不斉記憶型分子間共役付加反応及び Dieckmann 縮合の開発と応用

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略号表

Boc: *tert*-butoxycarbonyl

Bn: benzyl

Bz: benzoyl

^{i}Bu: isobutyl

^{t}Bu: *tert*-butyl

CAN: ammonium hexanitratocerate (IV)

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DIEA: *N*,*N*-diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DME: 1,2-dimethoxyethane

DMF: *N*,*N*-dimethylformamide

DMSO: dimethylsulfoxide

DPPA: diphenylphosphoryl azide

Et: ethyl

EDC・HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

FAB: fast atom bombardment

HMPA: hexamethylphosphoric triamide

HR: high resolution

IR: infrared absorption spectrometry

KHMDS: potassium bis(trimethylsilyl)amide

LiHMDS: lithium bis(trimethylsilyl)amide

LDA: lithium diisopropylamide

MS: mass spectrometry

MEM: methoxyethoxymethyl

MOM: methoxymethyl

Me: methyl

NCS: *N*-chlorosuccinimide

NaHMDS: sodium bis(trimethylsilyl)amide

NMR: nuclear magnetic resonance

^{i}Pr: isopropyl

PMB: *p*-methoxybenzyl

Ph: phenyl

L-Pro: L-proline

RPHPLC: reverse phase high performance liquid chromatography

r. t.: room temperature

SO_3・py: sulfer trioxide pyridine complex

THF: tetrahydrofuran

TBDPS: *tert*-butyldiphenylsilyl

TBAB: tetra-*n*-butylammonium bromide

TFA: trifluoroacetic acid

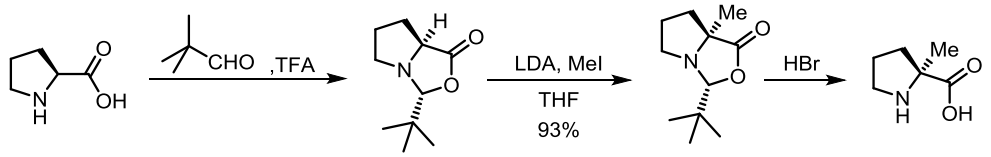
TMEDA: tetramethylethylenediamine

TMS: trimethylsilyl

Z(=Cbz): benzyloxycarbonyl

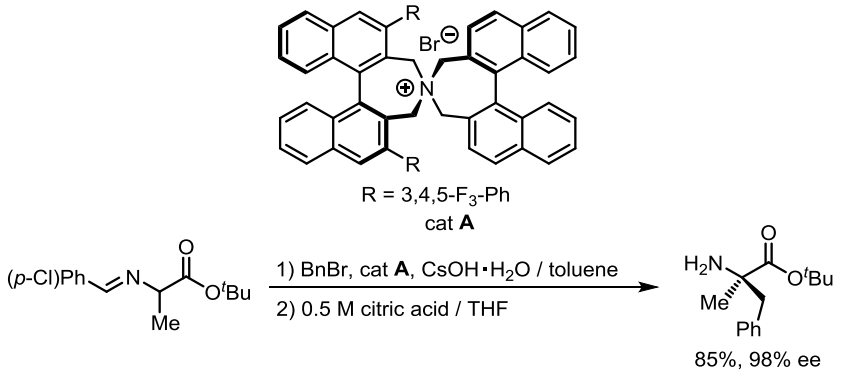
諸言

α, α -二置換 α -アミノ酸は有機化学や創薬化学において重要なツールとして利用されている。例えば、有機合成分野においては、キラルビルディングブロック、不斉触媒、不斉補助基、遷移金属触媒の配位子となるなど非常に有用な化合物群である。さらには天然物の構成単位にもしばしば見られるため、それ自身が合成ターゲットになることもある [1)]。また、創薬化学分野では、アミノ酸の脂溶性の増大、代謝安定性の向上など用途は多岐に渡る [2)]。その高い有用性のため、キラルなα, α -二置換 α -アミノ酸は、多くの研究者の合成研究ターゲットとなっている [3)]。例えば、Seebach らは、自己再生型不斉補助基を利用したジアステレオ選択的なエステルエノラートのアルキル化により、四置換炭素を構築している (Scheme 1-1) [4a, b)]。



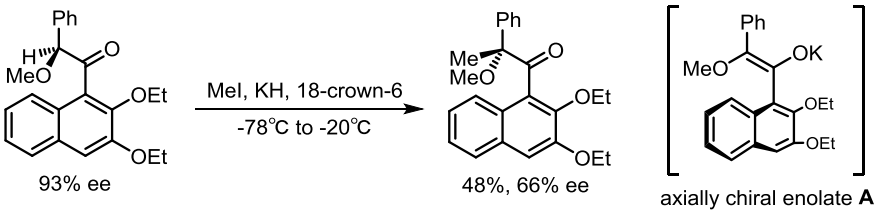
Scheme 1-1 自己再生型不斉補助基を用いたα, α −二置換 α −アミノ酸の合成例 (Seebach ら [4a,b)])

また、丸岡らは相関移動触媒 (PTC) を利用したアルキル化を報告している (Scheme 1-2) [5)]。その他にも数々の優れたα, α -二置換 α -アミノ酸合成法が報告されている [3)]。

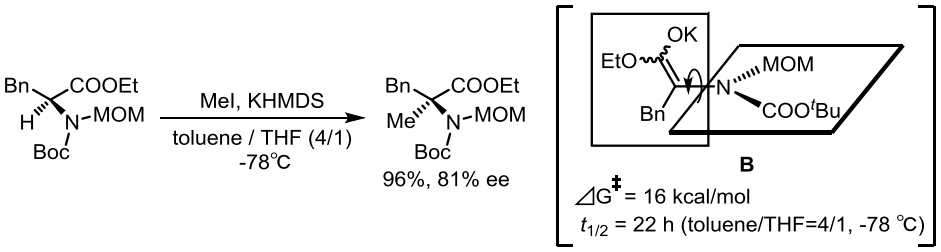


Scheme 1-2 PTC を用いたα, α −二置換 α −アミノ酸の合成例 (丸岡ら [5)])

一方 1991 年に川端らは、不斉が一見消失するエステルエノラートを経由する反応でも、軸性不斉を有する中間体 **A** を経由することで、中間体に動的なキラリティーが保持され不斉反応が進行する「不斉記憶型反応 (Memory of Chirality: MOC)」を報告している (Scheme 1-3) [6)]。2000 年には、この方法を α-アミノ酸誘導体へ展開し、*N*-Boc-*N*-MOM α-アミノ酸から生じるキラルな *C*-*N* 軸性不斉エノラート **B** を経由した不斉記憶型メチル化によりα-メチルアミノ酸の合成に成功している (Scheme 1-4) [7)]。この方法は、不斉触媒や不斉補助基を用いることなく、直接的にα, α -二置換 α -アミノ酸が得られるため、不斉触媒や不斉補助基を用いる方法に続く、第三の不斉合成法と言える。

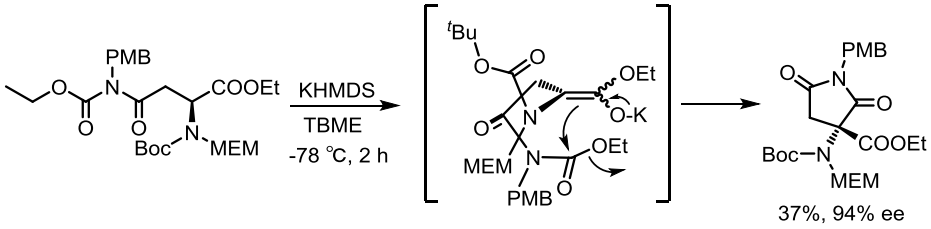


Scheme 1-3 不斉記憶型反応 (川端ら [6])



Scheme 1-4 不斉記憶型反応を用いた α, α −二置換 α −アミノ酸の合成 (川端ら [7])

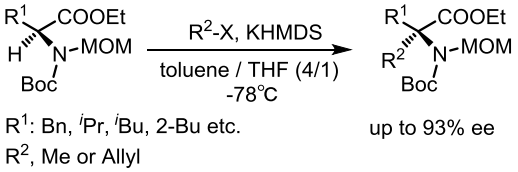
これまでに、この不斉記憶型の「分子内反応」を基盤として、アルキル化反応 [8]、共役付加反応 [9]、Dieckmann 縮合 [10]、アシル基転移反応 [11] やアリール化反応 [12] が報告されてきた。しかしながら、この内不斉記憶型 Dieckmann 縮合では、低収率という問題を抱えていた (Scheme 1-5)。



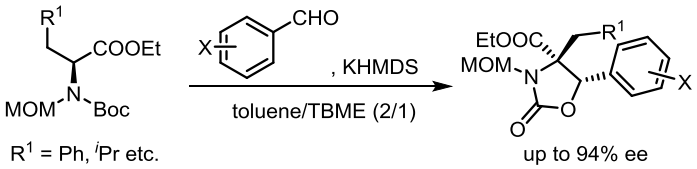
Scheme 1-5 不斉記憶型 Dieckmann 縮合

また、「分子間反応」としては、アルキル化反応 [7, 13]、アルドール反応 [14] を報告しているが、基質となる α-アミノ酸はラセミ化半減期の長いフェニルアラニン (Scheme 1-4 参照) やバリン、ロイシン、イソロイシンなどの基質に限られており (Scheme 1-6, 1-7)、ラセミ化半減期の短いアラニン誘導体への適用は達成されていなかった。

このような背景のもと著者は、上記問題の解決に向けて、不斉記憶型反応を中心とした新規α, α -二置換 α -アミノ酸の合成並びに不斉記憶型反応の応用研究を行った。



Scheme 1-6 分子間不斉記憶型アルキル化 [7, 13]



Scheme 1-7 不斉記憶型アルドール反応 [14)]

第一章 不斉記憶型分子間共役付加反応の開発と全合成への応用

第二章 改良型不斉記憶型 Dieckmann 縮合の開発

第三章 不斉記憶型反応を用いた新規アザエストラジオールの合成研究

第一章　不斉記憶型分子間共役付加反応の開発と全合成への応用

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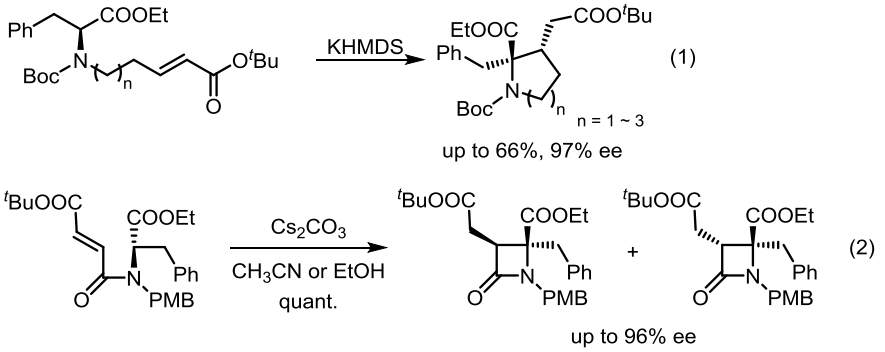
Org. Lett. **2013**, *15*, 864-867.

第一節 不斉記憶型分子間共役付加反応の開発

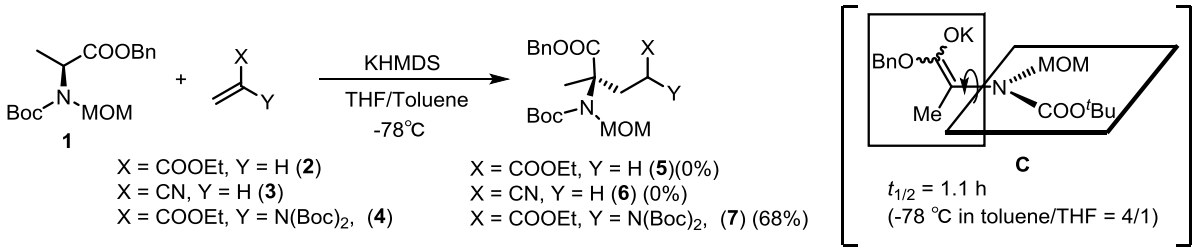
著者の所属する研究室では、これまでに不斉記憶型分子内共役付加反応を報告しており、五～七員環の含窒素ヘテロ環の合成ならびに多置換の新規 β-ラクタムの合成を報告している (Scheme 2-1) [9]。



Scheme 2-1 不斉記憶型分子内共役付加反応

しかしながら、合成法としてより自由度の大きい分子間共役付加反応の報告例は無く、分子間の不斉記憶型反応は前述通りメチル化、アリル化、アルドール反応に限られていた。不斉記憶型反応では、中間体の軸性不斉を有するキラルエノラートの軸の回転に伴うラセミ化と、目的とする反応が競合するため、生成物の光学純度が低下する問題が生じる。生成物の光学純度の低下を抑えるためには、軸性不斉エノラートの軸の回転 (ラセミ化) よりも速く目的の反応を進行させることが重要である。特に分子内反応に比べて反応速度の遅い分子間反応では、この問題が顕著になる。そのため、これまでの反応に用いられてきた基質となるアミノ酸は、そのエノラートのラセミ化半減期の比較的長い化合物に限られていた {例えば、フェニルアラニン由来のエノラート **B** (Scheme 1-3) のトルエン:THF=4:1 中の-78°C でのラセミ化半減期は 22 時間}。そこで、本研究では α-アミノ酸から生じるエノラートの中で最もラセミ化半減期の短くこれまで分子間不斉記憶型反応への適用が困難であったアラニン誘導体に着目し{エノラート **C** (Scheme 2-2) のトルエン:THF=4:1 中の-78°C でのラセミ化半減期は 1.1 時間: 未発表データ}、不斉記憶型分子間共役付加反応の開発を行うことにした。一方で、中間体キラルエノラートが最も短いラセミ化半減期を持つアラニン誘導体を用いた反応の開発に成功すれば、他の種々の α-アミノ酸を用いる幅広い分子間不斉記憶型反応への適用も可能になると考えられる。そこで、アラニン誘導体 **1** を用いて反応検討を行った。

まず、**1** より生じる *C-N* 軸性不斉エノラート **C** の短いラセミ化半減期を考慮して、速やかに反応が進行するマイケル受容体の探索を行った (Scheme 2-2)。塩基に KHMDS を用い、-78 °C で検討を行った結果、求電子剤としてアクリル酸エチル (**2**) やアクリロニトリル (**3**) を用いた場合は、付加体を殆ど与えなかったのに対し、共役付加後のエノラートアニオンの安定化を考慮した $N(Boc)_2$ 基を有するアクリル酸エステル **4** を用いると短時間で反応が進行し、目的の **7** を 1:1 のジアステレオマー混合物として 68%収率で得た。

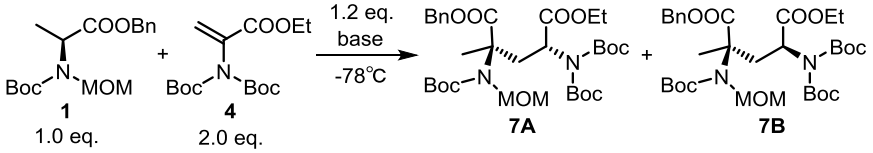


Scheme 2-2 マイケル受容体の探索

そこで、マイケル受容体を **4** に固定し反応検討を行った (Table 2-1)。Entry 1 は、Scheme 2-2 の条件であるが、トルエン/THF (4/1) の混合溶媒下、-78°C において、基質 **1** および **4** の混合溶液を塩基に 60 分かけて加えた後、10 分間撹拌した結果、化合物 **7** を 1/1 のジアステレオ混合物として収率 68%で得た。 この時、光学純度は 82% ee であった。塩基の検討では、NaHMDS の場合には収率は定量的であったが、光学純度が 63% ee と低下した (Entry 2)。LDA では、収率を 25%まで大幅に低下させた (Entry 3)。これら結果より引き続く検討は、光学純度が最も高い結果を与えた KHMDS を用いて行うこととした。溶媒検討では、トルエンを用いた場合は収率 75%、92% ee であった (Entry 4)。THF の比率の増加は光学純度を低下させた。トルエン/THF (1/1)では収率 56%、86% ee (Entry 5)、トルエン/THF (1/4)では収率 74%、光学純度は 87% ee (**7A**)、84% ee (**7B**) であった (Entry 6)、THF 単独では収率は定量的であったが、光学純度が 74% ee まで低下した (Entry 7)。この結果は、トルエンよりも配位性の高い THF の方が、キラルエノラートのアグリゲートが低次になり、エノラートの反応性を向上させただけでなく、ラセミ化半減期も同時に短くした結果と推測できる。トルエン/DMF (1/4)では、ジアステレオマー比が 1:2 に、光学純度が最高 94% ee (**7B**) へ僅かに改善したが、収率は 31% と低いものであった (Entry 8)。しかしながら、THF/DMF (1/1)を用いると、収率 83%、光学純度 93% ee (**7A**)、93% ee (**7B**)、ジアステレオマー比 1:2 とこれまでで最も良い結果となった (Entry 9)。DMF の添加は、キラルエノラートのラセミ化速度の増大にも増して目的の反応速度を向上させたため光学純度の向上につながったと考えている。このように、溶媒の選択とその比率がキラルエノラートのラセミ化と反応速度のバランスに重要であることが明らかとなった。

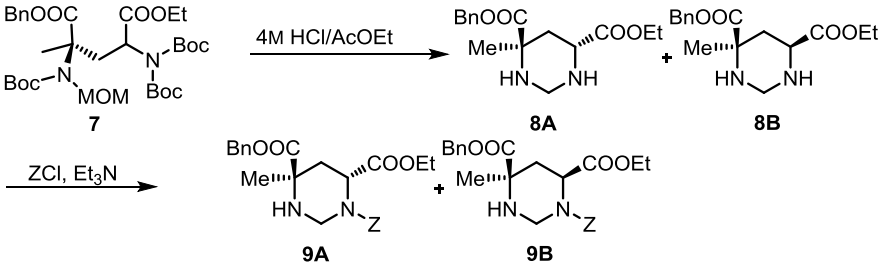
この反応では試薬の添加方法も重要であった。これまでは、基質を塩基に加えていたが、塩基を基質に加える手順に変えたところ、収率は定量的に、光学純度は 97% ee (**7A**)、97% ee (**7B**) を達成した (Entry 10)。この光学純度の向上は、発生させたエノラートを即座に大過剰のマイケルアクセプターで捕捉したことにより、軸性不斉エノラートのラセミ化が無視できるタイムスケールで共役付加反応が進行したためである。エノラートを発生させた後に親電子剤を添加した場合は、想定通り、キラルエノラートのラセミ化を伴うため光学純度を大幅に低下させた (Entry 11)。また、反応時間の延長は光学純度の低下を伴わなかったことから、逆マイケル反応は殆ど起こっていないと推察された (Entry 10 vs.12) (例えば、不斉記憶型分子内共役付加反応では、共役付加の可逆性により反応時間の延長に従い生成物の光学純度の低下が報告されている。[9b])。この反応はグラムスケールへのスケールアップにも対応でき、収率、光学純度、ジアステレオマー比を低下させることなく目的物を得た (Entry 13)。

Table 2-1 アラニン誘導体を用いる不斉記憶型分子間共役付加反応の検討



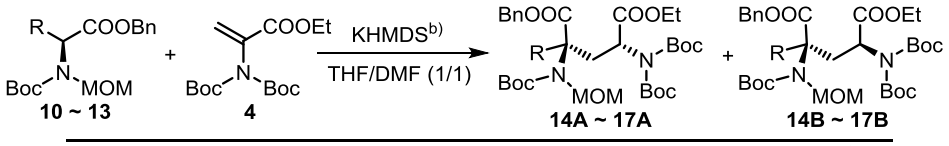
Entry	Base	Solvent	Time (min) for Addition[a)]	Time (min) for Reaction	Combined yield (%)	dr[b,c)] (**7A** / **7B**)	ee(%)[b)] **7A**	ee(%)[b)] **7B**
1	KHMDS[d)]	toluene/THF (4/1)	60	10	68	1 / 1	ND	82
2	NaHMDS[d)]	toluene/THF (4/1)	60	10	quant.	1 / 1	63	ND
3	LDA	toluene/THF (4/1)	60	10	25	1 / 1	ND	ND
4	KHMDS[e)]	toluene	60	10	75	1 / 1	92	92
5	KHMDS[e)]	toluene/THF (1/1)	60	10	56	1 / 1	ND	86
6	KHMDS[e)]	toluene/THF (1/4)	60	10	74	1 / 1	87	84
7	KHMDS[d)]	THF	60	10	quant.	1 / 1	74	ND
8	KHMDS[e)]	toluene/DMF (1/4)	60	10	31	1 / 1	91	94
9	KHMDS[d)]	THF/DMF (1/1)	60	10	83	1 / 2	93	93
10	KHMDS[d)]	THF/DMF (1/1)	35[f)]	10	quant.	1 / 2	97	97
11	KHMDS[d)]	THF/DMF (1/1)	30[g)]	10	70	1 / 2	22	22
12	KHMDS[d)]	THF/DMF (1/1)	35[f)]	120	90	1 / 2	ND	97
13[h)]	KHMDS[d)]	THF/DMF (1/1)	35[f)]	10	98	1 / 2	97	98

a) A solution of substrates **1** and **4** was added to a solution of base. b) The diastereomeric ratio and the enantiomeric excess were determined after conversion to **9A** and **9B.** c) The relative configuration was determined by NOESY spectrum of **8A** and **8B.** d) THF solution. e) Toluene solution. f) A KHMDS solution was added to a solution of **1** and **4.** g) A solution of **1** was treated with KHMDS for 30 min, and then a solution of **4** was added dropwise to the mixture. h) A gram scale reaction. ND : Not Determined



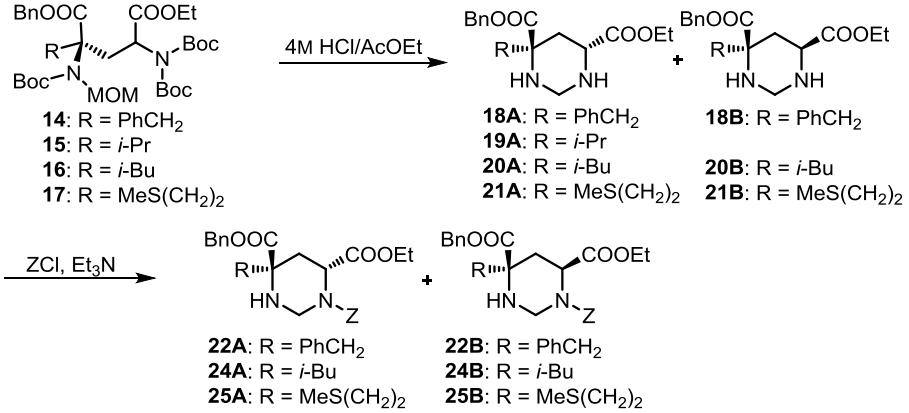
アラニン誘導体で不斉記憶型分子間共役付加反応を達成できたことから、他のアミノ酸への適用を同条件下に行った (Table 2-2)。フェニルアラニン誘導体 (**10**) においては、収率は定量的に進行し、ジアステレオマー比 3:2、それぞれ 97% ee、97% ee で目的の α, γ-ジアミノ酸誘導体 **14** を得た (Entry 1)。バリン誘導体 (**11**) は、反応速度が遅かったため反応温度を-40℃ まで上昇させて反応を行った (Entry 2)。その結果、**15A** を収率 50%、87% ee 単一のジアステレオマーとして得た。ロイシン誘導体 (**12**) は収率 62%、ジアステレオマー比 1:2、それぞれ 97% ee、97% ee で反応が進行し (Entry 3)、メチオニン誘導体 (**13**) においても収率は定量的に、ジアステレオマー比 1:2、それぞれ 91% ee、92% ee で目的物を与えた (Entry 4)。以上より、高収率、高立体選択的な不斉記憶型分子間共役付加反応の開発に成功した。

Table 2-2 種々のアミノ酸誘導体を用いる不斉記憶型分子間共役付加反応 [a)]



Entry	R	Time (h)	temp (℃)	Product	Combined yield (%)	dr[c, d)] (**A** / **B**)	ee (%)[c)] **A**	**B**
1	$PhCH_2$ (**10**)	0.3	-78	**14**	quant.	3 / 2	97	97
2	*i*-Pr (**11**)	24	-40	**15**	50	1 / 0	87	-
3	*i*-Bu (**12**)	2	-78	**16**	62	1 / 2	97	97
4	$MeS(CH_2)_2$ (**13**)	0.2	-78	**17**	quant.	1 / 2	91	92

a) A KHMDS solution was added to a solution of amino acids and **2.** b) THF solution c) The diastereomeric ratio and the enantiomeric excess were determined after conversion to **22A, 24A** or **25A** and **22B**, **24B** or **25B.** c) The relative configuration of **14** and **15** was determined by NOESY spectrum of (**18A**+**18B**) and **19A**, respectively.



14: R = $PhCH_2$
15: R = *i*-Pr
16: R = *i*-Bu
17: R = $MeS(CH_2)_2$

18A: R = $PhCH_2$
19A: R = *i*-Pr
20A: R = *i*-Bu
21A: R = $MeS(CH_2)_2$

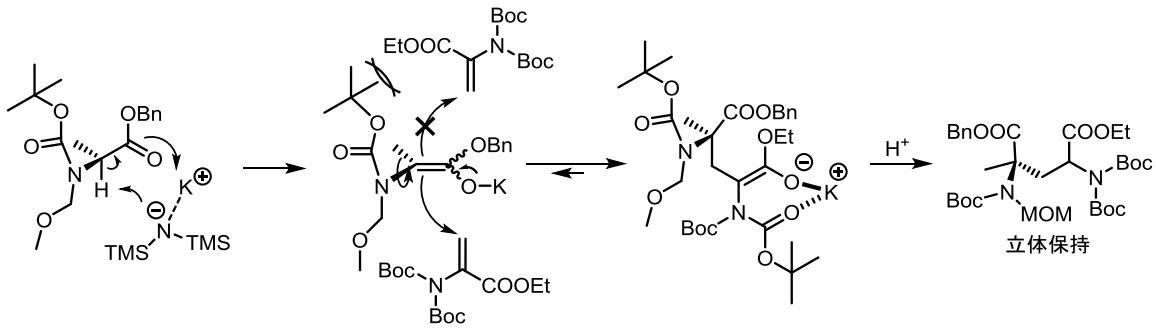
18B: R = $PhCH_2$
20B: R = *i*-Bu
21B: R = $MeS(CH_2)_2$

22A: R = $PhCH_2$
24A: R = *i*-Bu
25A: R = $MeS(CH_2)_2$

22B: R = $PhCH_2$
24B: R = *i*-Bu
25B: R = $MeS(CH_2)_2$

反応機構

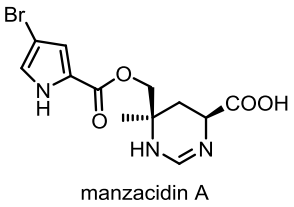
絶対配置は化合物 **7** を用いた海洋性天然物 manzacidin A の全合成により決定し、立体保持で進行していることを明らかとし (詳細は後述)、反応機構を次のように想定した (Scheme 2-3)。これまで報告された不斉記憶型反応では、*N*-Boc-*N*-アルキルアミノ酸誘導体の脱プロトン化は例外なく、脱プロトン化を起こす C(α)-H 結合が隣接する N-C(Boc)結合とアンチペリプラナーの配座から進行している [7-14)]。 その結果生成する軸性不斉エノラートに対しマイケルアクセプターは立体障害の小さい MOM 側からアプローチし、共役付加反応が進行し、全体として立体保持で反応が進行する。付加後のエノラートはカリウムとのキレートにより、逆マイケル付加反応が抑えられ収率よく目的物が得られていると考えられる。



Scheme 2-3 想定される反応機構

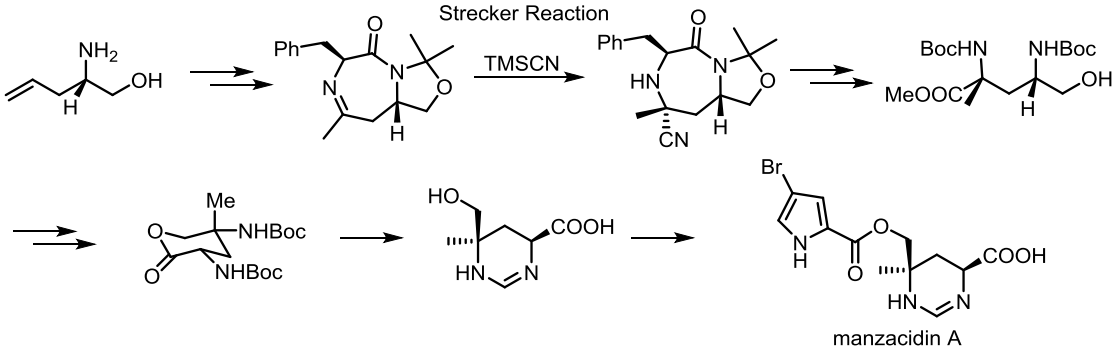
第二節 manzacidin A の全合成

上記の不斉記憶型分子間共役付加反応により得られるα,γ-ジアミノ酸誘導体 **7** を鍵中間体として海洋性アルカロイド manzacidin A[15] の全合成を行うこととした (Figure 2-1)。manzacidin A はブロモピロールアルカロイドの一種である。manzacidin A 自体の生物活性は報告されていないが、ブロモピロールアルカロイド類は α-アドレナリン受容体遮断作用、セロトニン受容体拮抗作用、アクトミオシン ATP アーゼの活性化作用など様々な薬理活性が報告されており、非常に興味深い化合物群である[15]。テトラヒドロピリミジン環 6 位に四置換炭素を有しており合成化学的にも興味が持たれる。 Manzacidin A の最初の全合成は、大船らにより不斉補助基を利用したジアステレオ選択的な不斉 Strecker 反応を利用して達成されており (Scheme 2-4)[16]、その他にも Du Bois[17] ら、丸岡ら[18]、Deng, L ら[19]、Sibi, M. P. ら[20]、市川ら[21] により達成されている。著者は、不斉記憶型分子間共役付加反応により得られた四置換炭素を manzacidin A の四置換炭素として利用し合成する逆合成経路を設定した (Scheme 2-5)。すなわち、manzacidin A はエステル部位で切断すると、ピロール部位 **26** とテトラヒドロピリミジン部位 **27** に分けられる。この **27** は、不斉記憶型分子間共役付加反応により得られた **7B** から環化、エステルの還元、窒素 α 位の酸化、脱保護により得られると考えた。

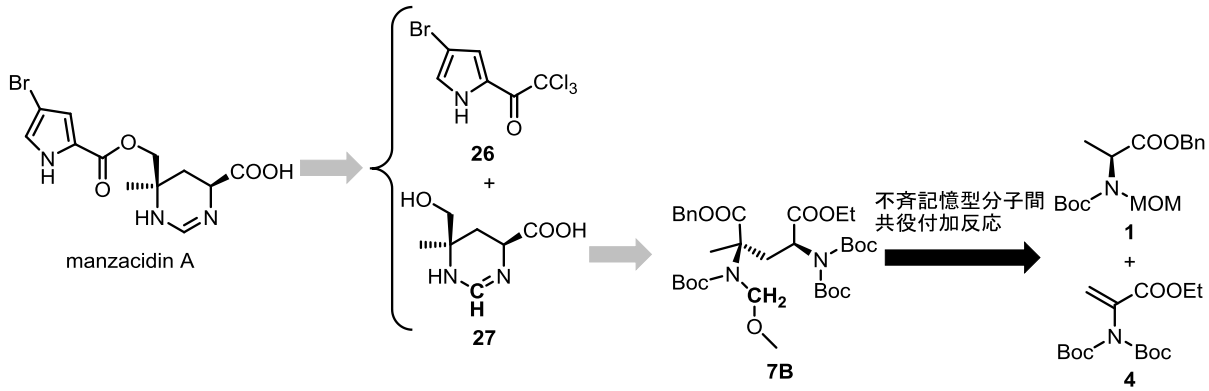


manzacidin A

Figure 2-1 manzacidin A の構造



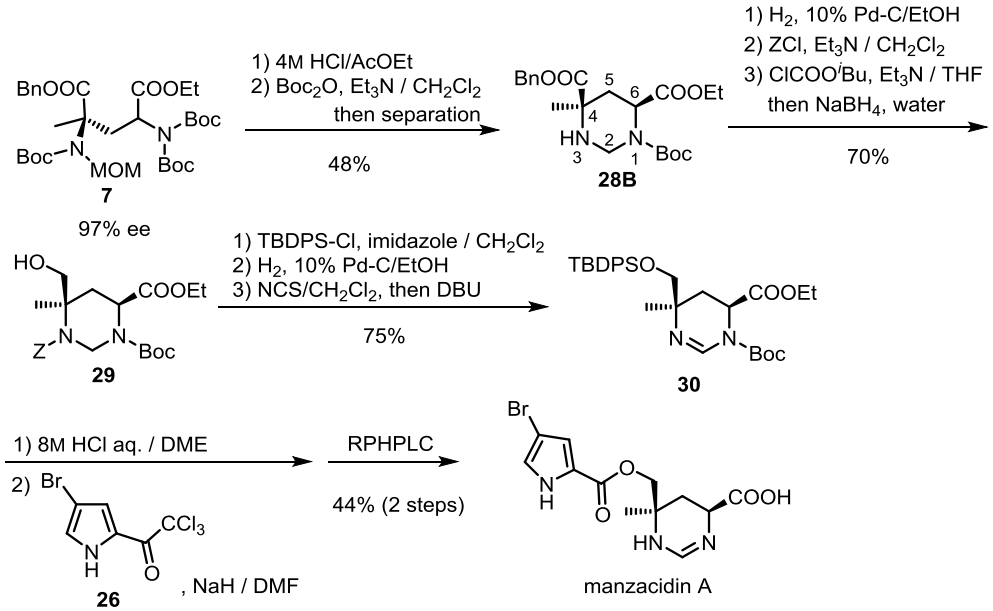
Scheme 2-4 manzacidin A の最初の全合成 (大船ら[16])



Scheme 2-5 manzacidin A の逆合成解析

実際の合成経路を下記に示す (Scheme 2-6)。ジアステレオ混合物 **7** の酸処理では、脱 Boc 化によ

り生じるアミンの *N*-MOM 基より生成するイミニウムへの付加により環化体が生成し、続く位置選択的な Boc 化後、ジアステレオマーを分離し **28B** を得た。**28B** の Bn 基を除去、3 位アミノ基の Z 基による保護、4 位カルボキシル基の混合酸無水物を経由した還元により **29** を得た。 **29** の水酸基の TBDPS 保護、Z 基の脱保護後、NCS による *N*-塩素化と続く DBU による脱塩化水素により **30** を得た。**30** の段階的な脱保護は失敗したが、塩酸を用いて一度にすべての保護基を除去することに成功した。この脱保護体を大船らの報告に基づきピロールエステル化し manzacidin A の合成を達成した。この化合物の ^{1}H NMR スペクトルを Figure 2-2 に示す。大船らの全合成品の NMR と良い一致を示した。さらに、比旋光度も報告と良い一致を示した {合成 manzacidin A $[\alpha]^{20}_D$ = -24.2 (c 0.7, MeOH), {lit.16 $[\alpha]^{27}_D$= -22.4 (c 0.52, MeOH)}。この合成により化合物 **7** の四置換炭素の絶対立体配置を *R* と決定し、不斉記憶型分子間共役付加反応が立体保持で進行することがわかった。



Scheme 2-6 manzacidin A の全合成

さらに、化合物 **28B** の 6 位エピマーである *R* 体ジアステレオマーも同様に *ent*-manzacidin C へ誘導し、manzacidin C と比旋光度の絶対値および各種スペクトルが一致することを確認した {合成 *ent*-manzacidin C $[\alpha]^{20}_D$ = -82.9 (c 0.45, MeOH), lit.16 manzacidin C $[\alpha]^{27}_D$= +89.3 (c 0.73, MeOH)}。Figure 2-3 には ^{1}H NMR の比較を示した。

以上のことより不斉記憶型分子間共役付加反応の開発に成功し、manzacidin A の全合成によりその有用性を示すことができた。

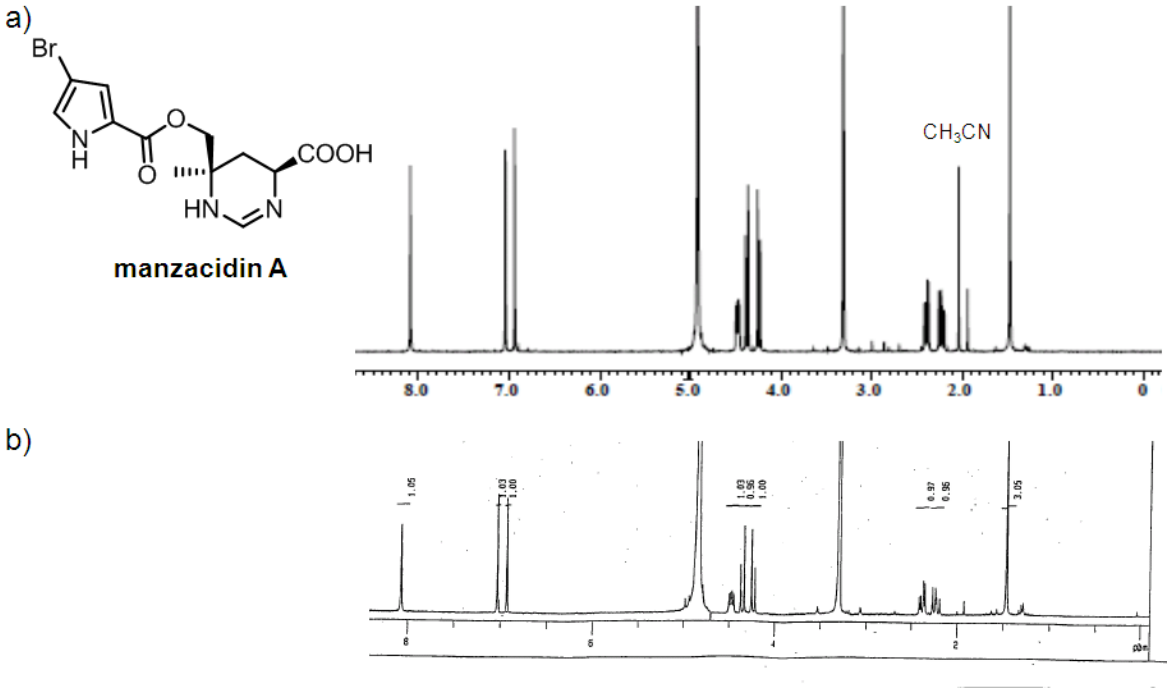


Figure 2-2 manzacidin A の ^{1}H NMR (CD_3OD) スペクトル、a) 著者らによる合成化合物、b) 大船らによる合成化合物.

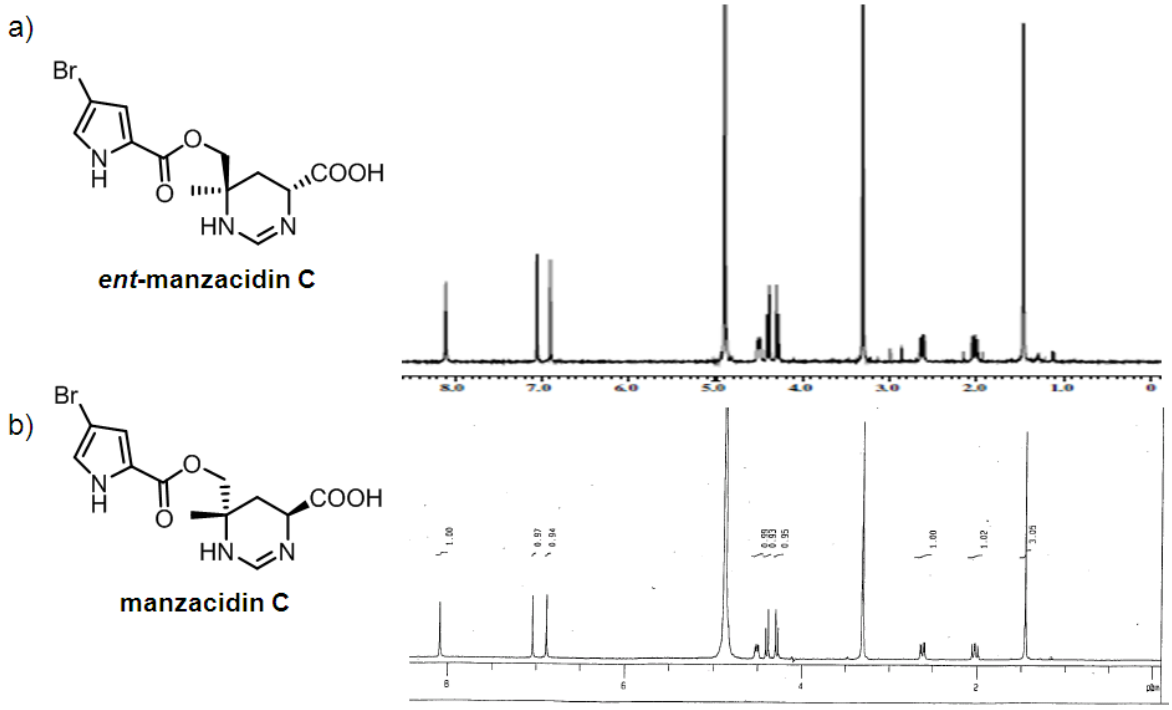
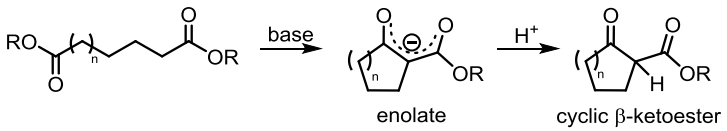


Figure 2-3 ^{1}H NMR (CD_3OD) スペクトル、a) 著者らによる合成 *ent*-manzacidin C、b) 大船らによる合成 manzacidin C.

第二章 改良型不斉記憶型 Dieckmann 縮合の開発

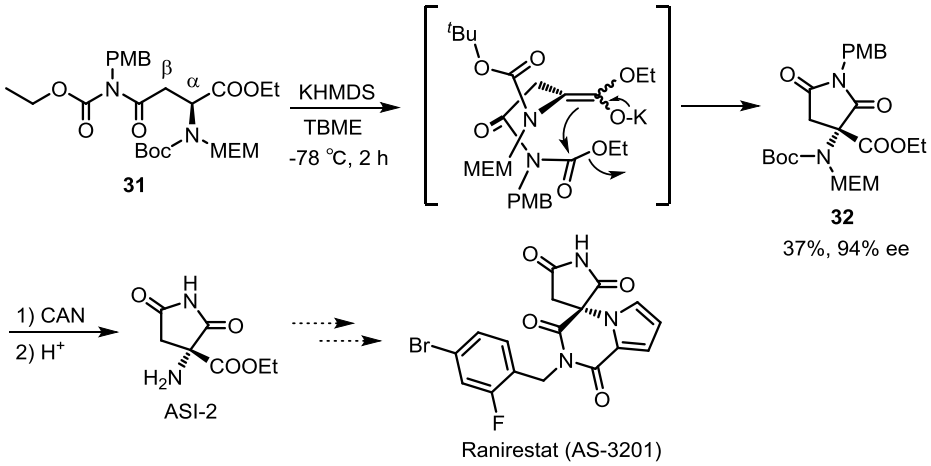
第一節 不斉記憶型 Dieckmann 縮合

Dieckmann 縮合は α-水素を有する分子内ジエステルから、環状 β-ケトエステルを合成する方法である (Scheme 3-1)[22] 。



Scheme 3-1 一般的な Dieckmann 縮合

当研究室の渡辺らは、2008 年に *C-N* 軸性不斉エノラートを用いた不斉記憶型 Dieckmann 縮合の開発を行い、アルドース還元酵素阻害剤 Ranirestat® [23]の合成中間体 ASI-2 の合成を報告している [10]。この不斉記憶型 Dieckmann 縮合では、アスパラギン誘導体 **31** から四置換炭素含有コハク酸イミド誘導体 **32** が得られる (scheme 3-2)。しかしながら、この方法は光学純度は良好なものの低収率であり改善が必要であった。そこで、高収率、高選択的な不斉記憶型 Dieckmann 縮合の開発を目的に研究を行うこととした。



Scheme 3-2 不斉記憶型 Dieckmann 縮合

この低収率の原因は基質 **31** (Scheme 3-2) のγ位にカルボニル基を有することによる α位と β位の脱プロトン化の競合であると考え、脱プロトン化の競合しない求電子側鎖を有する基質 **D** ~ **F** (Figure 3-1) を用いて検討を行うこととした。化合物 **D** からは γ-ラクタムアミノ酸誘導体 **G** が、化合物 **E** からは γ-ラクトンアミノ酸誘導体 **H** が、化合物 **F** からはインドリン-3-オン誘導体 **I** が得られると想定される。これまでに、**G** の様な単環性の四置換炭素含有 γ-ラクタムアミノ酸誘導体の構築は、Yang らにより、β-ケトエステルのニトロソアルドール反応において達成されている (Scheme 3-3)[24]。また、**H** の様な単環性の四置換炭素含有 γ-ラクトンアミノ酸誘導体の構築は、Rawal らによる β–ケトエステルへの不斉ヒドラジン化 [25]、Vedejs らによる不斉カルボキシル基転移反応と続くラクトン化 [26]や丸岡らによる不斉 Mannich 反応と続く還元によるラクトン化 [27]などにより達成され

ている (Scheme 3-4 ~ 6)。**I** の様な四置換炭素含有インドリン-3-オン誘導体の構築は Xu らにより、β-ケトエステルの不斉 Michael 付加反応[28]などにより達成されているが (Scheme 3-7)、これら化合物の合成を不斉記憶型 Dieckmann 縮合により達成された例はない。したがって、不斉記憶型 Dieckmann 縮合の開発は、四置換炭素含有環状 β-ケトエステル類の新たな直接的不斉構築法になると考えられる。

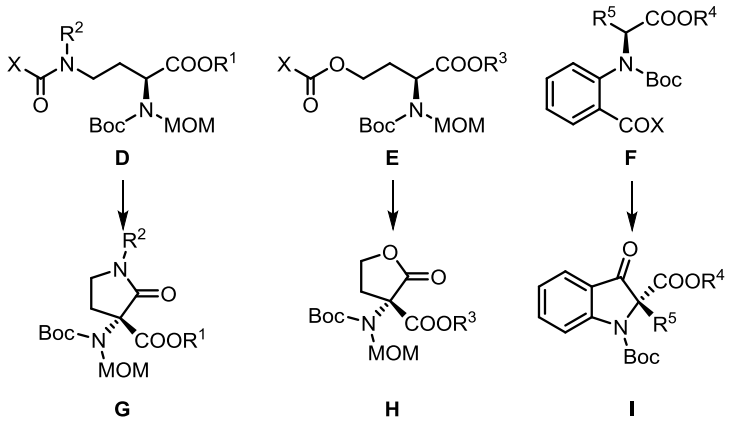
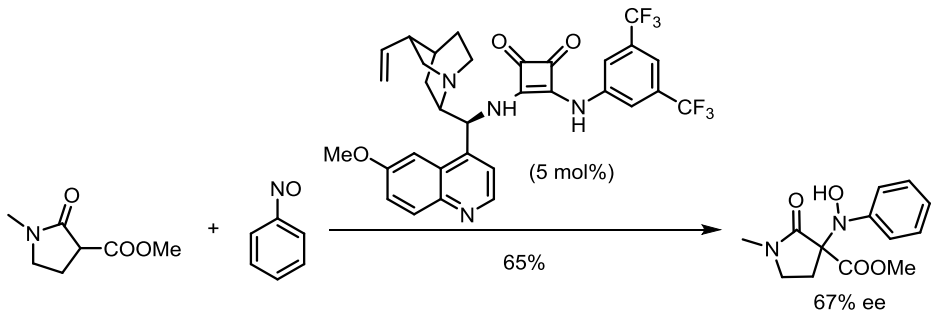
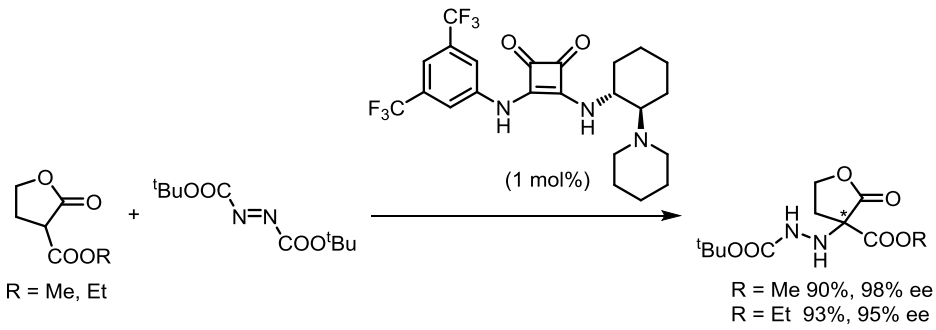


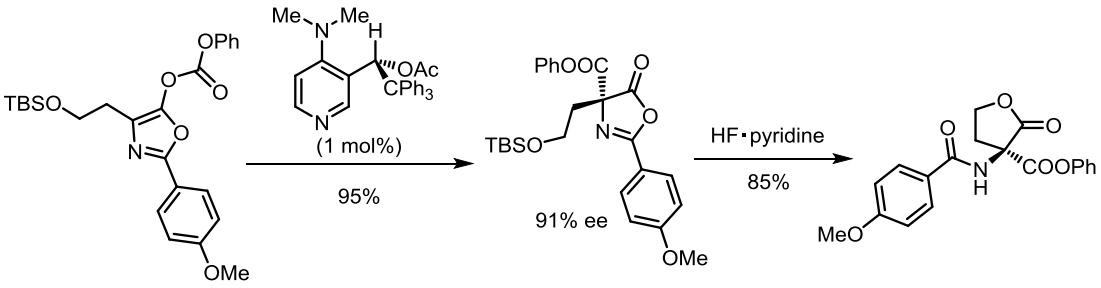
Figure 3-1 不斉記憶型 Dieckmann 縮合の標的反応



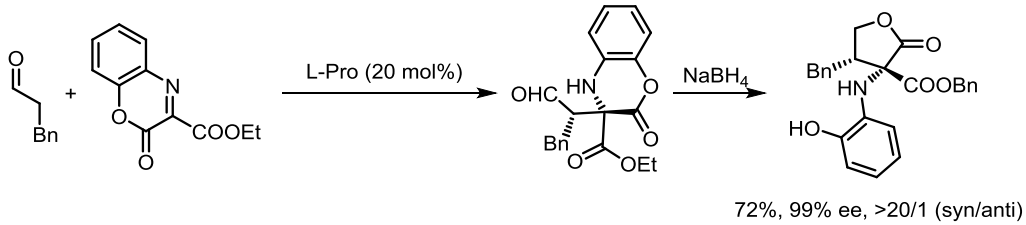
Scheme 3-3 β−ケトエステルのニトロソアルドール反応による四置換炭素含有γ−ラクタムアミノ酸の合成例（Yang ら[24]）



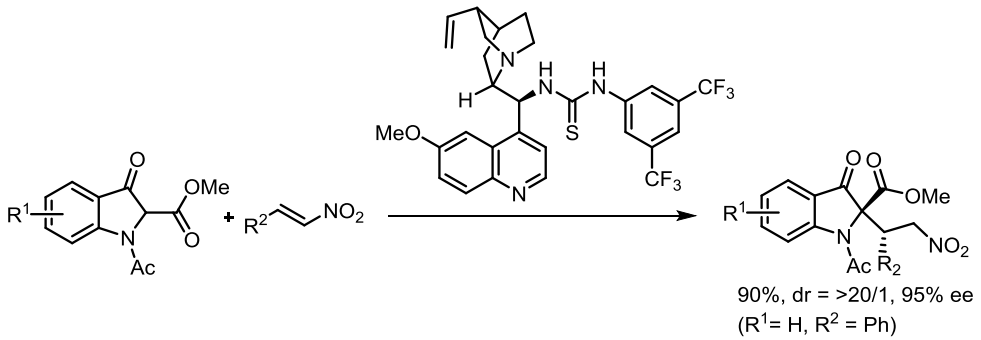
Scheme 3-4 β−ケトエステルの不斉ヒドラジン化（Rawal ら[25]）



Scheme 3-5　不斉カルボキシル基転移反応と続くラクトン化 (Vedejs ら [26])



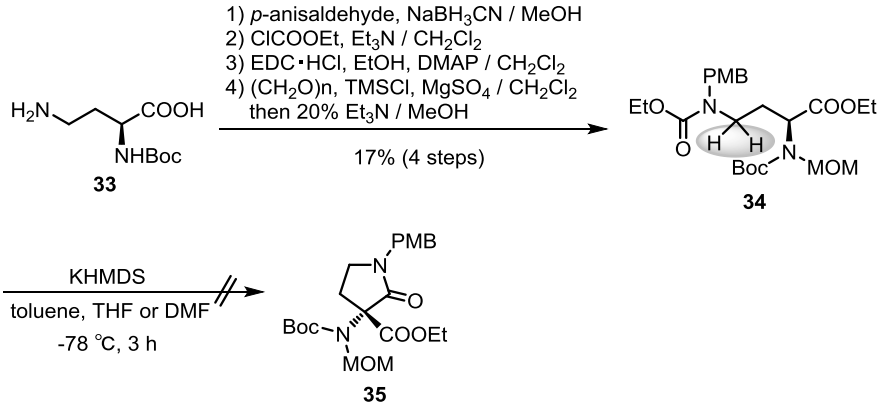
Scheme 3-6 不斉 Mannich 反応と続く還元によるラクトン化（丸岡ら [27]）



Scheme 3-7 不斉 Michael 付加反応によるインドリン-3-オン誘導体の合成（Xu ら [28]）

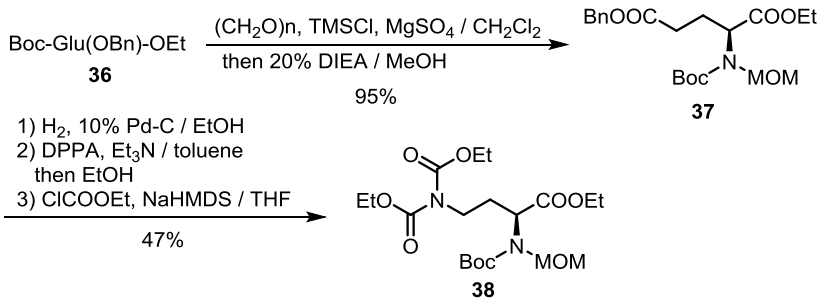
第二節 四置換炭素含有 γ-ラクタムアミノ酸誘導体の合成とその不斉構築

第一節で述べたように、アスパラギン誘導体 **31** の γ 位のカルボニル基の存在による α 位と β 位の脱プロトン化の競合を抑えることで目的の β-ケトエステルが得られると考え、γ 位のカルボニル基をメチレンに変換した化合物を合成し、不斉記憶型反応の検討を行った。反応に用いる基質の合成は、まず、既報通り Boc-グルタミンの Hoffmann 転位反応により得られた N^{α}-Boc-α,γ-ジアミノ酪酸 (**33**) [29]の *p*-アニスアルデヒドとの還元的-*N*-アルキル化による PMB 基の導入の後、第二級アミノ基をエトキシカルボニル化した。続いて α 位のカルボキシル基をエチルエステルへ変換したのち、アミド窒素に MOM 基を導入し不斉記憶型反応の前駆体 **34** を合成した。しかしながら、この **34** の KHMDS の処理では全く反応が進行しなかった (Scheme 3-8)。



Scheme 3-8 不斉記憶型 Dieckmann 縮合の初期検討

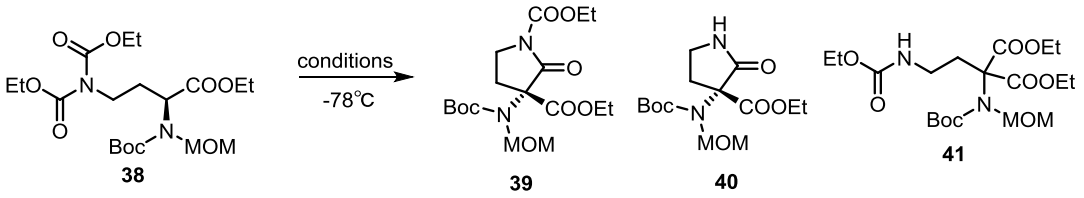
この原因はイミド構造がアミドになったことによる求電子側鎖の求電子性の低下と、γ 位の sp^2 のカルボニル炭素が sp^3 のメチレン炭素になったことによる配座自由度の向上が原因であると考えた。そこで、イミド構造を有したまま、エントロピー的に反応が有利に進行すると考えられる 2 つのエトキシカルボニル基を有するエキソイミド体 **38** を合成することにした。**38** の合成は Boc-Glu(OBn)-OEt (**36**) を出発原料として行い、カーバメート窒素の MOM 化を行い **37** へ誘導した後、接触還元によるベンジルエステルの脱保護と、続く Curtius 転位の後の中間体イソシアネートのエタノールでの捕捉によりエチルカーバメートへ変換した。最後にカーバメートの水素を理論量未満 (ラセミ化の抑制のため) の NaHMDS で脱プロトン化しクロロギ酸エチルと反応させることでジエトキシカルボニルアミノ体 **38** を得た (Scheme 3-9)。



Scheme 3-9 エキソイミド体 **38** の合成

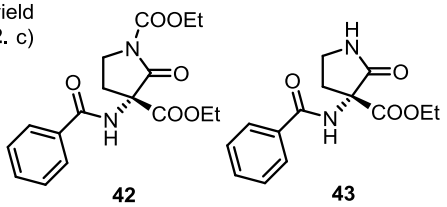
38 の不斉記憶型反応の検討結果を Table 3-1 に示す。溶媒に THF、塩基に KHMDS を用いて 30 分反応させたところ、目的とした γ-ラクタムアミノ酸 **39** の他に 1 位のエトキシカルボニル基が脱保護された **40** が得られた (Entry 1)。この **40** の光学純度は驚くべきことに 0% ee で完全なラセミ体であった。塩基として NaHMDS を用いた際には 22%収率で **39** が得られ、光学純度は 5% ee であった (Entry 2)。LiHMDS では全く反応が進行しなかった (Entry 3)。LDA では 5% 収率ながら 23% ee と改善した (Entry 4)。反応加速を期待した DMF を用いた反応では全く目的物は得られなかった (Entry 5)。また、LDA を用いて長時間の撹拌でも収率は改善しなかった (Entry 6) 。一方、HMPA を添加した反応では、γ-ラクタム誘導体 **40** の他にマロネート誘導体 **41** が得られた。

Table 3-1 エキソイミド体 38 の不斉記憶型反応の検討結果

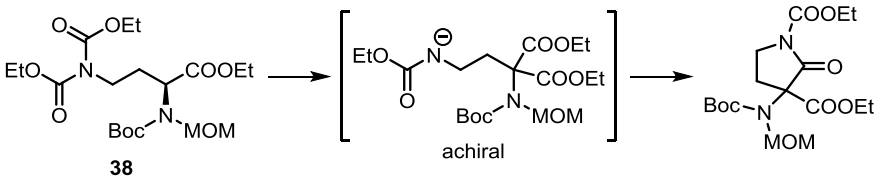


Entry	Base (sol.) (eq.)	Additive	Solvent	Time (h)	Yield 39	40	41
1	KHMDS (THF) (1.1)	-	THF	0.5	< 48%[a]	39% (0% ee[c])	
2	NaHMDS (THF) (1.1)	-	THF	0.5	22% (5% ee)[b]	-	
3	LiHMDS (THF) (1.1)	-	THF	0.5	-	-	
4	LDA (hex, THF) (1.1)	-	THF	0.5	5% (23% ee)[b]	-	
5	LDA (hex, THF) (1.1)	-	DMF	0.5	-	-	
6	LDA (hex, THF) (2)	-	THF	10	trace	16% (18% ee[c])	
7	LDA (hex, THF) (1.2)	HMPA (5 eq.)	THF	10	-	23%	37%

a) An unseparable mixture of **39** and **38** (ca. 30%). b) Chemical yield and enantiomeric excess were determined after convertion to **42.** c) The enantiomeric excess was determined after convertion to **43.**



上記結果において、 Entry 1 の条件で光学活性体が得られなかったこと、また、Entry 7 においてアキラルなジエチルマロネート誘導体が副生成物として得られていることから、この反応は *N-C* アシル基転移が起こり、アキラルなジエチルマロネートを経由して進行するものと想定した。(Scheme 3-10)。



Scheme 3-10 想定した反応機構

この推定メカニズムが正しければ、目的とした不斉記憶型 Dieckmann 縮合ではなく不斉記憶型 *C*-アシル化を経由することになる。本反応機構を精査すれば不斉記憶型 Dieckmann 縮合の開発につな

がると考え、検討を続けることとした。そこでまず、転移する置換基上の R が α 位に存在するエチルエステルの OEt と異なれば、不斉記憶型 *C*-アシル化により中間体マロネートはキラルになると考え (Figure 3-2)、基質 **38** のアミノ酸エチルエステルとは異なる *t*-ブトキシカルボニル基を側鎖窒素上に導入した **44** を用いて検討を行うこととした。

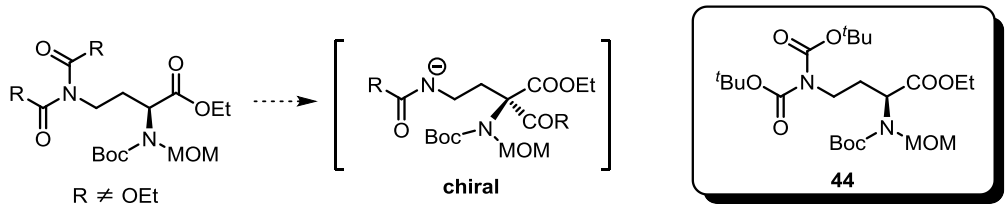
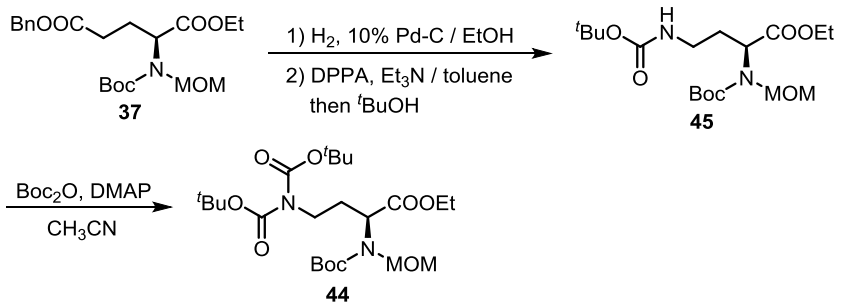


Figure 3-2 光学純度の向上を目的とした基質設計

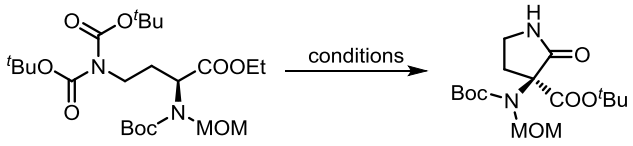
化合物 **44** の合成を Scheme 3-11 に記す。化合物 **37** の接触還元によるベンジルエステルの脱保護と、続く Curtius 転位の後の中間体イソシアネートの *t*-ブタノールでの捕捉により Boc 基へ変換した。次に、Boc_2O、DMAP を用いてアミド窒素上に2つ目の Boc 基を導入し *bis*-Boc アミノ体 **44** を得た。



Scheme 3-11 化合物 44 の合成

合成した **44** を用いて不斉記憶型反応の検討を行った (Table 3-2)。まず、溶媒に THF、塩基に KHMDS を用い、-78°C で反応を行った所、ピロリジン環の 1 位が脱保護され、エステル保護基が *t*-ブチル基に交換した γ-ラクタムアミノ酸誘導体 **46** を収率 10%で得た (Entry 1)。この化合物は想定通り光学活性体 (82% ee) であった。反応温度の-50°C への上昇は収率を 71% まで向上させたが、光学純度は 52% ee まで低下した (Entry 2)。しかしながら、この結果より -78°C でもエノラートの反応性を上げることで高い光学純度のまま収率は改善できると考え、溶媒検討を行うことにした。THF より配位性が高く、反応性の高いエノラートを発生すると期待できる DMF や DME を用いて反応させたところ、DMF、DME ともに収率の改善には至らず、特に DMF に至っては光学純度の大幅な低下を招いた。しかしながら、DME を用いた場合は光学純度が 94% ee と満足できる結果であった (Entry 3, 4)。そこで、より配位性が高く、反応性の高いエノラートの発生を期待して 18-crown-6 を THF 中で用いたところ収率は68%まで大幅に改善し、94% ee を達成した (Entry 5)。塩基の検討では、NaHMDS が最もよく 70%, 97% ee を達成した (Entry 6)。LiHMDS では全く反応が進行しなかった (Entry 7)。エーテル系ではなくアミン系の添加剤は全く効果が無かった (Entry 1 *vs.* Entry 8)。

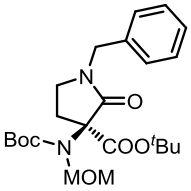
Table 3-2 エキソイミド体 **44** の不斉記憶型反応



44 **46**

Entry	Base (sol.) (eq.)	Additive (eq.)	Solvent (ratio)	Temp. (℃)	Time (h)	Yield (%)	ee[a] (%)
1	KHMDS (THF) (1.2)		THF	-78	12	10	82
2	KHMDS (THF) (1.2)		THF	-50	10	71	52
3	KHMDS (THF) (1.2)		THF/DMF (1/4)	-65	14	32	29
4	KHMDS (THF) (1.2)		THF/DME (1/1)	-78	12	4	94
5	KHMDS (THF) (1.2)	18-crown-6 (2.4)	THF	-78	12	68	94
6	NaHMDS (THF) (1.2)	15-crown-5 (2.4)	THF	-78	12	70	97
7	LiHMDS (THF) (1.2)	12-crown-4 (2.4)	THF	-78	12	-	
8	KHMDS (THF) (1.2)	TMEDA (5.0)	THF	-78	12	10	85

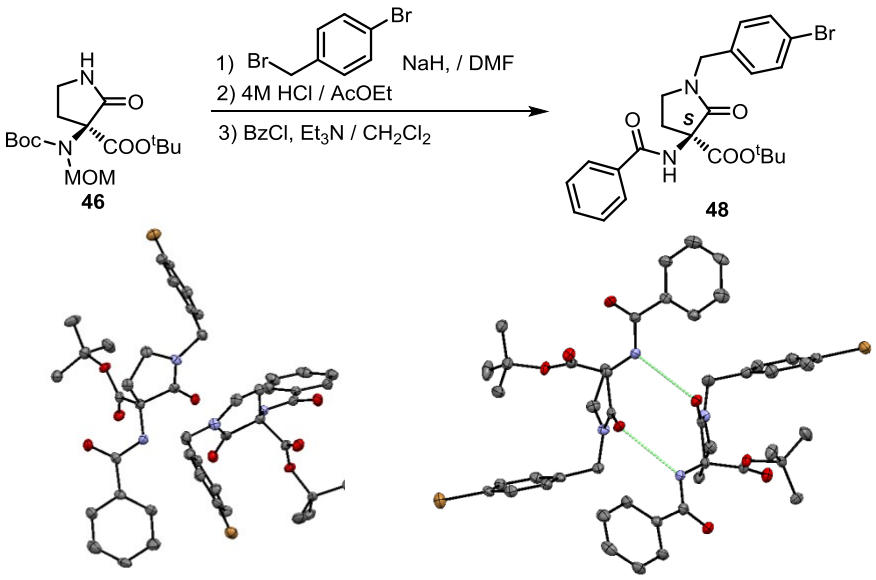
a) The enantiomeric excess was determined after conversion to **47**.



47

反応機構

化合物の **46** の絶対配置は誘導体の X-線結晶構造解析により行った。すなわち、1 位をブロモベンジル化後、Boc 基、MOM 基を *t*-ブチルエステル存在下選択的に除去し、ベンゾイル化し **48** を得た。**48** の単結晶 X-線構造解析により、四置換炭素の絶対配置は *S* であり、立体反転で本反応が進行することが判明した (Figure 3-3)。

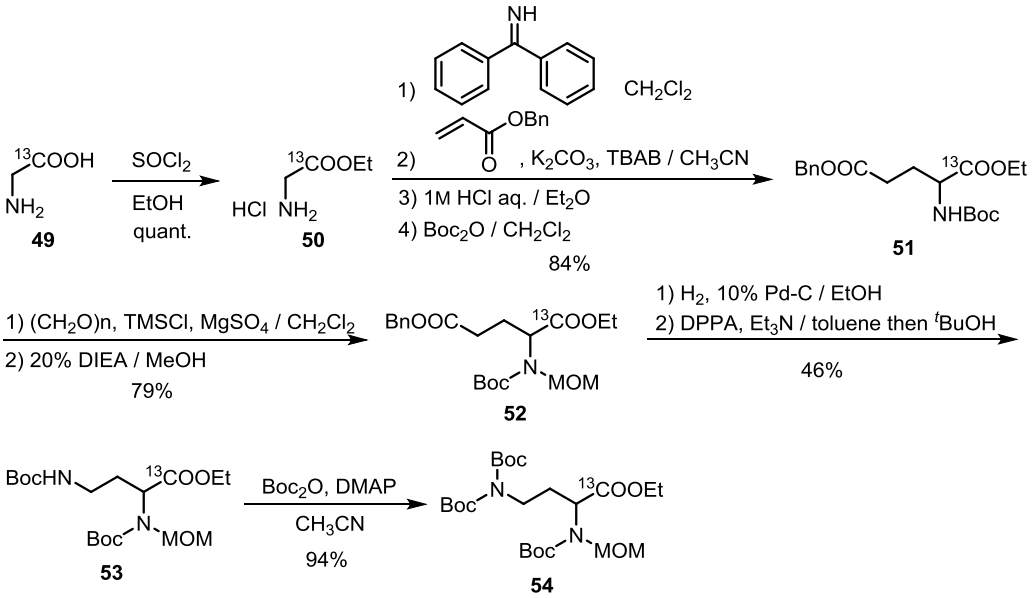


46 **48**

Figure 3-3 化合物 **48** の合成と **48** の X-線結晶構造（右図の緑点線は分子間での水素結合を示す）

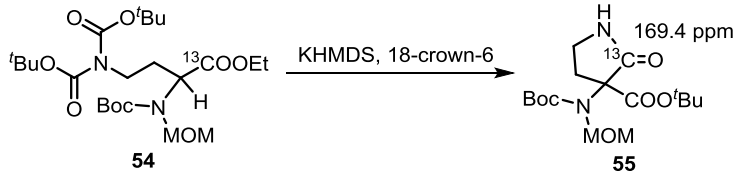
次に、Table 3-2 において基質と生成物の α-位のエステルがエチルから *t*-ブチルへ交換されていることから、基質エチルエステルカルボニル炭素に由来する生成物 **46** でのカルボニル基を ^{13}C ラベル

化した基質を用いて確認することにした。1-^{13}C ラベル体 **54** の合成は下記の様に行った (Scheme 3-12)。まず、1-^{13}C グリシン (**49**) を原料とし、エチルエステル化し **50** とした。次に、ベンゾフェノンイミノ化、アクリル酸ベンジルエステルに対するマイケル付加を行った後、ベンゾフェノンイミンを Boc 基へ変換し **51** とした。**51** からの誘導は Scheme 3-9, 3-11 と同様の方法で行い **54** を得た。



Scheme 3-12 ^{13}C ラベル体 **54** の合成

54 の γ-ラクタムアミノ酸への変換は、Table 3-2、entry 5 の方法に従い、KHMDS/18-crown-6 を用いて行い **55** を得た (Scheme 3-13)。化合物 **55** の ^{13}C NMR (DMSO-d_6) 測定ではラベル化された炭素のシグナルは 169.4 ppm であった。169.4 ppm に帰属される炭素シグナルはラクタム環 2 位のカルボニル炭素であったことからラクタム環 2 位がラベル化されていることが分かった。すなわち、基質 **44** のエチルエステルのカルボニル炭素は生成物 **46** の エステルカルボニルでなくラクタムカルボニルであることが分かった。



Scheme 3-13 ^{13}C ラベル体　**54** を用いた γ-ラクタムアミノ酸誘導体 **55** の合成

以上の結果より、Scheme 3-10 の想定は正しく、反応機構をまとめると次のようになる (Sheme 3-14)。

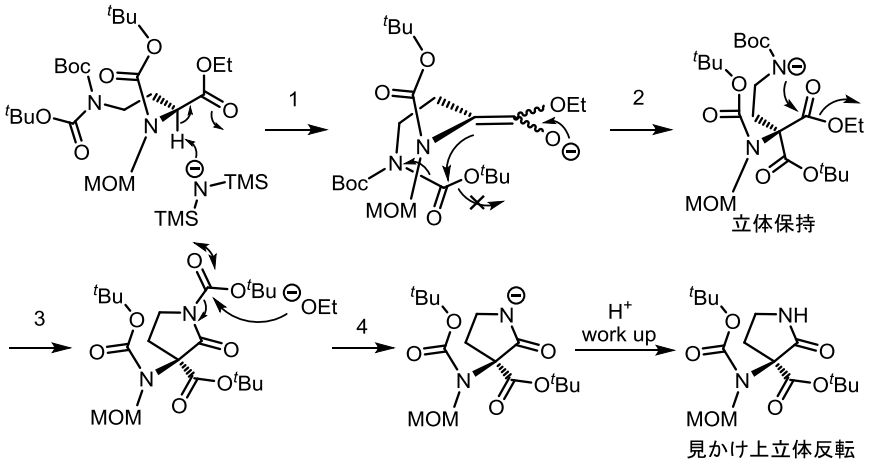
Step 1: Boc 基とアンチペリプラナーのコンホメーションにある α 水素が KHMDS により引き抜かれて *C-N* 軸性不斉エノラートが生成する。

Step 2: 軸性不斉エノラートは側鎖上の $N(Boc)_2$ 基と反応し、*tert*-ブトキシカルボニル化を立体障害の小さい *N*-MOM 基側から起こす (立体保持)。この際脱離するのは *t*-ブトキシドではなくカーバメート窒素上のアニオンである。これは、脱離基の共役酸の p*K*a で説明できる。すなわち、^{t}BuOH の p*K*a は 17 なのに対し、ウレタン上の *NH* の p*K*a は 15 付近と考えられることから、ウレタン窒素側へ脱離した方がアニオンが安定になるためである。これにより *t*-

ブチルエステルが α 位に転移する。

Step 3: 生じた窒素上のアニオンは立体障害の小さいエチルエステルにより化学選択的にアシル化を受け、γ-ラクタム環を形成する。転移した *t*-ブチルエステル部位とは異なるエステル部位と環化するので、一見立体反転した上でエステル交換したように見える。

Step 4: 生じるエトキシドはピロリジン環 1 位の Boc 基を攻撃し、*N*-Boc 基が脱保護され、目的物が得られる。



Scheme 3-14 反応機構のまとめ

最後の脱保護段階は、生成物を得るのに非常に重要である。一般的な Dieckmann 縮合は Scheme 3-1 の様に、生成する β-ケトエステルの α 位のプロトンが脱離したアルコキシドにより脱プロトン化されエノラートとして安定化するため、逆 Dieckmann 縮合は進行せずに目的物が得られる [22]。しかしながら、上記反応では得られた β-ケトエステルは四置換炭素を有しており、脱離するプロトンが無いため、反応性の高いアルコキシドが生じると Figure 3-4 のように逆 Claisen 縮合や逆 Dieckmann 縮合が起きる可能性がある。しかしながら、Scheme 3-14 に示すように、エトキシドの *N*-イミドへの攻撃によりアミドアニオンが生じるため、逆 Claisen 縮合や逆 Dieckmann 縮合が妨げられ目的物が収率よく得られたと考えられる。

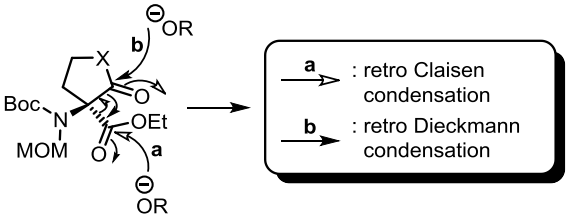
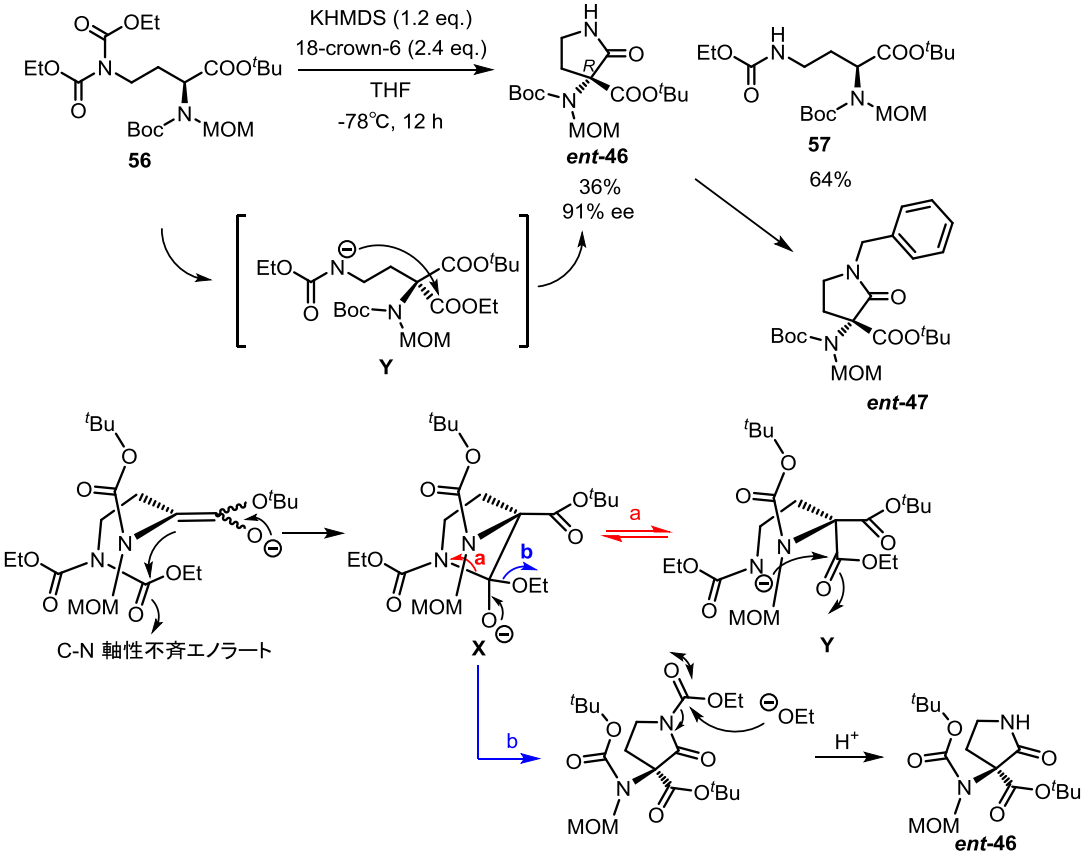


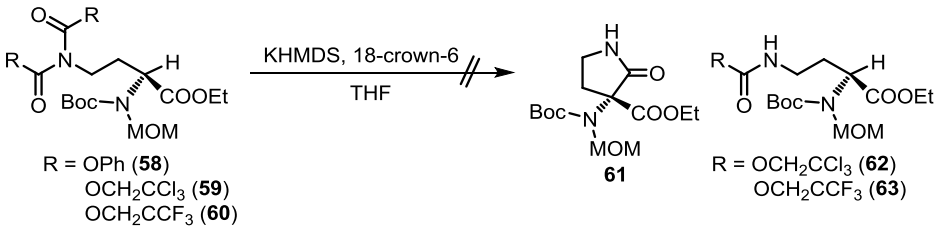
Figure 3-4 考えられる副反応

この反応機構は次の実験結果とも合致する。すなわち化合物 **44** の α 位エステルと側鎖アミノ保護基を入れ替えれば転移したエチルエステル側で環化するため立体保持で反応が進行すると考え **56** を合成し、不斉記憶型反応を行った (Scheme 3-15)。この結果、基質 **56** の側鎖エトキシカルボニル基の脱離を伴うため低収率ではあったが、予想通り立体保持で進行した化合物 ***ent*-46** を得た。絶対配置は、**46** と同様に *N*-ベンジル化により ***ent*-47** とし、キラルカラムを用いた HPLC における **47** 及びラセミ体との保持時間の比較により確認した。{ただし、この反応では、エトキシカルボニル基の転移後の中間体 **Y** は、四面体中間体 **X** から 経路 **a** を経由したものであるが、**a** を経由せず、直接的に経路 **b** を経由している可能性は完全に否定できない (この場合は、直接的に Dieckmann 縮合が進行したことになる)が、γ-ラクタムアミノ酸誘導体 **46** 合成の反応機構解析から中間体 **Y** を経由しているものと考えている}。



Scheme 3-15 立体保持で進行する形式的 Dieckmann 縮合

これら反応機構の解明により、γ-ラクタム合成は直接的な Dieckmann 縮合ではないことが明らかとなったため、直接的な不斉記憶型 Dieckmann 縮合の開発を目的とし、脱離基の共役酸の p*Ka* を考慮し、アニオンがより安定になるよう設計したビスフェノキシカルボニル基、ビス(2,2,2-トリクロロエトキシカルボニル)基やビス(2,2,2-トリフルオロエトキシカルボニル)を側鎖に導入した化合物 **58** ~ **60** を合成し検討を行ったが、全く目的物 **61** は得られず、**58** からは複雑な混合物を与え、**59** および **60** からは、側鎖アルコキシカルボニル基の脱保護が起こるのみであった (Scheme 3-16)。この脱保護は、反応系中の塩基が直接イミドを攻撃しているものと考察している。

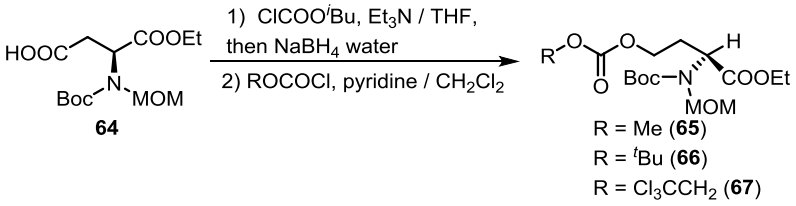


Scheme 3-16 直接的な不斉記憶型 Dieckmann 縮合に向けての試み

以上の結果より、γ-ラクタム合成を目的とした直接的な不斉記憶型 Dieckmann 縮合の開発は達成されなかったものの、不斉記憶型 *C*-アシル化を達成し、四置換炭素含有 γ-ラクタムアミノ酸の高エナンチオ選択的合成を行うことができた。直接的な不斉記憶型 Dieckmann 縮合の開発は他の基質で行うことにした。

第三節 四置換炭素含有 γ-ラクトンアミノ酸誘導体の合成

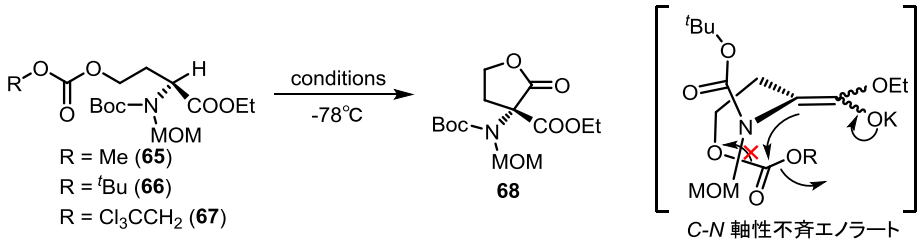
直接的な不斉記憶型 Dieckmann 縮合の開発を目指して、側鎖にカーボネート構造を有する基質 (**65**～**67**) より、γ-ラクトンアミノ酸誘導体の合成行うこととした。基質の合成はアスパラギン酸誘導体 (**64**) を出発原料とし[10]、混合酸無水物を経由した還元により生じた一級水酸基をカーボネートに変換して合成した (Scheme 4-1)。



Scheme 4-1 不斉記憶型 Dieckmann 縮合の前駆体カーボネートの合成

Table 4-1 には合成したカーボネートの不斉記憶型反応の検討結果を示した。メチルカーボネート **65** を THF 溶媒中-78°C で KHMDS (2.0 等量) で処理をすると、反応系が複雑になり全く目的物は得られなかった (Entry 1)。*t*-ブチルカーボネート **66** では反応が全く進行しなかった (Entry 2)。また、トリクロロエチルカーボネート **67** を同様に処理すると目的の γ-ラクトン **68** を 72%、63% ee で得た (Entry 3)。Entry 1 ～ 3 の結果より、脱離基として想定されるアルコキシド ($^-$OR) とホモセリン側鎖由来のアルコキシドの共役酸の p*K*a がほとんど変わらない場合 (MeOH およびホモセリン側鎖のアルコールはともに p*K*a 16 付近[30]) は、ホモセリン側に脱離することも考えられる上、Figure 3-4 で示したような逆 Claisen 縮合や逆 Dieckmann 縮合が起こり、様々な副反応が想定できる。一方、脱離基の共役酸の p*K*a が小さい場合 (2,2,2-トリクロロエタノールの p*K*a は 12 付近[30]) は想定通り、$^-$OR が安定なアニオンとして脱離し、直接的な Dieckmann 縮合が進行し、目的物が得られたと考えられる。KHMDS を 1.2 等量を用いた実験では、光学純度は 86% ee へ向上したものの収率は 43% へ低下した (Entry 4)。この条件では未反応の原料が多く残っていたので、エノラートが塩基や基質と mixed aggregate を形成し、反応を阻害したものと考えられる。溶媒検討では DMF、トルエンでは全く目的物は得られなかった (Entry 5、6)。一方、THF 溶媒への DME の添加は収率、光学純度を向上させることが分かった。10% DME/THF (v/v) 溶媒において KHMDS を 2.0 等量用いた場合は、収率 78%、79% ee へ向上した (Entry 7)。さらに、25% DME/THF (v/v) 溶媒で、収率 83%、92% ee を達成した (Entry 8)。同じエーテル系の溶媒である ジエチレングリコールジメチルエーテル (diglyme) を用いると大幅に収率が低下した (Entry 9)。次に 25% DME/THF (v/v) 溶媒に固定し、塩基の検討を行った。NaHMDS を用いた場合は収率 64%、86% ee (Entry 10)、LiHMDS を用いた場合は収率 87%、80% ee であった (Entry 11)。この光学純度の低下は、エノラートの低反応性に起因しており、*C-N* 軸性不斉エノラートのラセミ化が原因であると考えられる。これまでの検討結果は、基質の溶液に塩基を滴下して得られたものであるが、Entry 12 の様に塩基に基質を滴下する方法への変更では全く目的物は得られなかった。この γ-ラクトン合成では、前述の γ-ラクタム合成とは異なりクラウンエーテルは全く効果が見られなかった (Entry 13)。この反応では DMF、Diglyme、18-crown-6 など配位性が高く反応性の高いエノラートを発生させる溶媒や添加剤は、反応系を複雑にしてしまうことが分かる。エノラートと基質、塩基のアグリゲートの微妙なバランスが非常に重要であることがわかった。

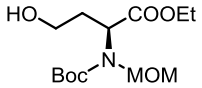
Table 4-1 不斉記憶型 Dieckmann 縮合による γ-ラクトンアミノ酸誘導体の合成

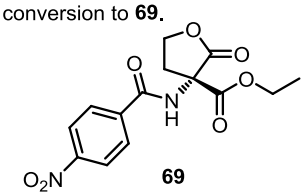


Entry	Substrate	Base (eq.)	Solvent	Time (h)	Procedure[a)]	Additive (eq.)	Yield (%)	ee (%)[b)]
1	**65**	KHMDS (2.0)	THF	10	I		-	-
2	**66**	KHMDS (2.0)	THF	10	I		-	-
3	**67**	KHMDS (2.0)	THF	10	I		72	63
4	**67**	KHMDS (1.2)	THF	10	I		43	86
5	**67**	KHMDS (1.2)	DMF	10	I		-	-
6	**67**	KHMDS (1.2)	PhMe	10	I		-	-
7	**67**	KHMDS (2.0)	THF/DME (9/1)	10	I		78	79
8	**67**	KHMDS (2.0)	THF/DME (3/1)	10	I		83	92
9	**67**	KHMDS (2.0)	THF/Diglyme (3/1)	10	I		21	89
10	**67**	NaHMDS (2.0)	THF/DME (3/1)	10	I		64	86
11	**67**	LiHMDS (2.0)	THF/DME (3/1)	10	I		87	80
12	**67**	KHMDS (2.0)	THF/DME (3/1)	6	II		-	-
13	**67**	KHMDS (2.0)	THF	10	I	18-crown-6 (2.4)	-	-

a) I: A solution of the base was added to a solution of the substrate . II: A solution of the substrate was added to a solution of the base . b) The enantiomeric excess was determined after conversion to **69**.

p*K*a of alcohols

	p*K*a (in water)
Cl_3CCH_2OH	12
MeOH	16
	~16
*t*BuOH	17



反応機構

化合物の **68** の絶対配置は誘導体の X-線結晶構造解析により行った。すなわち、%ee を決定した化合物 **69** (再結晶後 98% ee) のニトロ基を還元後、ブロモベンゾイル化し **70** へ誘導すると良好な結晶が得られたので、単結晶 X-線構造解析を行った (Figure 4-1)。その結果、絶対配置は *S* で、本不斉記憶型 Diekmann 縮合は立体保持進行することを確認した。

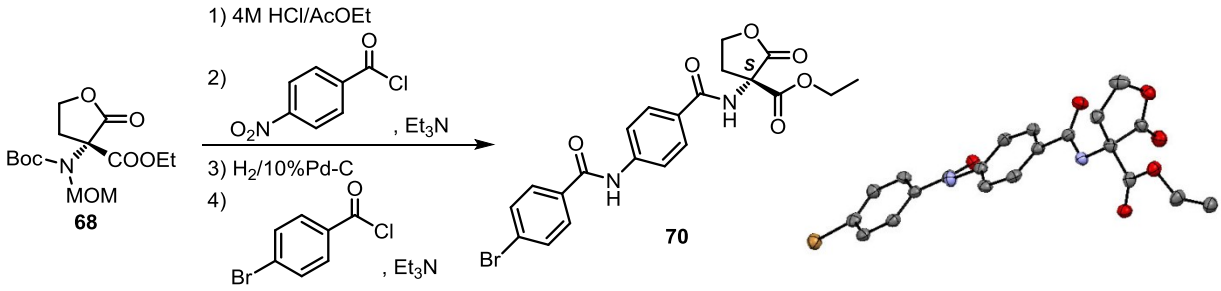
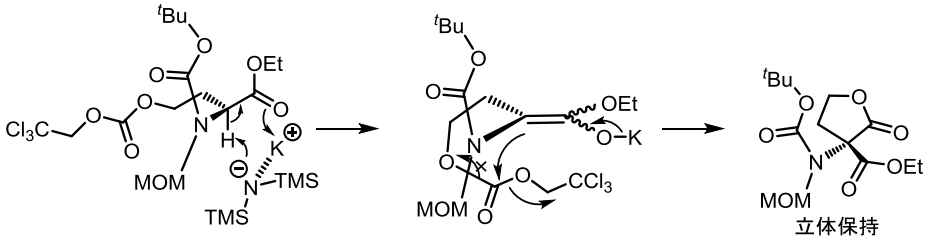


Figure 4-1 化合物 **70** の合成と X-線結晶構造

想定される反応機構は次の通りである (Scheme 4-2)。γ-ラクタム誘導体合成の際と同様の経路により脱プロトン化して得られた軸性不斉エノラートは、求電子剤のカーボネートと立体障害の小さい MOM 基側から反応し、共役酸の p*K*a の小さいトリクロロエトキシドを脱離しながら環化し、立体保持で四置換炭素を有するγ-ラクトン誘導体を与えると考えられる。

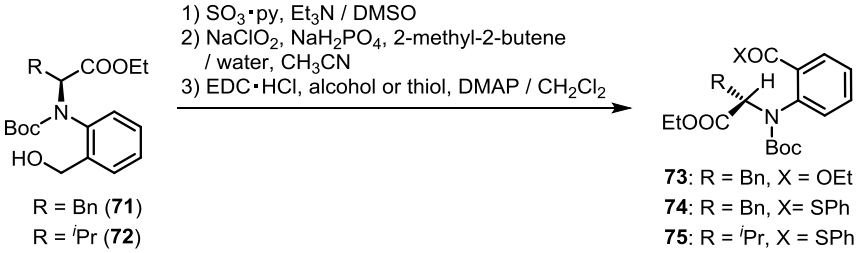


Scheme 4-2 想定される反応機構

以上の結果より、直接的な不斉記憶型 Dieckmann 縮合を用いた γ-ラクトンアミノ酸誘導体の合成を達成した。

第四節 四置換炭素含有 インドリン–3–オン誘導体の合成

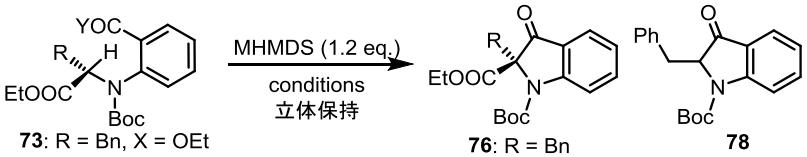
次に、直接的な不斉記憶型 Dieckmann 縮合の汎用性の拡大を目指して、*N*-アリールアミノ酸誘導体 (**73**～**75**) を合成し、反応検討を行うこととした。基質の合成は Ma ら、当研究室の門口らの報告に従いフェニルアラニン誘導体 (**71**) 、バリン誘導体 (**72**) を出発原料とし [31]、Parikh-Doering 酸化、Pinnick 酸化、エステル化により行った (Scheme 5-1)。



Scheme 5-1 不斉記憶型 Dieckmann 縮合に用いる *N*-アリールアミノ酸誘導体 **73**～**75** の合成

合成した **73**～**75** の不斉記憶型反応の検討結果を示した (Table 5-1)。ベンゼン環 *o*-位にエトキシカルボニル基を有する基質 **73** を用い、-78 °C、溶媒 THF、塩基 KHMDS で処理すると目的の四置換炭素含有インドリン-3-オン誘導体は得られず、脱エトキシカルボニル化した化合物 **78** を収率 72%で得た (Entry 1)。これは Figure 3-4 で述べたように、逆 Claisen 反応が起こったと考えられる。そこで、脱離基の由来のアニオンのカルボニル基への攻撃を抑制すべく、ソフトな脱離基を持つフェニルチオエステルを有する化合物 **74** を用いて反応を行った。溶媒に THF を用い、-78°C において塩基 KHMDS で処理すると想定通り目的の四置換炭素含有インドリン-3-オン誘導体 **76** を収率 54% で得た (Entry 2)。しかしながら、得られた **76** の光学純度は 18% ee と非常に低いものであった。そこで、反応性の高いエノラートを生成させることを目的とし、溶媒を THF から DMF に変更して反応を行った。その結果収率は 29% と低下したものの、光学純度は 56% ee まで改善した (Entry 3)。Entry 1～3 の検討は、基質に塩基を滴下していたので、塩基に基質を滴下する方法に変更したところ、収率 47%、光学純度 81% ee へ大幅に改善した (Entry 4)。更なる反応加速を期待して、18-crown-6 を添加したところ、収率 51%、92% ee に向上した (Entry 5)。塩基を NaHMDS に変更すると収率は変わらなかったが、99% ee を達成した (Entry 6)。これらの反応では、副生成物として *N*-Boc アントラニル酸が得られていた。この副生成物は、フェニルアラニンの β 位水素引き抜きによる E2 脱離体と思われ、これが収率が向上しない原因であると考えた (Scheme 5-2)。バリン誘導体 **75** は β 位に二つのメチル基が存在するため、E2 脱離を抑制できると考え、反応検討を行った。DMF 溶媒下、塩基として NaHMDS 、添加剤に 15-crown-5 を使用し 12 時間反応を行ったところ、**77** を収率 62%、99% ee で得た (Entry 7)。反応時間の延長により原料は消失し、収率 75%、99% ee を達成した (Entry 8)。反応温度を-40°C へと上昇させても光学純度の低下は見られなかった (Entry 9)。

Table 5-1 不斉記憶型 Dieckmann 縮合によるインドリン-3-オン誘導体の合成



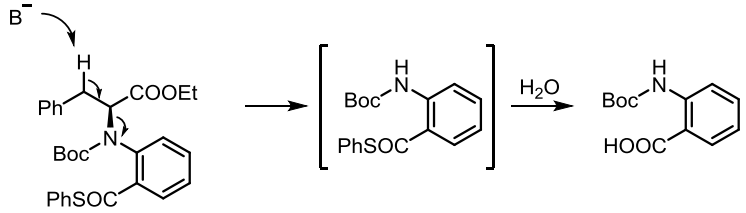
73: R = Bn, X = OEt
74: R = Bn, X= SPh
75: R = ^{i}Pr, X = SPh

76: R = Bn
77: R = *i*-Pr

78

Entry	Substrate	M	Additive (2.4 eq.)	Procedure[a)]	Solvent	Temp (℃)	Time (h)	Product	Yield (%)	ee (%)
1	**73**	K	-	I	THF	-78	1	**78**	72	
2	**74**	K	-	I	THF	-78	13	**76**	54	-18
3	**74**	K	-	I	DMF	-60	4.5	**76**	29	56
4	**74**	K	-	II	DMF	-70	1	**76**	47	81
5	**74**	K	18-crown-6	II	DMF	-70	4	**76**	51	92
6	**74**	Na	15-crown-5	II	DMF	-70	6	**76**	51	99
7	**75**	Na	15-crown-5	II	DMF	-70	12	**77**	62 (9)[b)]	99
8	**75**	Na	15-crown-5	II	DMF	-70	24	**77**	75	99
9	**75**	Na	15-crown-5	II	DMF	-40	6	**77**	73	99

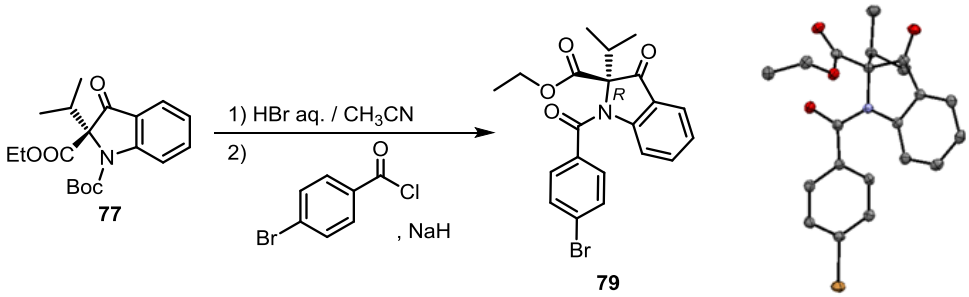
a) I: A solution of the base was added to a solution of the substrate. II : A solution of the substrate (and additive) was added to a base solution. b) A value in the parenthesis indicates the recovery yield (%) of the substrate (99% ee).



Scheme 5-2 想定される副反応

反応機構

化合物の **77** の絶対配置は誘導体の X-線結晶構造解析により行った。すなわち、化合物 **77** の *N*-Boc 基を脱保護後、ブロモベンゾイル化し **79** へ誘導すると良好な結晶が得られたので、単結晶 X-線構造解析を行った (Figure 5-1)。その結果、絶対配置は *R* であり、本反応が立体保持で進行することを確認した。



77

79

Figure 5-1 化合物 **79** の合成と **79** の X-線結晶構造

この反応の基質 **74**, **75** にはそれぞれ、回転障壁の高い結合の回転に伴う回転異性体が存在する。不斉記憶型反応はキラルエノラートのラセミ化を抑えるため低温で行うので、高い回転障壁により比較

的安定に存在する 2 つの回転異性体が脱プロトン化過程に影響を与えることが考えられる。そこで、化合物 **75** において回転障壁を算出し、この回転障壁の反応への影響について考察することにした。回転障壁の算出は DMF-d_7 中での温度可変 NMR (VT NMR) により求めた (Figure 5-2)[32] ,{この **75** の ^{1}H NMR における 20℃での異性体の比率は 60:40 (積分比より算出) であるが、50:50 と近似して行った。)。その結果回転障壁は、-70°C (DMF) で 16.2 kcal/mol であり、-70°C では約 10^{-5}/秒の速度で相互変換する 2 つの回転異性体の混合物と考えられる。この 2 つの回転異性体は Figure 5-2 に示す様に C(α)-N(Ar)Boc 軸の回転阻害に基づくものと考え、これらの回転異性体は、C(α)-H と N-C(Boc) がシンペリプラナーな配座を持つ **A** と、アンチペリプラナーな配座を持つ **B** の二種類と推定した。このような遅い相互変換は、低温の反応では脱プロトン化に影響を与えると考えられる。

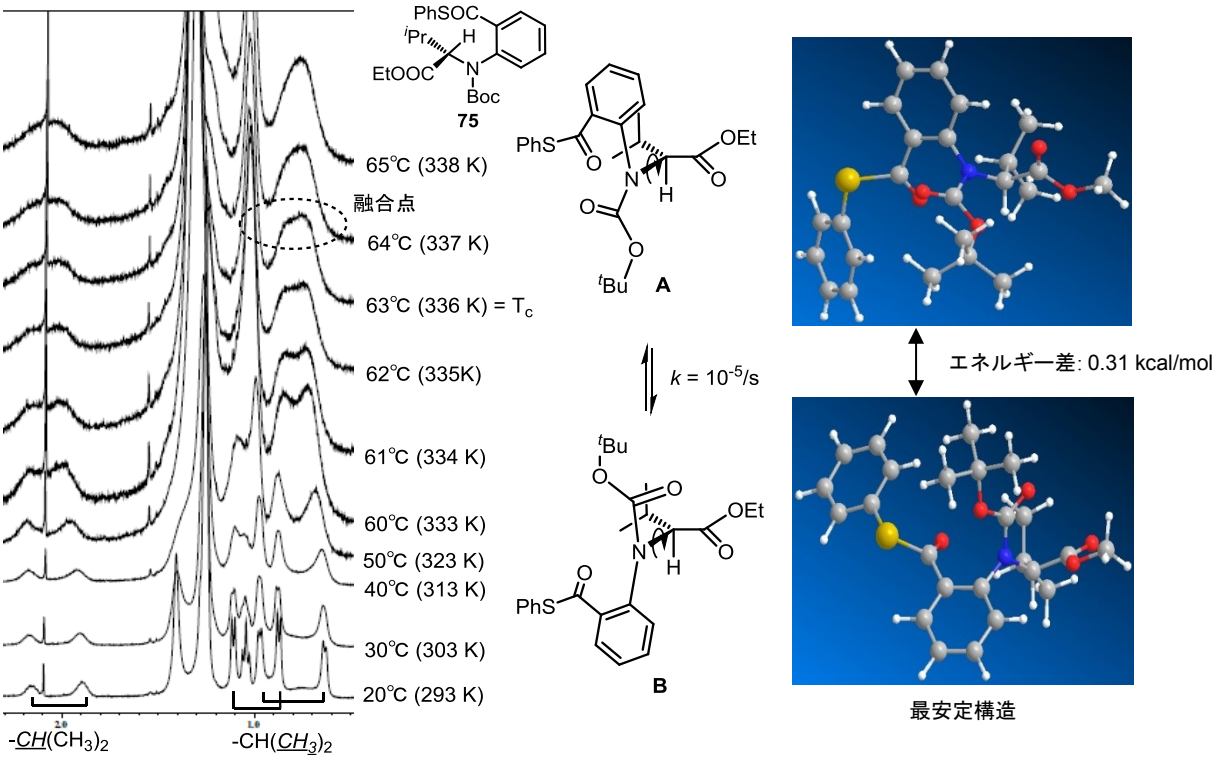
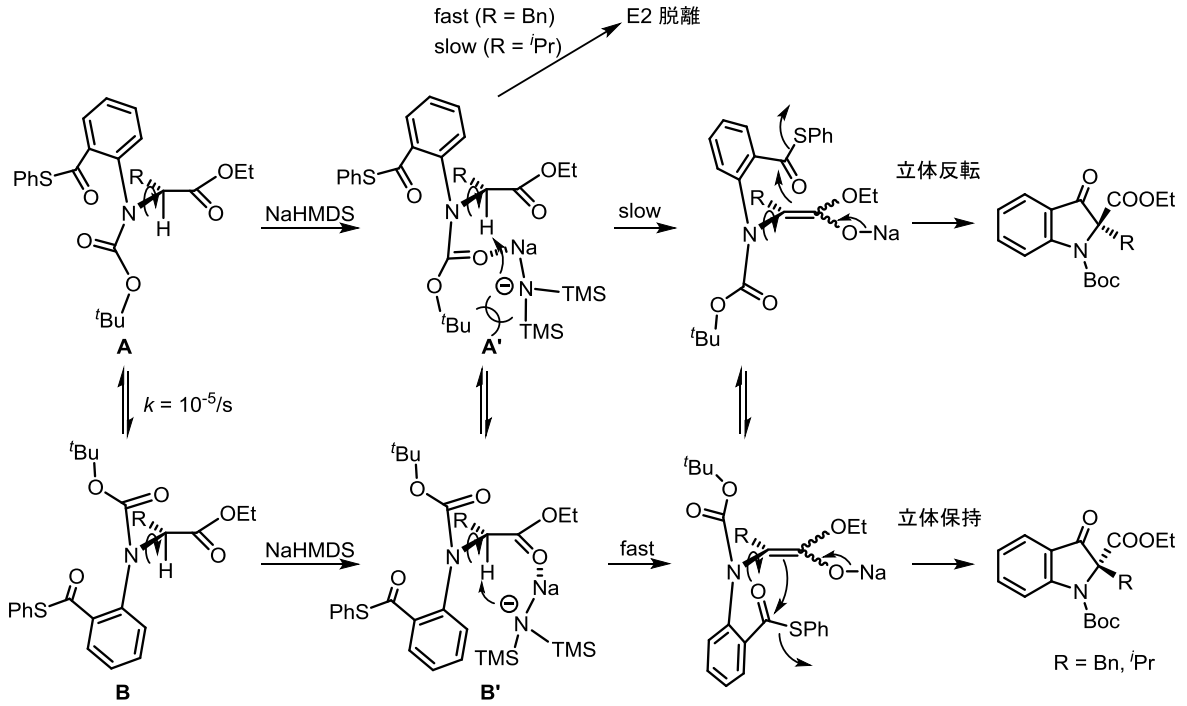


Figure 5-2 化合物 75 の ^{1}H vtNMR (DMF-d_7) の抜粋と構造最適化の結果 (B3LYP/6-31G* 計算)

まず、**75** のコンフォメーショナルサーチと続く DFT 計算により構造最適化を行った。その結果 **B** が最安定構造であった。 **A** / **B** 間のエネルギー差は 0.31 kcal/mol であり、化合物 **75** の 20 °C における回転異性体の比率 (60 : 40) と一致した。また、Table 5-1、Entry 7 より、反応 12 時間後も原料が回収され、この回収原料の光学純度は 99% ee である。このことは、片方の回転異性体からのみ脱プロトン化が起こることを示している。これらを考慮し、次の可能性を想定している (Scheme 5-3)。すなわち、メジャーな回転異性体 **B** (60%) は C(α)-H と N-C(Boc) がアンチペリプラナーな配座をとるため脱プロトン化が早く、エノラートの求電子部位との反応も非常に速く、高い光学純度で目的物が得られる。一方、マイナーな回転異性体 **A** (40%) は脱プロトン化が遅く、反応系中でメジャーな異性体へ徐々に変換され脱プロトン化を受ける。このことは、12 時間後に出発物質が 99%の光学純度で回収されたことに合致する (Entry 7)。反応時間を延長すると、このマイナー異性体もさらに異性化後に脱プロトン化を受け反応が進行するので、原料は消失し、収率が向上し、光学純度に影響を与え

ない (Entry 8)。一方、フェニルアラニン **74** のマイナー異性体は、異性化より E2 脱離の進行が早く、収率は 50% 程度で頭打ちしていると考えられる (Entry 4~6)。

主要な異性体は、最安定構造である **B** と推定した。このコンホメーションから脱プロトン化が起こり、生成した *C-N* 軸性不斉エノラートに対し、求電子剤のチオエステルは脱プロトン化が起こった側に存在するのでそのまま速やかに反応し立体保持で反応が進行する。一方、α 位の水素が Boc 基とシンペリプラナーにある **A** からの脱プロトン化が遅い原因は、下記の 2 点を考えている。① NaHMDS による脱プロトン化の際に、Boc 基と NaHMDS の立体障害が大きいこと。② 一般的に、脱プロトン化は、金属 (Scheme 5-3 では Na^+ を例に記載) がエステルカルボニル基に配位することにより α 位プロトンの酸性度が向上し、進行しやすくなると考えられる。異性体 **A** に KHMDS が共存すると Boc 基が *S*-cis コンホメーションを取り [8b]、Na^+ がエステルカルボニルでは無く、ルイス塩基性のより高い Boc 基のカルボニルに配位し、脱プロトン化過程を阻害していることが原因と考えられる。そのため脱プロトン化がほとんど進行せず、N-Cα軸の回転による **A'** の異性化によって **B'** に変換された後に脱プロトン化が進行すると考えられる。



Scheme 5-3 可能な反応機構

以上の結果より、不斉記憶型 Dieckmann 縮合を用いたインドリン–3–オン誘導体の合成を達成した。

第三章 不斉記憶型反応を用いた新規アザエストラジオールの合成研究

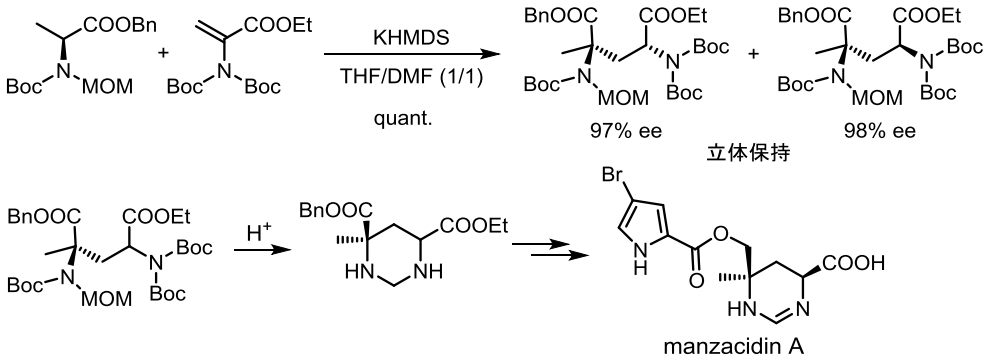
著者の所属する研究室ではこれまでに、不斉記憶型反応を利用したアルキル化反応[7,8]、共役付加反応[9]など数多くの四置換炭素含有アミノ酸の合成法を報告している。また、第一章に記述した様に、manzacidin A の全合成を達成しその有用性を示してきた。この度、さらなる有用性拡大を目的としてアザステロイドの合成を計画した[33]。ステロイドはほとんどの生物の生体内にて生合成され、生体維持に必要な細胞膜、胆汁酸の構成要素として利用されている他、性ホルモンとして重要な機能を果たしている。ステロイド骨格は 3 つのシクロヘキサン環と 1 つのシクロペンタン環から成る 4 縮合環炭素構造である。ステロイド骨格炭素の窒素に置換して得られる化合物は、生体必須物質にして普遍性が高いステロイドと立体配置が等しく、電子構造のみ異なる新規物質である。この新たなステロイドは構造有機化学的に非常に興味深くステロイド化学の新たな展開の可能性を秘めている。これまで医薬品としてステロイド骨格を有する様々な化合物が報告されているが、窒素原子への置換により生理活性、物性、安全性面でさらに新たな知見を得られることが期待できる。そこで今回、不斉記憶型反応を利用した新規アザエストラジオールの合成研究を行った。

結 論

不斉記憶型分子間共役付加反応の開発と全合成への応用ならびに不斉記憶型 Dieckmann 縮合の開発と反応機構の解明を行った。

第一章 不斉記憶型分子間共役付加反応の開発と全合成への応用

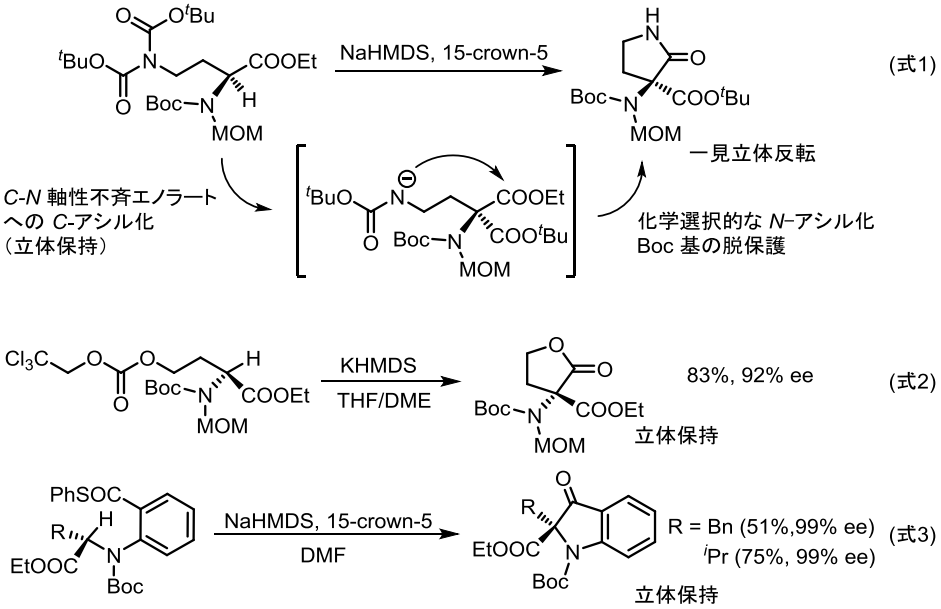
これまでの不斉記憶型反応で未解決課題であったラセミ化半減期の短いアラニン由来のキラルエノラートを中間体とする分子間共役付加反応の開発に成功した。マイケルアクセプターにビス(*t*-ブトキシカルボニル)アミノアクリル酸エチルを用い、溶媒に THF/DMF (1/1) の混合溶媒、-78°C で基質に塩基を添加することにより、高収率高選択的に α,γ-ジアミノ酸誘導体を得た。この α,γ-ジアミノ酸誘導体から、manzacidin A の全合成も達成し、改めて不斉記憶型反応の有用性を示すことができた (Scheme 7-1)。



Scheme 7-1 不斉記憶型分子間共役付加反応と manzacidin A 全合成

第二章 改良型不斉記憶型 Dieckmann 縮合の開発

まず、γ-ラクタムアミノ酸合成では基質にビス(*t*-ブトキシカルボニル)基を有する α,γ-ジアミノ酪酸誘導体を用いて検討を行った所、一見、Dieckmann 縮合が立体反転で進行しエステル交換した化合物が得られた。しかしながら詳細な反応機構解析により、直接的な Dieckmann 縮合は進行しておらず、不斉記憶型 *C*-アシル化に続く化学選択的な *N*-アシル化により本化合物が得られることを明らかとした (式 1)。これに対し、脱離基の安定性やソフト性を考慮し 2,2,2-トリクロロエチルカーボネートを有する基質より γ-ラクトンアミノ酸誘導体を (式 2)、*N*-アリールアミノ酸誘導体からインドリン-3-オン誘導体 (式 3) を高収率、高選択的に得る直接的な不斉記憶型 Diekmann 縮合を開発した (Scheme 7-2)。



Scheme 7-2 不斉記憶型 Dieckmann 縮合における不斉構築

第三章　不斉記憶型反応を用いた新規アザエストラジオールの合成研究

生命活動に必須の普遍物質であるステロイドと立体構造が等しく、電子構造のみが異なる新規物質の創製を目標として、アザエストラジオールの合成を不斉記憶型共役付加反応を鍵工程として検討した。

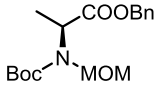
実験の部

General. ^{1}H NMR spectra were measured in $CDCl_3$ solution (TMS: 0.00 ppm), methanol-d_4 solution ($CD_2\underline{H}OD$: 3.31 ppm), C_6D_6 solution ($C_6D_5\underline{H}$: 7.15 ppm), DMSO-d_6 (CD_3SOCD_2H: 2.49 ppm) and DMF-d_7 (CD_6NCHO: 8.01 ppm) using JEOL ECX-400 (400 MHz) or JEOL ECA-600 (600 MHz) spectrophotometer, unless otherwise noted. ^{13}C NMR spectra were measured in $CDCl_3$ solution ($\underline{C}DCl_3$: 77.0 ppm), $(CD_3)_2SO$ solution ($(\underline{C}D_3)_2SO$: 39.5 ppm) and methanol-d_4 solution ($\underline{C}D_3OD$: 49.0 ppm) using JEOL ECX-400 (100 MHz) or JEOL ECA-600 (150 MHz) spectrophotometer, unless otherwise noted. Chemical shifts are reported in ppm. When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broadened. IR spectra were recorded on JASCO FT/IR-4200 spectrometer. Mass spectra were obtained on JEOL JMS-700. Elemental analyses were performed with CHN J-science-lab. Microcoder JM10. Optical rotations were determined on HORIBA SEPA-200. Flash column chromatography was performed on Silica Gel (SiliaFlash® F60). Thin layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel $60F_{245}$), and compounds were visualized with UV light and *p*-anisaldehyde stain, phosphomolybdic acid stain or ninhydrin stain. Preparative thin layer chromatography was performed on precoated plates (0.5 mm, silica gel Merck Kieselgel $60F_{245}$) and visualized with UV light. Melting points were measured with Yanaco MICRO MELTING POINT APPARATUS. Anhydrous THF was purchased from Kanto Kagaku and pre-treated with activated MS4Å. Anhydrous toluene was purchased from Wako and distilled from calcium hydride, and the distilled toluene was kept over MS4Å. Anhydrous DMF was purchased from Wako and distilled from P_2O_5 after being pre-treated with MS4Å for 1 day, and the distilled DMF was kept over MS4Å.

第一章 不斉記憶型分子間共役付加反応の開発と全合成への応用

Methoxymethylation of amino acid derivatives was carried out by reported method[34].

Preparation of **1(Ala derivative)**

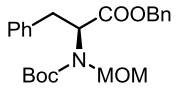


1

A solution of Boc-Ala-OBn (5.59 g, 20.0 mmol) in CH_2Cl_2 (200 mL) was added to a mixture of paraformaldehyde (0.901 g, 30.0 mmol) and $MgSO_4$ (20.0 g, 166 mmol) at rt. After the resulting mixture was cooled to 0 ˚C, TMSCl (6.52 g, 60.0 mmol) was added to the mixture. The suspension was stirred at rt for 17 h, and 20% Et_3N in MeOH (65 mL) was added to the suspension at 0 °C. The suspension was stirred at the same temperature for additional 30 min, and the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ (200 mL). The biphasic solution was extracted with $CHCl_3$ (50 mL×2), and the organic extracts were combined. The solution was washed with 10% aqueous solution of citric acid (100 mL) and brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10% to 20%) to give **1** as a colorless oil (4.45 g, 69%); $[\alpha]^{20}_{D}$= −13.7 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 2978, 2939, 1746, 1707, 1458, 1427, 1389, 1370, 1337, 1301,

1243, 1214, 1174, 1103, 1077, 1034; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.37 (5H, s), 1.46 (4H, s), 1.52 (3H, d, *J* = 7.3 Hz), 3.27 (1.3H, s), 3.31 (1.7H, s), 4.15 (0.55H, q, *J* = 7.3 Hz), 4.39 (0.45H, q, *J* = 7.3 Hz), 4.67-4.83 (2H, m), 5.10-5.20 (2H, m), 7.28-7.38 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 15.3, 15.9 (rotamer), 28.1, 28.2 (rotamer), 54.1, 54.7 (rotamer), 55.4, 55.7 (rotamer), 66.8, 66.9 (rotamer), 78.0, 78.3 (rotamer), 81.0, 81.1 (rotamer), 128.1, 128.3, 128.4, 128.5, 135.5, 135.8 (rotamer), 154.5, 154.9 (rotamer), 172.0, 172.1 (rotamer); MS(FAB) m/z $[M+Na]^+$ 346; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{17}H_{25}NO_5+Na]^+$ 346.1630, found 346.1631.

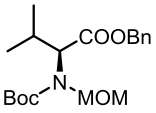
Preparation of **10** (Phe derivative)



10

A solution of Boc-Phe-OBn (1.35 g, 3.80 mmol) in CH_2Cl_2 (38 mL) was added to a mixture of paraformaldehyde (0.17 g, 5.70 mmol) and $MgSO_4$ (3.80 g, 31.5 mmol) at r. t. After the mixture was cooled to 0 ˚C, TMSCl (1.24 g, 11.4 mmol) was added to the mixture. The suspension was stirred at r. t. for 12 h, and 20% Et_3N in MeOH (13 mL) was added to the suspension at 0 °C. The suspension was stirred at the same temperature for additional 1.5 h, and the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ (50 mL). The biphasic solution was extracted with $CHCl_3$ (30 mL×2), and the organic extracts were combined. The solution was washed with 10% aqueous solution of citric acid (30 mL) and brine (30 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10% to 20%) to give **10** as a colorless oil (0.94 g, 62%); $[\alpha]^{20}_D$= – 85.4 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3031, 2976, 2932, 1742, 1707, 1496, 1454, 1428, 1388, 1369, 1345, 1297, 1256, 1219, 1171, 1141, 1092, 1060, 1023; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.43 (5.4H, s), 1.44 (3.6H, s), 3.00 (1.2H, s), 3.12 (1.8H, s), 3.19 (0.8H, dd, *J* = 10.1, 14.2 Hz), 3.40 (1.2H, dd, *J* = 5.0, 14.2 Hz), 3.86 (0.6H, d, *J* = 11.0 Hz), 3.99 (0.4H, d, *J* = 11.0 Hz), 4.21 (0.6H, dd, *J* = 5.0, 10.1 Hz), 4.29 (0.4H, dd, *J* = 5.0, 10.1 Hz), 4.56 (0.4H, d, *J* = 11.0 Hz), 4.70 (0.6H, d, *J* = 11.0 Hz), 5.12 (1H, d, *J* = 11.9 Hz), 5.23 (1H, d, *J* = 11.9 Hz), 7.15-7.35 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 28.2, 35.3, 36.2 (rotamer), 55.4, 55.9 (rotamer), 60.5, 60.7 (rotamer), 67.0, 67.1 (rotamer), 79.3, 79.4 (rotamer), 80.9, 81.2 (rotamer), 126.4, 126.6 (rotamer), 128.1, 128.3, 128.4, 128.4, 128.5, 129.2, 135.3, 135.6 (rotamer), 137.8, 138.1 (rotamer), 154.3, 154.8 (rotamer), 170.9, 170.9 (rotamer); MS(FAB) m/z $[M+Na]^+$ 422; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{23}H_{29}NO_5+Na]^+$ 422.1943, found 422.1954.

Preparation of **11** (Val derivative)

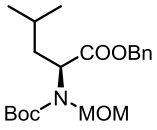


11

A solution of Boc-Val-OBn (1.33 g, 4.33 mmol) in CH_2Cl_2 (43 mL) was added to a mixture of paraformaldehyde (0.20 g, 6.49 mmol) and $MgSO_4$ (4.33 g, 35.9 mmol) at r. t. After the mixture was cooled

to 0 ˚C, TMSCl (1.41 g, 13.0 mmol) was added to the mixture. The suspension was stirred at r. t. for 12 h, and 20% Et_3N in MeOH (15 mL) was added to the suspension at 0 °C. The suspension was stirred at the same temperature for additional 1.5 h, and the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ (100 mL). The biphasic solution was extracted with $CHCl_3$ (50 mL×2), and the organic extracts were combined. The solution was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10% to 20%) to give **11** as a colorless oil (0.80 g, 51%); $[\alpha]^{20}_D$= –34.0 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 2971, 2934, 2876, 1742, 1707, 1459, 1427, 1389, 1369, 1335, 1295, 1255, 1172, 1120, 1084, 1004; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.92 (3H, d, *J* = 6.9 Hz), 1.00-1.05 (3H, m), 1.40 (4.5H, s), 1.46 (4.5H, s), 2.39 (1H, m), 3.22 (1.5H, s), 3.27 (1.5H, s), 3.80-3.83 (0.5H, m), 4.20-4.23 (0.5H, m), 4.67-4.82 (2H, m), 5.13 (1H, s), 5.14 (1H, s), 7.28-7.38 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 19.1, 19.2 (rotamer), 20.4, 21.2 (rotamer), 28.1, 28.3, 28.6 (rotamer), 55.8, 56.2 (rotamer), 63.3, 64.8 (rotamer), 66.5, 66.7 (rotamer), 77.6, 78.6 (rotamer), 80.9, 81.1 (rotamer), 128.0, 128.3, 128.4, 128.5, 135.5, 135.7 (rotamer), 155.2, 155.3 (rotamer), 171.0, 171.3 (rotamer); MS(FAB) m/z $[M+Na]^+$ 374; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{19}H_{29}NO_5+Na]^+$ 374.1943, found 374.1945.

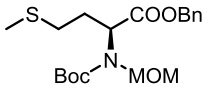
Preparation of **12** (Leu derivative)



12

A solution of Boc-Leu-OBn (1.61 g, 5.00 mmol) in CH_2Cl_2 (50 mL) was added to a mixture of paraformaldehyde (0.23 g, 7.50 mmol) and $MgSO_4$ (5.00 g, 41.5 mmol) at r. t. After the mixture was cooled to 0 ˚C, TMSCl (1.63 g, 15.0 mmol) was added to the mixture. The suspension was stirred at r. t for 5 h, and 20% Et_3N in MeOH (15 mL) was added at 0 °C. The suspension was stirred at the same temperature for additional 15 min and the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ (150 mL). The biphasic solution was extracted with $CHCl_3$ (100 mL×2), and the organic extracts were combined. The solution was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10% to 20%) to give **12** as a colorless oil (1.42 g, 78%); $[\alpha]^{20}_D$= –24.0 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 2959, 2871, 1742, 1707, 1460, 1421, 1389, 1368, 1299, 1257, 1175, 1124, 1085, 1011; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.93 (3.3H, d, *J* = 7.2 Hz), 0.94 (2.7H, d, *J* = 7.2 Hz), 1.39 (5H, s), 1.46 (4H, s), 1.61-1.71 (1H, m), 1.76-1.88 (2H, m), 3.24 (1.35H, s), 3.29 (1.65H, s), 4.25 (0.55H, dd, *J* = 6.9, 7.3 Hz), 4.53 (0.45H, dd, *J* = 6.9, 7.3 Hz), 4.62- 4.67 (1H, m), 4.77 (0.45H, d, *J* = 11.0 Hz), 4.84 (0.55H, d, *J* = 11.0 Hz), 5.09-5.19 (2H, m), 7.28-7.38 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 21.7, 21.7 (rotamer), 22.9, 23.1 (rotamer), 24.7, 24.8 (rotamer), 28.1, 28.2 (rotamer), 38.4, 39.1 (rotamer), 55.8, 56.1 (rotamer), 56.5, 57.1 (rotamer), 66.7, 66.8 (rotamer), 78.0, 78.3 (rotamer), 80.9, 81.0 (rotamer), 128.0, 128.2, 128.4, 128.5, 135.6, 135.7 (rotamer), 155.0, 155.3 (rotamer), 172.0, 172.2 (rotamer); MS(FAB) m/z $[M+Na]^+$ 388; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{20}H_{31}NO_5+Na]^+$ 388.2100, found 388.2111.

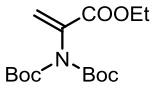
Preparation of **13** (Met derivative)



13

A solution of Boc-Met-OBn (1.55 g, 4.57 mmol) in CH_2Cl_2 (46 mL) added to a mixture of paraformaldehyde (0.23 g, 7.53 mmol) and $MgSO_4$ (4.57 g, 37.9 mmol) at r. t. After the mixture was cooled to 0 ˚C, TMSCl (1.49 g, 13.7 mmol) was added to the mixture. The suspension was stirred at r. t for 5 h, and 20% Et_3N in MeOH (14 mL) was added at 0°C. The suspension was stirred at the same temperature for additional 30 min and the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ (100 mL). The biphasic solution was extracted with $CHCl_3$ (50 mL×2), and the organic extracts were combined. The solution was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10%) to give **13** as a colorless oil (1.09 g, 62%); $[\alpha]^{20}_D$= –35.0 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 2976, 2924, 1742, 1707, 1455, 1427, 1390, 1369, 1341, 1298, 1219, 1170, 1090, 1044; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.38 (5H, s), 1.45 (4H, s), 2.04-2.26 (1H, m), 2.09 (3H, s), 2.34-2.43 (1H, m), 2.51-2.66 (2H, m), 3.26 (1.35H, s), 3.31 (1.65H, s), 4.32 (0.55H, dd, *J* = 5.5, 7.8 Hz), 4.47 (0.45H, dd, *J* = 6.9, 7.3 Hz), 4.63-4.69 (1H, m), 4.78 (0.45H, d, *J* = 11.0 Hz), 4.86 (0.55H, d, *J* = 11.0 Hz), 5.09-5.22 (2H, m), 7.28-7.40 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 15.1, 28.1, 28.1 (rotamer), 29.0, 29.6 (rotamer), 30.9, 55.8, 56.1 (rotamer), 57.6, 57.9 (rotamer), 67.0, 79.1, 79.2 (rotamer), 81.1, 81.3 (rotamer), 128.2, 128.3, 128.3, 128.4, 128.5, 135.3, 135.6 (rotamer), 154.7, 155.0 (rotamer), 171.2, 171.3 (rotamer); MS(FAB) m/z $[M+Na]^+$ 406; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{19}H_{29}NO_5S+Na]^+$ 406.1664, found 406.1674.

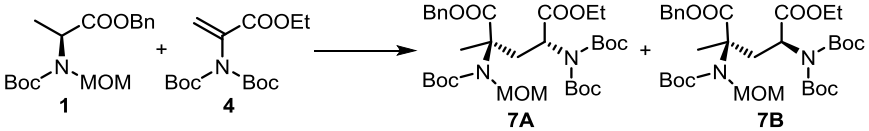
Preparation of **4**



4

To a solution of ethyl 2-(*tert*-butoxylcarbonyl)aminoacrylate[35] (12.4 g, 57.6 mmol) in CH_3CN (120 mL) were added DMAP (1.41 g, 11.5 mmol) and Boc_2O (12.6 g, 57.6 mmol) at r. t., sequentially, and the solution was stirred at r. t for 9.5 h. After removal of volatiles in vacuo, the residue was diluted with AcOEt (200 mL), and the solution was washed with 10% aqueous solution of citric acid (100 mL×2) and brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=20%) to give **4** as a colorless solid (17.5 g, 96%); IR (KBr) cm^{-1}: 2982, 2938, 2910, 1959, 1722, 1699, 1646, 1479, 1460, 1363, 1321, 1276, 1240, 1196, 1163, 1125, 1069, 1028; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, t, *J* = 6.9 Hz), 1.47 (18H, s), 4.26 (2H, q, *J* = 6.9 Hz), 5.64 (1H, s), 6.35 (1H, s); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.2, 27.8, 61.4, 83.0, 124.5, 150.6, 163.4; MS(FAB) m/z $[M+H]^+$ 316; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{15}H_{25}NO_6+H]^+$ 316.1760, found 316.1748.

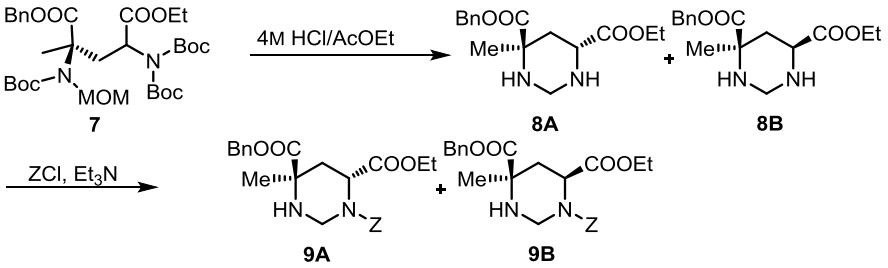
*Intermolecular conjugate addition reactions between **1** and **4** (Table 1, entry 13)*



To a solution of **1** (1.09 g, 3.37 mmol) and **4** (2.13 g, 6.74 mmol) in THF (12.1 mL)/DMF (20.2 mL) was added dropwise a solution of 0.5 M KHMDS in THF (8.09 mL, 4.04 mmol) over 25 min at –78 °C under Ar, and the solution was stirred at the same temperature for 10 min. The solution was poured into saturated aqueous solution of NH_4Cl (100 mL), and the solution was extracted with AcOEt (100 mL×2). The combined extracts were washed with water (100 mL), dried over Na_2SO_4 and filtrated. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt =10%, 20% to 30%) to give a 1/1 diastereomeric mixture of **7A** (97% ee) and **7B** (98% ee) as a colorless oil (2.15 g, 98%). Diastereomeric ratio and relative configuration of **7A** and **7B** were determined after their conversion to **8A** and **8B**. Enantiomeric excesses of **7A** and **7B** were determined after their conversion to **9A** and **9B**.

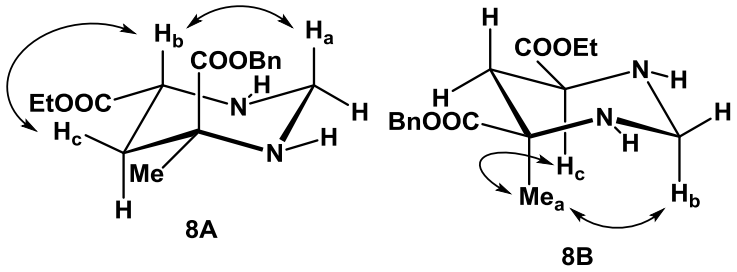
A 1/1 Diastereomeric mixture of **7A** and **7B**: IR (neat) cm^{-1}: 3091, 3066, 2980, 2935, 2828, 1794, 1745, 1704, 1497, 1478, 1457, 1368, 1301, 1253, 1145, 1094; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.21-1.28 (3H, m), 1.40-1.57 (30H, m), 2.22-2.41 (0.35H, m), 2.50-2.77 (0.65H, m), 2.89-3.15 (1H, m), 3.15-3.42 (3H, m), 4.10-4.17 (2H, m), 4.70 (0.65H, d, *J* = 11.9 Hz), 4.80 (0.35H, d, *J* = 11.9 Hz), 4.85-5.25 (4H, m), 7.27-7.39 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 14.1, 21.8, 27.9, 27.9, 36.2, 38.3, 54.5, 54.6, 55.4, 61.3, 61.4, 62.9, 66.8, 66.9, 75.5, 75.8, 81.0, 81.7, 83.0, 83.1, 128.1, 128.4, 135.5, 151.9, 154.8, 170.8, 171.1, 174.1; MS(FAB) m/z $[M+Na]^+$ 661; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{32}H_{50}N_2O_{11}+Na]^+$ 661.3312, found 661.3336.

*Determination of diastereomeric ratio, relative configuration, and ee of **7A** and **7B***



A mixture of **7A**/**7B** (4.28 g, 6.70 mmol) and 4 M HCl/AcOEt (34 mL) was stirred at r. t. for 30 min. The solution was concentrated in vacuo, and saturated aqueous solution of $NaHCO_3$ (200 mL) was added to the residue. The solution was extracted with AcOEt (50 mL×3), and the combined extracts were dried over Na_2SO_4 and filtered off. The filtrate was concentrated in vacuo to give a 1/1 diastereomeric mixture of **8A**/**8B** as a pale yellow oil (2.05 g, quant.); IR (neat) cm^{-1}: 3323, 3255, 3065, 3033, 2979, 1737, 1497, 1455, 1373, 1288, 1252, 1234, 1187, 1136, 1099, 1075, 1034; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.26 (1.95H, t, *J* = 7.5 Hz), 1.28 (1.05H, t, *J* = 7.5 Hz), 1.31 (1.05H, s), 1.36 (0.35H, dd, *J* = 12.8, 12.8 Hz), 1.49 (1.95H, s), 1,64 (0.65H, t, *J* = 11.4, 12.8 Hz,), 1.91-2.05 (2.65H, m), 2.54 (0.35H, dd, *J* = 3.2, 12.8 Hz), 3.45 (0.35H, dd, *J* = 2.8, 12.4 Hz), 3.62 (0.35H, d, *J* = 12.4 Hz), 3.73 (0.65H, dd, *J* = 3.7, 11.4 Hz), 3.84 (0.65H, d, *J* = 13.3 Hz), 3.90 (0.35H, d, *J* = 12.4 Hz), 4.00 (0.65Hz, d, *J* = 13.3 Hz), 4.11-4.22 (2H, m), 5.14 (0.65H, d, *J* = 12.4 Hz), 5.20 (0.65H, d, *J* = 12.4 Hz), 5.20 (0.35H, d, *J* = 12.4 Hz), 5.24 (0.35H, d, *J* = 12.4 Hz), 7.30-7.40 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 14.1, 20.3, 28.2, 37.2, 38.1, 53.5, 55.5, 55.6, 56.8, 58.6, 58.9, 61.1, 61.2, 67.0, 67.1, 128.1, 128.2, 128.4, 128.4, 128.6, 128.6, 135.4, 135.6, 172.4, 172.8, 175.0, 175.1; MS(FAB) m/z $[M+H]^+$ 307; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{16}H_{22}N_2O_4+H]^+$ 307.1658, found 307.1657. A small amount of a diastereomeric mixture of **8A**/**8B** was separated by preparative thin layer chromatography to determine each of relative configurations by

NOESY spectra

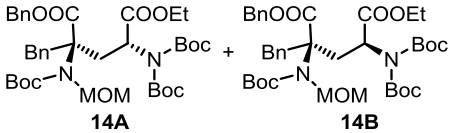


To a solution of **8A**/**8B** (38 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) were added Et_3N (15.3 mg, 0.15 mmol) and CbzCl (23.2 mg, 0.14 mmol) at 0 ˚C, successively, and the solution was stirred at r. t. for 5 h. After removal of volatiles in vacuo, the residue was purified by preparative thin layer chromatography (Hexane/AcOEt=33%) to give **9A** as a colorless oil (7.2 mg, 13%) and **9B** as a colorless oil (11.3 mg, 21%), respectively.

9A: 97% ee; $[\alpha]^{20}_D$=33.9 (c=0.36, $CHCl_3$); IR (neat) cm^{-1}: 3336, 3065, 3033, 2980, 1737, 1705, 1497, 1455, 1416, 1366, 1349, 1326, 1294, 1251, 1202, 1152, 1117, 1062, 1028; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.84-0.96 (3H, m), 1.30-1.41 (3H, m), 2.08 (1H, dd, *J* = 7.4, 13.7Hz), 2.11-2.24 (1H, m), 2.47 (1H, br s), 3.87-4.01 (2H, m), 4.33-4.50 (1H, m), 4.74-4.77 (0.5H, m), 4.85-4.90 (0.5H, m), 4.93-5.05 (2.5H, m), 5.13-5.24 (2.5H, m), 7.12-7.31 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 28.2, 34.0, 52.0, 52.6, 52.8 (rotamer), 56.1, 61.6, 67.3, 127.9, 128.1, 128.2, 128.5, 128.6, 135.3, 136.2, 153.7, 153.8 (rotamer), 171.6, 175.0; MS(FAB) m/z $[M+H]^+$ 441; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{24}H_{28}N_2O_6+H]^+$ 441.2026, found 441.2025; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=91.5/8/0.5, detection: 254 nm, retention time: t_{major}=30.3 min, t_{minor}=24.7 min.

9B: 98% ee; $[\alpha]^{20}_D$= –24.0 (c=0.50, $CHCl_3$); IR (neat) cm^{-1}: 3329, 3064, 3033, 2979, 2903, 1739, 1704, 1497, 1455, 1416, 1368, 1333, 1306, 1256, 1209, 1151, 1118, 1084, 1046, 1029; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.14-1.23 (3H, m), 1.32 (3H, s), 1.78-1.92 (3H, m), 2.81 (1H, dd, *J* = 15.1, 17.8 Hz), 3.92-4.20 (2H, m), 4.35-4. 45 (1H, m), 4.71-4.84 (2H, m), 5.03 (1H, d, *J* = 12.4 Hz), 5.15 (2H, s), 5.18 (1H, d, *J* = 12.4 Hz), 7.27-7.39 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 28.1, 34.9, 51.6, 52.0 (rotamer), 54.5, 54.6 (rotamer), 56.4, 61.4, 67.2, 67.5 (rotamer), 127.9, 128.1, 128.2, 128.4, 128.5, 128.6, 135.4, 136.2, 154.7, 155.8 (rotamer), 171.3, 174.2; MS(FAB) m/z $[M+H]^+$ 441; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{24}H_{28}N_2O_6+H]^+$ 441.2026, found 441.2025; HPLC conditions: column: CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=91.5/8/0.5, detection: 254 nm, retention time: t_{major}=22.2 min, t_{minor}=37.3 min.

*Reaction between **10** and **4** (Table 2-2, entry 1)*



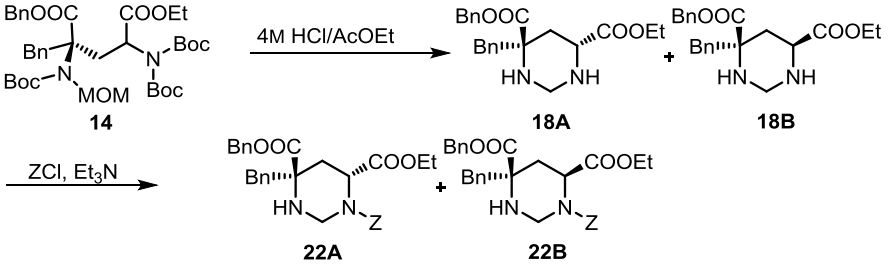
14A 14B

To a solution of **10** (0.16 g, 0.39 mmol) and **4** (0.25 g, 0.78 mmol) in THF (1.40 mL)/DMF (2.33 mL) was added dropwise a solution of 0.5 M KHMDS in THF (0.93 mL, 0.47 mmol) over 50 min at -78 ℃ under Ar, and the solution was stirred at the same temperature for 10 min. The solution was poured into saturated

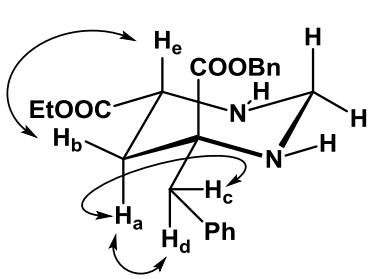
aqueous solution of NH_4Cl (20 mL), and the solution was extracted with AcOEt (20 mL×2). The combined extracts were washed with water (10 mL), dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10% to 50%) to give a 3/2 diastereomeric mixture of **14A** (97% ee) and **14B** (97% ee) as a colorless oil (0.278 g, quant.). Diastereomeric ratio and relative configuration were determined after their conversion to **18A** and **18B** Enantiomeric excesses of **14A** and **14B** were determined after their conversion to **22A** and **22B**.

A 3/2 Diastereomeric mixture of **14A** and **14B**: IR (neat) cm^{-1}: 3064, 3031, 2979, 2936, 2905, 2828, 1793, 1745, 1704, 1496, 1478, 1456, 1393, 1368, 1295, 1229, 1171, 1144, 1119, 1081, 1049; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.23-1.28 (3H, m), 1.41-1.51 (27H, m), 2.23-2.33 (0.4H, m), 2.82 (0.6H, m), 3.03 (1.2H, s), 3.13 (1.8H, s), 3.08-3.62 (3H, m), 4.11-4.23 (2H, m), 4.50-4.56 (0.8H, m), 4.61-4.84 (1H, m), 4.92-4.98 (1.2H, m), 5.09-5.19 (0.8H, m), 5.21-5.31 (1.2H, m), 7.04-7.11 (2H, m), 7.21-7.38 (8H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 27.8, 27.9, 28.2, 36.4, 37.6, 54.5, 54.5, 54.8, 61.5, 61.7, 65.3, 66.5, 67.0, 67.2, 75.3, 75.6, 81.0, 82.0, 83.3, 126.8, 127.8, 128.1, 128.6, 128.9, 130.7, 135.9, 151.6, 154.7, 170.6, 170.9, 172.3; MS(FAB) m/z $[M+Na]^+$ 737; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{38}H_{54}N_2O_{11}+Na]^+$ 737.3625, found 737.3643.

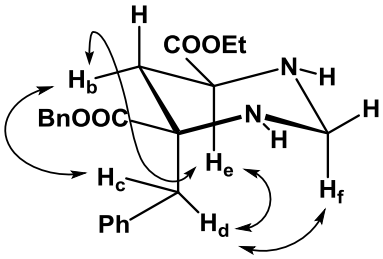
*Determination of diastereomeric ratio, relative configuration, and ee of **14A** and **14B***



A mixture of **14A**/**14B** (43 mg, 6.0×10^{-2} mmol) and 4 M HCl/AcOEt (0.6 mL) was stirred at r. t. for 30 min. The solution was basified with saturated aqueous $NaHCO_3$ solution. The solution was extracted with AcOEt (15 mL×2), and the combined extracts were dried over Na_2SO_4 and filtered off. The filtrate was concentrated in vacuo to give a 3/2 diastereomeric mixture of **18A**/**18B** as a pale yellow oil (23 mg, quant.); IR (neat) cm^{-1}: 3322, 3063, 3031, 2979, 2929, 2854, 1737, 1496, 1455, 1373, 1286, 1261, 1190, 1115, 1084, 1030; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.27 (1.2H, t, *J* = 7.3 Hz), 1.27 (1.8H, t, *J* = 7.3 Hz), 1.50 (0.6H, t, *J* = 12.8 Hz), 1.89 (0.4H, dd, *J* = 13.3, 13.6Hz), 2.04-2.22 (2.4H, m), 2.55 (0.6H, dd, *J* = 3.2, 13.3 Hz), 2.83 (0.6H, d, *J* = 13.3 Hz), 2.96 (0.6H, d, *J* = 13.3 Hz), 3.04 (0.4H, d, *J* = 13.7 Hz), 3.26 (0.4H, d, *J* = 13.7 Hz), 3.38 (0.6H, dd, *J* = 2.8, 12.4 Hz), 3.63 (0.6H, d, *J* = 12.4 Hz), 3.86 (0.4H, dd, *J* = 3.7, 10.1 Hz), 3.90 (0.6H, d, *J* =12.4 Hz), 4.00 (0.4H, d, *J* = 12.8 Hz), 4.07 (0.4H, d, *J* = 12.8 Hz), 4.11-4.25 (2H, m), 5.03 (0.4H, d, *J* = 11.8 Hz), 5.08 (0.4H, d, *J* = 11.8 Hz), 5.13 (1.2H, s), 6.97-7.08 (2H, m), 7.19-7.38 (8H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 36.6, 37.3, 39.6, 47.7, 53.7, 55.4, 55.7, 58.4, 61.1, 61.2, 63.0, 67.0, 67.0, 126.9, 127.2, 128.3, 128.4, 128.4, 128.4, 128.5, 128.6, 129.8, 130.0, 134.4, 135.1, 135.3, 135.8, 172.5 172.6, 173.8, 173.9; MS(FAB) m/z $[M+H]^+$ 383; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{22}H_{26}N_2O_4+H]^+$ 383.1971, found 383,1975. A small amount of a diastereomeric mixture of **18A**/**18B** was separated by preparative thin layer chromatography to determine each of relative configurations (See spectra data).



18A



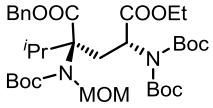
18B

To a solution of **18A**/**18B** in CH_2Cl_2 (0.6 mL) were added Et_3N (9.1 mg, 9.0×10^{-2} mmol) and CbzCl (13.3 mg, 7.8×10^{-2} mmol) at 0 ˚C, successively, and the solution was stirred at r. t. overnight. The solution was directly treated with preparative thin layer column chromatography (Hexane/AcOEt=50%) to give **22A** as a colorless oil (7 mg, 23%) and **226B** as a colorless oil (6 mg, 18%), respectively.

22A: 97% ee; $[\alpha]^{20}_D$=31.1 (c=0.35, $CHCl_3$); IR (neat) cm^{-1}: 3344, 3032, 2979, 1732, 1712, 1496, 1455, 1417, 1368, 1319, 1193, 1131, 1081, 1031; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.10-1.33 (3H, m), 2.10-2.28 (1H, m), 2.44 (1H, dd, *J* = 6.0, 13.8 Hz), 2.63-2.82 (1H, m), 2.91 (2H, s), 4.00-4.30 (2H, m), 4.30-4.54 (1H, m), 4.70-4.89 (1H, m), 4.95-5.21 (4H, m), 7.03-7.10 (2H, m), 7.16-7.20 (2H, m), 7.22-7.38 (6H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 33.1, 43.8, 52.5, 52.9 (rotamer), 53.1, 53.2 (rotamer), 60.8, 61.5, 67.5, 126.9, 127.9, 128.0, 128.4, 128.5, 128.6, 128.6, 130.2, 135.0, 135.4, 136.2, 154.7, 171.5, 174.2; MS(FAB) m/z $[M+H]^+$ 517; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{30}H_{32}N_2O_6+H]^+$ 517.2339, found 517.2333; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=89.5/10/0.5, detection: 254 nm, retention time: t_{major}=11.0 min, t_{minor}=14.7 min.

22B: 97% ee; $[\alpha]^{20}_D$= –20.5 (c=0.28, $CHCl_3$); IR (neat) cm^{-1}: 3327, 3063, 3032, 2980, 1739, 1705, 1604, 1496, 1455, 1415, 1369, 1333, 1257, 1204, 1134, 1085, 1060, 1029; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.12 (1.35H, t, *J* = 7.3 Hz), 1.18 (1.65H, t, *J* = 7.3 Hz), 1.96-2.04 (1H, m), 2.77-2.91 (2H, m), 2.97 (0.45H, d, *J* = 13.3 Hz), 2.99 (0.55H, d, *J* = 13.3 Hz), 3.85-4.15 (2H, m), 4.37 (0.45H, d, *J* = 12.8 Hz), 4.43 (0.55H, d, *J* = 12.8 Hz), 4.71-4.78 (1.45H, m), 4.84 (0.55H, d, *J* = 7.3 Hz), 4.90 (0.45H, d, *J* = 9.2 Hz), 4.93 (0.55H, d, *J* = 9.2 Hz), 5.05-5.13 (3H, m), 7.03-7.08 (2H, m), 7.19-7.40 (8H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 13.9, 33.2, 33.5 (rotamer), 46.8, 47.0 (rotamer), 51.6, 52.0 (rotamer), 54.3, 54.4 (rotamer), 60.4, 60.5 (rotamer), 61.4, 67.2, 67.5, 127.3, 127.8, 127.9, 128.1, 128.4, 128.5, 130.1, 130.2, 134.4, 135.0, 136.2, 154.6, 155.0 (rotamer), 171.3, 173.2; MS(FAB) m/z $[M+H]^+$ 517; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{30}H_{32}N_2O_6+H]^+$ 517.2339, found 517.2351; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=89.5/10/0.5, detection: 254 nm, retention time: t_{major}=15.9 min, t_{minor}=14.0 min.

*Reactions between **11** and **4** (Table 2-2, entry 2).*

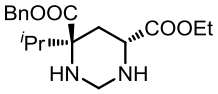


15A

To a solution of **11** (90.7mg, 0.26 mmol) and **4** (0.16 g, 0.52 mmol) in THF (0.93 mL)/DMF (1.55 mL) was added dropwise a solution of 0.5 M KHMDS in THF (0.62 mL, 0.31 mmol) over 30 min at –40 °C under Ar, and the solution was stirred at the same temperature for 24 h. The solution was poured into saturated

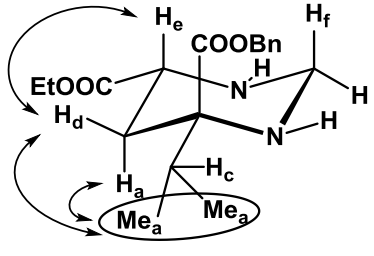
aqueous solution of NH_4Cl (20 mL), and the resulting solution was extracted with AcOEt (20 mL×2). The combined extracts were washed with water (20 mL×2), dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=15%) to give **15A** (85.2 mg, 50%, 87% ee) as the sole product; IR (neat) cm^{-1}: 2979, 2934, 1792, 1743, 1707, 1478, 1456, 1392, 1368, 1299, 1254, 1225, 1170, 1145, 1119, 1085, 1030; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.87-1.01 (6H, m), 1.20-1.28 (3H, m), 1.38-1.50 (27H, m), 2.40-2.61 (2H, m), 3.22-3.41 (4H, m), 4.12 (2H, q, *J* = 6.9 Hz), 4.49-4.61 (1H, m), 4.74-4.92 (1H, m), 5.01 (1H, d, *J* =12.4 Hz), 5.04-5.24 (1H, m), 5.16 (1H, d, *J* = 12.4 Hz), 7.25-7.40 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 14.1, 18.9, 19.1, 19.2, 27.8. 27.9, 28.1, 31.0, 33.8, 36.2, 38.3, 54.2, 54.5, 55.0, 55.4, 61.5, 66.5, 66.6, 68.7, 69.4, 75.9, 81.8, 82.9, 127.7, 128.1, 128.2, 128.4, 136.0, 149.6, 151.6, 154.9, 170.9, 171.1; MS(FAB) m/z $[M+Na]^+$ 689; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{34}H_{54}N_2O_{11}+Na]^+$ 689.3625, found 689.3635. Diastereomeric ratio, relative configuration and enantiomeric excess of **15A** were determined after their conversion to **19A**

*Determination of relative configuration and ee of **19A***



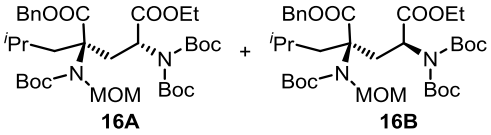
19A

A mixture of the compound **15A** (64 mg, 9.6×10^{-2} mmol) and 4 M HCl/AcOEt (1.0 mL) was stirred at r. t. for 30 min. The solution was basified with saturated aqueous $NaHCO_3$ solution. The solution was extracted with AcOEt (15 mL×2), and the combined extracts were dried over Na_2SO_4 and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by preparative thin layer chromatography (MeOH/$CHCl_3$=5%) to give **19A** as a pale yellow oil (8.8 mg, 28%, 87% ee).; IR (neat) cm^{-1}: 3324, 3065, 3033, 2967, 2936, 2877, 1731, 1498, 1456, 1390, 1373, 1352, 1290, 1257, 1190, 1148, 1097, 1054, 1028; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.85 (3H, d, *J* = 6.9 Hz), 0.90 (3H, d, *J* = 6.9 Hz), 1.29 (3H, t, *J* = 6.9 Hz), 1.38 (1H, dd, *J* = 12.4, 12.4 Hz), 1.76-1.85 (1H, m), 1.83 (2H, br s), 2.42 (1H, dd, *J* = 2.8, 12.4 Hz), 3.45 (1H, dd, *J* = 2.8, 12.4 Hz), 3.60 (1H, d, *J* = 12.4 Hz), 3.92 (1H, d, *J* = 12.4 Hz), 4.11-4.26 (2H, m), 5.18 (1H, d, *J* = 12.4 Hz), 5.25 (1H, d, *J* = 12.4 Hz), 7.32-7.40 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.3, 16.6, 16.8, 33.6, 37.1, 55.9, 58.9, 61.1, 65.5, 66.9, 128.5, 128.6, 128.7, 135.7, 173.1, 174.6; MS(FAB) m/z $[M+H]^+$ 335; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{18}H_{26}N_2O_4+H]$ 335.1971, found 335.1969; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=89.5/10/0.5, detection: 254 nm, retention time: t_{major}=8.5 min, t_{minor}=6.9 min.



19A

*Reaction between **12** and **4** (Table 2-2, entry 3)*

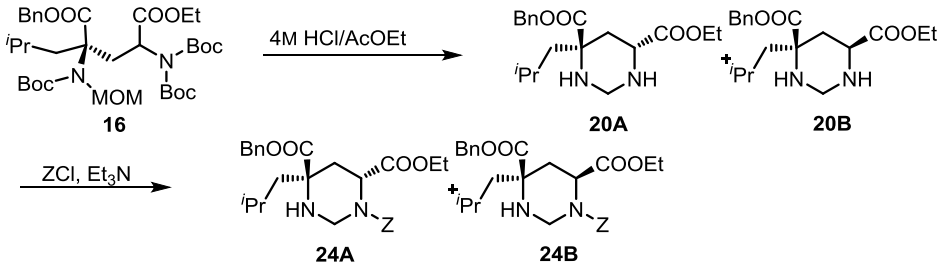


16A **16B**

To a solution of **14** (0.12 g, 0.34 mmol) and **4** (0.21 g, 0.68 mmol) in THF (1.22 mL)/DMF (2.03 mL) was added dropwise a solution of 0.5 M KHMDS in THF (0.81 mL, 0.41 mmol) over 30 min at –78°C under Ar, and the solution was stirred at the same temperature for 2 h. The solution was poured into saturated aqueous solution of NH_4Cl (30 mL), and the solution was extracted with AcOEt (20 mL×2). The combined extracts were washed with water (20 mL), dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10%) to give a 1/2 diastereomeric mixture of **16A** (97% ee) and **16B** (97% ee) as a colorless oil (0.14 g, 62%). Diastereomeric ratio of **16A**/**16B** was determined after their conversion into **20A**/**20B** by ^{1}H NMR. Enantiomeric excesses of **20A** and **20B** were determined after their conversion to **24A** and **24B**.

A 1/2 Diastereomeric mixture of **16A** and **16B**: IR (neat) cm^{-1}: 2979, 2934, 2873, 1797, 1744, 1704, 1456, 1392, 1367, 1297, 1255, 1221, 1146, 1080, 1033; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, m), 0.88 (1H, d, *J* = 6.9 Hz), 0.93 (2H, d, *J* = 6.9 Hz), 1.21-1.26 (3H, m), 1.39 (6H, s), 1.42 (3H, s), 1.49 (6H, s), 1.50 (12H, s), 1.58-1.75 (1H, m), 1.77-1.92 (1H, m), 1.98-2.18 (1H, m), 2.56 (0.35H, m), 2.73-2.77 (0.65H, m), 3.00-3.04 (0.65H, m), 3.13-3.22 (3H, m), 3.30-3.34 (0.35H, m), 4.09-4.17 (2H, m), 4.70 (0.65H, d, *J* = 12.0 Hz), 4.86-4.94 (1.7H, m), 5.04 (1.65H, m), 5.14 (1H, d, *J* = 12.4 Hz), 7.28-7.38 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 14.1, 14.1, 23.3, 23.4, 23.9, 24.7, 25.2, 27.8. 27.8, 27.9, 28.0, 28.0, 33.0, 35.1, 40.9, 54.3, 54.4, 55.3, 56.0, 61.4, 65.4, 65.6, 66.7, 66.8, 75.0, 75.6, 80.0, 81.7, 82.8, 83.0, 83.1, 127.9, 128.0, 128.2, 128.2, 128.5, 135.8, 152.0, 154.8, 155.0, 170.8, 171.1, 171.2, 172.9, 173.0; MS(FAB) m/z $[M+Na]^+$ 703; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{35}H_{56}N_2O_{11}+Na]^+$ 703.3782, found 703.3792.

*Determination of diastereomeric ratio and ee of **16A** and **16B***



16 **20A** **20B**

24A **24B**

A mixture of **16A**/**16B** (0.10 g, 0.15 mmol) and 4 M HCl/AcOEt (1.5 mL) was stirred at r. t. for 45 min. The solution was basified with saturated aqueous $NaHCO_3$ solution. The solution was extracted with AcOEt (20 mL×2), and the combined extracts were dried over Na_2SO_4 and filtered off. The filtrate was concentrated in vacuo to give a 1/2 diastereomeric mixture of **20A** and **20B** as a pale yellow oil (51 mg, quant.); IR (neat) cm^{-1}: 3326, 3033, 2956, 2870, 1737, 1497, 1456, 1372, 1348, 1286, 1262, 1215, 1186, 1146, 1029; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.76 (2H, d, *J* = 6.0 Hz), 0.84 (2H, d, *J* = 6.4 Hz), 0.93 (2H, d, *J* = 6.4 Hz), 1.25 (2H, t, *J* = 7.3 Hz), 1.28 (1H, t, *J* = 7.3 Hz), 1.35-1.58 (2.35H, m), 1.66-1.73 (1.65H, m), 1.92-2.03 (2.65H, m), 2.52 (0.35H, dd, *J* = 3.2, 13.3 Hz), 3.45 (0.35H, dd, *J* = 3.2, 12.4Hz), 3.66 (0.35H, d, *J* = 11.9 Hz), 3.70 (0.65H, d, *J* = 13.8 Hz), 3.77 (0.65H, dd, *J* = 3.2, 11.4 Hz), 3.89 (0.35H, d, *J* = 12.4 Hz), 3.99 (0.65Hz, d, *J* =

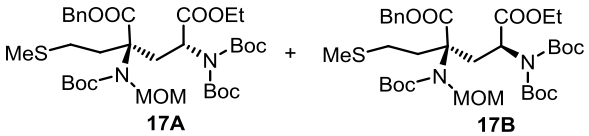
13.3 Hz), 4.09-4.24 (2H, m), 5.14 (1.4H, s), 5.17 (0.3H, d, J = 11.9 Hz), 5.24 (0.3H, d, J = 12.4 Hz), 7.32-7.40 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 14.1, 22.4, 23.2, 24.2, 24.2, 24.3, 37.7, 37.8, 40.2, 50.8, 53.6, 55.3, 55.5, 58.3, 59.2, 61.0, 61.1, 61.9, 66.9, 67.0, 128.4, 128.5, 128.6, 135.2, 135.4, 172.7, 172.8, 174.8, 175.4; MS(FAB) m/z $[M+H]^+$ 349; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{19}H_{28}N_2O_4+H]^+$ 349.2127, found 349.2119.

To a solution of **20A/20B** (49 mg, 0.14 mmol) in CH_2Cl_2 (1.4 mL) were added Et_3N (20.0 mg, 0.20 mmol) and CbzCl (28.8 mg, 0.18 mmol), and the solution was stirred at r. t. for overnight. The solution was directly treated with preparative thin layer chromatography (Hexane/AcOEt=33%) to give **24A** as a colorless oil (7.7 mg, 11%) and **24B** as a colorless oil (13 mg, 19%), respectively.

24A: 97% ee; $[\alpha]^{20}_D$=41.5 (c=0.39, $CHCl_3$); IR (neat) cm^{-1}: 3341, 3065, 3033, 2955, 2870, 1737, 1708, 1497, 1455, 1416, 1367, 1326, 1305, 1217, 1154, 1075, 1028; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.73 (3H, d, J = 6.4 Hz), 0.87 (3H, d, J = 6.4 Hz), 1.19-1.27 (3H, m), 1.60-1.72 (3H, m), 2.17 (2H, m), 2.62 (1H, br s), 4.10-4.23 (3H, m), 4.41 (0.4H, m), 4.58 (0.6H, m), 4.78-4.88 (1H, m), 5.04-5.19 (4H, m), 7.27-7.38 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 22.8, 24.2, 34.2, 34.4 (rotamer), 40.9, 52.3, 52.8, 59.1, 61.5, 67.4, 127.9, 128.1, 128.5, 128.5, 128.6, 135.2, 136.3, 135.4, 155.0, 171.7, 175.3; MS(FAB) m/z $[M+H]^+$ 483; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{27}H_{34}N_2O_6+H]^+$ 483.2495, found 483.2500; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=89.5/10/0.5, detection: 254 nm, retention time: t_{major}=8.8 min, t_{minor}=14.1 min.

24B: 97% ee; $[\alpha]^{20}_D$= –22.2 (c=0.64, $CHCl_3$); IR (neat) cm^{-1}: 3328, 3065, 3033, 2956, 2870, 1739, 1705, 1497, 1455, 1414, 1367, 1334, 1259, 1202, 1124, 1056; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.78 (3H, d, J = 6.4 Hz), 0.85 (3H, d, J = 6.4 Hz), 1.16-1.24 (3H, m), 1.44-1.50 (1H, m), 1.61-1.69 (2H, m), 1.84 (1H, dd, J = 6.9, 13.8 Hz), 2.78 (1H, t, J = 15.0 Hz), 3.99-4.20 (2H, m), 4.40-4.50 (1H, m), 4.70-4.78 (2H, m), 5.02 (1H, d, J = 12.4 Hz), 5.11-5.16 (2H, m), 5.15 (1H, d, J = 12.4 Hz), 7.28-7.38 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 23.7, 23.8, 24.3, 34.9, 35.2 (rotamer), 50.0, 51.7, 52.1 (rotamer), 54.1, 54.3 (rotamer), 59.3, 61.4, 67.2, 67.4 (rotamer), 127.9, 128.1, 128.4, 128.5, 128.5, 128.6, 135.2, 136.3, 154.6, 155.0 (rotamer), 171.4, 173.9; MS(FAB) m/z $[M+H]^+$ 483; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{27}H_{34}N_2O_6+H]^+$ 483.2495, found 483.2503; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=91.5/8/0.5, detection: 254 nm, retention time: t_{major}=15.3 min, t_{minor}=11.7 min.

*Reaction between **13** and **4** (Table 2-2, entry 4)*



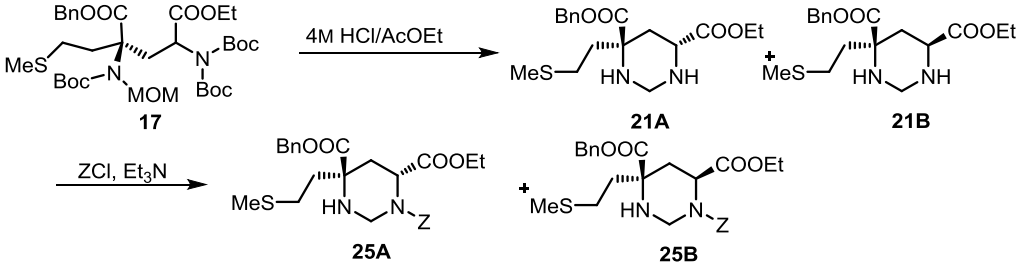
17A **17B**

To a solution of **13** (0.20 g, 0.52 mmol) and **4** (0.33 g, 1.04 mmol) in THF (1.88 mL)/DMF (3.13 mL) was added dropwise a solution of 0.5 M KHMDS in THF (1.25 mL, 0.626 mmol) for 25 min at –78 °C under Ar, and the solution was stirred at the same temperature for 10 min. The solution was poured into saturated aqueous solution of NH_4Cl (30 mL), and the solution was extracted with AcOEt (20 mL×2). The combined extracts were washed with water (20 mL), dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10% to 30%) to give a 1/2 diastereomeric mixture of **17A** (91% ee) and **17B** (92% ee) as a colorless oil (0.37 g, quant.).

Diastereomeric ratio of **17A**/**17B** was determined after their conversion into **21A**/**21B** by ^{1}H NMR. Enantiomeric excesses of **17A** and **17B** were determined after their conversion into **25A** and **25B.**

A 1/2 Diastereomeric mixture of **17A** and **17B**: IR (neat) cm^{-1}: 2980, 2934, 2830, 1792, 1741, 1704, 1477, 1456, 1368, 1300, 1256, 1234, 1173, 1145, 1081, 1022; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.21-1.28 (3H, m), 1.39 (6H, s), 1.43 (3H, s), 1.49 (18H, s), 1.98 (3H, s), 2.15 (1H, m), 2.32 (1H, m), 2.45-2.68 (2H, m), 2.97-3.00 (1H, m), 3.23 (3H, m), 4.10-4.18 (2H, m), 4.67 (1H, d, *J* = 12.4 Hz), 4.84-4.97 (2H, m), 5.05 (1H, d, *J* = 12.4 Hz), 5.20 (1H, d, *J* = 12.4 Hz), 7.31-7.39 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 14.1, 14.2, 15.3, 15.4, 27.9, 28.0, 28.1, 28.6, 32.5, 54.1, 54.3, 55.6, 61.5, 61.6, 65.8, 66.9, 67.0, 75.3, 75.8, 81.0, 81.2, 83,1, 83.3, 128.1, 128.4, 128.5, 135.6, 152.0, 152.1, 154.7, 170.7, 171.1, 171.2, 172.4, 172.4; MS(FAB) m/z $[M+Na]^+$ 721; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{34}H_{54}N_2O_{11}S+Na]^+$ 721.3346, found 721.3345.

*Determination of diastereomeric ratio and ee of **17A** and **17B***



A mixture of **17A**/**17B** (0.37 g, 0.52 mmol) and 4 M HCl/AcOEt (5.2 mL) was stirred at r. t. for 40 min. The solution was basified with saturated aqueous solution of $NaHCO_3$. The solution was extracted with AcOEt (30 mL×2), and the combined extracts were dried over Na_2SO_4 and filtered off. The filtrate was concentrated in vacuo to give a 1/2 diastereomeric mixture of **21A** and **21B** as a pale yellow oil (0.18 g, 94%); IR (neat) cm^{-1}: 3320, 3033, 2977, 2918, 2871, 1732, 1455, 1373, 1339, 1311, 1254, 1209, 1186, 1166, 1114, 1072, 1030; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.25-1.30 (3H, m), 1.40 (0.35H, t, *J* = 12.8 Hz), 1.57 (0.65H, dd, *J* = 11.9, 13.3 Hz), 1.80-1.89 (1H, m), 1.99 (3H, s), 2.01-2.12 (3H, m), 2.20-2.28 (1H, m), 2.30-2.38 (1H, m), 2.48-2.59 (1H, m), 3.44 (0.35H, dd, *J* = 3.2, 12.4 Hz), 3.65 (0.35H, d, *J* = 12.4 Hz), 3.72 (0.65H, d, *J* = 13.8 Hz), 3.77 (0.65H, dd, *J* = 2.7, 11.9Hz), 3.91 (0.35H, d, *J* = 12.4 Hz), 3.98 (0.65H, d, *J* = 12.4 Hz), 4.09-4.26 (2H, m), 5.12 (0.65H, d, *J* = 11.9 Hz), 5.21 (0.35H, d, *J* = 11.9 Hz), 5.23 (0.65H, d, *J* = 11.9 Hz), 5.25 (0.35H, d, *J* = 11.9 Hz), 7.32-7.40 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 14.3, 15.4, 15.5, 27.5, 28.7, 31.9, 36.6, 37.0, 40.9, 53.5, 55.0, 55.4, 58.3, 59.4, 61.0, 61.2, 61.9, 67.1, 67.2, 128.4, 128.4, 128.5, 128.6, 128.6, 135.2, 135.4, 172.4, 172.5, 174.0, 174.0; MS(FAB) m/z $[M+H]^+$ 367; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{18}H_{26}N_2O_4S+H]^+$ 367.1692, found 367.1701.

To a solution of **21A/21B** (60 mg, 0.14 mmol) in CH_2Cl_2 (1.6 mL) were added Et_3N (23.1 mg, 0.23 mmol) and CbzCl (33.5 mg, 0.20 mmol), and the solution was stirred at r. t. for overnight. The solution was concentrated in vacuo, and the residue was treated with preparative thin layer chromatography (Hexane/AcOEt 33%) to give **25A** as a colorless oil (7.5 mg, 9%) and **25B** as a colorless oil (19 mg, 23%), respectively.

25A: 91% ee; $[\alpha]^{20}_D$=49.3 (c=0.38, $CHCl_3$); IR (neat) cm^{-1}: 3335, 3065, 3033, 2976, 2962, 2919, 1736, 1706, 1417, 1366, 1290, 1273, 1203, 1166, 1112, 1083, 1028; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.18-1.29 (3H, m), 1.87-1.98 (4H, m), 2.11-2.27 (3H, m), 2.49 (1H, m), 2.60-2.73 (1H, m), 4.10-4.21 (3H, m), 4.40 (0.45H, m),

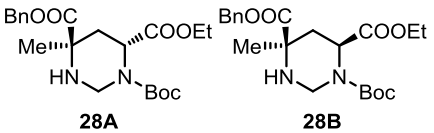
4.59 (0.55H, m), 4.78-4.90 (1H, m), 5.04-5.21 (4H, m), 7.28-7.38 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 15.5, 28.3, 33.2, 36.6, 51.9, 52.3, 52.4 (rotamer), 59.1, 61.6, 67.4 (rotamer), 67.6, 127.9, 128.1, 128.4, 128.5, 128.7, 135.1, 136.2, 151.0, 171.4, 174.2; MS(FAB) m/z $[M+H]^+$ 501; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{26}H_{32}N_2O_6S+H]^+$ 501.2059, found 501.2062; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=89.5/10/0.5, detection: 254 nm, retention time: t_{major}=16.7 min, t_{minor}=22.5 min.

25B: 92% ee; $[\alpha]^{20}_D$= –8.6 (c=0.92, $CHCl_3$); IR (neat) cm^{-1}: 3325, 3033, 2979, 1738, 1704, 1497, 1455, 1415, 1367, 1333, 1256, 1202, 1152, 1071, 1045, 1029; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.17-1.27 (3H, m), 1.73-1.81 (1H, m), 1.88 (1H, dd, *J* = 6.9, 14.2 Hz), 1.93-2.01 (4H, m), 2.11-2.20 (1H, m), 2.44 (1H, dt, *J* = 4.6, 12.4 Hz), 2.80 (1H, t, *J* = 15.0 Hz), 3.98-4.22 (2H, m), 4.47-4.52 (1H, m), 4.65 (1H, d, *J* = 12.8 Hz), 4.68 (0.5H, m), 4.78 (0.5H, m), 5.04 (1H, d, *J* = 12.4 Hz), 5.10-5.17 (2H, m), 5.19 (1H, d, *J* = 12.4 Hz), 7.28-7.38 (10H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 15.4, 27.8, 34.2 34.4 (rotamer), 40.4, 51.6, 52.0 (rotamer), 53.9, 54.1 (rotamer), 59.1, 61.5, 67.2, 67.4, 127.9, 128.1, 128.5, 128.6, 128.6, 135.1, 136.2, 154.5 (rotamer), 155.0, 171.3, 173.0; MS(FAB) m/z $[M+H]^+$ 501; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{26}H_{32}N_2O_6S+H]^+$ 501.2059, found 501.2062; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/Et_2NH=91.5/8/0.5, detection: 254 nm, retention time: t_{major}=22.9 min, t_{minor}=25.0 min.

Total Synthesis of manzacidin A (Scheme 2-6)

4-Benzyl 1-(*tert*-butyl) 6-ethyl-(4*R*,6*R*)-4-methyltetrahydropyrimidine-1,4,6(2*H*)-tricarboxylate (28A)

4-Benzyl 1-(*tert*-butyl) 6-ethyl (4*R*,6*S*)-4-methyltetrahydropyrimidine-1,4,6(2*H*)-tricarboxylate (28B)



28A **28B**

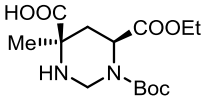
A mixture of **7A/7B** (0.39 g, 0.61 mmol) and 4 M HCl/AcOEt was stirred at r. t. for 1.5 h. The solution was concentrated in vacuo, and the residue was treated with AcOEt azeotrope. To the residue in CH_2Cl_2 (6 mL) were added Et_3N (0.184 g, 1.81 mmol) and Boc_2O (0.139 g, 0.635 mmol), and the solution was stirred at rt for overnight. The resulting mixture was diluted with AcOEt (50 mL), and washed with water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=15% to 50%) to give **28A** as a colorless oil (81.4 mg, 33%) and **28B** as a colorless oil (118 mg, 48%).

28A: 97% ee; $[\alpha]^{20}_D$=27.0 (c=1.20, $CHCl_3$); IR (neat) cm^{-1}: 3337, 2978, 2933, 1739, 1699, 1477, 1455, 1393, 1367, 1349, 1328, 1299, 1251, 1197, 1147, 1123, 1067; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, *J* = 6.9 Hz), 1.33 (3H, s), 1.36-1.50 (9H, m), 2.21 (2H, m), 2.43 (1H, br s), 4.16-4.25 (3H, m), 4.33-4.50 (0.5H, m), 4.55-4.85 (1.5H, m), 5.18 (2H, s), 7.30-7.42 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.3, 28.3, 34.1, 51.1, 52.1 (rotamer), 52.3, 52.8 (rotamer), 56.0, 62.3, 67.2, 80.5, 128.1, 128.4, 128.6, 135.3, 154.1, 171.8, 175.0; MS(FAB) m/z $[M+H]^+$ 407; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{21}H_{30}N_2O_6+H]^+$ 407.2182, found 407.2175.

28B: 98% ee; $[\alpha]^{20}_D$= –28.1 (c=1.02, $CHCl_3$); IR (neat) cm^{-1}: 3646, 2978, 2933, 1739, 1697, 1477, 1455, 1392, 1367, 1337, 1254, 1203, 1146, 1121, 1047; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.22 (3H, t, *J* = 6.8 Hz), 1.34 (3H, s), 1.37-1.50 (9H, m), 1.83 (1H, dd, *J* = 7.4, 14.2), 2.03-2.04 (1H, m), 2.79 (1H, dd, *J* = 13.5, 14.2 Hz), 3.94-4.15

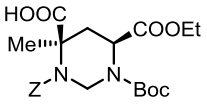
(2H, m), 4.29-4.37 (1H, m), 4.59-4.76 (2H, m), 5.04 (1H, d, *J* = 12.4 Hz), 5.17 (1H, d, *J* = 12.4 Hz), 7.34-7.37 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 13.9, 28.0, 28.1, 34.5, 34.7 (rotamer), 51.0, 52.2 (rotamer), 53.7, 54.7 (rotamer), 61.0, 67.0, 80.4, 128.0, 128.2, 128.5, 135.3, 154.0, 154.3 (rotamer), 171.5, 174.2; MS(FAB) m/z $[M+H]^+$ 407; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{21}H_{30}N_2O_6+H]^+$ 407.2182, found 407.2181.

(4*R*,6*S*)-1-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-4-methylhexahydropyrimidine-4-carboxylic acid



To a solution of **28B** (1.31 g, 3.22 mmol) in EtOH (28 mL) was added a suspension of 10% Pd-C (50 mg) in EtOH (20 mL), and the resulting suspension was stirred under H_2 atmosphere at r. t. for 45 min. The reaction mixture was diluted with MeOH to dissolve the white precipitate, and filtered to remove Pd-C. The filtrate was concentrated in vacuo to give the title compound as a colorless solid (0.988 g, 97%). For the elemental analysis, a small amount of the product was recrystallized from MeOH/Et_2O. Thus obtained product indicated 1/3 H_2O adduct; $[\alpha]^{20}_D$= –8.6 (c=1.00, MeOH); IR (KBr) cm^{-1}: 3107, 2980, 2935, 2878, 1744, 1712, 1628, 1590, 1476, 1418, 1394, 1368, 1340, 1284, 1251, 1208, 1156, 1128, 1035; ^{1}HNMR (400 MHz, CD_3OD) δ: 1.29 (3H, t, *J* = 6.9 Hz), 1.45-1.50 (12H, m), 1.94-2.04 (1H, m), 2.86 (0.5 H, d, *J* = 14.7 Hz), 2.92 (0.5 H, d, *J* = 14.7 Hz), 4.10-4.28 (2H, m), 4.59 (0.5H, d, *J* = 11.9 Hz), 4.71 (0.5H, d, *J* = 11.9 Hz), 4.74 (0.5H, d, *J* = 6.9 Hz), 4.81 (0.5H, d, *J* = 6.9 Hz), 5.06 (0.5H, d, *J* = 12.4 Hz), 5.15 (0.5H, d, *J* = 12.4 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.4, 26.0, 26.2 (rotamer), 28.3, 28.4 (rotamer), 33.4, 51.6, 53.0 (rotamer), 53.2, 54.3 (rotamer), 61.0, 62.9, 83.4, 83.6 (rotamer), 154.8, 155.0 (rotamer), 171.4, 171.5 (rotamer), 173.5; MS(FAB) m/z $[M+H]^+$ 317; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{14}H_{24}N_2O_6+H]^+$ 317.1713, found 317.1716; Elemental analysis (1/3 H_2O adduct), C, 52.16, H, 7.71, N, 8.69, found C, 52.05, H, 7.88, N, 8.53.

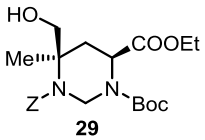
(4*R*,6*S*)-3-((Benzyloxy)carbonyl)-1-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-4-methylhexahydropyrimidine-4-carboxylic acid



To a solution of (4*R*,6*S*)-1-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-4-methylhexahydropyrimidine-4-carboxylic acid (0.37 g, 1.16 mmol) in CH_2Cl_2 (12 mL) were added Et_3N (0.13 g, 1.28 mmol) and CbzCl (0.21 g, 1.22 mmol) at 0 °C, and the solution was stirred at r. t. for 30 min. The resulting mixture was diluted with AcOEt (100 mL), and the solution was washed with 10% aqueous solution of citric acid (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), successively. The organic layer was dried over $MgSO_4$, and filtered off. The filtrate was concentrated in vacuo to give the title compound as a pale brown oil (0.52 g, quant.); $[\alpha]^{20}_D$=5.2 (c=0.84, $CHCl_3$); IR (neat) cm^{-1}: 3480, 3066, 2980, 2937, 2626, 1714, 1492, 1455, 1415, 1368, 1233, 1165, 1129, 1076, 1029, 1007; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.31 (3H, m), 1.40-1.44 (9H, m), 1.60-1.62 (3H, m), 2.17-2.42 (2H, m), 4.15-4.24 (2H, m), 4.38 (0.5H, dd, *J* = 6.0, 13.3 Hz), 4.46-4.51 (1H, m), 4.53 (0.5H, dd, *J* = 6.4, 12.8 Hz), 5.06-5.22 (2H, m), 5.84 (0.5H, d, *J* =

12.8 Hz), 5.98 (0.5H, d, *J* = 12.8 Hz), 7.26-7.38 (5H, m), 8.48 (1H, br s); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2 (rotamer), 20.0, 28.0, 28.1 (rotamer), 34.5, 34.7 (rotamer), 50.8, 50.9 (rotamer), 51.8, 52.0 (rotamer), 59.2, 59.2 (rotamer), 61.6, 67.6, 81.6, 81.6 (rotamer), 127.7, 127.8, 128.0, 128.1, 128.4, 135.7, 153.1, 153.3 (rotamer), 153.5, 153.6 (rotamer), 171.1, 171.4 (rotamer), 177.4; MS(FAB) m/z $[M+Na]^+$ 473; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{22}H_{30}N_2O_8+Na]^+$ 473.1900, found 473.1900.

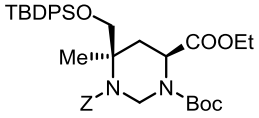
1-Benzyl 3-(*tert*-butyl) 4-ethyl (4*S*,6*R*)-6-(hydroxymethyl)-6-methyldihydropyrimidine-1,3,4(2*H*,4*H*)-tricarboxylate (29)



29

To a solution of (4*R*,6*S*)-3-((benzyloxy)carbonyl)-1-(*tert*-butoxycarbonyl)-6-(ethoxycarbonyl)-4-methylhexahydropyrimidine-4-carboxylic acid (0.40 g, 0.88 mmol) in CH_2Cl_2 (8.8 mL) were added Et_3N (0.11 g, 1.05 mmol) and isobutyl chloroformate (0.13 g, 0.92 mmol) at 0 ˚C, and the solution was stirred at the same temperature for 30 min. The resulting suspension was filtered off. The filtrate was added dropwise to the suspension of $NaBH_4$ (0.133 g, 3.51 mmol) in H_2O/THF (5 mL, 3/2, v/v) over 10 min at 0 ˚C, and the suspension was stirred for 30 min. The reaction was quenched by cautious addition of 10% aqueous solution of citric acid (30 mL), and the solution was extracted with AcOEt (30 mL×2). The combined extracts were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=35% to 75%) to give **29** as a colorless oil (0.27 g, 72%); $[\alpha]^{20}_D$=4.6 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3478, 3066, 3033, 2979, 2935, 2252, 1746, 1705, 1496, 1455, 1414, 1367, 1258, 1230, 1200, 1149, 1115, 1076, 1047, 1009; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.30 (3H, m), 1.36 (3H, s), 1.39-1.46 (9H, m), 1.82 (0.5H, dd, *J* = 5.5, 14.2 Hz), 1.90 (0.5H, dd, *J* = 6.0, 14.2 Hz), 2.33-2.40 (1H, m), 3.47 (1H, d, *J* = 10.5 Hz), 4.04 (1H, dd, *J* = 9.6, 10.5 Hz), 4.15-4.22 (2H, m), 4.33-4.41 (1.5H, m), 4.50 (0.5H, dd, *J* = 6.0, 13.3 Hz), 5.05-5.11 (1H, m), 5.16 (0.5H, d, *J* = 5.5 Hz), 5.19 (0.5H, d, *J* = 6.4 Hz), 5.89 (0.5H, d, *J* = 13.3 Hz), 6.06 (0.5H, d, *J* = 13.3 Hz), 7.29-7.39 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 14.1 (rotamer), 19.1, 28.0, 28.0 (rotamer), 34.0, 34.3 (rotamer), 51.4, 51.6 (rotamer), 52.2, 52.8 (rotamer), 58.3, 61.2, 67.1, 67.3 (rotamer), 68.1, 81.1, 127.5, 127.9, 128.1, 128.3, 128.4, 128.4, 135.8, 136.1 (rotamer), 153.2, 153.6 (rotamer), 154.3, 171.8, 172.0 (rotamer); MS(FAB) m/z $[M+Na]^+$ 459; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{22}H_{32}N_2O_7+Na]^+$ 459.2107, found 459.2115.

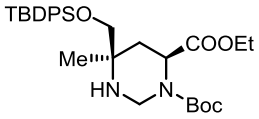
1-benzyl 3-(*tert*-butyl) 4-ethyl (4*S*,6*R*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6-methyldihydropyrimidine-1,3,4(2*H*,4*H*)-tricarboxylate



To a solution of **29** (0.26 g, 0.60 mmol) in CH_2Cl_2 (6 mL) were added imidazole (65 mg, 0.95 mmol)

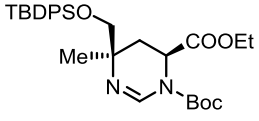
and *tert*-butyldiphenylchlorosilane (0.21 g, 0.77 mmol) at 0 ˚C, and the solution was stirred at r. t. for overnight. The resulting mixture was cautiously diluted with $CHCl_3$ (30 mL) and washed with saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4 and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (Hexane/AcOEt=10%) to give the title compound as a colorless oil (0.31 g, 77%); $[\alpha]^{20}_D$=12.2 (c=1.41, $CHCl_3$); IR (neat) cm^{-1}: 3070, 3032, 2976, 2932, 2894, 2858, 1960, 1892, 1747, 1697, 1589, 1538, 1490, 1472, 1455, 1410, 1366, 1282, 1258, 1226, 1199, 1151, 1113, 1031, 1008; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.01-1.04 (9H, m), 1.26-1.31 (3H, m), 1.35-1.44 (12H, m), 1.70-1.83 (1H, m), 2.59-2.68 (1H, m), 3.43-3.47 (1H, m), 4.17-4.28 (2H, m), 4.33 (0.6 H, dd, *J* = 5.0, 13.8 Hz), 4.44 (0.4H, dd, *J* = 5.0, 13.3 Hz), 4.42-4.50 (1H, m), 5.04-5.28 (2H, m), 5.93-6.14 (1H, m), 7.26-7.42 (11H, m), 7.56-7.59 (4H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 14.2 (rotamer), 19.2, 19.5 (rotamer), 26.7, 26.7 (rotamer), 28.1, 28.1 (rotamer), 34.3, 51.8, 52.0 (rotamer), 52.6, 53.1 (rotamer), 57.8, 66.8, 81.0, 127.6, 127.6, 127.9, 128.4, 128.4, 129.7, 132.8, 132.9 (rotamer), 133.2, 135.5, 135.5 (rotamer), 153.4, 154.3, 172.0, 172.3 (rotamer); MS(FAB) m/z $[M+Na]^+$ 697; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{38}H_{50}N_2O_7Si+Na]^+$ 697.3285, found 697.3284.

1-(*tert*-butyl) 6-ethyl (4*R*,6*S*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-methyltetrahydropyrimidine-1,6(2*H*)-dicarboxylate



To a solution of 1-benzyl 3-(*tert*-butyl) 4-ethyl (4*S*,6*R*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6 -methyldihydropyrimidine-1,3,4(2*H*,4*H*)-tricarboxylate (0.49 g, 0.73 mmol) in EtOH (10 mL) was added a suspension of 10% Pd-C (50 mg) in EtOH (10 mL), and the suspension was stirred under H_2 atmosphere at r. t. for 4 h. The resulting mixture was filtered, and the filtrate was concentrated in vacuo to give the title compound as a colorless oil (0.39 g, quant.); $[\alpha]^{20}_D$= –18.6 (c=0.74, MeOH); IR (KBr) cm^{-1}: 3330, 3071, 3049, 2963, 2931, 2858, 1740, 1699, 1589, 1473, 1462, 1428, 1392, 1366, 1334, 1301, 1252, 1199, 1167, 1112, 1090, 1052; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.08 (9H, s), 1.12 (3H, s), 1.18 (3H, t, *J* = 6.9 Hz), 1.44 (9H, s), 1.77 (1H, dd, *J* = 6.4, 14.2 Hz), 1.81 (1H, s), 2.17 (1H, m), 3.38 (1H, d, *J* = 10.1 Hz), 3.45 (1H, d, *J* = 10.1 Hz), 4.00-4.13 (2H, m), 4.22 (1H, d, *J* = 11.9 Hz), 4.38 (1H, br s), 4.53 (1H, m), 7.35-7.45 (6H, m), 7.61-7.65 (4H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 19.3, 24.7, 26.9, 28.2, 32.8, 51.8, 52.4, 53.3 (rotamer), 61.0, 68.7, 69.5 (rotamer), 80.4, 129.7, 129.7, 133.1, 133.2, 135.6, 135.6, 154.4, 172.6; MS(FAB) m/z $[M+H]^+$ 541; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{30}H_{44}N_2O_5Si+H]^+$ 541.3098, found 541.3100.

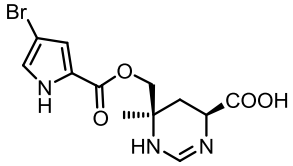
Ethyl {(4'*R*,6'*S*)-3'-*tert*-butoxycarbonyl-6'-(*tert*-butyldiphenylsiloxy)methyl-6'-methyl-3',4',5',6'-tetrahydropyrimidin-4'-yl}carboxylate (30)



30

To a solution of 1-(*tert*-butyl) 6-ethyl (4*R*,6*S*)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-methyltetrahydropyrimidine-1,6(2*H*)-dicarboxylate (0.13 g, 0.24 mmol) in CH_2Cl_2 (2.4 mL) was added *N*-chlorosuccinimide (NCS) (64 mg, 0.48 mmol) at 0 ˚C. After being stirred for 15 min at same temperature, DBU (0.148 g, 0.960 mmol) was added to the mixture and the resulting solution was stirred at r. t. for overnight. The solution was directly treated with flash silica-gel column chromatography (Hexane/AcOEt=15%) to give **30** as a colorless oil (0.13 g, quant.); $[\alpha]^{20}_D$= –46.3 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3071, 3049, 2966, 2932, 2858, 1730, 1647, 1590, 1473, 1462, 1428, 1392, 1370, 1311, 1256, 1197, 1166, 1140, 1112, 1032, 1009; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.08 (9H, s), 1.16 (3H, s), 1.23-1.27 (3H, m), 1.49 (9H, s), 1.93 (1H, m), 2.07 (1H, m), 3.42 (1H, d, *J* = 9.6 Hz), 3.64 (1H, d, *J* = 9.6 Hz), 4.09-4.15 (2H, m), 4.30 (1H, t, *J* = 6.7 Hz), 7.34-7.43 (6H, m), 7.61-7.65 (4H, m) 7.92 (0.6H, br s), 8.04 (0.4H, br s); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 14.1 (rotamer), 19.3, 23.1, 26.9, 27.9, 31.4, 51.3, 52.1 (rotamer), 61.3, 71.3, 83.4, 127.5, 129.6, 129.6, 133.2, 133.3, 135.6, 135.6, 141.3, 151.3, 171.0; MS(FAB) m/z $[M+H]^+$ 539; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{30}H_{42}N_2O_5Si+H]^+$ 539.2941, found 539.2939.

Manzacidin A

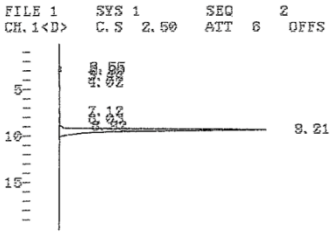


manzacidin A

To a solution of **30** (50 mg, 9.28×10^{-2} mmol) in 1,2-DME (0.47 mL) was added 8 M HCl aq. (116 μL), and the solution was stirred at 60 °C for 1 h. After addition of 8 M HCl aq. (116 μL), the solution was stirred at 60 °C for further 1.5 h. After addition of 8 M HCl aq. (116 μL), the solution was stirred at 60 °C for additional 1 h. The resulting mixture was diluted with 2 M HCl aq (3 mL) and the solution was washed with AcOEt (1 mL×2). The organic layer was extracted with 2 M HCl aq (2 mL), and all aqueous layers were combined. The aqueous layers were concentrated in vacuo. The residue was treated with Dowex-50W X4 (H^+ form) (2 g, water to 1 M NH_4OH) to give (4*S*, 6*R*)-6-hydroxymethyl-6-methyl-1,4,5,6-tetrahydropyrimidine-4-carboxylic acid as a white film (9.6 mg). To a solution of the compound in DMF (1.5 mL) was added NaH (60% in oil) (4.5 mg, 0.11 mmol), and the suspension was stirred at r. t. for 15 min. To the solution was added 4-bromo-2-trichloroacetylpyrrole (40.5 mg, 0.14 mmol), and the solution was stirred at r. t. for 4 h. After dilution with 2 M HCl aq. (3 mL) at 0 ˚C, the solution was washed with AcOEt (1 mL×2). The aqueous layer was concentrated in vacuo, and the residue was purified by RPHPLC (column: COSMOSIL 5C18-Ar-II 4.6ϕx250 mm, flow: 1 mL/min, detection: 254 nm, 20% CH_3CN/water containing 0.1% TFA) to give manzacidin A as a white amorphous solid (14 mg, 44%, 2 steps); $[\alpha]^{20}_D$ = –24.2 (c = 0.70, MeOH) {lit17 $[\alpha]^{27}_D$ = –22.4 (c = 0.52, MeOH)}; IR (neat) cm^{-1}: 3192, 2979, 1706, 1668, 1580, 1454, 1399, 1384, 1316, 1182, 1135, 1076; ^{1}H NMR (CD_3OD): δ 1.47 (3H, s), 2.22 (1H, dd, *J* =10.1, 14.0 Hz), 2.39 (1H, dd, *J* = 5.0, 14.0 Hz), 4.24 (1H, d, *J* = 11.4 Hz), 4.38 (1H, d, *J* = 11.4 Hz), 4.46 (1H, dd, *J* = 5.0, 10.1 Hz), 6.94 (1H, d, *J* = 1.2 Hz), 7.04 (1H, d, *J* = 1.2 Hz), 8.09 (1H, s); ^{13}CNMR (100 MHz, CD_3OD) δ: 24.0, 31.1, 49.4, 53.8, 68.8, 98.2, 118.5, 123.3, 125.4, 152.1, 160.6, 171.7; MS(FAB) m/z $[M+H]^+$ 344, 346, $[M+Na]^+$ 366, 368; HRMS (FAB) m/z

$[M+H]^+$ calcd for $[C_{12}H_{14}BrN_3O_4+H]^+$ 344.0246, 346.0227, found 344.0243, 346.0227.

RPHPLC chart



D-7500 INTEGRATOR REPORT

ANALYZED: 10/08/11 12:35 REPORTED: 10/08/11 12:55
SYSTEM : 1
METHOD : KH OPERATOR: HIRASE
CHANNEL : 1 <DIGITAL> SEQ : 2

FILE : 1 (07/10/02 15:35)
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	AREA	HEIGHT	CONC	BC
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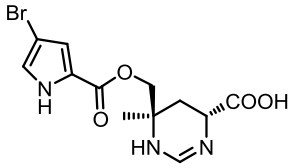
2	2.90	2884	315	0.710	VB
3	3.44	1920	98	0.473	BB
4	4.02	455	29	0.112	BB
5	7.12	270	23	0.066	BB
6	8.03	600	37	0.148	BB
7	8.92	4167	444	1.026	BV
8	9.21	391853	23097	96.479	VB
TOTAL		406154	24303	100.000	
PEAK REJ :		0			

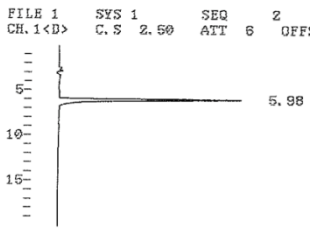
***ent*-Manzacidin C**



ent-manzacidin C

RPHPLC conditions; column: COSMOSIL 5C18-Ar-II 4.6ϕx250 mm, flow: 1 mL/min, detection: 254 nm, 20% CH_3CN/water containing 0.1% TFA; $[\alpha]^{20}_D$ = –82.9 (c = 0.45, MeOH); IR (neat) cm^{-1}: 2979, 1700, 1666, 1578, 1451, 1386, 1311, 1183, 1134; ^1H NMR (400 MHz, CD_3OD) δ: 1.45 (3H, s), 2.00 (1H, dd, *J* =10.5, 14.2 Hz), 2.61 (1H, dd, *J* = 5.5, 14.2 Hz), 4.27 (1H, d, *J* = 11.4 Hz), 4.38 (1H, d, *J* = 11.4 Hz), 4.48 (1H, dd, *J* = 5.5, 10.5 Hz), 6.90 (1H, d, *J* = 1.4 Hz), 7.05 (1H, d, *J* = 1.4 Hz), 8.10 (1H, s); ^{13}CNMR (100 MHz, CD_3OD) δ: 23.8, 32.4, 50.8, 53.4, 69.2, 98.2, 118.3, 123.3, 125.5, 152.0, 160.6, 172.1; MS(FAB) m/z $[M+H]^+$ 344, 346, $[M+Na]^+$ 366, 368; HRMS (FAB) m/z $[M+H]^+$ calcd for $[C_{12}H_{14}BrN_3O_4+H]^+$ 344.0246, 346.0227, found 344.0248, 346.0228.

RPHPLC chart



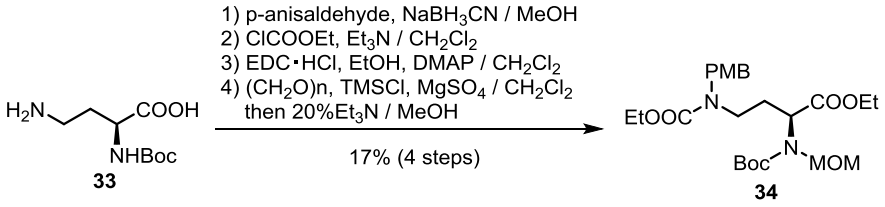
D-7500 INTEGRATOR REPORT

ANALYZED: 07/15/11 10:21 REPORTED: 07/15/11 10:41
SYSTEM : 1
METHOD : KH OPERATOR: HIRASE
CHANNEL : 1 <DIGITAL> SEQ : 2

FILE : 1 (07/10/02 15:35)
CALC-METHOD: AR/HI% <AREA> COMPONENT TBL : 0

NO.	RT	AREA	CONC	BC
1	5.98	273235	100.000	BB
TOTAL		273235	100.000	
PEAK REJ :		0		

Preparation of **Ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-(ethoxycarbonyl)(*p*-methoxybenzyl) aminobutanoate (34)**



To a suspension of 4-amino-2-(*tert*-Butoxycarbonyl)aminobutanoic acid (**33**)[29] (0.436 g, 2.00 mmol) in MeOH (10 mL) were added *p*-anisaldehyde (0.272 g, 2.00 mmol) and $NaBH_3CN$ (0.251 g, 4.00 mmol), and the suspension was stirred at r. t. for 6 h. The reaction mixture was concentrated in vacuo.

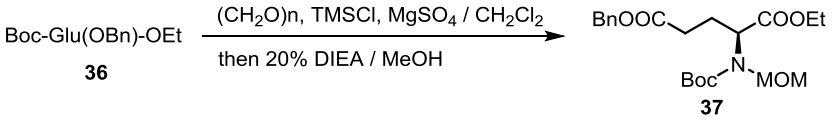
To the residue in CH_2Cl_2 (10 mL) were added Et_3N (0.243 g, 2.40 mmol) and ethyl chloroformate (0.217 g, 21.00 mmol) on ice, and the solution was stirred at r. t. for 10 h. To the solution was added AcOEt (70 mL), and the solution was 10% citric acid solution (30 mL×2) and brine (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was treated with flash silica-gel column chromatography (50 g, $CHCl_3$/MeOH 3%) to give crude 2-(*tert*-butoxycarbonyl)amino-4-(ethoxycarbonyl)(*p*-methoxybenzyl)aminobutanoic acid.

To the crude product in CH_2Cl_2 (8.2 mL) were added EtOH (0.113 g, 2.46 mmol), DMAP (20 mg, 0.164 mmol) and EDC・HCl (0.377 g, 1.97 mmol), and the solution was stirred at r. t. for 18 h. To the solution was added AcOEt (100 mL), and the solution was 10% citric acid solution (30 mL×2) and brine (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was treated with flash silica-gel column chromatography (15 g, Hexane/AcOEt 15%) to give crude ethyl 2-(*tert*-butoxycarbonyl)amino-4-(ethoxycarbonyl)(*p*-methoxybenzyl)aminobutanoate. To a mixture of paraformaldehyde (0.0374 g, 1.25 mmol) and $MgSO_4$ (0.832 g, 6.91 mmol) was added a solution of the crude product in CH_2Cl_2 (8.5 mL), and to the suspension was added TMSCl (0.271 g, 2.50 mmol) (distilled from CaH_2) on ice. The suspension was stirred at r. t. for 14 h. To the suspension was added 20% Et_3N/MeOH (2.5 mL) on ice, and the suspension was stirred at the same temperature for 30 min. To the suspension was added saturated aqueous $NaHCO_3$ solution (50 mL), and the solution was extracted with $CHCl_3$ (30 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (10 g, Hexane/AcOEt 20%) to give **34** as colorless oil (0.167 g, 17%, 4 steps). $[\alpha]^{20}_D$=-13.5 (c 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2979, 2936, 2836, 1740, 1702, 1612, 1513, 1470, 1425, 1389, 1368, 1300, 1248, 1175, 1092, 1035, 914, 860, 817, 773; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.23-1.29 (6H, m), 1.42 (5.5H, s), 1.48 (3.5H, s), 1.87-2.12 (1H, m), 2.25-2.41 (1H, m), 3.21-3.43 (4H, m), 3.79 (3H, s), 4.10-4.25 (4H, m), 4.38-4.45 (1H, m), 4.61-4.67 (1H, m), 4.70-4.85 (1H, m), 6.82-6.89 (2H, m), 7.12-7.30 (2H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 14.6, 28.0, 28.1 (rotamer), 29.1, 43.5, 44.2 (rotamer), 49.1, 49.6 (rotamer), 55.1, 55.7, 56.0 (rotamer), 56.3, 56.9 (rotamer), 61.1, 61.3, 78.4, 78.7 (rotamer), 81.0, 81.1 (rotamer), 113.7, 113.8 (rotamer), 128.4 (rotamer), 128.6, 129.0 (rotamer), 129.2, 129.8, 129.9 (rotamer), 154.8, 155.0 (rotamer), 156.3, 156.6 (rotamer), 158.8, 171.8;

MS(FAB) m/z $[M+Na]^+$ 505; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{24}H_{38}N_2O_8+Na]^+$ 505.2526, found 505.2531.

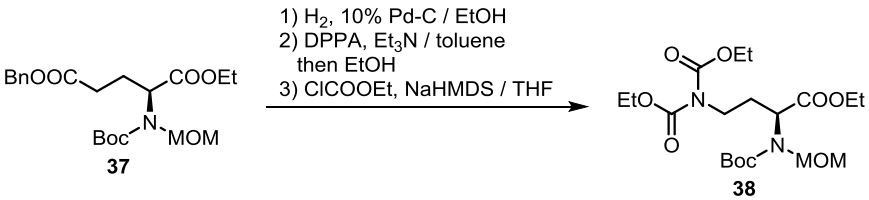
*Preparation of **38***

Benzyl 4-ethoxycarbonyl-4-(*tert*-butoxycarbonyl)(methoxymethyl)aminobutanoate (37)



To a mixture of paraformaldehyde (0.637 g, 21.2 mmol) and $MgSO_4$ (14.1 g, 117 mmol) was added a solution of Boc-Glu(OBn)-OEt (**36**) (5.17 g, 14.1 mmol) in CH_2Cl_2 (141 mL), and to the suspension was added TMSCl (4.60 g, 42.3 mmol) (distilled from CaH_2) on ice. The suspension was stirred at r. t. for 6 h. To the suspension was added 20% DIEA/MeOH (47 mL) on ice, and the suspension was stirred at the same temperature for 30 min. To the suspension was added saturated aqueous $NaHCO_3$ solution (200 mL), and the solution was extracted with $CHCl_3$ (100 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (200 g, Hexane/AcOEt 30%) to give **37** as colorless oil (5.47 g, 95%). $[\alpha]^{20}_D$=-24.5 (c 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2979, 2936, 1739, 1707, 1427, 1389, 1367, 1297, 1255, 1164, 1092, 1033, 913, 863, 751, 699; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.31 (3H, m), 1.42 (5.5H, s), 1.47 (3.5H, s), 2.10-2.19 (1H, m), 2.33-2.51 (3H, m), 3.32 (1.2H, s), 3.34 (1.8H, s), 4.08 (0.6H, dd, J = 6.0Hz, 9.3 Hz), 4.10-4.23 (2H, m), 4.31 (0.4H, dd, J = 6.0Hz, 9.3 Hz), 4.61-4.64 (1H, m), 4.76 (0.4H, d, J = 11.9 Hz), 4.80 (0.6 H, d, J = 11.9 Hz), 5.12 (2H, s), 7.31-7.38 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 24.8, 25.5 (rotamer), 28.1, 30.7, 55.9, 56.1 (rotamer), 57.9, 58.5 (rotamer), 61.2, 61.2 (rotamer), 66.3, 78.8, 79.3 (rotamer), 81.1, 81.3 (rotamer) 128.2, 128.5, 135.8, 135.9 (rotamer), 155.0, 157.1 (rotamer), 171.2, 172.8; MS(FAB) m/z $[M+Na]^+$ 432; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{21}H_{31}NO_7+Na]^+$ 432.1198, found 432.2004.

Ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-bis(ethoxycarbonyl)aminobutanoate (38)



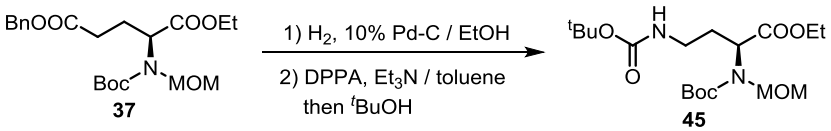
To a solution of **37** (2.69 g, 6.57 mmol) was added a suspension of 10% Pd-C (130 mg) in EtOH (66 mL), and the suspension was stirred under an H_2 atmosphere at r. t. for 14 h. The suspension was filtered to remove Pd-C. The filtrate was concentrated in vacuo to give crude carboxylic acid as colorless oil (2.16 g). To a solution of the residue in toluene (33 mL) were added Et_3N (1.33 g, 13.1 mmol) and DPPA (1.90 g, 6.90 mmol), and the solution was stirred at 80°C for 1 h. To the solution was added EtOH (3.03 g, 65.7 mmol), and the solution was stirred at 80°C for 12 h. To the solution was added toluene (33 mL), and the solution was washed with 10% citric acid solution (50 mL), brine $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue

was purified by flash silica-gel column chromatography (20 g, Hexane/AcOEt 10% to 50 %) to give 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-(ethoxycarbonyl) aminobutanoate (2.38 g). Thus obtained product (0.552 g, 1.52 mmol) was used in a following reaction. To a solution of the product (0.552 g) in THF (12.4 mL) was added a solution of 1.89 M NaHMDS (0.776 mmol, 1.45 mmol) at -78°C, and the solution was stirred at the same temperature for 10 min. To the solution was added a solution of ClCOOEt (0.181 g, 1.67 mmol) in THF (2 mL) by cannulation, and the solution was stirred for 1 h. The reaction mixture was added to saturated NH_4Cl aq. (20 ml), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (10 g, Hexane/AcOEt 10%) to give **38** as colorless oil (0.308 g, 47%)

$[\alpha]^{20}_D$=-21.7 (c 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2981, 2937, 1793, 1743, 1708, 1448, 1372, 1332, 1295, 1194, 1094, 914, 865, 777; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.20-1.31(9H, m), 1.41-1.46 (9H, m), 2.01-2.14 (1H, m), 2.30-2.40 (1H, m), 3.31-3.35 (3H, m), 3.98-4.26 (7H, m), 4.66-4.79 (2H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 28.0, 28.1(rotamer), 28.8, 29.8 (rotamer), 44.1, 44.2 (rotamer), 55.8, 56.0 (rotamer), 56.4, 57.1 (rotamer), 60.9, 61.2 (rotamer), 63.0, 78.4, 78.9 (rotamer), 81.0, 81.2 (rotamer), 153.4, 154.7, 154.9 (rotamer), 171.0, 171.1 (rotamer); MS(FAB) m/z $[M+Na]^+$ 457; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{19}H_{34}N_2O_9+Na]^+$ 457.2162, found 457.2168

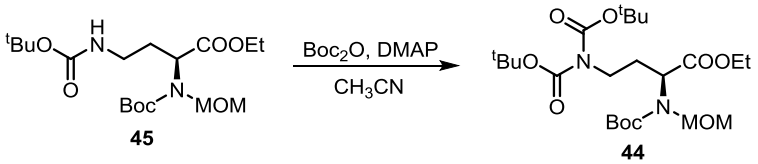
*Preparation of **44***

Ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-(*tert*-butoxycarbonyl) aminobutanoate (45)



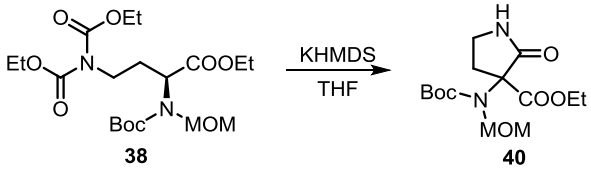
To a solution of **37** (10.5 g, 25.6 mmol) was added a suspension of 10% Pd-C (525 mg) in EtOH (256 mL), and the suspension was stirred under an H_2 atmosphere at r. t. for 6 h. The suspension was filtered to remove Pd-C. The filtrate was concentrated in vacuo to give crude carboxylic acid as colorless oil (8.40 g). To a solution of the residue in toluene (130 mL) were added Et_3N (5.18 g, 51.2 mmol) and DPPA (7.40 g, 26.9 mmol), and the solution was stirred under reflux for 35 min. To the solution was added ^{t}BuOH (19.0 g, 256 mmol), and the solution was stirred at 80°C for 2 days. The solution was washed with 10% citric acid solution (50 mL), brine $NaHCO_3$ solution (50 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (300 g, Hexane/AcOEt 15% to 100 %) to give **45** as colorless oil (7.89 g, 78.9%). $[\alpha]^{20}_D$=-42.7 (c 1.0, $CHCl_3$); IR (neat) cm^{-1}: 3373, 2979, 2935, 1741, 1712, 1523, 1429, 1391, 1367, 1298, 1250, 1174, 1098, 1031, 915, 864, 776; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.30 (3H, m), 1.44 (13H, s), 1.49 (5H, s), 1.95-2.11 (1H, m), 2.17-2.33 (1H, m), 2.99-3.20 (1H, m), 3.30-3.40 (4H, m), 4.02 (0.55H, dd, J = 5.5 Hz, 8.2 Hz), 4.10-4.23 (2H, m), 4.27-4.35 (0.45H, m), 4.67-4.82 (1H, m), 5.00 (1H, brs); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 28.1, 28.4, 29.9, 30.7 (rotamer), 37.3, 37.5 (rotamer), 56.0, 56.2 (rotamer), 56.6, 57.5 (rotamer), 61.2, 61.3 (rotamer), 79.1, 79.9, 81.2, 81.4 (rotamer) 154.9, 155.9 (rotamer), 171.4, 171.5; MS(FAB) m/z $[M+Na]^+$ 413; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{18}H_{34}N_2O_7+Na]^+$ 413.2264, found 413.2269

Ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-bis(*tert*-butoxycarbonyl) aminobutanoate (44)



To a solution of **45** (1.51 g, 3.87 mmol) in CH_3CN (39 mL) were added DMAP (47 mg, 0.387 mmol) and Boc_2O (1.01 g, 4.64 mmol), and the solution was stirred at r. t. for 11 h. To the solution were additionally added DMAP (47 mg, 0.387 mmol) and Boc_2O (0.422 g, 1.94 mmol), and the solution was stirred at r. t. for 11 h. To the solution was added AcOEt (50 mL) and the solution was washed with 10% citric acid (30 mL×2). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (100 g, Hexane/AcOEt 15 %) to give **44** as colorless oil (1.70 g, 89%). $[\alpha]^{20}_D$=-17.6 (c 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2979, 2936, 1790, 1743, 1709, 1450, 1393, 1366, 1302, 1280, , 1255, 1220, 1176, 1140, 1035, 915, 859, 776; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.30 (3H, m), 1.44-1.50 (27H, m), 2.00-2.16 (1H, m), 2.31-2.42 (1H, m), 3.36 (3H, s), 3.66-3.69 (2H, m), 4.01 (0.6H, t, J = 6.9 Hz), 4.10-4.25 (2H, m), 4.70-4.73 (1H, m), 4.78-4.83 (1H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.2, 28.0, 28.1(rotamer), 29.1, 30.1 (rotamer), 44.3, 56.0, 56.2 (rotamer), 56.8 (rotamer), 57.3, 61.3, 79.0, 81.3, 82.4, 152.4, 152.5, 152.6, 171.3, 171.4 (rotamer); MS(FAB) m/z $[M+Na]^+$ 513; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{23}H_{42}N_2O_9+Na]^+$ 513.2788, found 513.2791

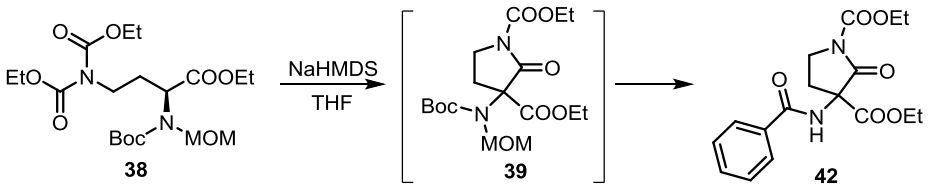
Ethyl 3-(*tert*-butoxycarbonyl)(methoxymethyl)amino-2-oxopyrrolidin-3-ylcarboxylate (40)



(Conditions of entry 1 in Table 3-1)

To a solution of **38** (54 mg, 0.124 mmol) in THF (1 mL) was added dropwise 0.53M KHMDS (in THF) (257 μL, 0.136 mmol) at -78°C. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was added to saturated NH_4Cl aq. (20 ml), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (5 g, Hexane/AcOEt 50% to 100%) to give **40** as colorless oil (15 mg, 39%, 0%ee). Enantiomeric excess of **40** was determined after conversion to **43**. ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.20-1.32 (3H, m), 1.44 (9H, s), 2.29-2.36 (1H, m), 3.19-3.30 (1H, m), 3.26 (3H, s), 3.36-3.50 (2H, m), 4.08-4.37 (2H, m), 5.01-5.22 (2H, m), 6.72 (1H, brs); ^{13}CNMR (100MHz, DMSO-d6) δ: 14.0, 28.1, 33.2, 34.5 (rotamer), 39.3, 55.5, 62.3, 68.3, 76.0, 76.1 (rotamer), 81.6, 82.0 (rotamer), 154.7, 154.8, 169.4, 170.6, 170.8 (rotamer); MS(FAB) m/z $[M+H]^+$ 317

Ethyl 3-benzoylamino-2-oxopyrrolidin-3-ylcarboxylate (40)

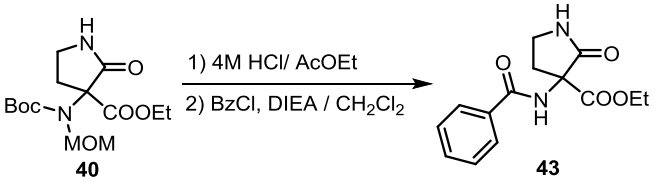


(Conditions of entry 2 in Table 3-1)

To a solution of **38** (48 mg, 0.110 mmol) in THF (1 mL) was added dropwise 1.89 M NaHMDS (in THF) (64 μL, 0.121 mmol) at -78°C. The reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was added to saturated NH_4Cl aq. (20 ml), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was treated with flash silica-gel column chromatography (10 g, Hexane/AcOEt 15% to 50%) to give crude **39** as colorless oil (23 mg).

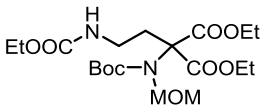
The residue **39** and 4M HCl/AcOEt (0.5 mL) was stirred at r. t. for 2 h. The solution was concentrated in vacuo, and to the residue in CH_2Cl_2 (0.6 mL) were added DIEA (15.2 mg, 0.118 mmol) and benzoyl chloride (9.2 mg, 6.5×10^{-2} mmol) on ice, and the solution was stirred at r. t. for 1 h. The reaction mixture was directly treated with preparative thin layer chromatography (AcOEt) to give **42** as colorless oil (8.6 mg, 22%, 2steps, 5% ee). ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.31 (3H, t, J = 7.1 Hz), 1.38 (3H, t, J = 7.1 Hz), 2.62-2.74 (2H, m), 3.95-3.97 (1H, m), 4.06-4.12 (1H, m), 4.24-4.36 (2H, m), 4.36 (2H, q, J = 7.1 Hz), 7.44-7.48 (2H, m), 7.54 (1H, t, J = 7.3 Hz), 7.81-7.84 (2H, m); HPLC conditions: column: DAICEL CHIRALPAK® AD-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH=80/20, detection: 254 nm, retention time: *t*minor=25 min, *t*major=28 min.

Ethyl 3-benzoylamino-2-oxopyrrolidin-3-ylcarboxylate (43)



A mixture of **40** (15 mg, 4.8×10^{-2} mmol) and 4M HCl/AcOEt (0.5 mL) was stirred at r. t. for 2 h. The solution was concentrated in vacuo, and to the residue in CH_2Cl_2 (0.5 mL) were added DIEA (12 mg, 9.6×10^{-2} mmol) and benzoyl chloride (7.5 mg, 5.3×10^{-2} mmol), and the solution was stirred at r. t. for 1 h. The reaction mixture was directly treated with preparative thin layer chromatography (AcOEt) to give **43** as colorless oil (3 mg, 23%). ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.30 (3H, t, J = 7.4 Hz), 2.62-2.70 (1H, m), 2.95-3.01 (1H, m), 3.59-3.70 (1H, m), 4.30 (2H, q, J = 7.4 Hz), 6.78 (1H, s), 7.38 (1H, s), 7.45 (2H, t, J = 7.3 Hz), 7.53 (1H, t, J = 7.3 Hz), 7.83-7.86 (2H, m); ^{13}CNMR (100MHz, $CDCl_3$) δ: 14.0, 32.4, 40.0, 62.9, 64.2, 127.2, 128.6, 132.0, 133.8, 167.0, 169.2, 171.6 HPLC conditions: column: DAICEL CHIRALCEL® OJ, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH=85/15, detection: 254 nm, retention time: t=22 min, t=27 min.

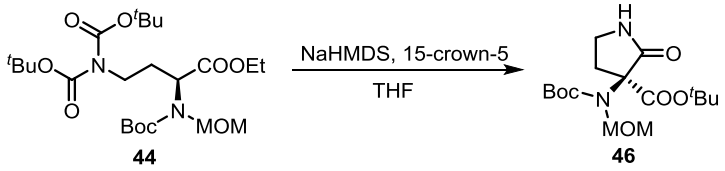
(Byproduct of entry 7 in Table 3-1)



41

IR (neat) cm^{-1}: 3384, 2981, 2934, 1712, 1530, 1451, 1370, 1298, 1252, 1208, 1173, 1097, 1031, 861, 758; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.20-1.37 (9H, m), 1.46 (9H, s), 2.40 (2H, t, J = 6.4 Hz), 3.36 (3H, s), 3.37-3.42 (2H, m), 4.06-4.11 (2H, m), 4.19-4.27 (4H, m), 4.93 (2H, s), 5.06 (1H. brs); ^{13}CNMR (100MHz, DMSO-d6) δ: 13.9, 14.6, 28.0, 34.5, 36.9, 56.0, 60.6, 68.8, 76.2, 82.0, 154.9, 156.5, 168.5; MS(FAB) m/z $[M+Na]^+$ 457; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{19}H_{34}N_2O_9+Na]^+$ 457.2162, found 457.2167

***tert*-Butyl 3-(*tert*-butoxycarbinyl)(methoxymethyl)amino-2-oxo-pyrrolidin-3-ylcarboxylate (46)**

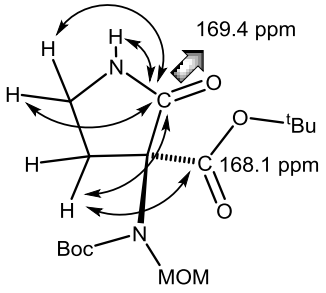


44 **46**

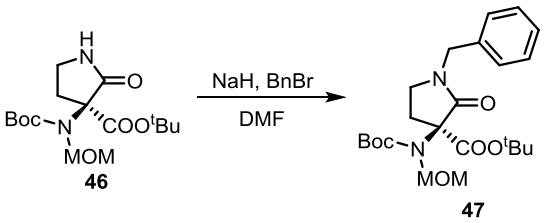
(Conditions of entry 6 in Table 3-2)

To a solution of **44** (55.5 mg, 0.113 mmol) in THF (1.06 mL) was added 15-crown-5 (60 mg, 0.271 mmol), and to the mixture was added dropwise 1.89M NaHMDS (in THF) (72 μL, 0.135 mmol) at -78°C. The reaction mixture was stirred at the same temperature for 12 h. The reaction mixture was added to saturated NH_4Cl aq. (20 ml), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (10 g, Hexane/AcOEt 50%, 100%) to give **46** as colorless solid (27 mg, 70%, 97% ee). Enantiomeric excess of **46** was determined after conversion to **47**. $[\alpha]^{20}_D$=102.2 (c 0.72, $CHCl_3$); IR (neat) cm^{-1}: 3317, 2979, 2933, 1710, 1456, 1371, 1298, 1257, 1160, 1084, 1033, 941, 849, 756;^{1}HNMR (400MHz, $CDCl_3$) δ: 1.46 (9H, s), 1.48 (9H, s), 2.29-2.36 (1H, m), 3.15-3.30 (1H, m), 3.27 (3H, s), 3.36-3.44 (2H, m), 4.95-5.22 (2H, m), 6.42 (1H, brs); ^{13}CNMR (100MHz, DMSO-d6) δ: 27.4, 27.8, 33.1, 34.5 (rotamer), 38.4, 54.9, 68.5, 75.1, 76.0 (rotamer), 80.6, 81.2 (rotamer), 154.3, 168.1, 169.4; MS(FAB) m/z $[M+H]^+$ 345; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{16}H_{28}N_2O_6+H]^+$ 345.2026, found 345.2023

Correlation in ^{1}H-^{13}C HMBC NMR (DMSO-d_6)



***tert*-Butyl 1-benzyl-3-(*tert*-butoxycarbinyl)(methoxymethyl)amino-2-oxo-pyrrolidin- 3-ylcarboxylate (47)**

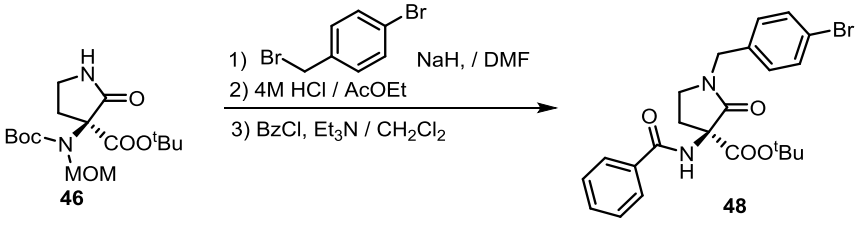


46 **47**

To a solution of **46** (5.2 mg, 1.51×10^{-2} mmol) in DMF (0.15 mL) were added NaH (60% in oil) (0.8 mg, 1.96×10^{-2} mmol) and Benzyl bromide (3.1 mg, 1.81×10^{-2} mmol) at r. t., and the solution was stirred at the same temperature for 40 min. To the solution was added 10% citric acid solution (5 mL), and the solution was extracted with AcOEt (10 mL×2). The extracts were combined, and to the solution was added hexane (10 mL). The solution was washed with water (5 mL×2). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography (Hexane/AcOEt 33 %) to give **47** as colorless solid (4.7 mg, 71%). $[\alpha]^{20}_{D}$=113.5 (c 0.805, $CHCl_3$); IR (KBr) cm^{-1}: 2980, 2931, 1751, 1700, 1454, 1370, 1305, 1263, 1154, 1082, 1041, 943, 911, 859, 764, 705; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.48 (9H, s), 2.15-2.22 (1H, m), 3.02-3.33 (3H, m), 3.21 (3H, s), 4.44 (1H, d, J = 14.7 Hz), 4.55 (1H, d, J = 14.7 Hz), 4.97-5.22 (2H, m), 7.23-7.34 (5H, m); ^{13}CNMR (100MHz, $CDCl_3$) δ: 27.7, 28.2, 31.0, 43.8, 47.5, 55.2, 69.2, 81.3, 82.0, 127.6, 128.1, 128.6, 135.7, 154.7, 160.8, 168.0; MS(FAB) m/z $[M+H]^+$ 435, $[M+Na]^+$ 457; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{23}H_{34}N_2O_6+H]^+$ 435.2495, found 435.2490; HPLC conditions: column: DAICEL CHIRALPAK® OD, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH=97/3, detection: 254 nm, retention time: tmajor=8.1 min, tminor=10.1min.

*Determination of absolutely configuration of **46***

***tert*-Butyl 1-(4-bromo)benzyl-3-(benzoyl)amino-2-oxo-pyrrolidin-3-ylcarboxylate (62)**



46 **48**

To a solution of **46** (67 mg, 0.195 mmol) in DMF (2 mL) were added NaH (60% in oil) (10 mg, 0.253 mmol) and *p*-bromobenzyl bromide (53.6 mg, 1.81×10^{-2} mmol) at r. t., and the solution was stirred at the same temperature for 40 min. To the solution was added AcOEt (30 mL), and the solution was washed with 10% citric acid solution (10 mL) and water (10 mL×2). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography (Hexane/AcOEt 33 %) to give 4-bromobenzylated compound as a colorless solid (82.5 mg). The solid was used in a following reaction without further purification. A mixture of the residue and 4M HCl/AcOEt (1.6 mL) was stirred at r. t. for 2.5 h. The solution was concentrated in vacuo, and to the residue in CH_2Cl_2 (1 mL) were added Et_3N (48.9 mg, 0.483 mmol) and benzoyl chloride (34 mg, 0.241 mmol), and the solution was stirred at r. t. for 1 h. To the solution was added $CHCl_3$ (30 mL), and the solution was washed with 10% citric acid solution (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography (1st

Hexane/AcOEt 20 % and 2nd toluene/AcOEt 5/1) to give **48** as colorless solid (22 mg). The solid was recrystallized from Et_2O/hexane, and was used in X-ray crystallography. $[\alpha]^{20}_D$=33.7 (c 0.330, $CHCl_3$); IR (KBr) cm^{-1}: 3353, 2973, 1756, 1709, 1654, 1522, 1485, 1368, 1287, 1261, 1157, 1113, 1068, 848, 713; ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.56-2.69 (1H, m), 3.40-3.49, 3.21 (3H, s), 4.36 (1H, d, J = 14.6 Hz), 4.72 (1H, d, J = 14.7 Hz), 7.23 (2H, d, J = 8.2 Hz), 7.43-7.54 (6H, m), 7.84-7.86 (2H, m); ^{13}CNMR (100MHz, $CDCl_3$) δ: 27.8, 29.6, 44.3, 47.0, 65.4, 84.1, 121.7, 127.2, 128.5, 129.9, 131.8, 131.9, 133.5, 134.9, 166.6, 168.6, 168.6; MS(FAB) m/z $[M+H]^+$ 473, 475; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{23}H_{25}BrN_2O_4+H]^+$ 473.1076, 475.1059 found 473.1067, 475.1057

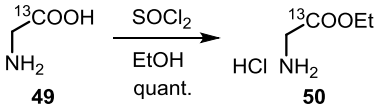
*X-ray structural analysis of **48***

Crystal Data of **48** $C_{23}H_{25}BrN_2O_4$, M = 473.36, space group P212121, a = 11.975 (4) Å, b = 12.732 (5) Å, c = 29.233(11) Å, α = 90°, β = 90°, γ = 90°, V = 4457(3) $Å^3$, Z = 8, ρ_{calcd} = 1.411Mg/m^3, $Mo_{K\alpha}$ radiation, λ = 0.71075 Å, μ = 1.875 mm–1, T = 103(2) K. The final *R1* and w*R2* were 0.0411 and 0.0747 for 618 parameters. CCDC 955163 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Determination of the reaction mechanism of γ-lactams

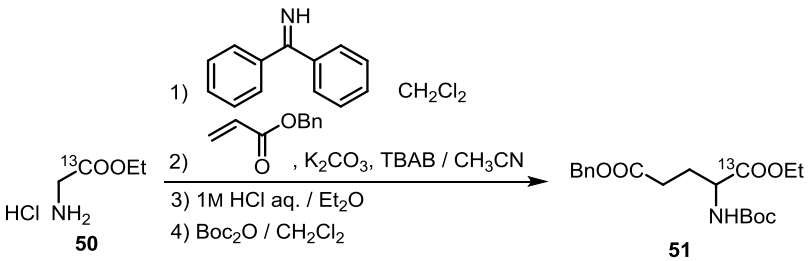
*Preparation of **54***

1-^{13}C Ethyl 2-aminoacetate hydrochloride (50)



A thionyl chloride (2.6 mL) was added dropwise to EtOH (15 mL) for 8 min on ice, and the solution was stirred at the same temperature for 2 min. To the mixture was added 1-^{13}C glycine (**49**) (1.00 g, 13.1 mmol) on ice, and the suspension was stirred at r. t. for 4 h. The suspension was additionally stirred at 40°C for 13 h. The suspension was concentrated in vacuo. The residue was suspended to Et_2O, and filtered to give **50** as a colorless solid (1.84 g, quant.). ^{1}HNMR (400MHz, DMSO-d_6) δ: 1.22 (3H, t, J = 7.3 Hz), 3.76 (2H, d, J = 6.4 Hz), 4.16 (1H, dd, J = 3.2Hz, 7.3 Hz), 4.20 (1H, dd, J = 3.2Hz, 7.3 Hz), 8.41 (3H, brs); ^{13}CNMR (100MHz, DMSO-d_6) δ: 14.0, 61.6, 167.7 (^{13}C labeled) (*C*H_2 signal was not be detected because this signal would hide in solvent peak. (^{13}C NMR of HCl-Gly-OEt indicated that *C*H_2 signal observed in 41.1 ppm in D_2O); MS(EI) m/z $[M]^+$ 104; HRMS(EI) m/z $[M]^+$ calcd for $[C_3{}^{13}CH_9NO_2]^+$ 104.0667, found 104.0666

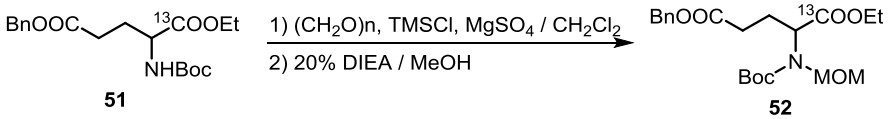
1-^{13}C 5-Benzyl 1-ethyl 2-(*tert*-butoxycarbonyl)aminopentanedioate (51)



To a suspension of **50** (0.703 g, 5.00 mmol) in CH_2Cl_2 (18 mL) was added benzophenonimine (0.906

g, 5.00 mmol), and the suspension was stirred at r. t. for 24 h. To the reaction mixture was added water (50 mL), and the biphasic solution was extracted with $CHCl_3$ (50 mL×2). The extracts were combined, and the solution was washed with brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (30 g, Hexane/AcOEt 10% to 50%) to give 1-^{13}C ethyl 2-(diphenylmethylene)aminoacetate as colorless oil (1.29 g). Thus obtained crude product (1.21 g) was used in a following reaction. To a solution of the residue (1.21 g, 4.51 mmol) in CH_3CN (16.5 mL) were added K_2CO_3 (1.87 g, 13.5 mmol) and tetra-*n*-butylammonium bromide (0.145 g, 0.451 mmol), and to the suspension was added dropwise benzyl acrylate (1.46 g, 9.02 mmol) in CH_3CN (3.5 mL) for 3 min. The suspension was stirred at r. t. for 3 h. The insoluble materials were filtered off, and the filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (20 g, Hexane/AcOEt 10% to 30%) to give 1-^{13}C 5-benzyl 1-ethyl 2-((diphenylmethylene)amino)pentanedioate as colorless oil (1.65 g, 85%). Thus obtained crude product (1.61 g) was used in a following reaction. To a solution of the residue (1.61 g, 3.74 mmol) in Et_2O (37.4 mL) was added 1M HCl aq. (18.7 mL, 18.7 mmol), and he biphasic solution was stirred at r. t. for 4.5 h. The organic layer was removed, and the aqueous layer was washed with Et_2O (10 mL). The aqueous layer was basified by $NaHCO_3$, and the solution was extracted with AcOEt (30 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. To the residue in CH_2Cl_2 (35 mL) was added Boc_2O (0.816 g, 3.74 mmol), and the solution was stirred at r. t. for 4 h. To the reaction mixture was added $CHCl_3$ (50 mL), and the solution was washed with 10% citric acid solution (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (20 g, Hexane/AcOEt 20%) to give **51** as a colorless solid (1.15 g, 84%). ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.27 (3H, t, J = 6.9 Hz), 1.44 (9H, s), 1.91-2.01 (1H, m), 2.14-2.26 (1H, m), 2.39-2.52 (2H, m), 4.16-4.22 (3H, m), 4.29-4.36 (1H, m), 5.12 (3H, m), 7.30-7.40 (5H, m); ^{13}CNMR (100MHz, $CDCl_3$) δ: 14.1, 27.4, 27.8, 28.3, 30.3, 52.8 (d, split by C-C coupling, J = 60.1 Hz), 61.6, 66.5, 80.0, 85.2, 128.3, 128.3, 128.6, 135.7, 146.7, 155.4, 172.2 (^{13}C labeled), 172.6; MS(FAB) m/z $[M+H]^+$ 367, $[M+Na]^+$ 389; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{18}{}^{13}CH_{27}NO_6+H]^+$ 367.1949, found 367.1950

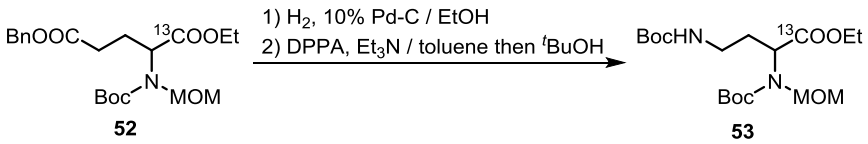
1-^{13}C 5-Benzyl 1-ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)aminopentanedioate (52)



To a solution of **51** (1.11 g, 3.03 mmol) in CH_2Cl_2 (30 mL) were added paraformaldehyde (0.136 g, 4.55 mmol) and $MgSO_4$ (3.03 g, 35.1 mmol) at r. t., and to the suspension was added TMSCl (0.988 g, 9.09 mmol) at 0°C. The suspension was stirred at r. t. for 9.5 h, and to the suspension was added 20% DIEA in MeOH (10 mL) at 0°C. The suspension was stirred at the same temperature for 30 min, and to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (50 mL). The biphasic solution was extracted with $CHCl_3$ (30 mL×2), and the extracts were combined. The solution was dried over Na_2SO_4, filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography

(Hexane/AcOEt 15% to 30 %) to give **52** as colorless oil (0.982 g, 79%). ^{1}HNMR (400MHz, $CDCl_3$) δ: 1.23-1.30 (3H, m), 1.43 (5.2H, s), 1.47 (3.8H, s), 2.10-2.22 (1H, m), 2.38-2.52 (3H, m), 3.32 (1.3H, s), 3.34 (1.7H, s), 4.06-4.34 (3H, m), 4.63 (1H, d, J = 11 Hz), 4.76 (0.42H ,d, J = 11 Hz), 4.80 (0.58H, d, J = 11 Hz), 5.12 (2H, s), 7.30-7.40 (5H, m); ^{13}CNMR (100MHz, $CDCl_3$) δ: 14.1, 24.8, 25.5 (rotamer), 28.1, 30.8, 55.9, 56.2 (rotamer), 57.9 (d, split by C-C coupling, J = 59.1 Hz), 58.5 (rotamer, d, split by C-C coupling, J = 59.1 Hz), 61.2, 61.2 (rotamer), 66.3, 78.8, 79.3 (rotamer), 81.1, 81.3 (rotamer), 128.2, 128.5, 135.8, 155.0, 171.2 (^{13}C labeled), 171.2 (^{13}C labeled) (rotamer), 172.2, 172.8 (rotamer); MS(FAB) m/z $[M+Na]^+$ 433; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{20}{}^{13}CH_{31}NO_7+Na]^+$ 433.2031, found 433.2032

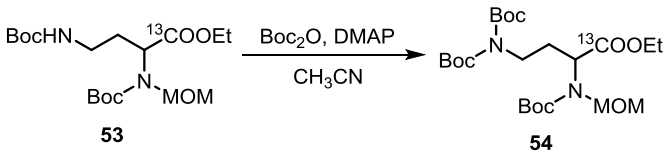
1-^{13}C Ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-(*tert*-butoxcarbonyl) aminobutanoate (53)



52 **53**

To a solution of **52** (0.948 g, 2.31 mmol) in EtOH (13 mL) was added a suspension of 10% Pd-C (50 mg) in EtOH (10 mL), and the suspension was stirred under an H_2 atmosphere at r. t. for overnight. The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was used in a next reaction without further purification. To a solution of the residue (0.740 g, 2.31 mmol) in toluene (12 mL) were added Et_3N (0.467 g, 4.62 mmol) and DPPA (0.636 g, 2.31 mmol), and the solution was stirred at 80°C for 30 min. To the solution was added ^{t}BuOH (1.71 g, 23.1 mmol), and the solution was stirred at 80°C for 68 h. To the solution was added toluene (50 mL), and the solution was washed with 10% citric acid solution (30 mL), brine (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (50 g, Hexane/AcOEt 20% to 35 %) to give **53** as colorless oil (0.414 g, 46%). ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.16-1.23 (3H, m), 1.36-1.41 (18H, m), 1.89-2.03 (1H, m), 2.10-2.24 (1H, m), 2.93-3.19 (1H, m), 3.11 (1H, m), 3.21-3.34 (4H, m), 3.92-4.28 (3H, m), 4.60-4.74 (3H. m), 3.39 (1.8H, s), 5.06 (1H, brs); ^{13}CNMR (100MHz, $CDCl_3$) δ: 13.9, 28.0, 28.2, 29.7, 30.6 (rotamer), 37.2, 37.3 (rotamer), 55.8, 56.0 (rotamer), 56.5 (d, split by C-C coupling, J = 61 Hz), 57.3 (d, split by C-C coupling, J = 61 Hz, rotamer), 61.0, 61.1 (rotamer), 78.8, 79.7 (rotamer), 81.0, 81.1 (rotamer), 154.8, 155.8 (rotamer), 171.2 (^{13}C labeled), 171.3 (rotamer, ^{13}C labeled); MS(FAB) m/z $[M+Na]^+$ 414; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{17}{}^{13}CH_{34}N_2O_7+Na]^+$ 414.2295, found 414.2302

1-^{13}C Ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-bis(*tert*-butoxcarbonyl) aminobutanoate (54)

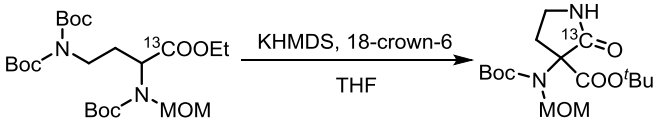


53 **54**

To a solution of **53** (0.372 g, 0.950 mmol) in CH_3CN (9.5 mL) were added DMAP (12 mg, 0.0950 mmol) and Boc_2O (0.249 g, 1.14 mmol), and the solution was stirred at r. t. overnight. To the solution

wereadditionally added DMAP (12 mg, 0.0950 mmol) and Boc_2O (0.249 g, 1.14 mmol), and the solution was stirred at 50°C for 2 h. The solution was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (20 g, Hexane/AcOEt 15 %) to give **54** as colorless oil (0.440 g, 94%). ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.15-1.22 (3H, m), 1.36-1.42 (27H, m), 1.93-2.07 (1H, m), 2.23-2.36 (1H, m), 3.28 (3H, s), 3.58-3.62 (2H, m), 3.90-4.18 (3H, m), 4.63 (1H. d, J = 10.6 Hz), 4.70-4.74 (1H, m); ^{13}CNMR (100MHz, $CDCl_3$) δ: 14.0, 27.8, 27.9 (rotamer), 28.9, 29.9 (rotamer), 44.0, 55.7, 55.9 (rotamer), 56.5 (d, split by C-C coupling, J = 61.5 Hz), 57.1 (d, split by C-C coupling, J = 61.5 Hz, rotamer), 61.0, 78.3, 78.8 (rotamer), 80.8, 81.0 (rotamer), 82.1, 152.2, 152.3 (rotamer), 154.5, 154.8, 170.0, 171.0 (^{13}C labeled), 171.1 (^{13}C labeled) (rotamer); MS(FAB) m/z $[M+Na]^+$ 514; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{22}{}^{13}CH_{42}N_2O_9+Na]^+$ 514.2820, found 514.2821

2-^{13}C *tert*-Butyl 3-(*tert*-butoxycarbinyl)(methoxymethyl)amino-2-oxopyrrolidin-3- ylcarboxylate (55)

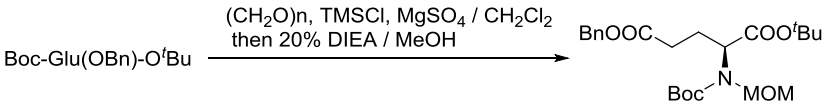


54 **55**

A solution of 18-crown-6 (71 mg, 0.269 mmol) in THF (0.87 mL) was added to **54** (56 mg, 0.112 mmol), and to the mixture was added dropwise 0.53M KHMDS (in THF) (0.253 mL, 0.134 mmol) at -78°C. the reaction mixture was stirred at the same temperature for 12 h. The reaction mixture was added to saturated NH_4Cl aq. (20 ml), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (10 g, Hexane/AcOEt 50%) to give **55** as colorless oil (36 mg, 94%). ^{1}HNMR (400MHz, DMSO-d_6) δ: 1.36 (9H, s), 1.40 (9H, s), 2.03-2.23 (1H, m), 2.92-3.02 (1H, m), 3.13 (3H, s), 3.13-3.24 (2H, m), 4.82-5.01 (2H, m), 8.32 (1H,s); ^{13}CNMR (100MHz, DMSO-d6) δ: 27.4, 27.8, 33.1, 34.5 (rotamer), 38.4, 38.4 (rotamer), 54.9, 68.5 (d, split by C-C coupling, J = 47 Hz, rotamer), 75.1., 76.0 (rotamer), 80.6, 81.2 (rotamer), 154.3, 168.1, 169.4 (^{13}C labeled); MS(FAB) m/z [M+H]+ 346, $[M+Na]^+$ 368, HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{15}{}^{13}CH_{28}N_2O_6+H]^+$ 346.2057, found 346.2059

Preparation of tert-Butyl 2-(tert-butoxycarbonyl)(methoxymethyl)amino-4-(ethoxycarbonyl) aminobutanoate (56)

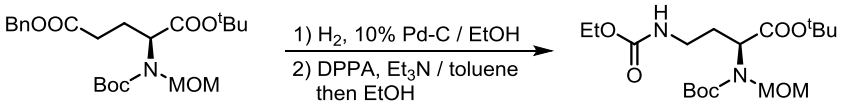
Benzyl 4-(*tert*-butoxycarbonyl)-4-(*tert*-butoxycarbonyl)(methoxymethyl)aminobutanoate



To a mixture of paraformaldehyde (0.288 g, 9.61 mmol) and $MgSO_4$ (6.39 g, 53.1 mmol) was added a solution of Boc-Glu(OBn)-O^{t}Bu (2.52 g, 6.40 mmol) in CH_2Cl_2 (64 mL), and to the suspension was added TMSCl (2.09 g, 19.2 mmol) (distilled from CaH_2) on ice. The suspension was stirred at r. t. for 14 h. To the suspension was added 20% DIEA/MeOH (21 mL) on ice, and the suspension was stirred at the same temperature for 30 min. To the suspension was added saturated aqueous $NaHCO_3$ solution (200 mL), and the

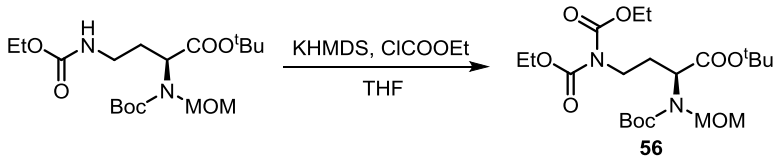
solution was extracted with $CHCl_3$ (100 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (150 g, Hexane/AcOEt 5%, 10%) to give the title compound as colorless oil (1.69 g, 61%). $[\alpha]^{20}_D$=-14.7 (c 0.785, $CHCl_3$); IR (neat) cm^{-1}: 2977, 2936, 1738, 1707, 1426, 1367, 1254, 1160, 1092, 914, 746, 699; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.41-1.50 (18H, m), 2.32-2.53 (3H, m), 3.31-3.38 (3H, m), 3.99-4.06 (0.5H, m), 4.15-4.25 (0.5H, m), 4.59-4.66 (2H, m), 4.72-4.78 (1H, m), 5.12 (2H, s), 7.29-7.39 (5H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 24.9, 25.5 (rotamer), 28.0, 28.2, 30.9, 55.9, 56.2 (rotamer), 58.7, 59.3 (rotamer), 66.3, 78.9, 79.4 (rotamer), 80.9, 81.2 (rotamer) 81.4, 81.5 (rotamer), 128.2, 128.5, 135.8, 154.7, 155.3 (rotamer), 170.0, 170.3 (rotamer), 172.8, 172.9 (rotamer); MS(FAB) m/z $[M+Na]^+$ 460; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{23}H_{35}NO_7+Na]^+$ 460.2311, found 460.2313

***tert*-Butyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-(ethoxycarbonyl) aminobutanoate**



To a solution of benzyl 4-(*tert*-butoxycarbonyl)-4-(*tert*-butoxycarbonyl)(methoxymethyl) aminobutanoate (1.69 g, 3.86 mmol) was added a suspension of 10% Pd-C (85 mg) in EtOH (77 mL), and the suspension was stirred under an H_2 atmosphere at r. t. for 2 h. The suspension was filtered to remove Pd-C. The filtrate was concentrated in vacuo to give crude carboxylic acid as colorless oil (1.38 g). To a solution of the residue in toluene (20 mL) were added Et_3N (0.781 g, 7.72 mmol) and DPPA (1.06 g, 3.86 mmol), and the solution was stirred under reflux for 15 min. To the solution was added EtOH (1.78 g, 38.6 mmol), and the solution was stirred at 80°C for 1 h. To the solution was added AcOEt (50 mL), and the solution was washed with 10% citric acid solution (30 mL), brine $NaHCO_3$ solution (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (100 g, Hexane/AcOEt 10%, 15%, 20% to 50 %) to give the title compound as colorless oil (0.941 g, 62.3%). $[\alpha]^{20}_D$=-35.5 (c 1.08, $CHCl_3$); IR (neat) cm^{-1}: 3356, 2979, 2935, 1708, 1529, 1428, 1391, 1368, 1300, 1252, 1158, 1098, 1041, 963, 916, 849, 758; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.20-1.27 (3H, m), 1.42-1.48 (18H, m), 1.94-2.05 (1H, m), 2.13-2.25 (1H, m), 3.00-3.16 (1H, m), 3.30-3.45 (4H, m), 3.87-3.99 (0.5H, m), 4.04-4.24 (2.5H, m), 4.61-4.73 (1.5H, m), 4.86 (0.5H, d, J = 10.5 Hz), 5.15-5.23 (0.5H, m), 5.25-5.32 (0.5 H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.6, 27.9, 27.9 (rotamer), 28.2, 29.9, 30.5 (rotamer), 37.7 37.8 (rotamer), 56.0, 56.2 (rotamer), 57.4, 58.5 60.6, 79.2, 80.2 (rotamer), 81.0, 81.3 (rotamer), 81.6, 154.9, 155.1 (rotamer), 156.6, 170.1, 170.4; MS(FAB) m/z $[M+Na]^+$ 413; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{18}H_{34}N_2O_7+Na]^+$ 413.2264, found 413.2266

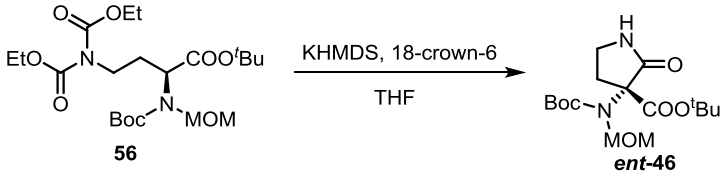
***tert*-Butyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-bis(ethoxycarbonyl) aminobutanoate (56)**



56

To a solution of *tert*-Butyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-(ethoxycarbonyl) aminobutanoate (0.180 g, 0.461 mmol) in THF (3.7 mL) was added dropwise 0.52M KHMDS in THF (0.877 mL, 0.452 mmol) over 5 minute-periods at -78°C. To the solution was added ClCOOEt (60 mg, 0.553 mmol), and the solution was stirred at -78°C for 15 min. The solution was added to saturated aqueous NH_4Cl solution (20 mL), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was washed with water (20 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (20 g, Hexane/AcOEt 15%) to give **56** as colorless oil (90 mg, 42%). $[\alpha]^{20}_{D}$=-11.5 (c 0.625, $CHCl_3$); IR (neat) cm^{-1}: 2979, 2936, 1793, 1707, 1451, 1371, 1332, 1287, 1156, 1094, 915, 864, 776; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.33 (6H, t, J = 6.9 Hz), 1.45-1.49 (18H, m), 2.04-2.13 (1H, m), 2.28-2.37 (1H, m), 3.36 (3H, s), 3.71-3.83 (2H, m), 3.94-4.01 (0.5H, m), 4.14-4.19 (0.5H, m), 4.23-4.29 (4H, m); 4.66-4.79 (2H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 27.9, 27.9 (rotamer), 28.1, 28.2 (rotamer), 29.0, 29.7 (rotamer), 44.3, 44.3 (rotamer), 55.3, 56.0 (rotamer), 57.3, 57.9 (rotamer), 62.9, 62.9 (rotamer), 78.6, 78.9 (rotamer), 80.8, 81.8 (rotamer), 81.3, 81.4, 153.5, 154.5, 155.3 (rotamer), 169.9, 170.1 (rotamer); MS(FAB) m/z $[M+Na]^+$ 485; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{21}H_{38}N_2O_9+Na]^+$ 485.2475, found 485.2475

(*R*)-*tert*-Butyl 3-(*tert*-butoxycarbonyl)(methoxymethyl)amino-2-oxopyrrolidin-3-carboxylate (*ent*-46)

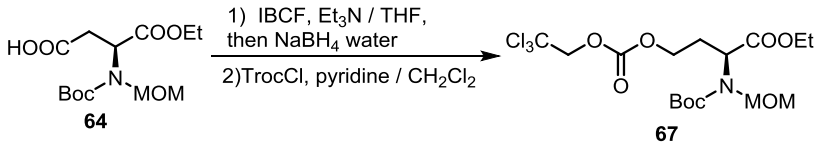


56 **ent-46**

To a solution of **56** (90 mg, 0.195 mmol) was added a solution of 18-crown-6 (0.123 g, 0.468 mmol) in THF (1.5 mL) was added dropwise 0.515M KHMDS in THF (0.453 mL, 0.233 mmol) for 5 minute at -78°C, and the solution was stirred at -78°C for 12 h. The solution was added to saturated aqueous NH_4Cl solution (20 mL), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (3 g, Hexane/AcOEt 20% and 50%) to give ***ent*-46** as colorless oil (24 mg, 36%, 91% ee). Enantiomeric excess of ***ent*-46** was determined after *N*-benzylation same as compound **47**. HPLC conditions: column: DAICEL CHIRALPAK® OD, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH/ =97/3, detection: 254 nm, retention time: tmajor=10.1 min, tminor=8.2 min.

第三節 四置換炭素含有 γ-ラクトンアミノ酸誘導体の合成

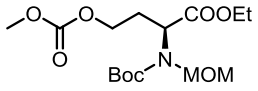
Preparation of **(*S*)-Ethyl 2-[(*tert*-butoxycarbonyl)(methoxymethyl)amino]-4-{[(2,2,2-trichloroethoxy) carbonyl]oxy}butanoate (67)**



64 **67**

To a solution of **64**[10] (0.615 g, 2.01 mmol) in THF (10 mL) were added Et_3N (0.244 g, 2.41 mmol) and isobutyl chloroformate (0.303 g, 2.22 mmol) on ice, and the solution was stirred at the same temperature for 20 min. The suspension was filtered, and to the filtrate was added a solution of $NaBH_4$ (0.228 g, 6.03 mmol) in water (2 mL) on ice, and the suspension was stirred for 40 min. To the solution was added AcOEt (100 mL), and the solution was washed with saturated aqueous $NaHCO_3$ solution (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (30 g, Hexane/AcOEt 50%) to give homoserine derivative as colorless oil. To a solution of the residue (0.414 g) in CH_2Cl_2 (7 mL) was added pyridine (7 mL) at r. t., and to the solution was added Troc-Cl (0.331 g, 1.56 mmol) on ice, and the solution was stirred at the same temperature for 150 min. The solution was concentrated in vacuo, and the residue was treated with column chromatography (30g, Hexane/AcOEt 10%) to give **67** as colorless oil (0.646 g, 98%) $[\alpha]^{20}_D$=-27.3 (c 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2979, 2936, 1762, 1709, 1428, 1392, 1369, 1251, 1175, 1100, 1031, 1004, 916, 861, 820, 782, 730, 573; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.25-1.32 (3H, m), 1.45 (5.4H, s), 1.48 (3.6H, s), 2.17-2.35 (1H, m), 2.49-2.58 (1H, m), 3.37 (3H, s) 4.10-4.42 (5H, m), 4.66 (1.2H, d, J = 10.5 Hz), 4.77 (2H, s), 4.79 (0.4H, d, J = 11.0 Hz), 4.85(0.4H, d, J = 11 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 28.1, 28.8, 29.6 (rotamer), 55.9, 55.9, 56.1 (rotamer), 56,.1 (rotamer), 61.2, 61.3 (rotamer), 65.9, 66.0 (rotamer), 76.6, 79.4, 81.2, 81.4 (rotamer), 94.3, 153.7, 154.4, 154.8 (rotamer), 170.8; MS(FAB) m/z $[M+Na]^+$ 488 (100%), 490 (90%), 492 (29%), ; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{16}H_{25}{}^{35}Cl_3NO_8+Na]^+$ 488.0622, found 488.0626

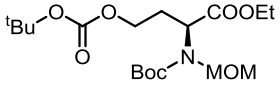
(*S*)-Ethyl 2-{(*tert*-butoxycarbonyl)(methoxymethyl)amino}-4-{(methoxycarbonyl)oxy}butanoate (65)



65

The preparation of **65** was conducted in same procedure of synthesis of **67**. ClCOOMe was used in the place of $ClCOOCH_2CCl_3$. $[\alpha]^{20}_D$=-33.4 (c 1.55, $CHCl_3$); IR (neat) cm^{-1}: 2979, 1750, 1709, 1443, 1390, 1368, 1272, 1175, 1099, 1031, 916, 862, 792; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.31 (3H, m), 1.44 (5.4H, s), 1.48 (3.6H, s), 2.13-2.30 (1H, m), 2.44-2.53 (1H, m), 3.37 (3H, s), 3.78 (3H, s), 4.10-4.30 (5H, m), 4.64 (1H, d, J = 11 Hz), 4.82 (0.4H, d, J = 11.0 Hz), 4.86 (0.6H, d, J = 11.0 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.0, 28.0, 28.9, 29.8 (rotamer), 54.6, 55.9, 56.1, 61.2, 61.3 (rotamer), 64.7, 79.3, 81.1, 81.3 (rotamer), 154.5, 154.8 (rotamer),155.5, 170.9; MS(FAB) m/z $[M+Na]^+$ 372 ; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{15}H_{27}NO_8+Na]^+$ 372.1634, found 372.1639

(*S*)-Ethyl 2-{(*tert*-butoxycarbonyl)(methoxymethyl)amino}-4-{(methoxycarbonyl)oxy}butanoate (66)



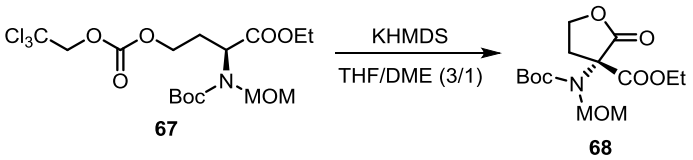
66

To a solution of ethyl 2-(*tert*-butoxycarbonyl)(methoxymethyl)amino-4-hydroxybutanoate (0.321 g, 1.10 mmol) which is intermediate of preparation of **67** in CH_3CN (5.5 mL) were added DMAP (3 mg, 0.110 mmol) and Boc_2O (0.288 g, 1.32 mmol), and the solution was stirred at r. t. for 13 h. The reaction mixture

was concentrated in vacuo. The residue was treated with column chromatography (40 g, Hexane/AcOEt 20% to 50%) to give **66** as colorless oil (0.148 g, 34%). $[\alpha]^{20}_{D}$=-34.1 (c 1.1, $CHCl_3$); IR (neat) cm^{-1}: 2980, 2936, 1742, 1710, 1461, 1427, 1391, 1368, 1281, 1255, 1166, 1099, 1032, 916, 859, 793, 773; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.24-1.32 (3H, m), 1.44-1.48 (18H, m), 2.10-2.30 (1H, m), 2.42-2.51 (1H, m), 3.37 (3H, s), 4.09-4.28 (5H, m), 4.62 (1H, d, J = 11 Hz), 4.81 (0.4H, d, J = 11.0 Hz), 4.87 (0.6H, d, J = 11.0 Hz); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 14.1, 27.7, 28.1, 28.8, 29.7 (rotamer), 55.9, 56.0 (rotamer) 56.2, 61.1, 61.2 (rotamer), 63.7, 79.3, 81.1, 81.3 (rotamer), 81.9, 82.0 (rotamer), 153.3, 154.5, 154.9 (rotamer), 171.1; MS(FAB) m/z $[M+Na]^+$ 414; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{18}H_{33}NO_8+Na]^+$ 414.2104, found 414.2108

(*S*)-Ethyl

3-(*tert*-butoxycarbonyl)(methoxymethyl)amino-2-oxo-1,2,3,4-tetrahydrofuran-3-yl-carboxylate (68)

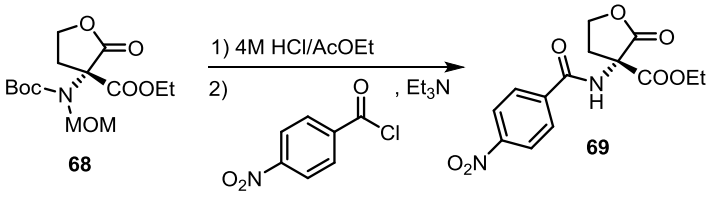


(Conditions of entry 8 in Table 4-1)

To a solution of **67** (58.9 mg, 0.126 mmol) in a mixture of THF (0.462 mL) and 1,2-DME (0.315 mL) was added dropwise a solution of 0.521 M KHMDS in THF (0.483 mL, 0.252 mmol) for 8 minute at -78°C, and the solution was stirred at -78°C for 10 h. The solution was added to saturated aqueous NH_4Cl solution (20 mL), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (10 g, Hexane/AcOEt 15% and 70%) to give **68** as colorless oil (33.3 mg, 83%, 92% ee). Enantiomeric excess of **68** was determined after conversion to **69**. $[\alpha]^{20}_{D}$=-37.0 (c 1.1, $CHCl_3$); IR (neat) cm^{-1}: 2980, 2934, 1782, 1739, 1712, 1474, 1460, 1371, 1297, 1256, 1216, 1166, 1101, 1083, 1031, 959, 859, 758; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.26-1.32 (3H, m), 1.47 (9H, s), 2.58-2.66 (1H, m), 3.15-3.35 (4H, m), 4.12-4.35 (2H, m), 4.43 (t, J = 7.3 Hz), 4.90 (1 H, d, J = 10.0 Hz)), 4.98-5.18 (1H, m) ; ^{13}CNMR (100 MHz, $CDCl_3$) δ: 13.9, 28.0, 34.1, 34.9 (rotamer), 55.4, 62.8, 66.5, 67.1 (rotamer), 76.1, 82.4, 154.2, 167.2, 170.2; MS(FAB) m/z [M+H]+ 318, $[M+Na]^+$ 340; HRMS(FAB) m/z $[M+Na]^+$ calcd for $[C_{14}H_{23}NO_7+Na]^+$ 340.1372, found 340.1374.

*Determination of ee of **68***

Preparation of **Ethyl 3-(4-nitrobenzoyl)amino-2-oxo-1,2,3,4-tetrahydrofuran-3-yl-carboxylate (69)**

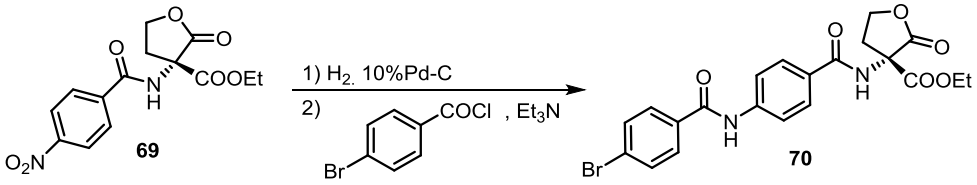


A mixture of **68** (9 mg, 2.84×10^{-2} mmol) and 4M HCl / AcOEt (0.3 mL) was stirred at r. t. for 1 h. The solution was concentrated in vacuo. To the solution of the residue in CH_2Cl_2 (0.3 mL) were added Et_3N

(8.6 mg, 8.51×10^{-2} mmol) and 4-nitrobenzoyl chloride (5.3 mg, 2.84×10^{-2} mmol), and the solution was stirred at r. t. for 1 h. The solution was treated with preparative thin layer chromatography to give **69** as a colorless solid (7.2 mg, 78%). $[\alpha]^{20}_{D}$=-7.95 (c 1.1, $CHCl_3$); IR (KB**r**) cm^{-1}: 3344, 1767, 1732, 1663, 1603, 1530, 1484, 1354, 1327, 1302, 1270, 1216,1177, 1122, 1022, 954, 716, 526 ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.4 Hz), 2.84 (0.35H, dd, J = 3.2Hz, 7.8Hz), 2.87 (0.65H, J = 3.2Hz, 7.8Hz), 2.93 (0.65H, t, J = 9.2Hz), 2.96 (0.35H, t, J = 9.2Hz), 4.59 (0.35H, dd, J = 7.8Hz, 9.2Hz), 4.61(0.65H, dd, J = 7.8Hz, 9.2Hz), 4.73 (0.65H, dd, J = 3.2Hz, 9.2Hz), 4.75(0.65H, 3.2Hz, 9.2Hz), 7.56 (1H, brs), 8.01 (2H, d, J = 8.7Hz), 8.33 (2H, d, J = 8.7Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 32.5, 63.1, 64.0, 66.6, 123.9, 128.5, 137.9, 150.2, 164.6, 170.6; MS(FAB) m/z [M+H]+ 323 $[M+Na]^+$ 345, HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{14}H_{14}N_2O_7+H]^+$ 323.0879, found 323.0879; HPLC conditions: column: DAICEL CHIRALPAK® AS-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH=70/30 detection: 254 nm, retention time: major=30.0 min, minor=24.9 min.

*Determination of absolutely configuration of **68***

Preparation of **Ethyl 3-[4-[(4-bromobenzoyl)amino]benzoyl}amino-2-oxo-1,2,3,4-tetrahydrofuran-3-yl-carboxylate (70)**



To a solution of **69** (98% ee, 12 mg, 3.7×10^{-2} mmol) in EtOH (1 mL) was added a suspension of 10% Pd-C (30 mg) in EtOH (4 mL) was stirred under an H_2 atmosphere at r. t. for 3 h. The insoluble materials were filtered off, and the filtrate was concentrated in vacuo. To the residue in CH_2Cl_2 (4 mL) were added Et_3N (4.1 mg, 4.1×10^{-2} mmol) and *p*-bromobenzoyl chloride (8.2 mg, 3.7×10^{-2} mmol), and the solution was stirred at r. t. for 3 h. The solution was diluted with AcOEt (40 mL), and the solution was washed with 10% citric acid (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by flash silica-gel column chromatography (5 g, Hexane/AcOEt 40%) to give **70** as colorless solid (9 mg). The solid was recrystallized from $CHCl_3/Et_2O$ to obtain the crystalline solid for X-ray crystallography. ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.33 (3H, t, J = 6.9 Hz), 2.77 (0.4H, dd, J = 3.2Hz, 7.8Hz), 2.81 (0.6H, J = 3.2Hz, 7.8Hz), 2.90 (0.6H, t, J = 9.6Hz), 2.93 (0.4H, t, J = 9.6Hz), 4.24-4.37 (2H, m), 4.56 (0.4H, dd, J = 7.8Hz, 9.6Hz), 4.58 (0.6H, dd, J = 7.8Hz, 9.6Hz), 4.71 (0.4H, dd, J = 3.2Hz, 9.6Hz), 4.74 (0.6H, 3.2Hz, 9.6Hz), 7.41 (1H, brs), 7.62 (2H, d, J = 8.7Hz), 7.73 (4H, s), 7.79 (2H, d, J = 8.7Hz), 8.41 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 32.7, 62.9, 63.8, 66.7, 119.7, 126.9, 127.7, 128.4, 128.9, 132.0, 133.2, 141.6, 164.9, 165.7, 167.9, 171.6; MS(FAB) m/z [M+H]+ 475, 477, $[M+Na]^+$ 497, 499, HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{21}H_{19}{}^{79}BrN_2O_6+H]^+$ 475.0505, found 475.0495, $[C_{21}H_{19}{}^{81}BrN_2O_6+H]^+$ 477.0487, found 477.0486

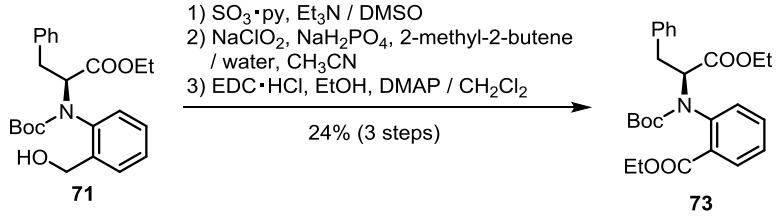
X-ray structural analysis of **70**

Crystal Data of **70**: $C_{21}H_{19}BrN_2O_6$, M = 475.29, space group P21, a=7.5060(14) Å, b=5.4543(7) Å, c=23.444(3) Å, α = 90°, 90.984(10)°, γ = 90°, V = 959.6(3) $Å^3$, Z = 2, ρ_{calcd} = 1.645 Mg/m^3, $Mo_{K\alpha}$ radiation,λ = 0.71075 Å, μ = 2.186 mm–1, T = 103(2) K. The final *R1* and w*R2* were 0.0360 and 0.0741 for 272 parameters. CCDC

955164 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

第四節 四置換炭素含有 インドリン–3–オン誘導体の合成

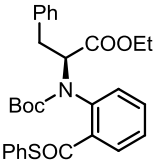
Preparation of **(*S*)-ethyl 2-([*tert*-butoxycarbonyl]{2-[ethoxycarbonyl]phenyl}amino)-3-phenylpropanoate (73)**



To a solution of **71**[31b] (2.11 g, 5.28 mmol) in DMSO (53 mL), and to the solution were added Et_3N (5.34 g, 52.8 mmol) and SO_3·pyridine (3.36 g, 21.1 mmol) on water bath, and the solution was stirred at r. t. for 1 h. To the suspension was added 10% citric acid solution (100 mL) on ice bath, and the solution was extracted with AcOEt (50 mL×2). The extracts were combined, and the solution was washed with water (30mL×2). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (100 g, Hexane/AcOEt 30%) to give the aldehyde as a colorless solid (1.99 g). Thus obtained aldehyde was used a following reaction without further purification. To a solution of the residue in CH_3CN (100 mL) were added a solution of $NaClO_2$ (1.47 g, 15.0 mmol) in water (20 mL), 2-methyl-2-butene (3.51 g, 50.0 mmol) and a solution of NaH_2PO_4 (1.80 g, 15.0 mmol) in water (20 ml) on ice bath, and the solution was stirred at r. t. for 24 h. To the suspension was added a solution of Na_2SO_3 (0.63 g) in water (2 mL) on ice bath, and the suspension was stirred at the same temperature for 1 h. To the suspension was added 10% citric acid solution (50 mL), and the solution was extracted with AcOEt (50 mL×3). The extracts were combined, and the solution was washed with brine (30 mL). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (150 g, Hexane/AcOEt 30% and 70%) to give the carboxylic acid as colorless oil (1.85 g). The 0.203 g of the product was used in a following reaction. To a solution of the residue (0.203 g) in CH_2Cl_2 (4.9 mL) were added EtOH (0.113 g, 2.45 mmol), DMAP (6 mg, 4.91×10^{-2}mmol) and EDC·HCl (0.122 g, 0.638 mmol), and the solution was stirred at r. t. for 9 h. The reaction mixture was treated with flash silica-gel column chromatography (20 g, Hexane/AcOEt 15%, 40%) to give **73** as colorless oil (61 mg, 24%, 3 steps). $[\alpha]^{20}_D$=24.3 (c 1.04, $CHCl_3$); IR (neat) cm^{-1}: 3064, 3028, 2980, 2934, 1705, 1601, 1492, 1453, 1368, 1324, 1291, 1254, 1201, 1166, 1093, 1048, 1020, 858, 753, 702;^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.02-1.09 (2.1H, m), 1.1-1.15 (0.9H, m), 1,26 (4.7H, s),), 1.31 (4.1H, s), 1.35 (1.5H, s), 1.34-1.39 (3 H, m) 1.45 (2.3H, s), 1.52 (0.7H, s), 2.56-2.79 (1.4H, m), 3.38 (0.23 H, dd, J = 3.7 Hz, 13.7 Hz), 3.48 (0.07 H, d, J = 14.2 Hz), 3.62 (0.23H, d, J = 13.7 Hz), 3.65 (0.07H, d, J = 14.2 Hz), 4.01-4.36 (4H, m), 4.45 (0.07H, d, J =7.8 Hz), 4.59 (0.23H, dd, J = 3.6 Hz, 9.2 Hz),4.82 (0.18H, dd, J = 6.4 Hz, 10.5 Hz), 4.97 (0.52H, dd, J = 6.8 Hz, 9.6 Hz), 6.93-6.99 (1.25 H, m), 7.13-7.24 (3H, m), 7.32-7.43 (1H, m), 7.50-7.60 (1H, m), 7.68-7.72 (0.75H, m), 7.89-7.95 (1H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 13.9 (rotamer), 14.1 (rotamer),

14.3 (rotamer), 14.4, 28.1, 28.3 (rotamer), 36.7, 37.4 (rotamer), 37.5 (rotamer), 60.8 (rotamer), 61.0, 61.1 (rotamer), 61.2, 61.3 (rotamer), 61.6, 62.5 (rotamer), 65.6 (rotamer), 80.7, 81.0 (rotamer), 81.4 (rotamer), 126.3 (rotamer), 126.7, 126.8 (rotamer), 126.8 (rotamer), 127.5, 127.9 (rotamer),128.2, 128.3, 128.3 (rotamer), 129.2, 129.4 (rotamer), 130.9, 131.0 (rotamer), 131.0 (rotamer), 132.4, 132.7 (rotamer), 132.8 (rotamer), 136.6 (rotamer), 136.8, 138.7, 138.8 (rotamer), 139.1 (rotamer), 153.5 (rotamer), 154.2, 166.1, 173.4; MS(FAB) m/z $[M+H]^+$ 442, $[M+Na]^+$ 464; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{25}H_{31}NO_6+H]^+$ 442.2230, found 442.2234.

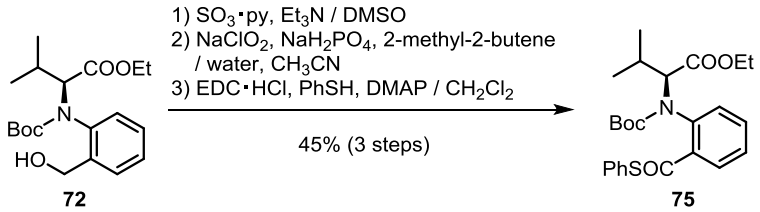
Preparation of (*S*)-ethyl 2-([*tert*-butoxycarbonyl]{2-[(phenylthio)carbonyl]phenyl}amino)-3-phenylpropanoate (74)



74

The 1.34 g of carboxylic acid, which described above was used in a following reaction. To a solution of the residue (1.34 g) in CH_2Cl_2 (32 mL) were added thiophenol (0.714 g, 6.48 mmol), DMAP (40 mg, 0.324 mmol) and EDC·HCl (0.807 g, 4.21 mmol), and the solution was stirred at r. t. for 22 h. To the reaction mixture was added $CHCl_3$ (50 mL), and the solution was washed with 10% citric acid (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The reaction mixture was purified by flash silica-gel column chromatography (150 g, Hexane/AcOEt 10%, 15%) to give **74** as pale yellow oil (0.885 g, 45%, 3 steps). $[\alpha]^{20}_D$=21.8 (c 0.903, $CHCl_3$); IR (KBr) cm^{-1}: 3063, 3027, 2978, 2934, 2902, 1731, 1699, 1687, 1596, 1575, 1485, 1455, 1448, 1442, 1391, 1367, 1328, 1308, 1293, 1271, 1256, 1200, 1169, 1062, 1020, 905, 880, 861, 771, 744, 700, 687, 664, 653;^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.93-1.17 (3H, m), 1.32 (4.1H, s), 1.35 (1.4H, s), 1.44 (2.6H, s), 1.49 (0.9H, s), 2.48-2.56 (0.75H, m), 2.77-2.93 (0.75H, m), 3.40-3.69 (0.5H, m), 3.95-4.19 (2H, m), 4.29-4.37 (0.25H, m), 4.74 (0.25H, dd, J =5.0 Hz, 11.5 Hz), 4.89 (0.5H, dd, J = 5.5 Hz, 11.0 Hz), 7.02-7.24 (5H, m), 7.42-7.61 (7.25H, m), 7.79 (0.75H, d, J = 7.8 Hz), 7.91-7.98 (1H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 13.7, 13.8 (rotamer), 28.0, 28.2 (rotamer), 36.9, 37.6 (rotamer), 60.7, 62.0, 62.7 (rotamer), 81.0, 81.6 (rotamer), 126.1 (rotamer), 126.6, 127.7 (rotamer), 127.8, 128.0 (rotamer),128.1, 128.1 (rotamer), 128.8, 129.3, 129.4 (rotamer), 129.5, 131.4, 131.9 (rotamer), 132.5, 132.7 (rotamer), 132.9 (rotamer), 134.6 (rotamer), 134.8, 135.0 (rotamer), 136.4 (rotamer), 136.6, 136.7 (rotamer), 137.2, 153.7, 154.0 (rotamer), 173.3, 189.4; MS(FAB) m/z $[M+H]^+$ 506, $[M+Na]^+$ 528; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{29}H_{31}NO_5S+H]^+$ 506.2001, found 506.2008.

Preparation of **(*S*)-ethyl 2-([*tert*-butoxycarbonyl]{2-[(phenylthio)carbonyl]phenyl}amino)-3-methylbutanoate (75)**



72 **75**

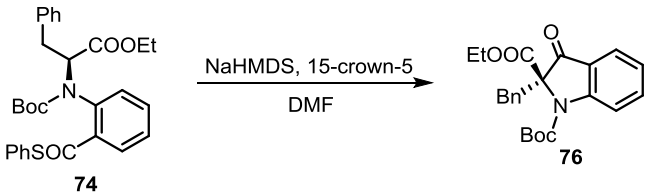
To a solution of **72**[31b] (3.67 g, 10.4 mmol) in DMSO (104 mL), and to the solution were added Et_3N (10.5 g, 104 mmol) and SO_3·pyridine (6.65 g, 41.8 mmol) on water bath, and the solution was stirred at r. t. for 2 h. To the suspension were added crashed ice (30 mL) and 10% citric acid solution (150 mL), and the solution was extracted with AcOEt (100 mL×2). The extracts were combined, and the solution was washed with 10% citric acid solution (50 mL×2) and brine (30 mL). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the crystalline solid was collected with AcOEt. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (30 g, Hexane/AcOEt 15%) to give the aldehyde as a colorless solid (2.06 g). Thus obtained aldehyde was used a following reaction without further purification. To a solution of the aldehyde (2.06 g) in CH_3CN (120 mL) were added a solution of $NaClO_2$ (1.74 g, 17.7 mmol) in water (35 mL), 2-methyl-2-butene (4.14 g, 59.1 mmol) and a solution of NaH_2PO_4 (2.12 g, 17.7 mmol) in water (35 ml) on ice bath, and the solution was stirred at r. t. for 2 days. To the suspension was added a solution of Na_2SO_3 (1.49 g) in water (5 mL) on ice bath, and the suspension was stirred at the same temperature for 1 h. To the suspension was added 10% citric acid solution (200 mL), and the solution was extracted with AcOEt (100 mL×2). The extracts were combined, and the solution was washed with brine (100 mL). The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by flash silica-gel column chromatography (150 g, $CHCl_3$/MeOH 5%) to give the carboxylic acid as colorless oil (2.16 g). To a solution of the residue in CH_2Cl_2 (30 mL) were added thiophenol (0.977 g, 8.87 mmol), DMAP (72 mg, 0.591 mmol) and EDC·HCl (1.36 g, 7.09 mmol), and the solution was stirred at r. t. for 2 h. To the reaction mixture was concentrated in vacuo. The reaction mixture was purified by flash silica-gel column chromatography (150 g, Hexane/AcOEt 10%, 15%) to give **75** as colorless oil (1.36 g, 29%, 3 steps). $[\alpha]^{20}_{D}$=3.08 (c 1.01, $CHCl_3$); IR (KBr) cm^{-1}: 2979, 2934, 2874, 1739, 1699, 1593, 1573, 1479, 1454, 1387, 1312, 1252, 1294, 1171, 1134, 1032, 896,760, 689; ^{1}HNMR (400 MHz, DMF-d7) δ: 0.64 (1H, d, J = 5.5 Hz), 0.88 (2H, d, J = 6.4 Hz), 0.98 (1H, d, J = 5.5 Hz), 1.05 (1H, t, J = 6.9 Hz), 1.12 (2H, d, J = 6.4 Hz), 1.23-1.32 (8H, m), 1.41 (3H, s), 1.86-1.95 (0.65H, m), 2.12-2.22 (0.35 H, m), 3.90-4.01 (0.7 H, m), 4.14-4.31 (1.3H, m), 4.35 (0.65H, m), 4.60 (0.35H, d, J = 9.6 Hz), 7.38-7.43 (0.35H, m), 7.50-7.65 (6.35H, m), 7.70-7.86 (1.65H, m), 8.07-8.17 (0.65H, m); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 13.9, 14.3 (rotamer), 18.7, 19.0, 19.3 (rotamer), 21.8, 22.5 (rotamer), 27.6 (rotamer), 28.0, 28.2 (rotamer), 30.5 (rotamer), 60.5 (rotamer), 60.7, 66.2, 66.5 (rotamer), 80.7, 80.8 (rotamer), 127.3 (rotamer), 127.6, 128.8, 129.1, 129.2, 129.5, 131.4 (rotamer), 131.8, 132.3, 132.7 (rotamer), 134.6, 134.7, 135.1 (rotamer), 154.0, 154.1 (rotamer), 170.0, 172.5 (rotamer), 189.4; MS(FAB) m/z $[M+H]^+$ 458, $[M+Na]^+$ 480; HRMS(FAB) m/z $[M+H]^+$ calcd for $[C_{25}H_{32}NO_5S+H]^+$ 458.2001, found 458.1196;

[Computational Details (Figure 5-2)]

Geometry optimization was performed with SPARTAN'10 build 1.1.0. The ground-state geometrie of **75** was determined by means of the following successive steps: Conformational search with MMFF, HF, then DFT

calculation with B3LYP functionals. The basis sets of employed were for HF geometry optimization, 3-21G*, and DFT geometry optimization, 6-31G*. Conformer A: SCF Done: E = -1761.122272 A. U. after 1 cycle. Conformer B: SCF Done: E = -1761.122763 A. U. after 1 cycle.

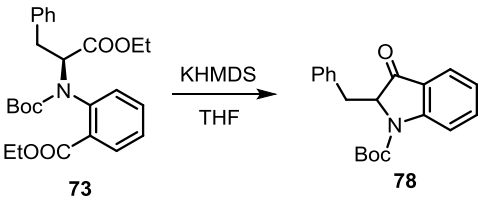
Ethyl 1-(*tert*-butoxycarbonyl)-2-benzyl-3-oxoindolin-2-carboxylate (76)



(Conditions of entry 6 in Table 5-1)

To a solution of 1.04 M NaHMDS in THF (0.160 mL, 0.166 mmol) in DMF (0.22 mL) at -70°C was added a solution of **74** (70 mg, 0.138 mmol) and 15-crown-5 (73 mg, 0.331 mmol) in DMF (1 mL), and the solution was stirred at -70°C for 4 h. The solution was added to saturated aqueous NH_4Cl solution (20 mL), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography (Hexane/AcOEt 33%) to give **76** as pale yellow oil (28 mg, 54%, 99% ee). $[\alpha]^{20}_D$= 137.7 (c 0.80, $CHCl_3$); IR (neat) cm^{-1}: 3031, 2980, 2936, 1757, 1714, 1606, 1469, 1366, 1308, 1252, 1161, 1109, 1072, 1010, 842, 758, 702; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.23 (3H, t, J = 6.9 Hz), 1.63-1.67 (9H, m), 3.68-3.91 (2H, m), 4.06-4.40 (2H, m), 6.95-7.03 (6H, m), 7.44-7.56 (2.25H, m), 8.08 (0.75H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 28.3, 39.1, 62.4, 76.1, 83.2, 116.2, 122.5, 123.1, 123.9, 127.0, 128.0, 129.6, 134.4, 137.3, 149.9, 154.1, 166.3, 194.0; MS(FAB) m/z $[M]^+$ 395 $[M+Na]^+$ 418 HRMS(FAB) m/z $[M]^+$ calcd for $[C_{23}H_{25}NO_5]^+$ 395.1733, found 395.1734.; HPLC conditions: column: DAICEL CHIRALCEL® OD-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH=99/1 detection: 254 nm, retention time: major=7.61 min, minor= not detected

1-(*tert*-Butoxycarbonyl)-2-benzyl-3-indolinone (78)

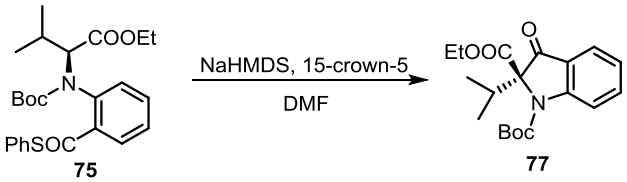


(Conditions of entry 1 in Table 5-1)

In the case of the use of **73** (61 mg, 0.138 mmol) as substrate and KHMDS (0.318 mL, 0.166 mmol) as base in THF (1.06 mL), the conpound **78** was obtained (32 mg, 72%). IR (neat) cm^{-1}: 2978, 2931, 1712, 1607, 1525, 1470, 1374, 1288, 1254, 1151, 1068, 1008, 757, 700; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.65 (9H, s), 3.38 (1H, dd, J = 3.2 Hz, 13.8 Hz), 3.45-3.54 (1H, m), 4.45-4.51 (1H, m), 6.98 (1H, t, J = 7.4 Hz), 7.02-7.11 (5H, m), 7.46 (1H, t, J = 7.4 Hz), 7.55(1H, d, J = 6.9 Hz), 7.96 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): 28.4, 36.6, 65.9, 82.6, 116.4, 122.7, 123.4, 124.2, 126.7, 128.0, 129.5, 134.6, 136.8, 150.9, 198.9; MS(FAB) m/z

$[M]^+$ 324 HRMS(FAB) m/z $[M]^+$ calcd for $[C_{20}H_{21}NO_3+H]^+$ 324.1600, found 324.1600

Ethyl 1-(*tert*-butoxycarbonyl)-2-isopropyl-3-oxoindolin-2-carboxylate (9177)

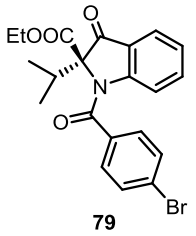


(Conditions of entry 8 in Table 5-1)

To a solution of 1.04M NaHMDS in THF (0.101 mL, 0.104 mmol) at -70°C was added a solution of **75** (40 mg, 8.74×10^{-2} mmol) and 15-crown-5 (46 mg, 0.210 mmol) in DMF (0.77 mL), and the solution was stirred at -70°C for 24 h. The solution was added to saturated aqueous NH_4Cl solution (20 mL), and the solution was extracted with AcOEt (20 mL×2). The extracts were combined, and the solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo. The residue was purified by preparative thin layer chromatography (Hexane/AcOEt 17%) to give **77** as colorless oil (23 mg, 75%, 99% ee). $[\alpha]^{20}_D$= 267 (c 0.77, $CHCl_3$); IR (neat) cm^{-1}: 2977, 2936, 1759, 1716, 1606, 1469, 1371, 1344, 1254, 1229, 1161, 1055, 759; ^{1}HNMR (400 MHz, $CDCl_3$) δ: 0.99 (3H, d, J = 7.4 Hz), 1.01 (3H, d, J = 7.3 Hz), 1.17 (3H, t, J = 7.3 Hz), 1.55 (9H, s), 2.91-3.01 (1H, m), 4.03-4.30 (2H, m), 7.16 (1H, t, J = 7.8 Hz), 7.65 (1H, t, J = 7.8 Hz), 7.71 (1H, d, J = 7.8 Hz), 8.28 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 16.9, 18.7, 28.1, 33.4, 61.7, 77.9, 83.3, 117.0, 123.3, 124.0, 137.2, 150.5, 166.3, 194.7; MS(FAB) m/z $[M]^+$ 347, $[M+Na]^+$ 418, HRMS(FAB) m/z $[M]^+$ calcd for $[C_{19}H_{25}NO_5]^+$ 347.1733, found 347.1729; HPLC conditions: column: DAICEL CHIRALCEL® OD-H, flow rate: 1 mL/min, eluent: Hexane/*i*-PrOH=99/1 detection: 254 nm, retention time: major=5.9 min, minor= 5.4 min

Determination of absolutely configuration of 77

Preparation of **Ethyl 1-(4-bromobenzoyl)-2-isopropyl-3-oxoindolin-2-carboxylate (79)**



To a solution of **77** (22 mg, 6.33×10^{-2} mmol) in CH_3CN (0.9 mL) was added 47% HBr aq. (0.1 mL), and the solution was stirred at r. t. for overnight. The reaction mixtrue was concentrated in vacuo, and the crystalline solid was collected with AcOEt. The filtrate was concentrated in vacuo, and the residue was treated with preparative thin layer chromatography (Hexane/AcOEt=3/1). Thus obtained aldehyde was used a following reaction without further purification.

To a solution of the residue in DMF (1.2 mL) were added NaH (2.2 mg, 5.6×10^{-2} mmol) and 4-bromobenzoyl chloride (10.4 mg, 4.8×10^{-2} mmol, and the solution was stirred at r. t. for 1 h. To the suspension were added AcOEt (20 mL) and hexane (5 mL). The solution was washed with water (5 mL×3).

The solution was dried over Na_2SO_4, and filtered off. The filtrate was concentrated in vacuo, and the residue was purified by preparative thin layer chromatography (Hexane/AcOEt=3/1) to give **79** as a colorless solid (9 mg, 49%). ^{1}HNMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.9 Hz), 1.18 (3H, t, J = 6.8 Hz), 3.11-3.22 (1H, m), 4.12-4.20 (1H, m), 4.22-4.30 (1H, m), 6.32 (1H, d, J = 8.2 Hz), 7.14 (1H, t, J = 7.4 Hz), 7.34 (1H, t, J = 6.8 Hz), 7.46 (2H, d, J = 8.2 Hz), 7.65 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 14.0, 17.2, 19.4, 33.9, 62.0, 116.1, 124.0, 124.5, 124.9, 126.3, 129.4, 132.4, 134.4, 136.3, 153.2, 165.5, 167.3, 194.1; MS(FAB) m/z $[M+H]^+$ 430, 432, HRMS(FAB) m/z $[M]^+$ calcd for $[C_{21}H_{20}BrNO_4+H]^+$ 430.0649, 432.0649, found 430.0654, 432.0636

X-ray structural analysis of **79**

Crystal Data of **79**: $C_{21}H_{20}BrNO_4$, M = 430.29, space group P212121, a=10.2892(1) Å, 11.8272(2) Å, 15.7226(3) Å, α = 90°, 90°, γ = 90°, V = 1913.32(5) Å^3, Z = 4, ρ_{calcd} = 1.494 Mg/m^3, $Mo_{K\alpha}$ radiation,λ = 0.71075 Å, μ = 2.175 mm–1, T = 103(2) K. The final *R1* and w*R2* were 0.0237 and 0.0532 for 324 parameters. CCDC 955165 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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