Synthesis of Chiral Diamines and Aminoalcohols
and
Development of Practical Synthetic Procedures of Anti-infective Drugs

Kenji Izumi

Contents

Abbreviation

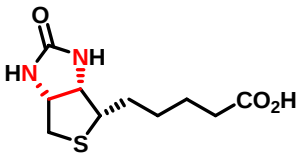
Ac	acetyl
API	Active Pharmaceutical Ingredients
Bn	benzyl
BOC	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
Bz	benzoyl
Cp	cyclopentadienyl
DCC	dicyclohexylcarbodiimide
DHP	dehydropeptidase
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ration
de	diastereomeric excess
ee	enantiomeric excess
ent	enantiomer
Et	ethyl
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
IR	infrared spectrum
LDA	lithium diisopropylamide
Me	methyl
Ms	methansulfonyl

MS	mass spectrometry
Naph	naphthalene
NMR	nuclear magnetic resonance
Ph	phenyl
PMZ	4-methoxybenxyl
PNB	4-nitrobenzyl
PNZ	4-nitrobenzyloxycarbonyl
i-Pr	isopropyl
Py	pyridine
SAR	structure activity relationships
Sm	samarium
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl
Tr	triphenylmethyl
Val	valine

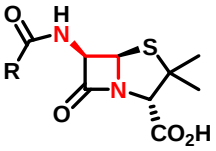
Introduction and Summary

Synthesis of Chiral Diamines and Aminoalcohols

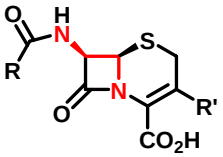
Optically pure vicinal diamines have played significant roles in organic chemistry due to their broad utility, serving both as useful units for many biologically active compounds and as important chiral ligands or chiral auxiliaries for asymmetric synthesis.[1] For example, biotin which is an essential cofactor of carboxylase-catalyzed



Biotin (Vitamin H)



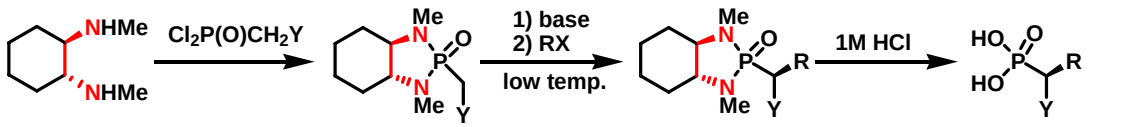
Penicillins



Cephalosporins

reactions, is one of the many compounds found in nature that contain the 1,2-diamino moiety in their skeletons.[1] The well-known antibiotics penicillins and cephalosporins also contain a 2,3-diamino carboxylic acid unit, incorporated into penam and cephem structures, respectively.[1] Hanessian and others have demonstrated the usefulness of

Scheme 1



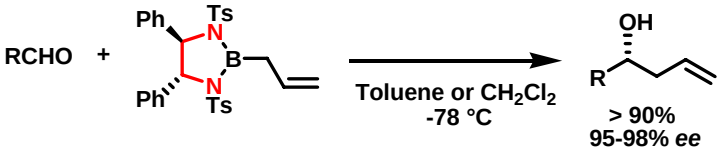
Y = Me, Ph, Cl, N_3

71-84%
68-98% *de*

Y = Me, Ph, Cl, NH_2

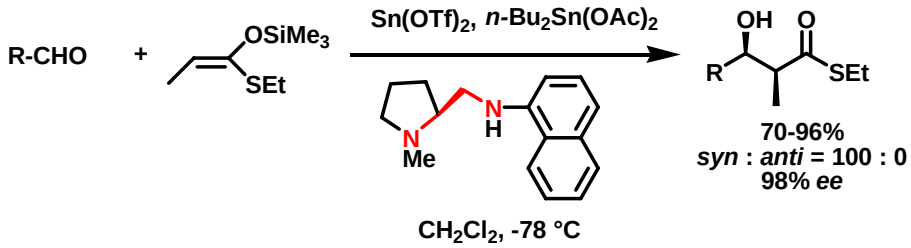
chiral bicyclic phosphonamides as chiral auxiliaries in organic synthesis, which are important surrogates for carboxylic acids[2] (Scheme 1). The allylborane derivative derived from a 1,2-diamine was shown to be an excellent reagent for the enantioselective alkylation of aldehyde.[1] The adducts are useful precursors of

Scheme 2



β-hydroxy- and *γ*-hydroxy- carboxylic acid derivatives[3] (Scheme 2). Kobayashi and Mukaiyama et al. have shown that asymmetric aldol reactions of achiral silylenol ethers can be performed with excellent stereochemical control by the combined use of tin(II) triflate, dibutyltin diacetate and a chiral 1,2-diamine.[4] Thus, when a vicinal diamine was

Scheme 3



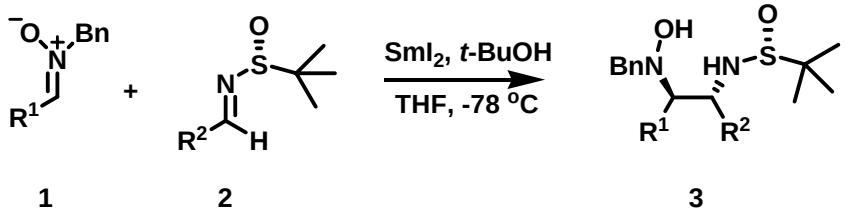
used in a stoichiometric fashion in the reaction of the silyl enol ether with various

aldehydes, the *syn*-aldol products were formed exclusively (Scheme 3).

These applications have led to much recent attention on the development of methods for the preparation of optically pure vicinal diamines, but highly efficient asymmetric synthesis of enantiopure vicinal diamines remains challenging. Among the approaches developed, such as resolution,[5] asymmetric diamination,[6] aza-Henry reaction,[7] nucleophilic addition to imine derivatives[8] and alkylation of glycine amide derivatives,[9] those that involve stereoselective C-C bond formation are of particular interest.

We have reported the first use of samarium diiodide-induced cross-coupling reaction of nitrones **1** with chiral *N*-*tert*-butanesulfinyl imines **2** for the asymmetric synthesis of unsymmetrical vicinal diamines **3**[10] (Scheme 4). This was the first

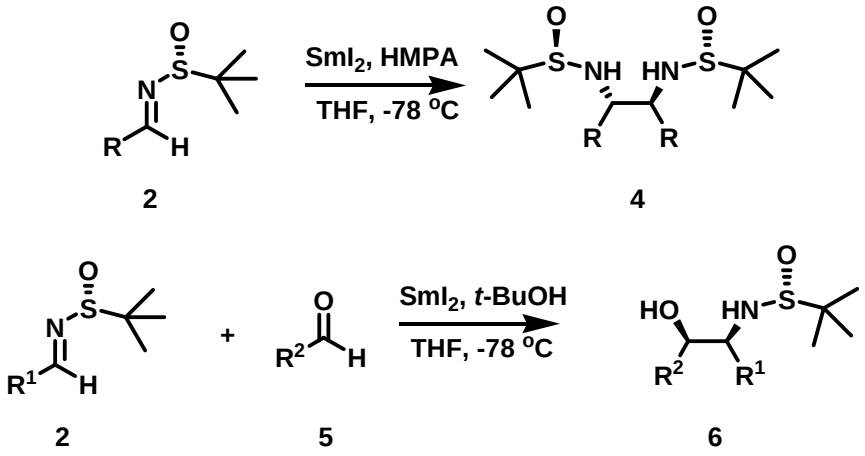
Scheme 4



successful example of highly diastereoselective and enantioselective cross-coupling reaction between two different imine species. It provides straightforward access to enantiopure vicinal diamines that are widely applicable for asymmetric synthesis after further transformation of the obtained products. In the course of this study, two new reaction systems were discovered, which allow convenient synthesis of enantiopure C_2-symmetrical vicinal diamines **4**[11] and enantiopure β-amino alcohols **6**.[12] These compounds can also be efficiently prepared under suitable reaction conditions (Scheme

5).

Scheme 5



For the synthesis of enantiopure C_2-symmetrical vicinal diamines **4**, an efficient reductive homocoupling reaction of aromatic *N*-*tert*-butanesulfinyl imines **2** in the presence of samarium diiodide and HMPA was developed, which generates C_2-symmetrical l,2-diamines in a stereoselective manner. Its simple experimental procedure and mild reaction conditions make this highly diastereoselective and enantioselective homocoupling reaction a convenient, practical and straightforward approach to the synthesis of enantiomerically enriched C_2-symmetrical vicinal diamines.

For the synthesis of enantiomerically pure *β*-amino alcohols **6**, a highly efficient and practical approach was developed via the samarium diiodide-mediated reductive cross-coupling reaction of chiral *N*-*tert*-butanesulfinyl imines **2** with aldehydes **5**. This method was found to be very effective for the preparation of a broad range of chiral

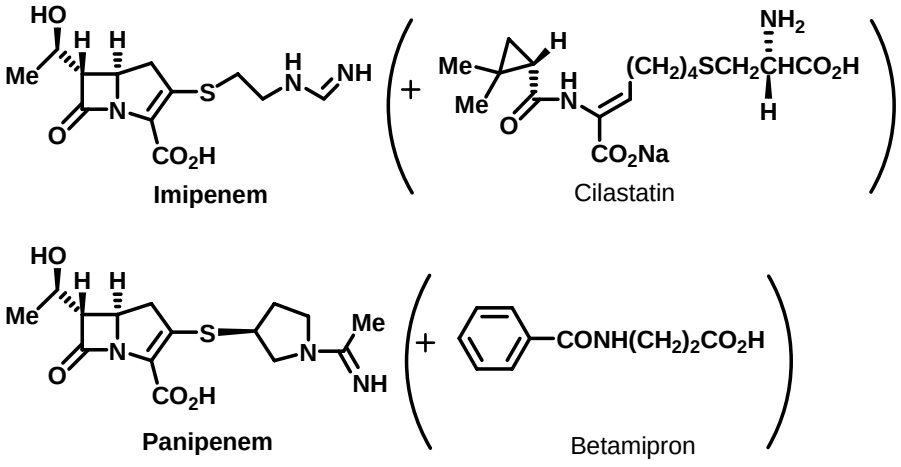
β-amino alcohols, including functionalized ones under mild conditions. The diastereoselectivities and enantioselectivities of this reaction are excellent in most cases. Moreover, it provides a solution to the long-standing issue of direct construction of enantiopure *β*-amino alcohols via a pinacol-type cross-coupling reaction between carbonyl compounds and imines.

Development of Practical Synthetic Procedures of Anti-infective Drugs

An antibiotic is a chemical compound that inhibits or abolishes the growth of microorganisms, such as bacteria, fungi or protozoans. While the term originally referred to any agent with biological activity against living organisms, "antibiotic" now is used to refer to substances with anti-bacterial, anti-fungal, or anti-parasitical activity.

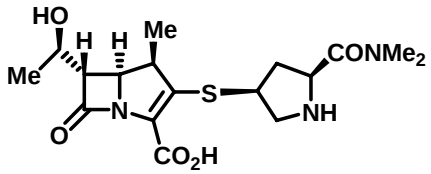
The first antibiotic compounds used in modern medicine were produced and isolated from living organisms, such as the penicillin class produced by fungi in the genus *Penicillium* or streptomycin from bacteria of the genus *Streptomyces*. Advances in organic chemistry now allow many antibiotics to be obtained by chemical synthesis.

Carbapenem compounds are a kind of antibiotic which can inhibit cell-wall synthesis. They are noted for their broad and potent antibacterial activity.[13] Imipenem,[14] Panipenem,[15] Meropenem,[16] Biapenem[17] and Ertapenem[18] have been marketed. In the

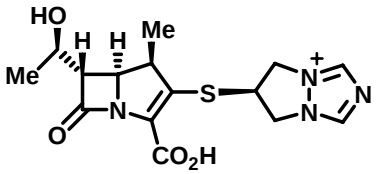


cases of Meropenem, Biapenem and Ertapenem, the introduction of a 1β-methyl group to the carbapenem skeleton enhances metabolic stability to renal dehydropeptidase-1

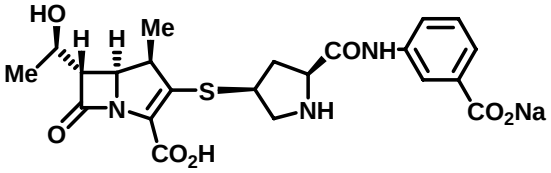
(DHP-1) and leads to high antibacterial potency.[19] On the other hand, in the cases of Imipenem and Panipenem, they are used in combination with Cilastatin and Betamipron, respectively, because of their instability against DHP-1.



Meropenem



Biapenem



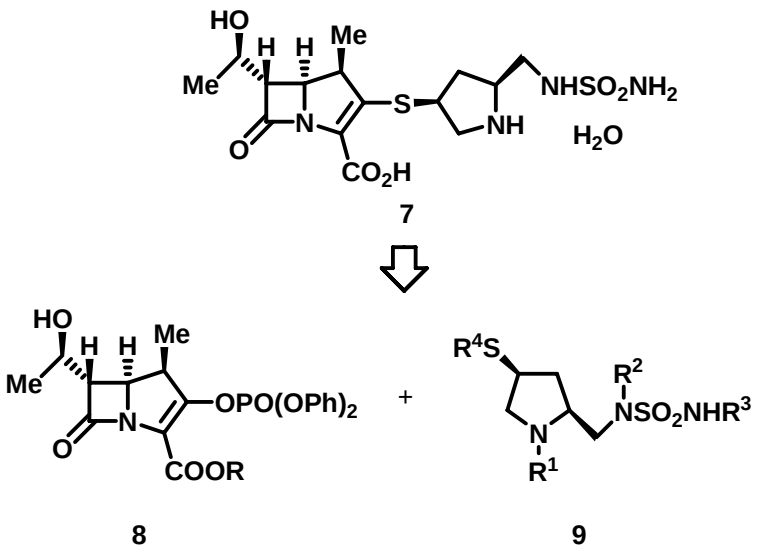
Ertapenem

A novel parenteral 1β-methylcarbapenem antibiotic, Doripenem hydrate **7**, was discovered by Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan.[20] Its synthesis, biology and structure activity relationships (SAR) have been reported.[20,21] Doripenem hydrate **7** exhibits potent, broad and well-balanced antibacterial activity against a wide range of both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*.

Doripenem hydrate **7** can be assembled from *p*-nitrobenzyl-protected 1β-methylcarbapenem enol phosphate **8** and the 2-aminomethylpyrrolidin-4-ylthio-containing side chain **9**, using the conventional retrosynthetic analysis of the carbapenem (Scheme 6). Described here are the manufacturing processes of Doripenem hydrate **7** via a deprotection reaction[22] and of the side chain **9**.[23]

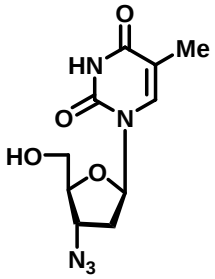
Doripenem hydrate **7** can be manufactured using a practical multikilogram-scale synthesis method via a deprotection reaction of a protected Doripenem prepared from enol phosphate **8** and the side chain **9**. *p*-Toluidine and most other organic impurities can be effectively removed using THF/water and $MgCl_2$. This process requires no chromatographic purification and affords Doripenem hydrate **7** as a sterile crystalline monohydrate in good yield. It has been scaled up to over 25 kg at a commercial plant to manufacture Doripenem hydrate **7** for commercial supply.

Scheme 6

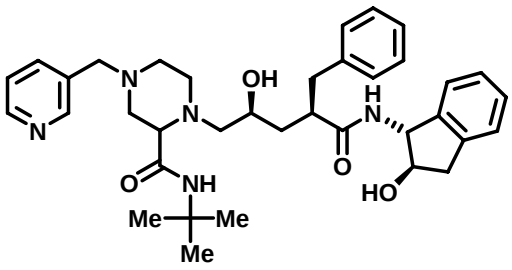


The side chain **9** can be obtained in an overall yield of 55-56% (via six reactions with an average yield of 91%) without chromatographic purification, cryogenic temperature or haloalkane solvent and with only short operating periods of time. This makes it practical, efficient and applicable to industrial use. This new process also has been scaled up in the commercial plant to produce over 400 kg of the side chain **9**.

To treat human immunodeficiency virus (HIV) infection, inhibitors of its replication enzymes, reverse transcriptase, AZT for example, and protease, Indinavir for example,



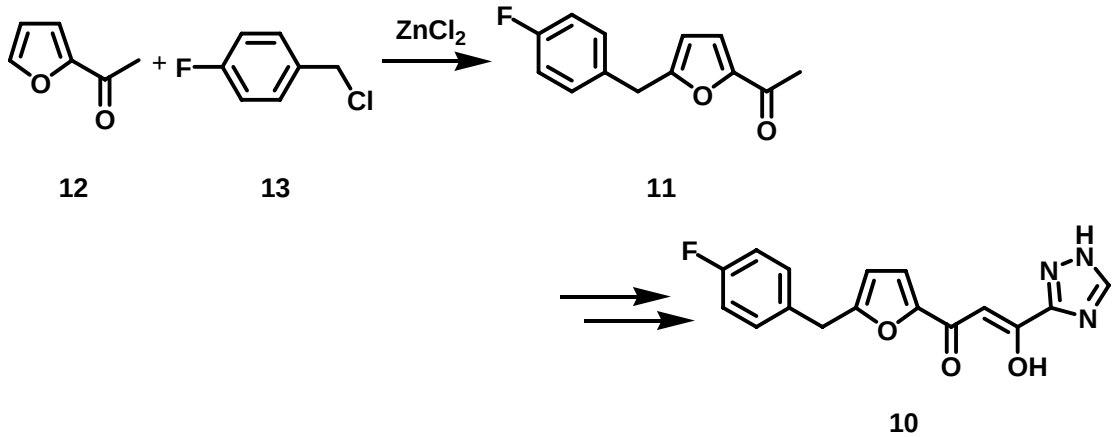
AZT



Indinavir

have been used.[24] Combinational use of these inhibitors has greatly reduced both the mortality and morbidity of HIV-infected patients. However, when complex combination therapy is continued, considerable toxicity is encountered and drug-resistant HIV strains emerge. To resolve these issues, there is a need for new inhibitors.[25] Recently, another HIV replication enzyme, integrase, has been considered an attractive therapeutic target,

Scheme 7



12 13 11

10

because HIV cannot replicate without integrating with a host chromosome.[26] An inhibitor of integrase, compound S-1360 (**10**), was discovered by the Discovery Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan.[27] A low-cost and reliable synthesis method was needed to prepare S-1360 on a large scale. Continuous efforts led to the development of two procedures for one-step synthesis of **11,** which is a key intermediate in the synthesis of **10** via Friedel-Crafts benzylation.

Compounds **12**, **13** and the reagent $ZnCl_2$ are inexpensive and Friedel-Crafts benzylation is effective and economical for the synthesis of **11**. For small-scale synthesis in a laboratory, reaction with anhydrous $ZnCl_2$ in CH_2Cl_2 can be used. However, for large-scale synthesis, reaction with water should be adopted to protect the environment and reduce safety risks. These procedures should be modified to allow their use for synthesizing 5-substituted-2-furyl ketones.

In sum, highly efficient and practical synthesis methods were developed to obtain C_2-symmetrical vicinal diamines and β-amino alcohols with diastereoselectivities and enantioselectivities, which are excellent in most cases. They provide a solution to the long-standing problem of the difficulty of direct construction of enantiopure C_2-symmetrical vicinal diamines and β-amino alcohols, and their application is expected to make a large contribution to the asymmetric synthesis.

Also reported are practical manufacturing methods for two kinds of anti-infective drugs, 1β-methylcarbepenem antibiotic, Doripenem hydrate and HIV integrase inhibitor, S-1360. Theses methods are not only economically sound but also help protect the environment and reduce safety risk.

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Chapter 1

Synthesis of Chiral Diamines and Aminoalcohols

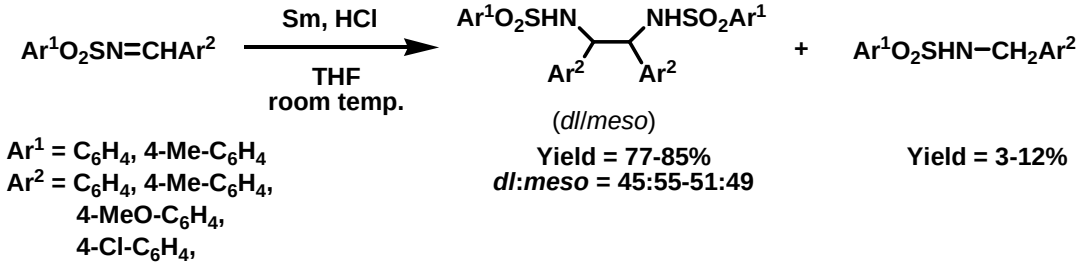
Abstract: An efficient and straightforward method was developed for the preparation of highly enantiomerically enriched C_2-symmetrical vicinal diamines by the reductive homocoupling reaction of aromatic *N*-*tert*-butanesulfinyl imines in the presence of samarium diiodide and HMPA. It offers an access to a variety of enantiopure C_2-symmetrical 1,2-diamines in a very mild and practical way.

A highly efficient and practical approach was also developed for the synthesis of enantiomerically pure *β*-amino alcohols by the samarium diiodide-mediated reductive cross-coupling reaction of chiral *N*-*tert*-butanesulfinyl imines with aldehydes. It offers a solution to the long-standing difficulty of direct construction of enantiopure *β*-amino alcohols via pinacol-type cross-coupling reaction between carbonyl compounds and imines.

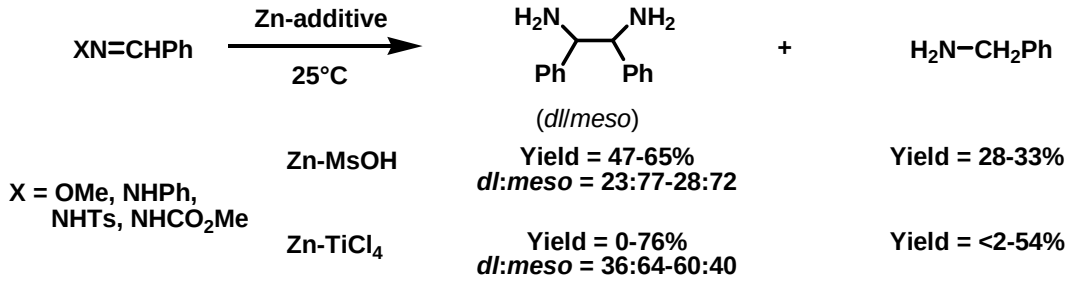
1-1. Highly Diastereoselective and Enantioselective Synthesis of Enantiopure C_2-Symmetrical Vicinal Diamines

Enantiopure vicinal diamines are of great importance in organic chemistry because of their presence in many biologically active compounds and their use as versatile chiral ligands or auxiliaries in asymmetric synthesis.[1] Much effort has been devoted to the

Scheme 1



Scheme 2



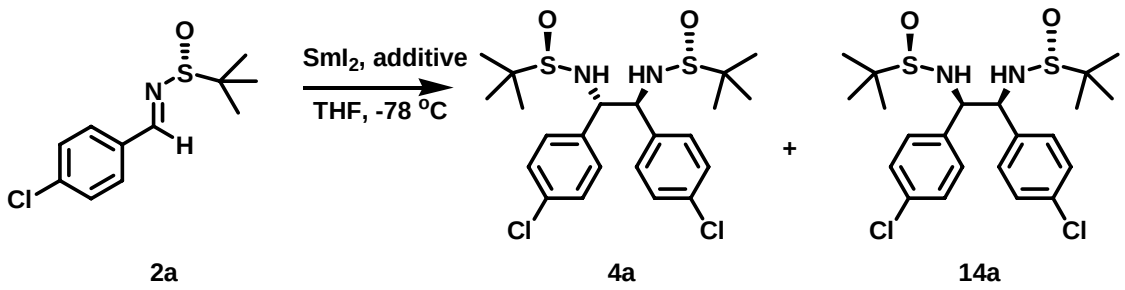
development of methods for preparing them.[1-3] The most straightforward and promising approach is a method based on the reductive coupling reaction of imine species promoted by a reducing agent.[3] In recent decades, a number of reaction systems have

been developed for this transformation, but very often have low stereoselectivity[4] (Scheme 1[4c] and 2[4d]). Highly efficient asymmetric synthesis of enantiopure vicinal diamines remains a significant synthetic challenge.

We have reported the first use of samarium diiodide-induced cross-coupling reaction of nitrones with chiral *N*-*tert*-butanesulfinyl imines for the asymmetric synthesis of unsymmetrical vicinal diamines.[5] Excellent enantioselectivities as well as high diastereoselectivities were observed in this reaction. The reaction gives access to a variety of highly enantiomerically enriched unsymmetrical vicinal diamines after further transformation of the obtained products. Continuing work[6] on the samarium diiodide-mediated reductive coupling reaction revealed that enantiomerically enriched C_2-symmetrical vicinal diamines can also be effectively prepared under the proper reaction conditions.

During the course of our studies on the above-mentioned cross-coupling reactions, we observed minor formation of the homocoupling product of *N*-*tert*-butanesulfinyl imine **2a** upon treatment with 2 equiv of samarium diiodide in the presence of nitrone. This suggested the potential of using a reductive homocoupling reaction to synthesize

Scheme 3



chiral C_2-symmetrical diamines. To our knowledge, no radical reaction of *N*-*tert*-butanesulfinyl imines[7] has been documented previously. Our initial investigations were carried out using (*R*)-sulfinyl aldimine **2a** as a substrate under various reaction conditions (Scheme 3).

As anticipated, the homocoupling reaction of sulfinyl aldimine **2a** successfully proceeded in the presence of 2 equiv of samarium diiodide in THF at -78 °C to produce both the *d*/*l*- and the *pseudo-meso*-adduct in a total yield of 81%.[8] The *d*/*l*-adduct **4a** is slightly superior to the *pseudo-meso*-adduct **14a** with a ratio of 1.4:1 (Table 1, entry 1). No significant improvement was found when *tert*-butyl alcohol or NiI_2[9] was added to

Table 1 Initial Examination of the Reductive Homocoupling Reaction Conditions

entry	additive	yield (%)[a]	**4a**:**14a**[b]
1		81	1.4:1
2	*t*- BuOH (2.0 equiv)	77	1.7:1
3	NiI_2 (2%)	72	1.7:1
4	**HMPA (2.0 equiv)**	**99**	**only 4a**
5[c]	HMPA (1.2 equiv)	96	6:1

[a] Total isolated yield of *d*/*l*- and *pseudo-meso* -products. [b] Determined by the individual isolated yield of **4a** and **14a** after flash column chromatography.

[c] Performed with 1.2 equiv of SmI_2.

the reaction system (entries 2 and 3). Very gratifyingly, when 2 equiv of HMPA[10] was added, the coupling reaction proceeded smoothly to give only the *d*/*l*-product **4a** as a single diastereomer in an almost quantitative yield of 99% (entry 4). The structure of the obtained diamine product **4a** was unambiguously established by X-ray analysis, and the stereochemistry of the two newly formed carbon centers was revealed to possess the

(*S*,*S*)-configuration (Figure 1). Further experiments showed that the stereoselectivity of

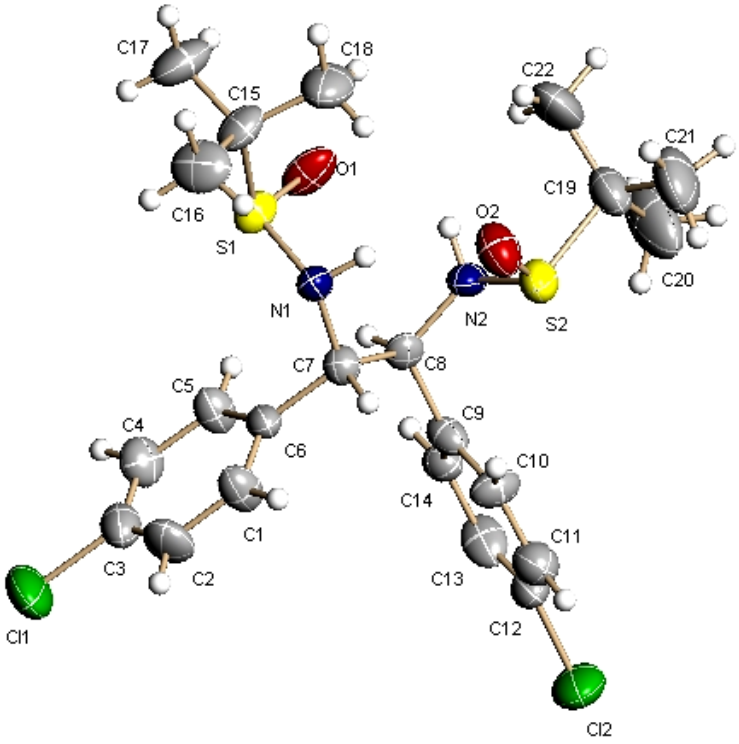


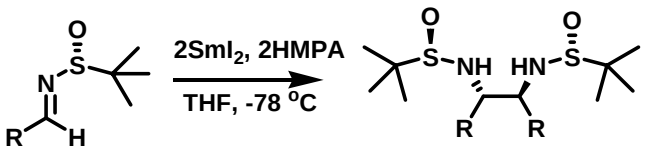
Figure 1 X-ray Crystal Structure of Homocoupling Product **4a**

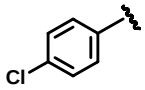
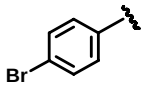
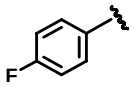
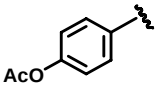
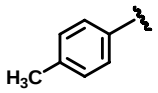
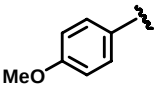
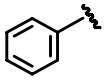
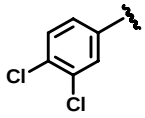
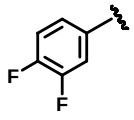
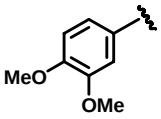
the reaction was largely affected by the reaction conditions. A decrease in the amount of both samarium diiodide and HMPA from 2 to 1.2 equiv led to the formation of the *pseudo-meso*-product **14a**. As a result, a 6:1 mixture of diastereomeric diamine **4a** and **14a** was obtained, although the yield remained high (entry 5). These results suggest that the presence of a suitable amount of donor ligand HMPA in conjunction with samarium diiodide is critical for achieving good stereoselectivity.

On the basis of the established optimum reaction conditions used in entry 4 of Table 1, a variety of other enantiomerically pure aromatic *N*-*tert*-butanesulfinyl imines were employed as substrates to determine the generality of this reductive homocoupling

reaction. As summarized in Table 2, imines containing either electron-withdrawing or electron-donating substituents were all successfully coupled to afford the corresponding sulfinyl 1,2-diamines. In most cases, the reactions proceeded to completion in 2-3 h, giving *d*/*l*-adducts **4** as the only products in moderate to excellent yields.[11] In accordance with earlier studies on the cross-coupling reaction,[5] electron-donating substituted imines were relatively less reactive and gave a lower yield of homocoupling products (entries 5, 6 and 10). Interestingly, a significant HMPA effect was found in the cases of methoxy-substituted imines **2f** and **2j**; when the amount of HMPA added was increased from 2 to 6 equiv, a dramatic improvement of the coupling yield from 58 to 80% and from 52 to 85% was observed, respectively (entries 6 and 10).[12] We presume that this may be due to an increase of the reduction potential of samarium diiodide by HMPA; however, no obvious increase of the yields in the cases of **2e** and **2g** was observed (entries 5 and 7). Nonsubstituted imine **2g** appears to be the least reactive under the current reaction conditions (entry 7). Notably, for those diamines obtained in entries 1, 2, 4 and 6, the *para*-halogen, acetoxy or methoxy substituent on the benzene ring would be a useful function for further attachment onto solid support materials such as via *O*-alkylation or Suzuki coupling reactions.[13] The obtained diamine products with different electronic properties would also be very useful chiral ligands in asymmetric reactions.

Table 2 Samarium Diiodide-mediated Reductive Homocoupling Reaction of Chiral *N-tert*-Butane Sulfinyl Imines[a]

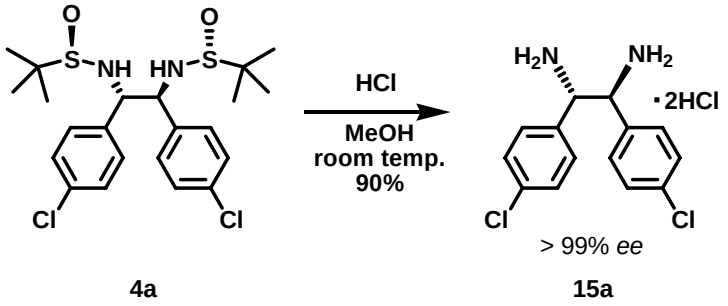


entry	R	substrate	product	yield (%)[b]	*dr*
1		**2a**	**4a**	99	>99:1
2		**2b**	**4b**	93	93:7
3		**2c**	**4c**	83	>99:1
4		**2d**	**4d**	61	>99:1
5		**2e**	**4e**	71(72)[c]	>99:1
6		**2f**	**4f**	58(80)[c]	>99:1
7		**2g**	**4g**	25(30)[c]	>99:1
8		**2h**	**4h**	81	81:19
9		**2i**	**4i**	69	>99:1
10		**2j**	**4j**	52(85)[c]	>99:1

[a]All reactions were performed using 2.0 equiv of SmI_2 and 2.0 equiv of HMPA in THF at -78 °C unless otherwise noted. [b]Isolated yield. [c]Performed with 6 equiv of HMPA.

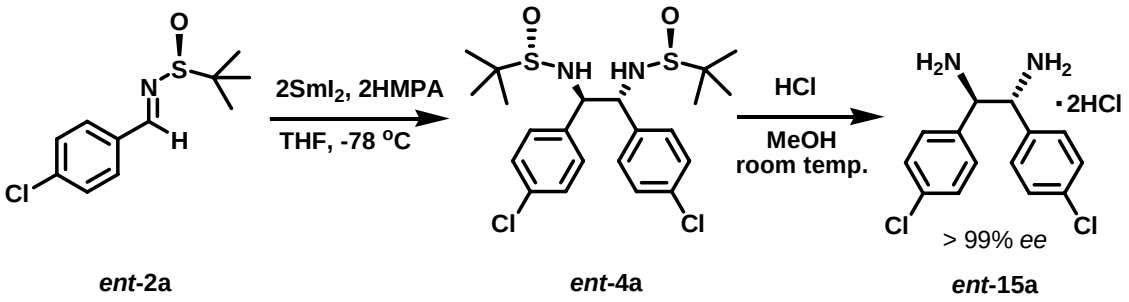
Conversion of the homocoupling products to the corresponding free diamines has also been examined. As exemplified by the reaction of **4a** shown in Scheme 4, the chiral

Scheme 4



4a **15a**

Scheme 5

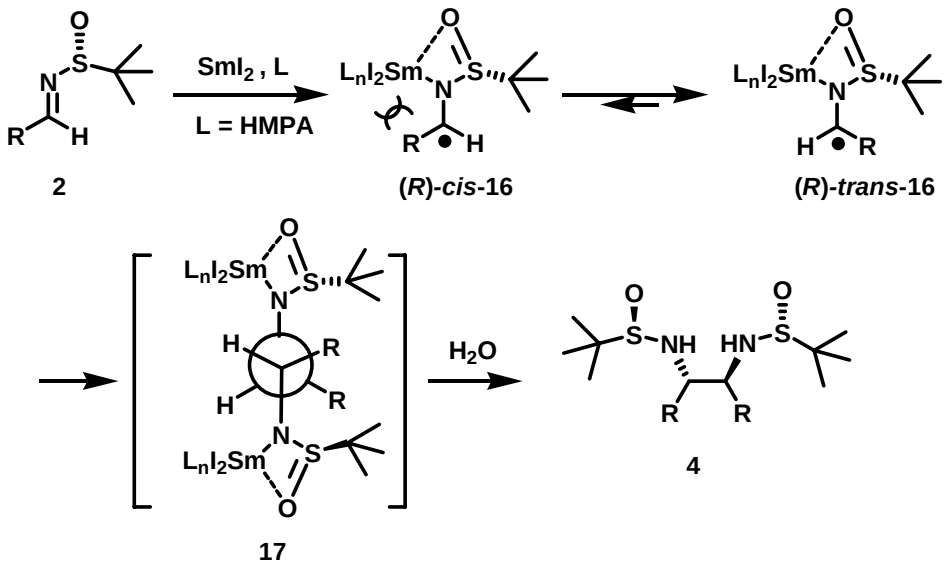


***ent*-2a** ***ent*-4a** ***ent*-15a**

free diamine **15a** can be readily obtained by removal of the *N*-*tert*-butanesulfinyl group under acidic conditions. On the other hand, ***ent*-15a** can be synthesized from ***ent*-4a**, which is obtained by the homocoupling reaction of (*S*)-sulfinyl aldimine ***ent*-2a** (Scheme 5). To determine the *ee*, the enantio-purities were then ascertained by chiral HPLC analysis of the corresponding diacetates. The diacetates of diamines **15a**, ***ent*-15a**, **15b**, ***ent*-15b** and **15f**, ***ent*-15f** each showed an extremely high *ee* of > 99%.

On the basis of known samarium diiodide chemistry[14] and the observed stereoselectivity, a plausible reaction mechanism is presented in Scheme 6. Upon treatment of samarium diiodide in THF and HMPA, sulfinyl imine substrate **2** undergoes one-electron reduction to give a radical intermediate **(*R*)-*cis*-16**. Due to the bulkiness of the samarium complex with HMPA, **(*R*)-*cis*-16** is rapidly transformed into a structurally more stable intermediate **(*R*)-*trans*-16**. During the homocoupling reaction, the *tert*-butanesulfinyl group serves as a powerful chiral directing group; the *Re*-face approach of the formed radical intermediate **(*R*)-*trans*-16** occurs predominantly because of steric repulsion between the two bulky *tert*-butanesulfinyl groups on the nitrogen atoms. The excellent diastereoselectivity and enantioselectivity of the reaction can thus

Scheme 6 Proposed Reaction Mechanism



be explained by assuming the transition state **17**. Enantiomerically enriched

C_2-symmetrical vicinal diamine **4** is then obtained after quenching with water.

In summary, a new reaction system is offered that allows efficient reductive homocoupling reaction of aromatic *N*-*tert*-butanesulfinyl imines in the presence of samarium diiodide and HMPA to generate C_2-symmetrical l,2-diamines in a very mild and stereoselective way. The simple experimental procedures and their mild reaction conditions make this highly diastereoselective and enantioselective homocoupling reaction a convenient, practical and straightforward approach to the synthesis of enantiomerically enriched C_2-symmetrical vicinal diamines. Further studies aimed at exploring the applicability of these new C_2-symmetrical vicinal diamines in asymmetric reactions are in progress.

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11. See footnotes of Table 2 for details.
12. When 8 equiv of HMPA was employed, no further improvement of the yield was observed.
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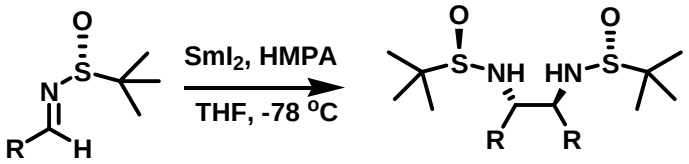
Experimental Section

1. General Procedure for the Homocoupling Reaction of Chiral *N-tert*-Butylsulfinyl Imines.



To a solution of freshly prepared samarium diiodide (1.0 mmol) in THF (5 mL), HMPA (1.0 mmol) in THF (1 mL) was added at -78 °C. After approximately 30 min, sulfinyl imine (0.5 mmol) in THF (6 mL) was added dropwise and the mixture was stirred at -78 °C for another 2-3 h. After completion of the reaction had been confirmed by TLC analysis, a saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added to the mixture, which was then extracted with EtOAc. Purification by flash column chromatography afforded the desired homocoupling product.

2. Characterization of the Obtained Optically Active C_2-Symmetrical 1,2-Diamines.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(4-chlorophenyl)-2-(2-methylpropane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4a). mp 94-98 °C; $[\alpha]_D^{20}$ = -43.6° (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 18H), 4.87 (t, *J* = 2.4 Hz, 2H), 5.96 (s, 2H), 7.09 (dd, *J* = 6.6, 1.8 Hz, 4H), 7.20 (dd, *J* = 6.6, 2.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.63, 56.47, 59.75, 128.46, 130.01, 133.53, 138.83; FT-IR (KBr, cm^{-1}): 3198, 2994, 1595, 1494, 1033, 750; ESI-MS (m/z): 489.1 (M^+).

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(4-bromophenyl)-2-(2-methyl-propane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4b). mp 152 °C; $[\alpha]_D^{20}$ = -52.0° (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 18H), 4.85 (m, 2H), 5.97 (m, 2H), 7.03 (dd, *J* = 6.6, 1.8 Hz, 4H), 7.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.63, 56.49, 59.81, 121.77, 130.34, 131.41, 137.33; FT-IR (KBr, cm^{-1}): 3198, 1489, 1038; ESI-MS (m/z): 578.9 $(M + H)^+$; HR-MS for $C_{22}H_{30}N_2O_2S_2Br_2$ (M^+): calcd. 577.0188, found: 577.0200.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(4-fluorophenyl)-2-(2-methyl-propane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4c). $[\alpha]_D^{20}$ = -41.0° (*c* 1.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 18H), 4.89 (s, 2H), 5.93 (s, 2H), 6.91 (td, *J* = 8.7, 2.1 Hz, 4H), 7.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.63, 56.38, 59.95, 115.00, 115.28, 130.25, 130.36, 134.18, 134.23, 160.33, 163.60; ^{19}F NMR (282 MHz, $CDCl_3$): δ -114.5 (m); FT-IR (KBr, cm^{-1}): 3287, 3191, 2966, 1604, 1515, 1226, 1060, 1032; ESI-MS (m/z): 457.3 $(M + H)^+$; HR-MS for $C_{22}H_{30}N_2O_2S_2F_2Na$ (M^+ + Na): calcd. 479.1609, found: 479.1622.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(4-acetoxyphenyl)-2-(2-methyl-propane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4d). $[\alpha]_D^{20}$ = -44.2° (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (s, 18H), 2.25 (s, 6H), 4.89 (s, 2H), 5.93 (s, 2H), 6.94 (d, *J* = 5.4 Hz, 4H), 7.15 (d, *J* = 5.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.05, 22.61, 56.37, 59.98, 121.14, 129.59, 135.83, 149.88, 169.01; FT-IR (KBr, cm^{-1}): 3203, 1762, 1510, 1370, 1201, 1040; ESI-MS (m/z): 537.3 $(M + H)^+$; HR-MS for $C_{26}H_{37}N_2O_6S_2$ $(M + H)^+$: calcd. 537.2087, found: 537.2089.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(4-methylphenyl)-2-(2-methyl-propane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4e). mp 68 °C; $[\alpha]_D^{20}$ = -58.6° (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 18H), 2.27 (s, 6H), 4.96 (s, 2H), 5.88 (s, 2H), 7.01 (d, *J* = 8.1 Hz, 4H), 7.08 (d, *J* = 8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.03, 22.60, 56.09, 60.51, 128.60, 128.70, 135.29, 137.01; FT-IR (KBr, cm^{-1}): 3194, 1516, 1475, 1363, 1037; ESI-MS (m/z): 449.2 $(M + H)^+$; HR-MS for $C_{24}H_{36}N_2O_2S_2Na$ $(M + Na)^+$: calcd. 471.2110, found: 471.2104.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(4-methoxyphenyl)-2-(2-methy-lpropane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4f). $[\alpha]_D^{20}$ = -52.7° (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 18H), 3.74 (s, 6H), 4.92 (s, 2H), 5.86 (s, 2H), 6.73 (dd, *J* = 6.9, 2.4 Hz, 4H), 7.12 (dd, *J* = 6.9, 2.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.68, 55.07, 56.14, 60.44, 113.41, 129.93, 130.50, 158.71; FT-IR (KBr, cm^{-1}): 3209, 2958, 1613, 1515, 1250, 1034; ESI-MS (m/z): 481.2 $(M + H)^+$; HR-MS for $C_{24}H_{36}N_2O_4S_2Na$ $(M + Na)^+$: calcd. 503.2008, found: 503.2019.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bisphenyl-2-(2-methylpropane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S*'(*R*)] (4g). $[\alpha]_D^{20}$ = -32° (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 18H), 4.94 (s, 2H), 5.90 (s, 2H), 7.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.67, 56.32, 60.54, 127.51, 128.06, 128.73, 138.51; FT-IR (KBr, cm^{-1}): 3236, 2950, 1055, 1043; ESI-MS (m/z): 421.2 $(M + H)^+$; HR-MS for $C_{22}H_{33}N_2O_2S_2$ $(M + H)^+$: calcd. 421.1978, found: 421.1967.

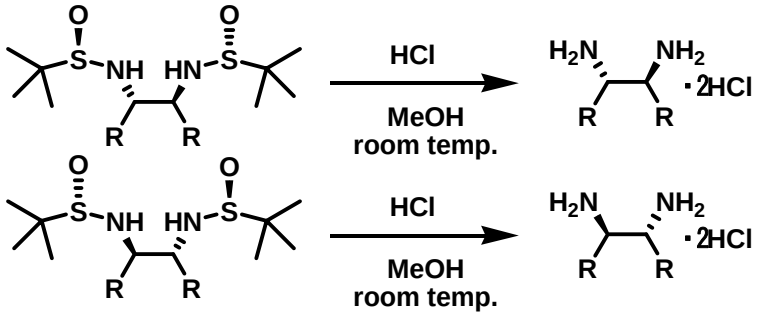
(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(3,4-dichlorophenyl)-2-(2-me-

thylpropane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S'*(*R*)] (4h). $[\alpha]_D^{20}$ = -45.3° (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (s, 18H), 4.83 (s, 2H), 5.99 (s, 2H), 6.96 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.62, 56.66, 59.38, 127.89, 130.31, 130.59, 132.13, 132.63, 138.30; FT-IR (KBr, cm^{-1}): 3224, 1474, 1033; ESI-MS (m/z): 559.1 $(M + H)^+$; HR-MS for $C_{22}H_{28}N_2O_2S_2Cl_4Na$ $(M + Na)^+$: calcd. 579.0238, found: 579.0245.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(3,4-difluorophenyl)-2-(2-methylpropane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S'*(*R*)] (4i). $[\alpha]_D^{20}$ = -36.3° (*c* 1.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 18H), 4.83 (s, 2H), 5.98 (s, 2H), 6.87 (m, 2H), 7.04 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.59, 56.54, 59.59, 117.04, 117.27, 117.55, 117.78, 124.64, 124.68, 124.72, 124.77, 135.18, 135.25, 135.31, 147.97, 148.14, 148.31, 148.47, 151.28, 151.44, 151.60, 151.77; FT-IR (KBr, cm^{-1}): 3175, 1521, 1280, 1033; ESI-MS (m/z): 493.1 $(M + H)^+$; HR-MS for $C_{22}H_{28}N_2O_2S_2F_4Na$ $(M + Na)^+$: calcd. 515.1421, found: 515.1404.

(1*S*,2*S*)-2-Methylpropane-2-sulfinic acid [1,2-bis(3,4-dimethoxyphenyl)-2-(2-methylpropane-2-sulfinylamino)ethyl]amide-, [*S*(*R*),*S'*(*R*)] (4j). $[\alpha]_D^{20}$ = -22.7° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 18H), 3.77 (s, 6H), 3.83 (s, 6H), 4.91 (s, 2H), 5.91 (s, 2H), 6.70 (m, 4H), 6.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.68, 55.66, 55.75, 56.17, 60.45, 110.22, 112.11, 120.76, 130.91, 148.17, 148.42; FT-IR (KBr, cm^{-1}): 3209, 2958, 1518, 1261, 1028; ESI-MS (m/z): 541.3 $(M + H)^+$; HR-MS for $C_{26}H_{41}N_2O_6S_2$ $(M + H)^+$: calcd. 541.2400, found: 541.2417.

3. Conversion of the Homocoupling Product 4 to Free Diamine 15.



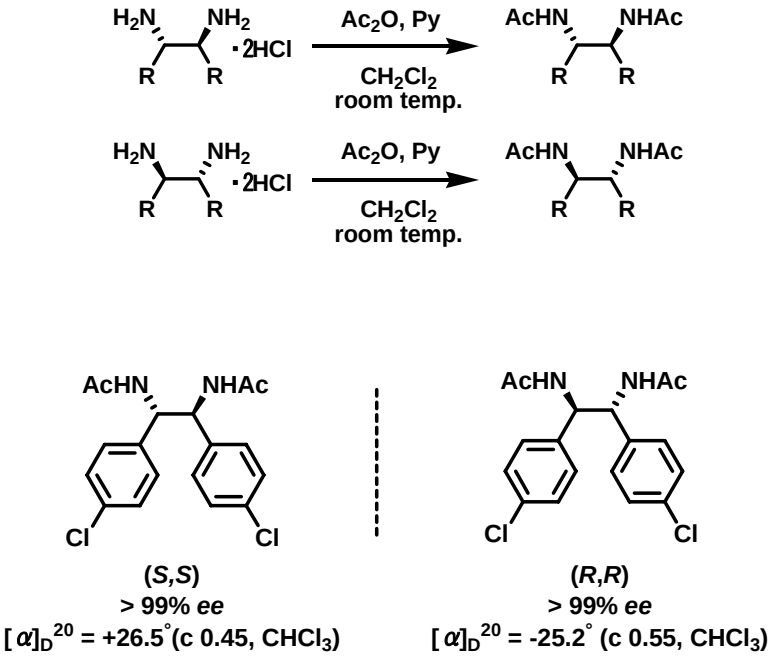
To a solution of the obtained homocoupling product (0.2 mmol) in MeOH (2.0 mL), 4 N HCl (0.5 mL) in 1,4-dioxane (2.0 mmol) was added. The mixture was stirred at 25 °C for 30 min and then concentrated. The resulting solid was recrystallized using a mixture of MeOH and Et_2O to provide the free diamine.

(1*S*,2*S*)-1,2-Bis(4-chlorophenyl)ethane-1,2-diamine dihydrochloride (15a) and **(1*R*,2*R*)-1,2-Bis(4-chlorophenyl)ethane-1,2-diamine dihydrochloride (*ent*-15a).** $[\alpha]_D^{20}$= +35.0° (*c* 0.70, CH_3OH) for **(*S, S*)-15a**; $[\alpha]_D^{20}$ = -36.3° (*c* 1.00, CH_3OH) for **(*R, R*)-*ent*-15a**; ^{1}H NMR (300 MHz, CD_3OD): δ 5.12 (s, 2H), 7.37 (m, 8H); ^{13}C NMR (75 MHz, CD_3OD): δ 57.95, 130.62, 131.40, 132.01, 137.27.

(1*S*,2*S*)-1,2-Bis(4-bromophenyl)ethane-1,2-diamine dihydrochloride (15b) and **(1*R*,2*R*)-1,2- Bis(4-bromophenyl)ethane-1,2-diamine dihydrochloride (*ent*-15b).** ^{1}H NMR (300 MHz, CD_3OD): δ 5.11 (s, 2H), 7.30 (d, *J* = 6.6 Hz, 4H), 7.54 (d, *J* = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, CD_3OD): δ 58.04, 125.43, 131.57, 132.53, 133.68.

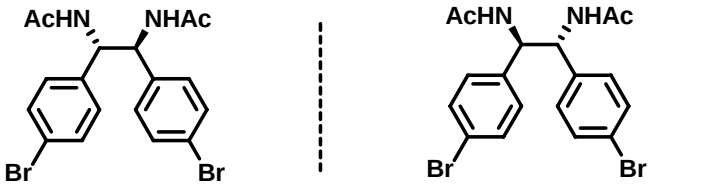
(1*S*,2*S*)-1,2-Bis(4-methoxyphenyl)ethane-1,2-diamine dihydrochloride (15f) and **(1*R*,2*R*)-1,2-Bis(4-methoxyphenyl)ethane-1,2-diamine dihydrochloride (*ent*-15f).** ^{1}H NMR (300 MHz, CD_3OD): δ 3.77 (s, 6H), 5.00 (s, 2H), 6.91 (d, J = 8.4 Hz, 4H), 7.23 (d, J = 8.7 Hz, 4H); ^{13}C NMR (75 MHz, CD_3OD): δ 55.90, 58.22, 115.66, 124.74, 131.14, 162.33.

4. Determination of the Enantiomeric Excess.



***N*-[(1*S*,2*S*)-2-Acetylamino-1,2-bis(4-chlorophenyl)ethyl]acetamide** and ***N*-[(1*R*,2*R*)-2-Acetylamino-1,2-bis(4-chlorophenyl)ethyl]acetamide**. HPLC: Daicel Chiralpak AD-H column, detected at 254 nm, eluent: hexane/2-propanol = 80/20 (v/v); ^{1}H NMR (300 MHz, CD_3OD): δ 1.96 (s, 6H), 5.18 (s, 2H), 7.10 (d, J = 8.7 Hz, 4H), 7.18 (d, J = 8.4 Hz, 4H); ^{13}C NMR (75 MHz, CD_3OD): δ 22.66, 58.65, 129.48, 130.40,

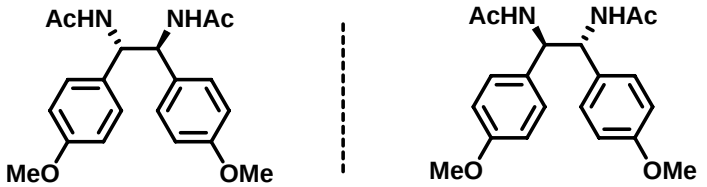
134.40, 139.42, 172.96; FT-IR (KBr, cm^{-1}): 3290, 1650, 1552, 1093; ESI-MS (m/z): 365.1 $(M + H)^+$.



(*S*,*S*)
> 99% *ee*
$[\alpha]_D^{20}$ = +57.8° (c 0.30, $CHCl_3$)

(*R*,*R*)
> 99% *ee*
$[\alpha]_D^{20}$ = -52.7°(c 0.27, $CHCl_3$)

***N*-[(1*S*,2*S*)-2-Acetylamino-1,2-bis(4-bromophenyl)ethyl]acetamide** and ***N*-[(1*R*,2*R*)-2-Acetylamino-1,2-bis(4-bromophenyl)ethyl]acetamide** HPLC: Daicel Chiralpak AD-H column, detected at 254 nm, eluent: hexane/2-propanol = 90/10 (v/v); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ (4/1)): δ 1.86 (s, 6H), 5.01 (s, 2H), 6.90 (d, J = 8.1 Hz, 4H), 7.20 (d, J = 8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ (4/1)): δ 22.42, 57.33, 121.48, 129.06, 131.44, 137.28, 171.45; FT-IR (KBr, cm^{-1}): 3289, 1650, 1550, 1011; ESI-MS (m/z): 455.0 (M^+); HR-MS for $C_{18}H_{18}N_2O_2Br_2Na$ $(M + Na)^+$: calcd. 474.9627, found: 474.9620.



(*S*,*S*)
> 99% *ee*
$[\alpha]_D^{20}$ = +132.6° (c 0.38, $CHCl_3$)

(*R*,*R*)
> 99% *ee*
$[\alpha]_D^{20}$ = -135.2° (c 0.40, $CHCl_3$)

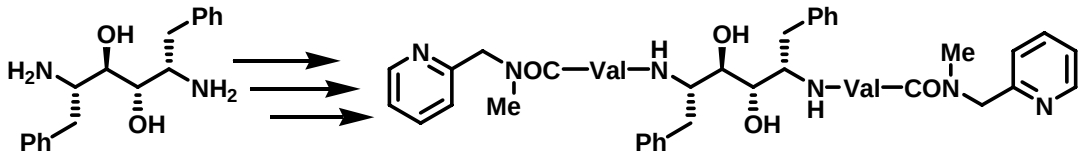
***N*-[(1*S*,2*S*)-2-Acetylamino-1,2-bis(4-methoxyphenyl)ethyl]acetamide** and

***N*-[(1*R*,2*R*)-2-Acetylamino-1,2-bis(4-methoxyphenyl)ethyl]acetamide** HPLC: Daicel Chiralpak AD-H column, detected at 254 nm, eluent: hexane/2-propanol = 90/10 (v/v); ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ (10/1)): δ 1.87 (s, 6H), 3.78 (s, 6H), 5.01 (s, 2H), 6.59 (d, J = 6.6 Hz, 4H), 6.94 (d, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.55, 54.89, 57.69, 113.59, 128.49, 130.62, 158.54, 171.27; FT-IR (KBr, cm^{-1}): 3289, 1650, 1551, 1011; ESI-MS (m/z): 357.2 $(M + H)^+$; HR-MS for $C_{20}H_{24}N_2O_4Na$ $(M + Na)^+$: calcd. 379.1628, found: 379.1634.

1-2. Highly Efficient and Direct Approach for Synthesis of Enantiopure *β*-Amino Alcohols

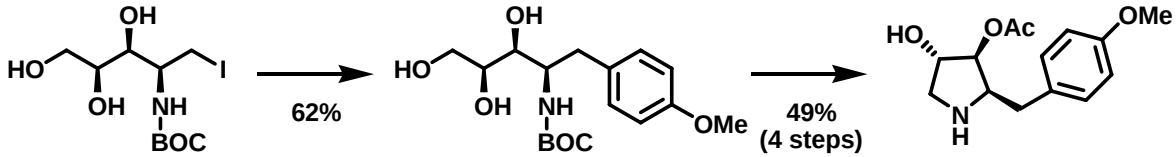
Optically active *β*-amino alcohols are versatile building blocks for medicinal chemistry and natural product synthesis[15] (Schemes 7[16] and 8). They have also been

Scheme 7



A-77003

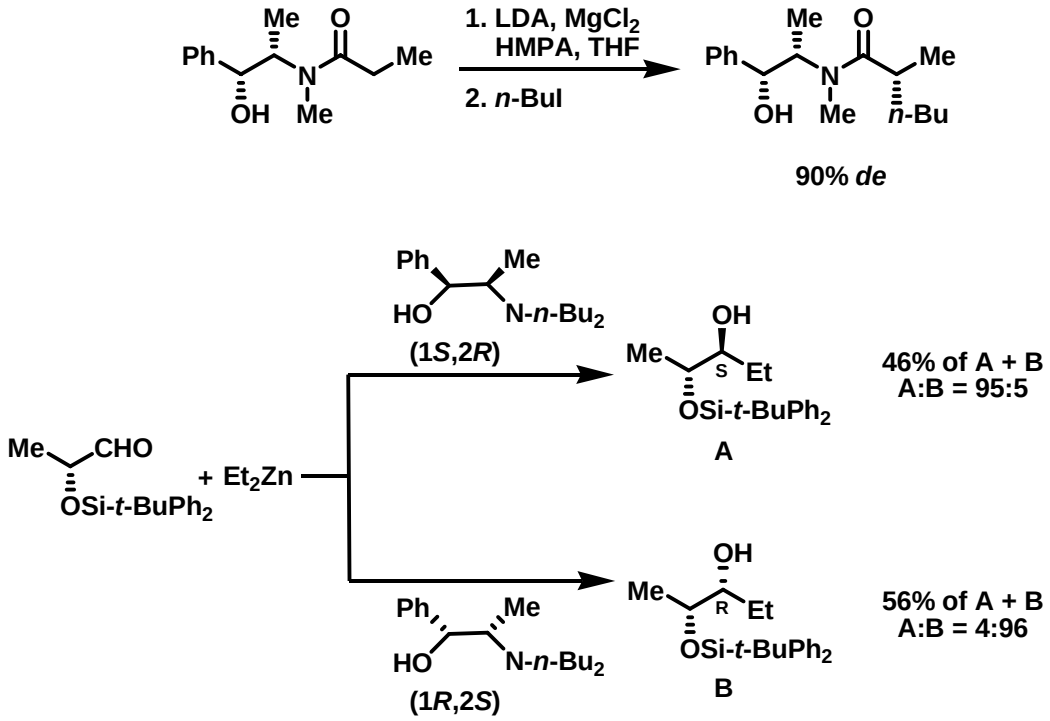
Scheme 8



(+)-Anisomycin

used as powerful chiral ligands or auxiliaries in asymmetric synthesis[17] (Scheme 9). Due to their importance, considerable efforts have been made to develop efficient methods for their preparation.[18] Among them, the pinacol-type cross-coupling reaction between carbonyl compounds and imines is one of the most direct ways to construct *β*-amino alcohols. However, a serious issue is the difficulty of achieving both

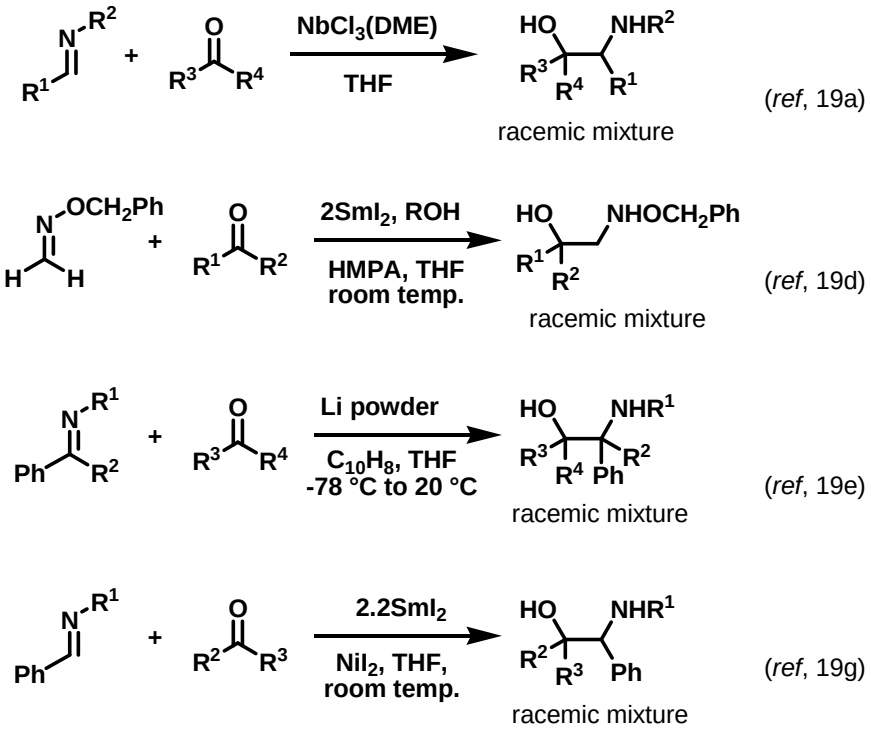
Scheme 9



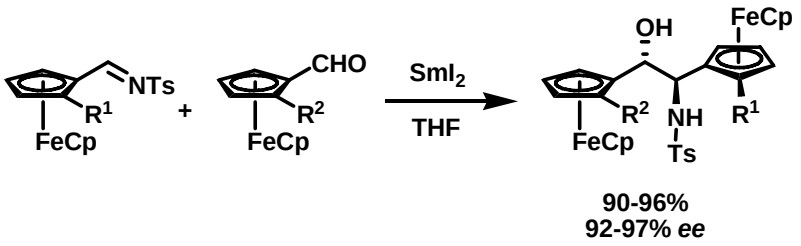
good chemoselectivity and stereoselectivity. Because of this, only a few examples of intermolecular cross-coupling reaction to form racemic *β*-amino alcohols have been reported[19] (Scheme 10); the development of a highly diastereoselective and enantioselective cross pinacol coupling reaction remains a significant synthetic challenge.

Although the asymmetric synthesis of *β*-amino alcohols by cross pinacol coupling reaction using planar chiral substrates has been realized,[20] the products are limited to ferrocenyl or $Cr(CO)_3$ aromatic derivatives (Scheme 11). The need remains for new approaches with broader substrate generality. As described in the previous section, our laboratory documented the first use of samarium diiodide-induced cross-coupling

Scheme 10



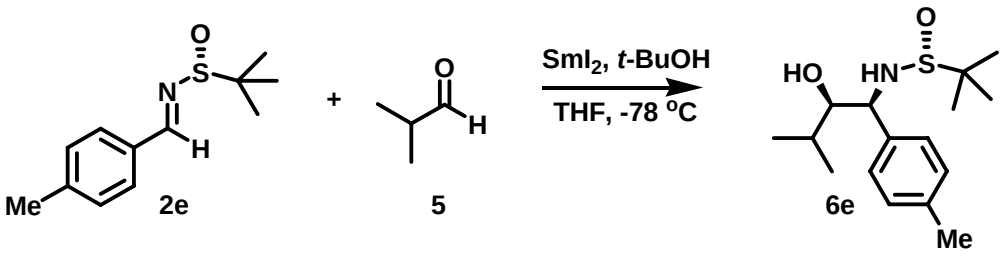
Scheme 11



reaction of nitrones with chiral *N-tert*-butanesulfinyl imines[21] for the asymmetric synthesis of unsymmetrical vicinal diamines.[22] This success suggested that it might be possible to extend this approach to the asymmetric synthesis of vicinal amino alcohols.

This led to our discovery that the cross-coupling reaction between chiral *N*-*tert*-butanesulfinyl imines and aldehydes in the presence of samarium diiodide could afford *β*-amino alcohols with excellent enantiomeric excesses and good yields.

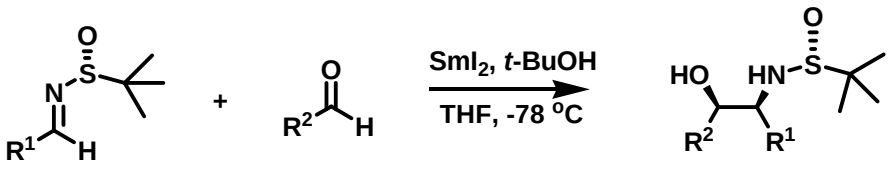
Scheme 12



The cross-coupling reaction of *N*-sulfinyl imine **2e** with benzaldehyde was initially examined using previously reported reaction conditions.[22] However, the result was disappointing with the formation of a considerable amount of pinacol from benzaldehyde and no desired cross-coupling product. With *p*-tolualdehyde, a trace amount of the cross-coupling product was observed. Next, attention was forcused on aliphatic aldehydes.[23] Fortunately, when isobutyraldehyde **5** (1.2 equiv) was used as the substrate, the reaction proceeded smoothly in the presence of 2 equiv of samarium diiodide. After 4 h, the expected *β*-amino alcohol derivative **6e** was obtained in 88% yield with extremely high diastereoselectivity (> 99% *de*)[24] (Scheme 12), and no pinacol formation was detected. Subsequent optimization of the reaction conditions led to further improvement of the yield (92%) with a little more excess (1.5 equiv) of aldehyde substrate. *tert*-Butyl alcohol was found to be essential for the achievement of a high yield.[25]

The success of the cross-coupling reaction between *N*-sulfinyl imine **2e** and isobutyraldehyde prompted us to extend the general scope of the reaction. Under the optimized conditions, we were pleased to find that a series of *N*-sulfinyl imines reacted with various aldehydes smoothly to give the desired cross-coupling products in good to excellent yields with extremely high diastereomeric ratios (up to > 99:1) (Table 3). Relatively lower yields (70-71%) were observed in the cases of aromatic imine substrates having *para*-Br and Cl substituents because of the formation of some homocoupling products (entries 8 and 9). As previously described,[26] these two substrates are subject to easy homocoupling reaction under similar reaction conditions. Fortunately, the absolute structure of the obtained cross pinacol product was unambiguously established by X-ray crystallography, and the stereochemistry of the two newly formed carbon centers was revealed to possess (*R*,*S*)-configuration (Figure 2). When the R^1 or R^2 substituent became bulkier, the coupling reaction still proceeded well (entries 2, 3, 12 and 13). In the reaction with isobutyraldehyde, a variety of substituted aromatic imines gave similar selectivities (entries 1 and 6-13), suggesting that the diastereoselectivity was primarily controlled by the stereochemistry of the *N*-sulfinyl group rather than by the electronic effect. However, the diastereoselectivity was found to be influenced by the steric hindrance of the aldehyde substrate (entries 1-5). The use of less hindered aldehydes, such as hexanal and 3-phenylpropanal, resulted in a decrease in diastereoselectivity (91:9 and 88:12) (entries 4 and 5). In addition to the aromatic *N*-sulfinyl imines, we evaluated the cross-coupling reaction of aliphatic imines with isobutyraldehyde and found that the reactions could equally be accomplished with high yields and high diastereomeric ratios (entries 14-17). Thus, the reaction substrate scope could be greatly expanded, indicating the excellent

Table 3 Samarium Diiodide-induced Reductive Cross-coupling Reaction of *N-tert*-Butanesulfinyl Imines with Aldehydes[a]



2 **5** **6**

entry	R^1	R^2	6	T (h)	yield (%)[b]	*dr*[c]	*ee*[d]
1	4-$CH_3C_6H_4$	*i*-Pr	**6e**	4	92	>99:1	98
2	4-$CH_3C_6H_4$	C_6H_{11}	**6e'**	7	90	99:1	>99
3	4-$CH_3C_6H_4$	$(Et)_2CH$	**6e''**	7	73	>99:1	99
4	4-$CH_3C_6H_4$	*n*-C_5H_{11}	**6e'''**	7	90	91:9	95
5	4-$CH_3C_6H_4$	PhC_2H_4	**6e''''**	7	95	88:12	95
6	Ph	*i*-Pr	**6g**	7	86	99:1	97
7	4-FC_6H_4	*i*-Pr	**6c**	4	89	98:2	>99
8	4-ClC_6H_4	*i*-Pr	**6a**	4	71	99:1	98
9	4-BrC_6H_4	*i*-Pr	**6b**	4	70	>99:1	>99
10	4-$AcOC_6H_4$	*i*-Pr	**6d**	4	82	>99:1	>99
11	4-$CH_3OC_6H_4$	*i*-Pr	**6f**	4	84	>99:1	>99
12	3,4-$(MeO)_2C_6H_3$	*i*-Pr	**6j**	7	90	>99:1	>99
13	2,4-$(MeO)_2C_6H_3$	*i*-Pr	**6k**	7	73	>99:1	>99
14	*i*-Pr	*i*-Pr	**6l**	6	88	>99:1	98
15	$PhCH_2CH_2$	*i*-Pr	**6m**	6	87	96:4	>99
16	$CH_3(CH_2)_4$	*i*-Pr	**6n**	6	95	98:2	97
17	$BnOCH_2$	*i*-Pr	**6o**	8	82	>99:1	97

[a]See experimental section for reaction details. [b]Isolated yield. [c]According to HPLC-MS and ^{1}H NMR of the crude materials. [d]Enantiomeric excess for the free *β*-amino alcohols after acidic hydrolysis of **6**; see experimental section for details.

compatibility and efficiency of the method. Notably, for those *β*-amino alcohol products **6a**, **6b**, **6d** and **6f**, the *para*-halogen, acetoxy or methoxy substituent on the benzene ring would be a useful functionality for further modification, such as adjustment of the

solubility or attachment onto support materials via *O*-alkylation or coupling reactions.[27] For the product **6o**, it is also worth noting that removal of the *N*-sulfinyl and benzyl

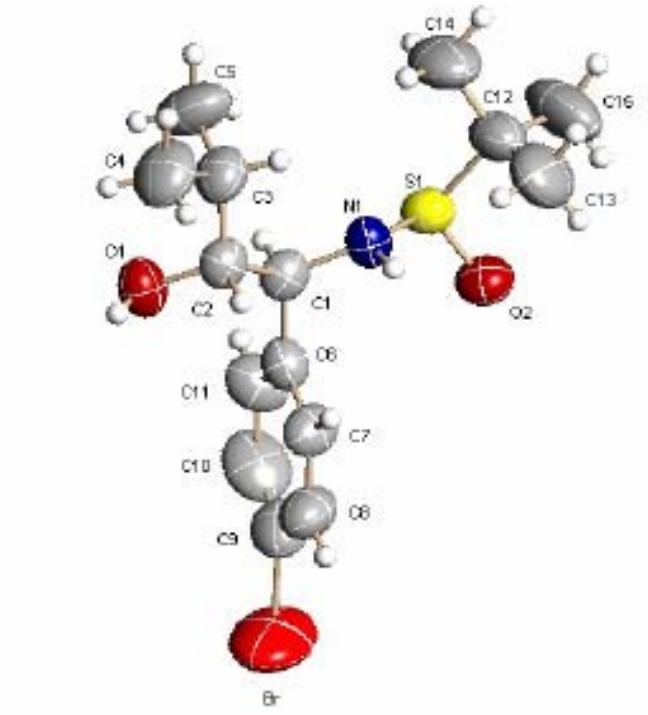


Figure 2 X-ray Crystal Structure of Cross-coupling Product **6b**

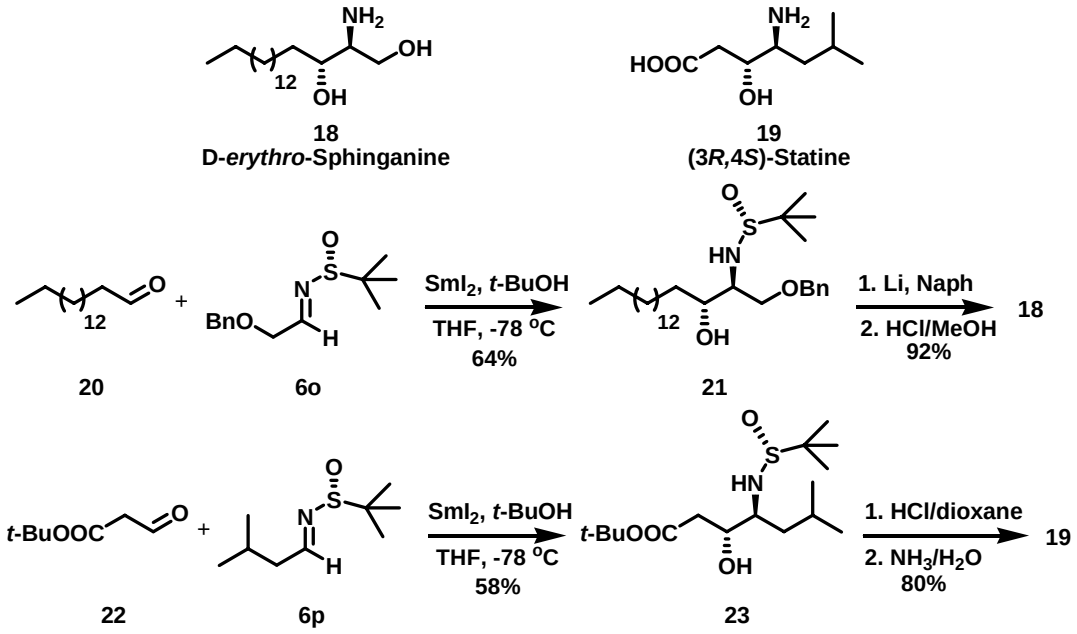
groups will afford the chiral 2-amino-1,3-propanediol derivative, which is, from the synthesis viewpoint, a very useful building block.

Cleavage of the sulfinyl group under acidic conditions (HCl/MeOH) was subsequently accomplished to afford *β*-amino alcohols in high yields. Very gratifyingly, excellent enantiomeric excesses (> 95% *ee*) were observed in all cases (Table 3). These results clearly indicate that the *N*-sulfinyl group serves as a powerful chiral directing group and affects the stereoselectivity of the reaction.

As described above, this highly diastereoselective and enantioselective cross pinacol

coupling reaction offers a significantly more efficient and direct method for construction of *β*-amino alcohol scaffolds. To further demonstrate its synthetic value, the rapid preparation of two biologically active compounds D-*erythro*-sphinganine (**18**) and (3*R*,4*S*)-statine (**19**) was carried out (Scheme 13).

Scheme 13



The cross-coupling reaction of palmitaldehyde **20** (4 equiv)[28] with imine **6o** was performed at -78 °C under standard conditions to provide **21** as a single diastereomer in 64% yield.[29] Removal of the benzyl and sulfinyl groups gave D-*erythro*-sphinganine (**18**) in 92% overall yield with 97% *ee*.

When aldehyde **22** (2 equiv) was treated with *N*-sulfinyl imine **6p** under similar reaction conditions, **23** was isolated in 58% yield with 99% *de*. The *tert*-butyl ester and *N*-sulfinyl group were then easily cleaved by acidic hydrolysis in one step to afford optically pure (3*R*,4*S*)-statine (**9**) in high yield. This approach represents one of the most

convenient and direct syntheses of **18** and **19** reported to date.[30]

In summary, we have developed a highly efficient and practical approach to the synthesis of enantiomerically pure *β*-amino alcohols by the samarium diiodide-mediated reductive cross-coupling reaction of chiral *N*-*tert*-butanesulfinyl imines with aldehydes. This method has been found to be very effective for the preparation of a broad range of chiral *β*-amino alcohols, including functionalized ones under mild conditions. Diastereoselectivities and enantioselectivities in this reaction are excellent in most cases. Moreover, it provides a solution to the long-standing problem of the difficulty of direct construction of enantiopure *β*-amino alcohols via the pinacol-type cross-coupling reaction between carbonyl compounds and imines. Both this methodology and the obtained *β*-amino alcohols should be widely applicable in asymmetric synthesis.

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28. A larger excess was used for its poor solubility in THF at -78 °C.

29. Yield based on consumed starting material.

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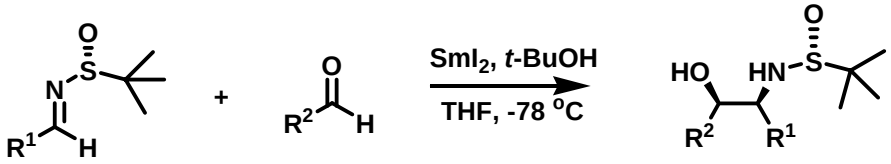
Experimental Section

1. General Procedure for the Reductive Cross-coupling Reaction of *N-tert*-Butyl-sulfinyl Imines with Aldehydes.



To a solution of freshly prepared samarium diiodide (1.0 mmol) in THF (5 mL) cooled, a mixture of *tert*-butyl alcohol (1.0 mmol), aldehyde (0.75 mmol) and chiral *N-tert*-butanesulfinyl imine (0.5 mmol) in THF (6 mL) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 2-3 h. When R^1 = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4 or 4-$AcOC_6H_4$, a mixture of *tert*-butyl alcohol and aldehyde was first added, and *N-tert*-butylsulfinyl imine was then added dropwise to minimize the homocoupling reaction. After completion of the reaction had been confirmed by TLC analysis, a saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added to the mixture, which was then extracted with EtOAc. Purification by flash column chromatography afforded the desired homocoupling product.

2. Characterization of the Obtained Optically Active *β*-Amino Alcohols.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-*p*-tolylbutyl] amide-, [*S*(*R*)] (6e). $[\alpha]_D^{20}$ = -48.2° (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ

0.94 (d, *J* = 5.1 Hz, 3H), 0.96 (d, *J* = 5.1 Hz, 3H), 1.22 (s, 9H), 1.49 (m, 1H), 2.07 (br, 1H), 2.33 (s, 3H), 3.61 (br, 1H), 3.68 (d, *J* = 5.7 Hz, 1H), 4.45 (t, *J* = 4.8 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.26, 19.32, 21.09, 22.57, 30.17, 55.96, 60.42, 78.82, 128.39, 129.31, 135.39, 137.85; FT-IR (KBr, cm^{-1}): 3346, 1463, 1031; ESI-MS (m/z): 298.3 $(M + H)^+$; HR-MS for $C_{16}H_{27}NO_2SNa$ $(M + Na)^+$: calcd. 320.1655, found: 320.1634.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-cyclohexyl-2-hydroxy-1-*p*-tolylethyl]- amide-, [*S*(*R*)] (6e'). $[\alpha]_D^{20}$ = -53.8° (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (s, 9H, *J* = 7.2 Hz), 1.24-1.26 (m, 4H), 1.72-1.90 (m, 6H), 2.34 (s, 3H), 3.66 (dd, *J* = 4.2, 7.2 Hz, 1H), 3.77 (d, *J* = 5.7 Hz, 1H), 4.47 (t, *J* = 4.9 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.12, 22.63, 25.59, 25.86, 26.33, 28.27, 29.55, 39.67, 56.03, 60.00, 78.05, 128.38, 129.36, 135.56, 137.80; FT-IR (KBr, cm^{-1}): 3346, 1463, 1031; ESI-MS (m/z): 338 $(M + H)^+$; HR-MS for $C_{19}H_{31}NO_2SNa$ $(M + Na)^+$: calcd. 360.1967, found: 360.1974.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-3-ethyl-2-hydroxy-1-*p*-tolylpentyl]-amide-, [*S*(*R*)] (6e''). $[\alpha]_D^{20}$ = -36.0° (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (q, *J* = 3.0 Hz, 6H), 1.19 (s, 9H), 1.21-1.56 (m, 5H), 1.76 (br, 1H), 2.33 (s, 3H), 3.64 (d, *J* = 5.4 Hz, 1H), 3.85 (br, 1H), 4.45 (t, *J* = 5.4 Hz, 1H), 7.15(d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.50, 10.61, 20.01, 21.10, 21.29, 22.59, 41.69, 56.03, 60.42, 74.90, 128.30, 129.40, 135.77, 137.86; FT-IR (KBr, cm^{-1}): 3370, 3336, 2967, 1513, 1466, 1033; ESI-MS (m/z): 326.3 $(M + H)^+$; HR-MS for $C_{18}H_{31}NO_2SNa$ $(M + Na)^+$: calcd. 348.1968, found: 348.1989.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-1-*p*-tolylheptyl]amide-, [*S*(*R*)] (6e''''). $[\alpha]_D^{20}$ = -30.2° (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.9 Hz), 1.12-1.20 (m, 2H), 1.28 (s, 9H), 1.29-1.36 (m, 6H), 2.34 (s, 3H), 3.78 (s, 1H), 3.96 (t, *J* = 4.5 Hz, 1H), 4.35 (dd, *J* = 3.6, 5.4 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.90, 21.00, 22.46, 22.58, 25.51, 31.64, 33.29, 56.13, 62.17, 73.60, 128.11, 129.07, 135.23, 137.50; FT-IR (KBr, cm^{-1}): 3300, 2959, 2919, 1462, 1046; ESI-MS (m/z): 326.2 $(M + H)^+$; HR-MS for $C_{18}H_{32}NO_2S$ $(M + H)^+$: calcd. 326.2148, found: 326.2144.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-4-phenyl-1-*p*-tolylbutyl] amide-, [*S*(*R*)] (6e''''). $[\alpha]_D^{20}$ = -53.8° (*c* 1.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 1H), 1.22 (s, 8H), 1.23-1.26 (m, 1H), 1.48-1.50 (m, 1H), 2.33 (s, 3H), 2.78-2.83 (m, 1H), 2.64-2.67 (m, 1H), 3.95 (s, 1H), 3.99 (d, *J* = 6.3 Hz, 1H), 4.37 (dd, *J* = 5.1, 9.6 Hz, 1H), 7.13-7.28 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.01, 22.62, 32.17, 35.10, 56.21, 62.26, 73.02, 128.09, 128.22, 128.27, 128.33, 129.19, 135.10, 137.67, 141.70; FT-IR (KBr, cm^{-1}): 3377, 3024, 2857, 1047, 1038; ESI-MS (m/z): 360 $(M + H)^+$; HR-MS for $C_{21}H_{30}NO_2S$ $(M + H)^+$: calcd. 360.1992, found: 360.1998.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-phenylbutyl] amide-, [*S*(*R*)] (6g). $[\alpha]_D^{20}$ = -51.3° (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J* = 6.9 Hz, 6H), 1.21 (s, 9H), 1.48 (m, 1H), 2.00 (br, 1H), 3.63 (br, 1H), 3.74 (d, *J* = 5.7 Hz, 1H), 4.49 (dd, *J* = 5.7, 4.5 Hz, 1H), 7.31-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.29, 19.33, 22.59, 30.17, 56.05, 60.61, 78.85, 128.19, 128.52, 128.64, 138.40; FT-IR (KBr, cm^{-1}): 3410, 3327, 2956, 1475, 1041, 699; ESI-MS (m/z): 284.2

$(M + H)^+$; HR-MS for $C_{15}H_{25}NO_2SNa$ $(M + Na)^+$: calcd. 306.1498, found: 306.1515.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-*p*-fluorophenylbutyl]amide-, [*S*(*R*)] (6c). $[\alpha]_D^{20}$ = -42.1° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, *J* = 1.5 Hz, 3H), 0.96 (d, *J* = 1.5 Hz, 3H), 1.22 (s, 9H), 1.24-1.27 (m, 1H), 2.12 (d, *J* = 2.1 Hz, 1H), 3.61 (dd, *J* = 3.9, 7.8 Hz, 1H), 3.70 (d, *J* = 5.7 Hz, 1H), 4.48 (dd, *J* = 5.7, 9.3 Hz, 1H), 7.05 (d, *J* = 18.1 Hz, 2H), 7.42 (d, *J* = 18.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.34, 19.15, 22.49, 30.21, 56.05, 60.01, 78.99, 115.19, 115.47, 130.25, 130.35, 134.39, 134.44, 160.69, 163.96; FT-IR (KBr, cm^{-1}): 2961, 2872, 1604, 1511, 1048; ESI-MS (m/z): 302.2 $(M + H)^+$; HR-MS for $C_{15}H_{25}NO_2SF$ $(M + H)^+$: calcd. 302.1584, found: 302.1583.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-*p*-chlorophenylbutyl]amide-, [*S*(*R*)] (6a). $[\alpha]_D^{20}$ = -35.8° (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.6 Hz, 6H), 1.21 (s, 9H), 1.45 (m, 1H), 2.27 (br, 1H), 3.60 (m, 1H), 3.81 (m, 1H), 4.44 (m, 1H), 7.30 (dd, *J* = 2.4, 6.6 Hz, 2H), 7.36 (dd, *J* = 2.4, 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.37, 19.18, 22.53, 30.25, 56.12, 60.11, 78.99, 128.69, 130.03, 133.90, 137.04; FT-IR (KBr, cm^{-1}): 3344, 2961, 1492, 1031; ESI-MS (m/z): 318.2 $(M + H)^+$; HR-MS for $C_{15}H_{24}NO_2SClNa$ $(M + Na)^+$: calcd. 340.1108, found: 340.1113.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-*p*-bromophenylbutyl]amide-, [*S*(*R*)] (6b). $[\alpha]_D^{20}$ = -26.7° (*c* 0.75, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.9 Hz, 6H), 1.20 (s, 9H), 1.45 (m, 1H), 2.35 (d, *J* = 5.1 Hz, 1H),

3.58 (m, 1H), 3.84 (d, J = 6.6 Hz, 1H), 4.41 (dd, J = 6.6, 4.5 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.37, 19.18, 22.52, 30.25, 56.13, 60.16, 78.98, 122.07, 130.36, 131.60, 137.61; FT-IR (KBr, cm^{-1}): 3340, 2958, 1487, 1031; ESI-MS (m/z): 362.3 $(M + H)^+$; HR-MS for $C_{15}H_{24}NO_2SBrNa$ $(M + Na)^+$: calcd. 384.0603, found: 384.0614.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-*p*-acetoxyphenylbutyl]amide-, [*S*(*R*)] (6d). $[\alpha]_D^{20}$ = -40.0° (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, J = 6.6 Hz, 6H), 1.19 (s, 9H), 1.46 (m, 1H), 2.29 (s, 3H), 2.33 (br, 1H), 3.56 (br, 1H), 3.78 (d, J = 6.0 Hz, 1H), 4.45 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.29, 19.23, 21.09, 22.53, 30.07, 56.03, 60.03, 78.77, 121.52, 129.69, 136.07, 150.23, 169.36; FT-IR (KBr, cm^{-1}): 3298, 3177, 2961, 1768, 1749, 1507, 1370, 1222, 1199, 1058, 1003; ESI-MS (m/z): 342.1 $(M + H)^+$; HR-MS for $C_{17}H_{27}NO_4SNa$ $(M + Na)^+$: calcd. 364.1553, found: 364.1547.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-*p*-methoxyphenylbutyl]amide-, [*S*(*R*)] (6f). $[\alpha]_D^{20}$ = -38.1° (*c* 1.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 0.97 (s, 3H), 1.22 (s, 9H), 1.25-1.29 (m, 1H), 2.06 (d, J = 4.2 Hz, 1H), 3.63 (m, 2H), 3.80 (s, 3H), 4.45 (t, J = 4.8 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.23, 19.20, 22.49, 30.13, 55.07, 55.91, 60.19, 78.87, 113.81, 129.65, 130.51, 159.15; FT-IR (KBr, cm^{-1}): 3504, 3139, 2962, 1515, 1247, 1039, 1001; ESI-MS (m/z): 314 $(M + H)^+$; HR-MS for $C_{16}H_{27}NO_3SNa$ $(M + Na)^+$: calcd. 336.1609, found: 336.1607.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-3,4-dimethoxy-phenylbutyl]amide-, [*S*(*R*)] (6j). $[\alpha]_D^{20}$ = -35.2° (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 3H), 0.99 (s, 3H), 1.24 (s, 9H), 2.01 (d, *J* = 4.2 Hz, 1H), 3.59-3.64 (m, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.43 (dd, *J* = 5.1, 9.6 Hz, 1H), 6.86 (dd, *J* = 6.0, 8.7 Hz, 1H), 6.99 (dd, *J* = 4.8, 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.07, 19.29, 22.46, 30.06, 55.66, 55.80, 55.88, 60.52, 78.77, 110.93, 111.79, 120.71, 130.98, 148.69; FT-IR (KBr, cm^{-1}): 3428, 2960, 2837, 1522, 1041, 1025; ESI-MS (m/z): 344 $(M + H)^+$; HR-MS for $C_{17}H_{29}NO_4SNa$ $(M + Na)^+$: calcd. 366.1709, found: 366.1712.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-2,4-dimethoxy-phenylbutyl]amide-, [*S*(*R*)] (6k). $[\alpha]_D^{20}$ = -49.6° (*c* 0.70, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.22 (s, 9H), 1.73-1.80 (m, 1H), 1.94 (s, 1H), 3.68 (s, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.13 (dd, *J* = 7.5, 16 Hz, 1H), 4.47 (dd, *J* = 7.5, 15 Hz, 1H), 6.46-6.49 (m, 2H), 7.27 (dd, *J* = 3.6, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.31, 19.74, 22.49, 29.67, 55.21, 55.33, 55.77, 59.17, 78.10, 99.12, 104.47, 119.77, 130.95, 157.93, 160.48; FT-IR (KBr, cm^{-1}): 3541, 2964, 1612, 1071; ESI-MS (m/z): 344.2 $(M + H)^+$; HR-MS for $C_{17}H_{29}NO_4SNa$ $(M + Na)^+$: calcd. 366.1709, found: 366.1706.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-1-isopropyl-3-methylbut-yl]amide-, [*S*(*R*)] (6l). $[\alpha]_D^{20}$ = -62.8° (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.91-0.97 (m, 9H), 1.09 (d, *J* = 5.1 Hz, 3H), 1.26 (s, 9H), 1.66 (d, *J* = 4.8 Hz, 1H), 1.91-1.95 (m, 1H), 2.20-2.25 (m, 1H), 3.16-3.20 (m, 1H), 3.23 (d, *J* = 6.6 Hz, 1H), 3.34 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.62, 16.79, 19.81, 20.87, 22.70,

27.25, 29.28, 56.10, 62.70, 78.15; FT-IR (KBr, cm^{-1}): 3367, 2964, 2874, 1473, 1035; ESI-MS (m/z): 250.2 $(M + H)^+$; HR-MS for $C_{12}H_{27}NO_2SNa$ $(M + Na)^+$: calcd. 272.1654, found: 272.1657.

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-3-methyl-1-phenethylbutyl]amide-, [*S*(*R*)] (6m). $[\alpha]_D^{20}$ = -118.8° (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.26 (s, 9H), 1.66-1.68 (m, 1H), 1.91-2.05 (m, 2H), 2.64-2.69 (m, 1H), 2.87-2.89 (m, 1H), 3.20 (dd, *J* = 2.1, 9.0 Hz, 2H), 3.31-3.38 (m, 2H), 7.18-7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.64, 19.69, 22.72, 28.55, 30.25, 31.66, 55.68, 58.09, 80.35, 125.90, 128.35, 128.55, 141.51; FT-IR (KBr, cm^{-1}): 3370, 2959, 5870, 1042; ESI-MS (m/z): 312.2 $(M + H)^+$; HR-MS for $C_{17}H_{29}NO_2SNa$ $(M + Na)^+$: calcd. 334.1811, found: 334.1813.

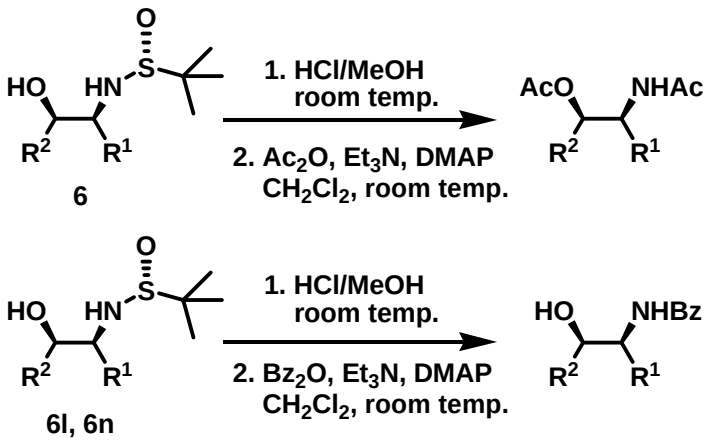
2-Methylpropane-2-sulfinic acid [(*S*)-1-((*R*)-1-hydroxy-2-methylpropyl)hexyl] amide-, [*S*(*R*)] (6n). $[\alpha]_D^{20}$ = -99.6° (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (dd, *J* = 4.2, 6.6 Hz, 6H), 1.02 (d, *J* = 6.3 Hz, 3H), 1.26 (s, 9H), 1.27-1.34 (m, 4H), 1.54-1.75 (m, 4H), 2.87 (s, 1H), 3.17 (d, *J* = 3.9 Hz, 1H), 3.24 (t, *J* = 6.6 Hz, 1H), 3.35-3.39 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.00, 19.02, 19.58, 22.46, 22.64, 25.49, 26.88, 30.13, 31.60, 55.59, 58.74, 79.99; FT-IR (KBr, cm^{-1}): 3303, 3207, 2958, 1058, 1038, 998; ESI-MS (m/z): 278.2 $(M + H)^+$; HR-MS for $C_{14}H_{31}NO_2SNa$ $(M + Na)^+$: calcd. 300.1968, found: 300.1970.

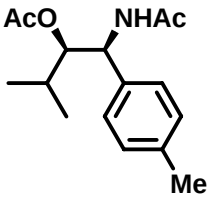
2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-1-benzyloxymethyl-2-hydroxy-3-methylbutyl]amide-, [*S*(*R*)] (6o). $[\alpha]_D^{20}$ = -46.0° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz,

$CDCl_3$): δ 0.90-0.96 (dd, J = 6.6 Hz, 6H), 1.25 (s, 9H), 1.75-1.77 (m, 1H), 2.57 (d, J = 5.7 Hz, 1H), 3.38-3.46 (m, 2H), 3.78-3.92 (m, 2H), 4.00 (d, J = 7.8 Hz, 1H), 4.45-4.63 (AB, J_{AB} = 11.7 Hz, 2H), 7.30-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.37, 19.30, 22.56, 30.14, 55.89, 56.92, 70.34, 73.50, 76.58, 127.86, 128.45, 137.51; FT-IR (film, cm^{-1}): 3400, 2960, 1072, 1051; ESI-MS (m/z): 328.3 $(M + H)^+$; HR-MS for $C_{17}H_{29}NO_3SNa$ $(M + Na)^+$: calcd. 350.1760, found: 350.1764.

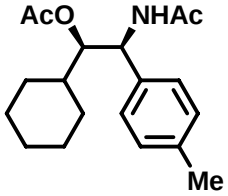
3. Determination of the Diastereoselectivity and the Enantiomeric Excess.

The diastereoselectivity of the reaction was determined by HPLC-MS and ^{1}H NMR of the crude products. The major diastereomer was then separated by column chromatography. The optical purities of the obtained *β*-amino alcohol products were determined by measuring the *ee* values of their diacetates or benzoylate derivatives.

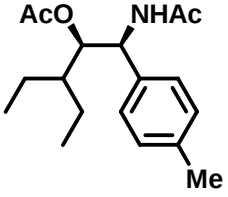




Acetic acid (*R*)-1-[(*S*)-acetylamino-*p*-tolylmethyl]-2-methylpropyl ester. HPLC: Chiralpak OD column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); $[\alpha]_D^{20}$ = +153.6° (*c* 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.77-1.83 (m, 1H), 1.91 (s, 3H), 1.94 (s, 3H), 2.32 (s, 3H), 4.99 (dd, *J* = 6.6, 12.6 Hz, 1H), 5.22 (dd, *J* = 5.4, 8.7 Hz, 1H), 6.39 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.59, 19.47, 20.77, 21.05, 23.29, 29.24, 53.80, 79.88, 127.72, 129.02, 135.35, 137.33, 169.08, 171.14; FT-IR (KBr, cm^{-1}): 3282, 2966, 1745, 1655, 1235; ESI-MS (m/z): 278 $(M + H)^+$; HR-MS for $C_{16}H_{23}NO_3Na$ $(M + Na)^+$: calcd. 300.1570, found: 300.1573.

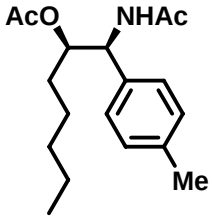


Acetic acid (1*R*,2*S*)-2-acetylamino-1-cyclohexyl-2-*p*-tolylethyl ester. HPLC: Chiralcel OD column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); $[\alpha]_D^{20}$ = +116.3° (*c* 0.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.00-1.78 (m, 11H), 1.89 (d, *J* = 3.0 Hz, 3H), 1.93 (d, *J* = 3.0 Hz, 3H), 2.27 (s, 3H), 4.95 (dd, *J* = 4.8, 7.2 Hz, 1H), 5.20 (dd, *J* = 4.8, 8.4 Hz, 1H), 6.35 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H); FT-IR (KBr, cm^{-1}): 3293, 2933, 2854, 1743, 1731, 1654, 1234; ESI-MS (m/z): 318 $(M + H)^+$; HR-MS for $C_{19}H_{28}NO_3$ $(M + H)^+$: calcd. 318.2064, found: 318.2063.

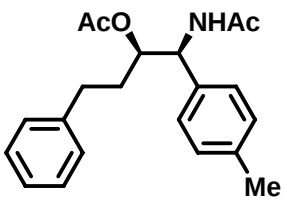


Acetic acid (*R*)-1-[(*S*)-acetylamino-*p*-tolylmethyl]-2-ethylbutyl ester. HPLC: Chiralpak AD-H column, detected at 254 nm, eluent: hexane/2-propanol = 80/20 (v/v); mp 105 °C; $[\alpha]_D^{20}$ = +127.2° (*c* 0.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.81-1.22 (m, 6H),

1.43-1.55 (m, 5H), 1.93 (s, 3H), 1.96 (s, 3H), 2.34 (s, 3H), 5.17 (dd, *J* = 5.7, 8.1 Hz, 1H), 5.26 (dd, *J* = 5.7, 8.1 Hz, 1H), 6.16 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.58, 10.91, 20.63, 20.74, 21.01, 21.64, 23.20, 53.67, 77.42, 127.73, 128.91, 135.50, 137.15, 169.05, 170.95; FT-IR (KBr, cm^{-1}): 3271, 2964, 1737, 1651, 1519, 1240; ESI-MS (m/z): 306 $(M+H)^+$; HR-MS for $C_{18}H_{27}NO_3Na$ $(M+Na)^+$: calcd. 328.1883, found: 328.1884.

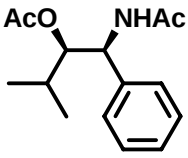


Acetic acid (*R*)-1-[(*S*)-acetylamino-*p*-tolylmethyl]hexyl ester. HPLC: Chiralpak AD-H column, detected at 214 nm, eluent: hexane/2-propanol = 90/10 (v/v); $[\alpha]_D^{20}$ = +83° (*c* 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, *J* = 6.9 Hz, 3H), 1.23-1.49 (m, 8H), 1.97 (s, 3H), 2.00 (s, 3H), 1.77-1.83 (m, 1H), 2.33 (s, 3H), 5.14 (dd, *J* = 7.2, 12 Hz, 1H), 6.52 (d, *J* = 6.6 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.90, 21.01, 21.04, 22.40, 23.32, 25.16, 31.00, 31.40, 55.63, 77.43, 127.48, 129.03, 134.87, 137.28, 169.23, 171.26; FT-IR (KBr, cm^{-1}): 3244, 2960, 1736, 1648, 1244; ESI-MS (m/z): 306 $(M+H)^+$; HR-MS for $C_{18}H_{27}NO_3Na$ $(M+Na)^+$: calcd. 328.1883, found: 328.1886.

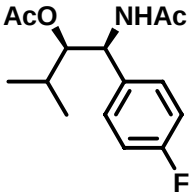


Acetic acid (*R*)-1-[(*S*)-acetylamino-*p*-tolylmethyl]-3-phenylpropyl ester. HPLC: Chiralpak AD column, detected at 254 nm, eluent: hexane/2-propanol = 80/20 (v/v); $[\alpha]_D^{20}$ = +69.5° (*c* 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-1.28 (m, 2H), 1.93 (s, 3H), 1.98 (s, 3H), 2.31 (s, 3H), 2.56-2.66 (m, 2H), 5.14-5.21 (m, 2H), 6.56 (d, *J* = 7.2 Hz, 1H), 7.08-7.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.96, 21.04, 23.31,

31.84, 32.84, 55.69, 75.48, 125.99, 127.41, 128.27, 128.39, 129.11, 134.64, 137.43, 140.91, 169.32, 171.28; FT-IR (KBr, cm^{-1}): 3356, 2955, 1731, 1653, 1244; ESI-MS (m/z): 340 $(M + H)^+$; HR-MS for $C_{21}H_{25}NO_3Na$ $(M + Na)^+$: calcd. 362.1727, found: 362.1722.

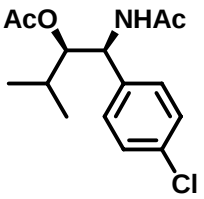


Acetic acid (*R*)-1-[(*S*)-acetylaminophenylmethyl]-2-methylpropyl ester. HPLC: Chiralpak AD-H column, detected at 254 nm, eluent: hexane/2-propanol = 80/20 (v/v); $[\alpha]_D^{20}$ = +164.7° (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.81-1.87 (m, 1H), 1.92 (s, 6H), 5.01 (t, *J* = 6.3 Hz, 1H), 5.25 (dd, *J* = 6.0, 8.7 Hz, 1H), 6.68 (s, 1H), 7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.48, 19.50, 20.72, 23.29 29.21, 54.06, 79.75, 127.68, 127.81, 128.32, 138.42, 169.18, 171.14; FT-IR (KBr, cm^{-1}): 3645, 3314, 1730, 1650, 1548, 1247; ESI-MS (m/z): 264 $(M + H)^+$; HR-MS for $C_{15}H_{22}NO_3$ $(M + H)^+$: calcd. 264.1597, found: 264.1597.

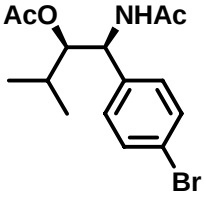


Acetic acid (*R*)-1-[(*S*)-acetylamino-(4-fluorophenyl)methyl]-2-methylpropyl ester. HPLC: Chiralcel OD column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); $[\alpha]_D^{20}$ = +123.1° (*c* 0.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.75-1.82 (m, 1H), 1.97 (s, 3H), 1.98 (s, 3H), 4.94 (dd, *J* = 4.8, 7.2 Hz, 1H), 5.24 (dd, *J* = 5.4, 8.4 Hz, 1H), 6.21 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.11, 19.42, 20.65, 23.12, 29.10, 53.37, 79.32, 115.01, 129.45, 134.55, 162.00, 169.33, 170.99; FT-IR (KBr, cm^{-1}): 3277, 2968, 1743, 1513, 1232; ESI-MS (m/z): 281 (M^+); HR-MS for

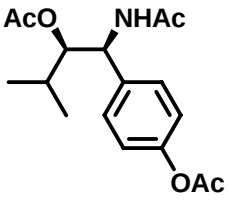
$C_{15}H_{20}NO_3NaF$ $(M + Na)^+$: calcd. 304.1570, found: 304.1321.



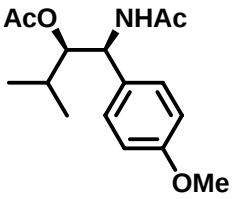
Acetic acid (*R*)-1-[(*S*)-acetylamino-(4-chlorophenyl)methyl]-2-methylpropyl ester. HPLC: Chiralpak AD column, detected at 214 nm, eluent: hexane/2-propanol = 80/20 (v/v); $[\alpha]_D^{20}$ = +153.7° (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.78-1.84 (m, 1H), 1.92 (s, 3H), 1.96 (s, 3H), 4.95 (t, *J* = 6.9 Hz, 1H), 5.21 (dd, *J* = 5.7, 8.4 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.49, 19.46, 20.75, 23.27, 29.22, 53.06, 79.65, 128.46, 129.17, 133.44, 137.04, 169.19, 171.21; FT-IR (KBr, cm^{-1}): 3302, 2976, 1737, 1646, 1542, 1236; ESI-MS (m/z): 298 $(M + H)^+$; HR-MS for $C_{15}H_{20}NO_3NaCl$ $(M + Na)^+$: calcd. 320.1024, found: 320.1024.



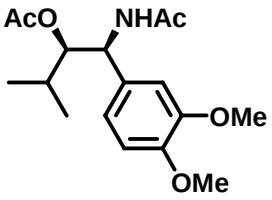
Acetic acid (*R*)-1-[(*S*)-acetylamino-(4-bromophenyl)methyl]-2-methylpropyl ester. HPLC: Chiralpak AD column, detected at 254 nm, eluent: hexane/2-propanol = 80/20 (v/v); $[\alpha]_D^{20}$ = +155.6° (*c* 0.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.78-1.84 (m, 1H), 1.92 (s, 3H), 1.95 (s, 3H), 4.95 (dd, *J* = 5.7, 6.6 Hz, 1H), 5.19 (dd, *J* = 6.3, 8.1 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.44, 19.47, 20.75, 23.25, 29.19, 53.66, 79.53, 121.58, 129.52, 131.40, 137.59, 169.21, 171.19; FT-IR (KBr, cm^{-1}): 3305, 2974, 1737, 1646, 1539, 1236; ESI-MS (m/z): 342 $(M + H)^+$; HR-MS for $C_{15}H_{20}NO_3NaBr$ $(M + Na)^+$: calcd. 364.0519, found: 364.0516.



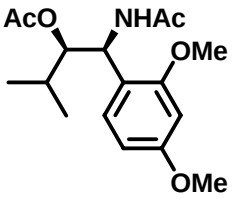
Acetic acid (*R*)-1-[(*S*)-(4-acetoxyphenyl)acetylaminomethyl]-2-methylpropy-l ester. HPLC: Chiralpak AS column, detected at 214 nm, eluent: hexane/2-propanol = 90/10 (v/v); $[\alpha]_D^{20}$ = +111.1° (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 1.79-1.84 (m, 1H), 1.95 (s, 3H), 1.97 (s, 3H), 2.28 (s, 3H), 4.97 (dd, *J* = 5.4, 7.2 Hz, 1H), 5.27 (dd, *J* = 5.4, 8.7 Hz, 1H), 6.22 (d, *J* = 6.0 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.50, 19.45, 20.74, 21.11, 23.23, 29.23, 53.46, 79.64, 121.44, 128.96, 136.03, 149.97, 169.18, 169.44, 171.14; FT-IR (KBr, cm^{-1}): 3587, 3287, 1737, 1658, 1550, 1238; ESI-MS (m/z): 322 $(M + H)^+$; HR-MS for $C_{17}H_{24}NO_5$ $(M + H)^+$: calcd. 322.1649, found: 322.1646.



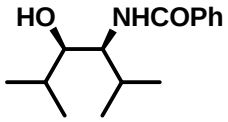
Acetic acid (*R*)-1-[(*S*)-acetylamino-(4-methoxyphenyl)methyl]-2-methylpro-pyl ester. HPLC: Chiralpak AD column, detected at 254 nm, eluent: hexane/2-propanol = 90/10 (v/v); $[\alpha]_D^{20}$ = +161.2° (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.76-1.83 (m, 1H), 1.94 (s, 3H), 1.97 (s, 3H), 3.79 (s, 3H), 4.98 (dd, *J* = 5.7, 12.6 Hz, 1H), 5.20 (dd, *J* = 5.7, 8.4 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.57, 19.44, 20.80, 23.31, 29.26, 53.46, 55.14, 79.86, 113.68, 128.98, 130.51, 158.93, 169.05, 171.10; FT-IR (KBr, cm^{-1}): 3318, 3290, 1746, 1729, 1641, 1517, 1258; ESI-MS (m/z): 294 $(M + H)^+$; HR-MS for $C_{16}H_{23}NO_4Na$ $(M + Na)^+$: calcd. 316.1519, found: 316.1519.



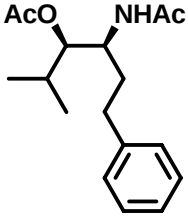
Acetic acid (*R*)-1-[(*S*)-acetylamino-(3,4-dimethoxyphenyl)-methyl]-2-met-hylpropyl ester. HPLC: Chiralpak AD column, detected at 254 nm, eluent: hexane/2-propanol = 90/10 (v/v); $[\alpha]_D^{20}$ = +120.3° (*c* 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.77-1.82 (m, 1H), 1.89 (s, 3H), 1.90 (s, 3H), 3.81 (s, 3H), 4.99 (dd, *J* = 6.3, 12.6 Hz, 1H), 5.15 (dd, *J* = 6.6, 8.4 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.26, 19.50, 20.76, 23.25, 29.20, 53.66, 55.69, 55.76, 79.41, 110.83, 111.42, 120.00, 131.09, 148.33, 148.49, 169.10, 170.88; FT-IR (KBr, cm^{-1}): 3328, 3271, 2933, 1749, 1644, 1521, 1230; ESI-MS (m/z): 324 $(M + H)^+$; HR-MS for $C_{17}H_{25}NO_5Na$ $(M + Na)^+$: calcd. 346.1625, found: 346.1626.



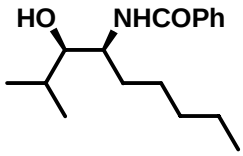
Acetic acid (*R*)-1-[(*S*)-acetylamino-(2,4-dimethoxyphenyl)-methyl]-2-methy-lpropyl ester. HPLC: Chiralcel OD column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); $[\alpha]_D^{20}$ = +113.3° (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.61-1.74 (m, 1H), 1.75 (s, 3H), 2.18 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 5.19-5.21 (m, 2H), 6.37-6.44 (m, 1H), 6.63 (d, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.85, 20.05, 20.52, 23.62, 28.49, 52.20, 55.26, 55.57, 77.54, 99.01, 103.92, 118.84, 131.17, 158.56, 160.35, 168.92, 170.36; FT-IR (KBr, cm^{-1}): 3300, 2965, 1741, 1653, 1509, 1239; ESI-MS (m/z): 324 $(M + H)^+$; HR-MS for $C_{17}H_{25}NO_5Na$ $(M + Na)^+$: calcd. 346.1625, found: 346.1628.



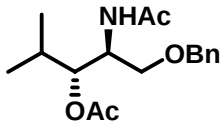
***N*-[(1*S*,2*R*)-2-Hydroxy-1-isopropyl-3-methylbutyl]benzamide.** HPLC: Chiralpak AS column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); $[\alpha]_D^{20}$ = +13.1° (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, *J* = 3.0 Hz, 6H), 1.00 (d, *J* = 3.0 Hz, 6H), 1.81-1.87 (m, 1H), 2.08 (d, *J* = 3.3 Hz, 1H), 2.22-2.28 (m, 1H), 3.41 (d, *J* = 6.3 Hz, 1H), 4.20-4.26 (m, 1H), 6.28 (d, *J* = 9.6 Hz, 1H), 7.40-7.50 (m, 3H), 7.77 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.81, 16.97, 19.86, 21.07, 30.33, 55.20, 77.96, 126.83, 128.57, 131.41, 134.79, 167.46; FT-IR (KBr, cm^{-1}): 3451, 3384, 2964, 1641, 1522, 1319; ESI-MS (m/z): 250 $(M + H)^+$; HR-MS for $C_{15}H_{23}NO_2Na$ $(M + Na)^+$: calcd. 272.1621, found: 272.1615.



Acetic acid (1*R*,2*S*)-2-acetylamino-1-isopropyl-4-phenylbutyl ester. HPLC: Chiralpak AD column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); $[\alpha]_D^{20}$ = +27.6° (*c* 0.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, *J* = 2.1 Hz, 3H), 0.90 (d, *J* = 2.1 Hz, 3H), 1.55-1.58 (m, 1H), 1.81-1.87 (m, 2H), 1.97 (s, 3H), 2.07 (s, 3H), 2.60-2.69 (m, 2H), 4.30 (t, *J* = 3.3 Hz, 1H), 4.65 (dd, *J* = 4.5, 6.9 Hz,1H), 5.72 (d, *J* = 9.3 Hz, 1H), 7.16-7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.87, 19.07, 20.93, 23.39, 29.66, 31.57, 32.27, 49.57, 81.19, 125.92, 128.30, 128.39, 141.63, 169.75, 171.44; FT-IR (KBr, cm^{-1}): 3285, 2966, 1739, 1651, 1552, 1237; ESI-MS (m/z): 292 $(M + H)^+$; HR-MS for $C_{17}H_{25}NO_3Na$ $(M + Na)^+$: calcd. 314.1727, found: 314.1728.

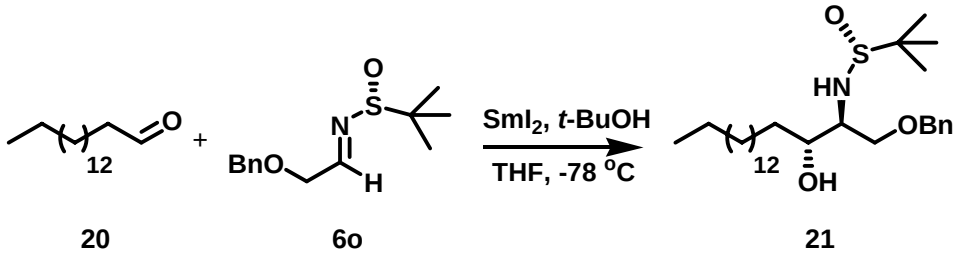


***N*-[(*S*)-1-[(*R*)-1-Hydroxy-2-methylpropyl]hexyl]benzamide.** HPLC: Chiralpak AS column, detected at 214 nm, eluent: hexane/2-propanol = 95/5 (v/v); mp 92 °C; $[\alpha]_D^{20}$ = -43.9° (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 7.5 Hz, 3H), 1.02 (d, *J* = 7.5 Hz, 3H), 1.29-1.78 (m, 9H), 2.23 (s, 1H), 3.35 (d, *J* = 7.5 Hz, 1H), 4.32 (t, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 8.7 Hz, 1H), 7.39-7.52 (m, 3H), 7.76-779 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04, 18.90, 19.29, 22.56, 25.87, 27.71, 31.20, 31.84, 51.56, 80.03, 126.88, 128.52, 131.37, 134.71, 167.16; FT-IR (KBr, cm^{-1}): 3312, 2956, 1634, 1539; ESI-MS (m/z): 278 $(M+H)^+$; HR-MS for $C_{17}H_{27}NO_2Na$ $(M+Na)^+$: calcd. 300.1934, found: 300.1937.



Acetic acid (1*R*,2*S*)-2-acetylamino-3-benzyloxy-1-isopropylpropyl ester. HPLC: Chiralcel AD column, detected at 214 nm, eluent: hexane/2-propanol = 90/10 (v/v); $[\alpha]_D^{26}$ = +17.2° (c 3.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (s, 3H), 0.91 (s, 3H), 1.87-1.91 (m, 1H), 1.94 (s, 3H), 1.98 (s, 3H), 3.44-3.46 (m, 1H), 4.31-4.39 (m, 1H), 4.43-4.49 (m, 2H), 4.89-4.93 (m, 1H), 6.05 (d, *J* = 9.0 Hz, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.41, 19.71, 20.76, 23.32, 29.02, 48.94, 68.43, 73.28, 76.52, 127.72, 127.88, 128.32, 137.64, 169.51, 170.63; FT-IR (film cm^{-1}) 3282, 2968, 1740, 1652, 1372, 1238; ESI-MS (m/z): 308.2 $(M+H)^+$, 330.1 $(M+Na)^+$; HR-MS for $C_{17}H_{25}NO_4Na$ $(M+Na)^+$: calcd. 330.1676, found: 330.1677.

4. Synthesis of D-*erythro*-sphinganine.

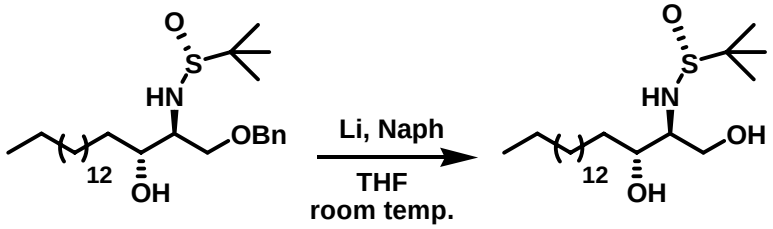


20 **6o** **21**

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-1-benzyloxymethyl-2-hydroxyheptadecyl]amide-, [*S*(*R*)] (21). To a solution of samarium diiodide (1.0 mmol) in THF (5 mL), a solution of imine 2-methylpropane-2-sulfinic acid [2-benzyloxy-eth-(E)-yl-idene]amide-, [*S*(*R*)] (**6o**) (121 mg, 0.48 mmol), palmitaldehyde (**20)** (450 mg, 2.0 mmol) and *tert*-butyl alcohol (95 μL, 1.0 mmol） in THF (10 mL) was dropped slowly at -78 °C. The mixture was stirred vigorously at the same temperature for 13 h and then quenched with saturated $Na_2S_2O_3$ solution (1 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated brine and then dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. After flash silica gel chromatography, the starting imine **6o** was recovered (19 mg) and the product **21** (129 mg, 64% yield based on the consumed starting material) was obtained as a yellow oil. Due to the poor solubility of long chained palmitaldehyde in THF, a larger excess (4 equiv) was employed to obtain a better result.

$[\alpha]_D^{26}$ = -23.9° (*c* 2.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86-0.88 (m, 3H), 1.24-1.25 (m, 35H), 1.40-1.47 (m, 2H), 2.49 (d, *J* = 6.6 Hz, 1H), 3.33 (m, 1H), 3.69 (m, 1H), 3.74-3.89 (m, 1H), 3.96-3.99 (d, *J* = 8 Hz, 2H), 4.44-4.64 (AB, J_{AB} =11.7 H*z,* 2H), 7.28-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.13, 22.64, 22.68, 25.83, 29.35, 29.54, 29.57, 29.60, 29.64, 29.67, 29.68, 31.91, 33.83, 55.96, 59.03, 70.10, 73.21, 73.50,

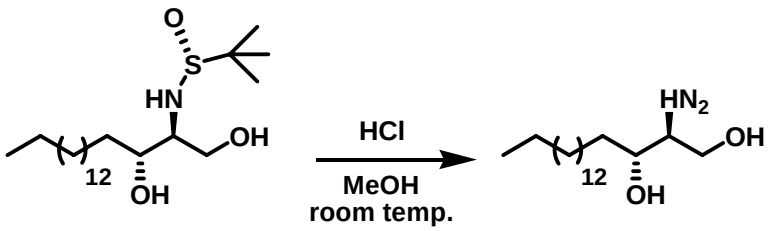
127.92, 127.94, 128.50, 137.48; FT-IR (film cm^{-1}) 3410, 2925, 2855, 1467, 1456, 1073, 1051; MALDI-TOF-MS (m/z): 496 $(M + H)^+$; HR-MS for $C_{29}H_{54}NO_3S$ $(M + H)^+$: calcd. 496.3819, found: 496.3820.



21

2-Methylpropane-2-sulfinic acid [(1*S*,2*R*)-2-hydroxy-1-hydroxymethylheptadecyl]amide-, [*S*(*R*)]. To a solution of naphthalene (3.5 g, 27.3mmol) in THF (20 mL), lithium (0.1 g, 14.4 mmol) was added. The mixture, stirred at room temperature for 2 h, formed a dark green solution. This solution was dropped into a solution of **21** (33 mg, 0.065 mmol) in dry THF (2 mL) at 0 °C until the dark green color did not disappear. The mixture was stirred for 0.5 h at room temperature and then quenched with MeOH. The solvent was removed *in vacuo* and purification by flash silica gel chromatography provided the product (25 mg, 94 %) as colorless needles.

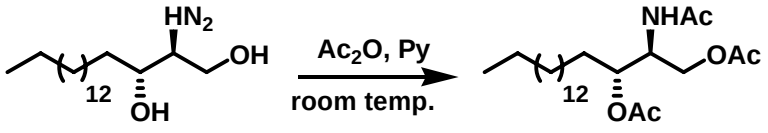
mp 41-43 °C; $[\alpha]_D^{27}$ = -17.0° (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.84-0.88 (m, 3H), 1.24-1.50 (m, 37H), 2.04 (br, 1H), 3.13-3.17 (m, 1H), 3.66 (m, 1H), 3.83-3.95 (m, 2H), 4.08-4.10 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.10, 25.66, 25.84, 29.34, 29.54, 29.56, 29.63, 29.64, 29.65, 29.67, 31.90, 34.33, 56.17, 61.91, 62.39, 73.92; FT-IR (film cm^{-1}): 3370 (br, s), 2924, 2854, 1468, 1048; ESI-MS (m/z): 406.2 $(M + H)^+$, 428.1 $(M + Na)^+$; HR-MS for $C_{22}H_{48}NO_3S$ $(M + H)^+$: calcd. 406.3349, found: 406.3348.



18

D-*erythro*-sphinganine (18). To a solution of the above obtained compound (18 mg, 0.044 mmol) in dry MeOH (2 mL), a solution of dry HCl in 1,4-dioxane (5.8 N, 30 μL) was added. The mixture was stirred at room temperature for 0.5 h and then 1 N NaOH aqueous solution was added to the mixture carefully to adjust the pH to 9. The solvent was then removed *in vacuo* and purification by flash silica gel chromatography provided product **18** (13 mg, 98 %) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$/MeOH): δ 0.83-0.88 (m, 3H), 1.24-1.45 (m, 28H), 3.00-3.04 (m, 1H), 3.29-3.31 (m, 1H), 3.59-3.63 (m, 1H), 3.66-3.69 (m, 1H), 3.74-3.79 (m, 1H); ^{13}C NMR (75MHz, $CDCl_3$/MeOH): δ 14.42, 23.40, 26.73, 30.12, 30.30, 30.44, 32.70, 33.95, 57.69, 60.06, 71.08; FT-IR (film cm^{-1}): 3359 (br, s), 2924, 2854; ESI-MS (m/z): 302.3 $(M + H)^+$; HR-MS for $C_{18}H_{40}NO_2$ $(M + H)^+$: calcd. 302.3053, found: 302.3057.



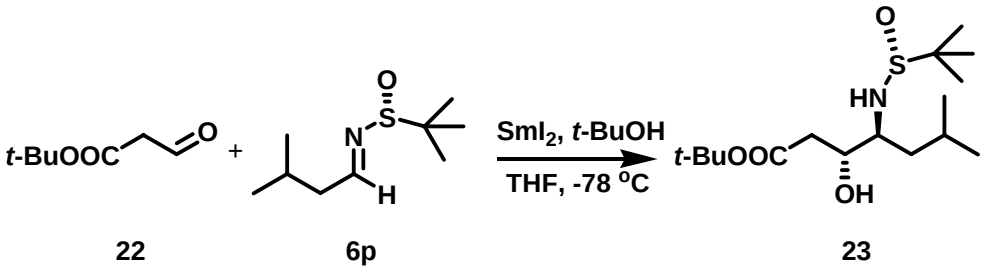
18

Acetic acid (*R*)-1-[(*S*)-2-acetoxy-1-acetylaminoethyl]hexadecyl ester. The

absolute configuration of **18** was further proved by the [α]$_D$ of its triacetate derivative.

[α]$_D^{27}$ = +17.3° (*c* 0.55, $CHCl_3$) [lit. [α]$_D^{20}$ = +17.4° (*c* 1.0, $CHCl_3$) *J. Org. Chem.* **2000**, *65*, 3538]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84-0.88 (m, 3H), 1.23-1.36 (m, 26H), 1.55-1.59 (m, 2H), 1.98 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 4.02-4.07 (dd, *J* = 3.6, 3.9 Hz, 1H), 4.20-4.26 (m, 1H), 4.33-4.39 (m, 1H), 4.86-4.92 (AB, J_{AB} = 6 Hz, 1H), 5.43 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.08, 20.78, 20.96, 22.64, 23.32, 25.32, 29.31, 29.40, 29.49, 29.60, 29.63, 31.44, 31.87, 50.45, 62.56, 73.91, 169.74, 170.90, 170.98; FT-IR (film cm^{-1}): 3302, 2919, 2850, 1734, 1648, 1544; ESI-MS (m/z): 428.2 $(M + H)^+$, 450.1 $(M + Na)^+$; HR-MS for $C_{24}H_{45}NO_5Na$ $(M + Na)^+$: calcd. 450.3190, found: 450.3191.

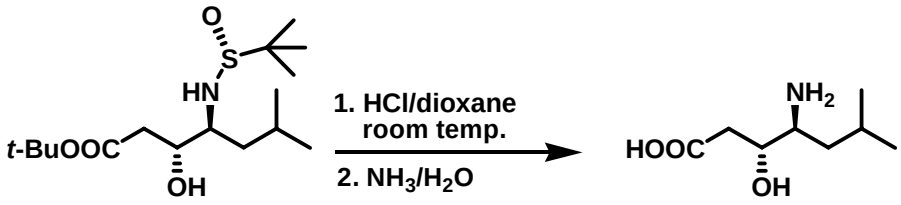
5. Synthesis of (3*R*,4*S*)-Statine.



22 **6p** **23**

(3*R*,4*S*)-3-Hydroxy-6-methyl-4-(2-methylpropane-2-sulfinylamino)heptanoic acid *tert*-butyl ester-, [*S*(*R*)] (23). Following the general procedure, 2.0 equiv of 3-oxo-propionic acid *tert*-butyl ester (**22)** was used in this reaction, and the reaction mixture was stirred for 6 h. After general workup, the crude product was purified by column chromatography on silica gel to give **23** (58 %).

$[\alpha]_D^{20}$ = -85° (*c* 0.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 1.15-1.35 (m, 10H), 1.43 (s, 9H), 1.53-1.58 (m, 1H), 1.73-1.76 (m, 1H), 2.29-2.48 (m, 2H), 3.28-3.36 (m, 1H), 3.37 (d, *J* = 1.2 Hz, 1H), 3.66 (d, *J* = 3.9 Hz, 1H), 3.95 (dd, *J* = 4.5, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.21, 22.66, 23.50, 23.84, 27.96, 38.10, 38.35, 55.87, 58.32, 71.39, 81.20, 171.77; FT-IR (KBr, cm^{-1}): 3290, 2962, 1722, 1366, 1157, 1028; ESI-MS (m/z): 336 $(M + H)^+$; HR-MS for $C_{16}H_{33}NO_4SNa$ $(M + Na)^+$: calcd. 358.2022, found: 358.2022.



23 **19**

(3*R*,4*S*)-Statine (19). To a solution of HCl in dioxane (5.8 N, 0.5 mL), the coupling product **23** (42 mg, 0.125 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was washed with ether and the separated aqueous layer was neutralized with ammonia. After concentration under reduced pressure, the resulting residue was purified by preparative TLC (silica gel) to give (3*R*,4*S*)-statine **19** (18 mg, 80 %).

$[\alpha]_D^{20}$ = -18.6° (*c* 0.08, H_2O) [lit. $[\alpha]_D^{20}$ = -19° (*c* 0.73, H_2O); For (3*S*,4*R*)-statine, $[\alpha]_D^{20}$= +18° (*c* 0.88, H_2O), *J. Med. Chem.* **1979**, *22*, 577]; ^1H NMR (300 MHz, D_2O): δ 0.77 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 1.30-1.38 (m, 2H), 1.51-1.55 (m, 1H), 2.32 (m, *J* = 4.8 Hz, 2H), 3.29-3.32 (m, 1H), 4.11-4.13 (m, 1H); FT-IR (KBr, cm^{-1}): 2961, 2871, 1721, 1183; ESI-MS (m/z): 176.2 $(M + H)^+$; HR-MS for $C_8H_{18}NO_3$

$(M + H)^+$: calcd. 176.1281, found: 176.1284.

Chapter 2

Development of Practical Synthetic Procedures of Anti-infective Drugs

Abstract: A practical large-scale process is described for the synthesis of Doripenem hydrate, a novel parenteral 1β-methylcarbapenem antibiotic, from *p*-nitrobenzyl-protected enol phosphate and the side chain, *N*-(*p*-nitrobenzyl-oxycarbonyl)-protected aminomethylpyrrolidine. Also presented are the synthesis of its side chain via an original procedure and a practical large-scale process using an improved procedure.

In the case of the synthesis of Doripenem hydrate, we found effective extraction conditions to remove *p*-toluidine and most other organic impurities by using a THF/water system containing an inorganic salt. The new process requires no chromatographic purification and several kilograms of Doripenem hydrate could be successfully prepared by this process.

With respect to the side chain, *trans*-4-hydroxy-*L*-proline was converted via an efficient process to (2*S*,4*S*)-4-acetylthio-2-(*N*-sulfamoyl-*tert*-butoxycarbonyl- aminomethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine in 55-56% overall yield *via* a six-step sequence, which included two alternative synthetic routes to the side chain. This process does not require chromatographic purification, cryogenic temperature or haloalkane solvents and has short operating times. Several kilograms of the side chain were

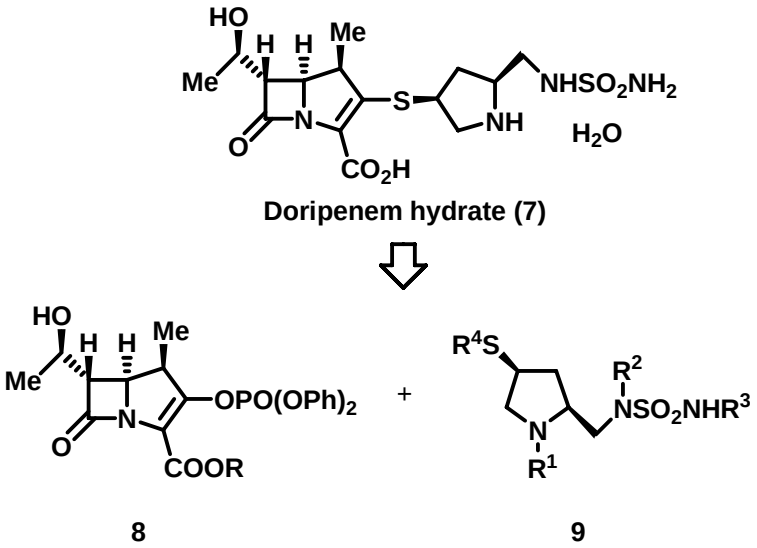
successfully prepared by this process.

Practical one-step synthesis of 5-(4-fluorobenzyl)-2-furyl methyl ketone, which is a key intermediate in the synthesis of HIV integrase inhibitor S-1360, was accomplished by Friedel-Crafts benzylation of 2-furyl methyl ketone with 4-fluorobenzyl chloride in the presence of $ZnCl_2$. Two reaction conditions and the subsequent reaction treatment procedures are described. The reaction under anhydrous condition in CH_2Cl_2 provides a convenient procedure for isolating the product. Under aqueous conditions, this is a large-scale ecologically friendly and safe manufacturing process.

2-1. Practical Large-scale Synthesis of Doripenem Hydrate: a Novel 1*β*-Methylcarbapenem Antibiotic

Doripenem hydrate **7**, which was discovered by Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan and launched in 2005, is a novel parenteral 1*β*-methylcarbapenem antibiotic.[1] Compound **7** exhibits potent, broad and well-balanced antibacterial activities against a wide range of both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*.

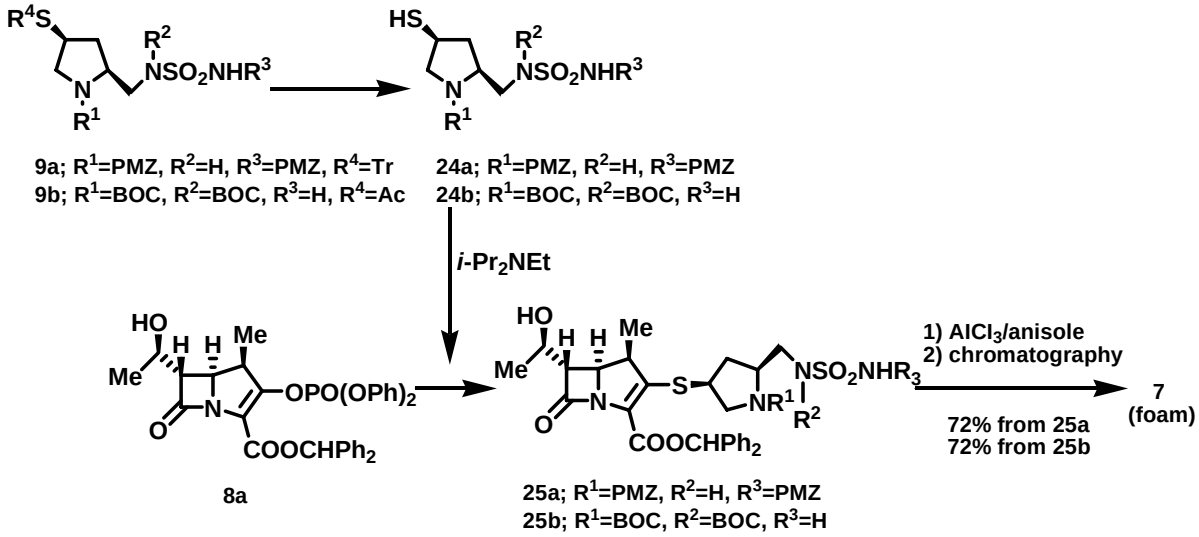
Scheme 1



According to conventional retrosynthetic analysis, Doripenem hydrate can be assembled from enol phosphate **8** and the 2-aminomethylpyrrolidin-4-ylthio-containing side chain **9** (Scheme 1). In the medicinal chemical route (Scheme 2),[1,2] compound **7**

was prepared by deprotection of compound **25a** or **25b** with $AlCl_3$-anisole.[3] Compound **25a** or **25b** was synthesized from the diphenylmethyl-protected enol phosphate **8a** and

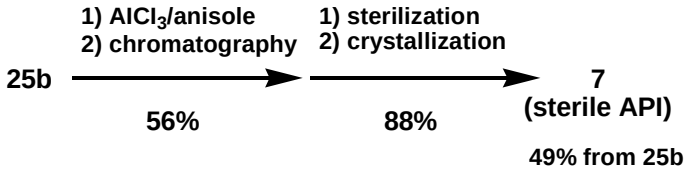
Scheme 2 Original Process for Medicinal Chemistry Synthesis (Bench Scale)



N-*p*-methoxybenzyl(= PMZ)-protected aminomethylpyrrolidine **9a** or *N*-BOC-protected aminomethylpyrrolidine **9b**, respectively. Although this route facilitated SAR (structure activity relationship) studies and led to rapid optimization of lead derivatives, it had several drawbacks for multikilogram-scale preparation of compound **7**. Compound **7** was isolated as a foam. The original route required chromatographic purification on Diaion HP-20. In the first-generation process (Scheme 3), we succeeded in obtaining compound **7** as a crystalline monohydrate. However, the process still required chromatographic purification and the yield (49%) of compound **7** from compound **25b** through the deprotection, purification and crystallization steps on a pilot scale was lower than that (63%) on a bench scale. Investigation of the reason for this showed that

the step yield of the deprotection reaction on the pilot scale was the same with that on the bench scale. The step yield of the crystallization including sterilization on the pilot

Scheme 3 First-generation Process (Pilot Scale)



scale was also the same as that on the bench scale (88%). However, the step yields of purification by chromatography on the bench and on the pilot scales were 72% and 56%, respectively. During chromatography and concentration of the eluents, decomposition of the target comound **7** occurred, resulting in a 16% yield decrease due to longer operating time on the pilot scale. To increase the yield and avoid chromatographic purification, we developed an improved process which dispensed with the purification step. This led to an efficient and practical synthesis[4a] of compound **7** from *p*-nitrobenzyl(= PNB)-protected enolphophate **8b**[5,6] and *N*-(*p*-nitrobenzyloxycarbonyl(= PNZ))-protected aminomethylpyrrolidine **9c**.[4a,4b] This process is amenable to large-scale production. Enol phosphate **8b** is also used for the synthesis of ertapenem as a starting material.[7] An efficient and practical large-scale synthesis of aminomethylpyrrolidine **9c** is described in the next section.[4b] Both enolphophate **8b** and aminomethylpyrrolidine **9c** are now commercially available.

Both deprotection processes, i.e., cleavage of *N*-BOC- or *N*-PMB-group using Lewis acid $AlCl_3$-anisole and catalytic hydrogenolysis of *N*-PNZ-group using Pd/C, to

give compound **7** required chromatographic purification on Diaion HP-20 to remove impurities in the original and the first-generation processes (Scheme 2,3)[1,2] and the improved process (Scheme 4). An $AlCl_3$–anisole system was used for the deprotection. The reaction mixture contained aluminum ion and numerous organic impurities (anisole, methoxybenzene derivatives and unknown water-soluble organic compounds). Anisole and methoxybenzene derivatives are easily removed by extraction. However, aluminum ion and several unknown organic impurities could not be removed completely by extraction using acetylacetone. They remained in the API (Active Pharmaceutical Ingredients) if chromatographic purification was not done. On the other hand, after replacing the *N*-BOC- or *N*-PMZ-group with the *N*-PNZ-group, we tried deprotection by catalytic hydrogenolysis with Pd/C. However, chromatographic purification was still necessary because the reaction mixture contained numerous kinds of impurities (*p*-toluidine, and several unknown water-soluble organic compounds) which could not be removed completely by extraction because of their high solubility in water.

In the catalytic hydrogenolysis process, we found an extremely effective extraction process to remove *p*-toluidine and most of the other organic impurities using a THF/water system coupled with an inorganic salt to achieve a salting-out effect. The number of phase cuts, % recovery and purity of compound **7** were examined by using a model system for the extraction in the presence of various inorganic salts. The aqueous layer was washed with THF (38 mL) until its amount was less than 5.5 g. The results are summarized in Table 1. The most important parameter is % purity. The theoretical water content is 4.1% by weight. With $MgCl_2$ and LiCl (entries 1 and 2), the amount of the residual inorganic salt was less than 0.1% because of their high solubility in aqueous MeOH. However, the other salts (entries 3 to 7) remained in the product (8–30% by

weight) because of their poor solubility in aqueous MeOH. LiCl required more phase cuts than $MgCl_2$. Therefore, we chose $MgCl_2$ as an additive. After the hydrogenolysis, $MgCl_2$ was added to the reaction mixture. As expected, the aqueous layer contained less

Table 1 Screening of Inorganic Salts as Additives in Model System for Extraction after Deprotection of Compound **25c**[a]

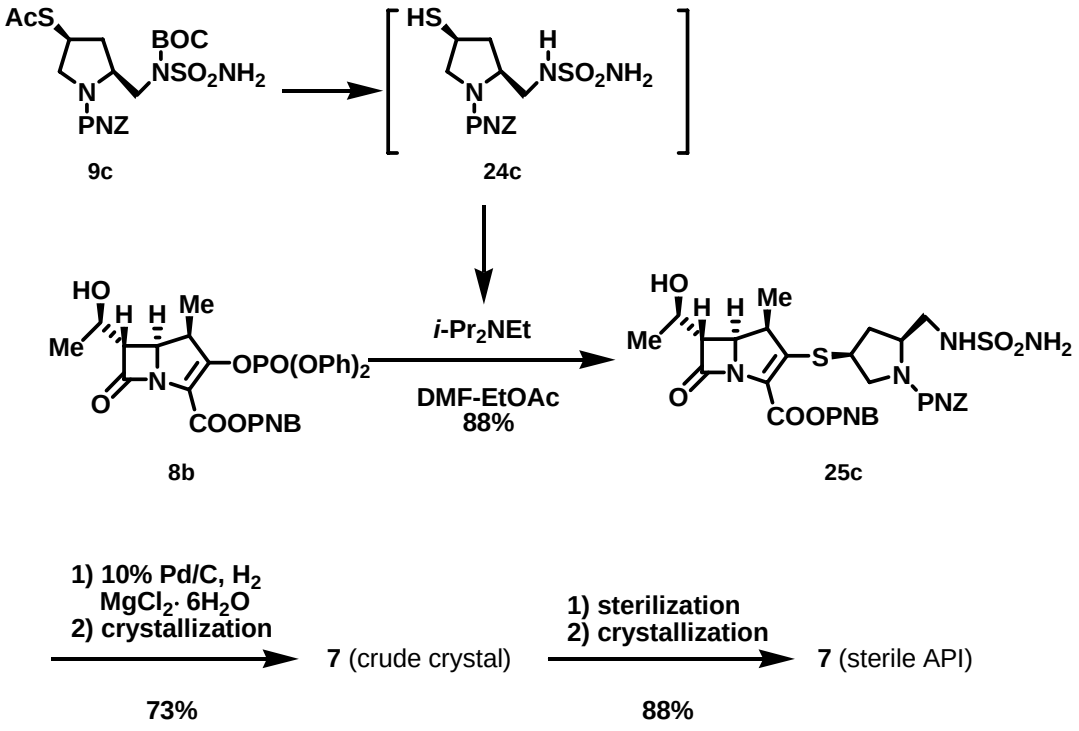
entry	salt	number of phase cuts, time	wt of aq layer, g	% recovery of **7**	% purity[c] of **7**
1	$MgCl_2$	4	3.5	82	97
2	LiCl	6	5.4	84	96
3	NaBr	4	3.3	84	88
4[b]	$BaCl_2$	3	3.1	38	88
5[b]	NaCl	5	3.9	90	83
6[b]	KCl	4	3.0	83	77
7	KBr	3	4.0	86	66
8	$CaCl_2$	5	4.2	no crystallization occurred	

[a]Extraction conditions: **7** (1.0 g) in THF (15.6 mL)-water (10.4 mL); after addition of a salt (1.2 g), the aqueous layer was separated. Crystallization was carried out as described in the Experimental Section. [b]Before crystallization, inorganic salt which precipitated from the aqueous layer was removed by filtration. [c]wt % measured by HPLC analysis.

than 0.1% *p*-toluidine by weight after extraction. Interestingly, $MgCl_2$ increased the solubility of compound **7** in the aqueous layer.[8] Thus, $MgCl_2$ was also used as an additive in the biphasic reaction mixture to prevent precipitation during the hydrogenolysis and extraction. In a pilot procedure, the number of phase cuts was reduced by addition of THF after hydrogenolysis to shorten operating periods of times. In order to increase the yield and avoid chromatographic purification, we developed the synthesis procedure for compound **7** shown in Scheme 4. Compound **25c** was

synthesized by the coupling reaction between PNB-protected enol phosphate **8b** and *in situ* intermediate mercaptopyrrolidine **24c**, which was prepared from *N*-PNZ-protected aminomethylpyrrolidine **9c**, in 88% yield. Catalytic hydrogenolysis of compound **25c** with Pd/C in the presence of $MgCl_2$ in aqueous THF followed by the improved work-up

Scheme 4 Improved Process



(removal of Pd/C by filtration, extraction, crystallization) afforded compound **7** as a non-sterile crystalline powder in 73% yield. The non-sterile crystals were sterilized and recrystallized to give compound **7** as a sterile API in 88% yield. The overall yield of compound **7** from compound **25c** was 64%, which was 15% higher than that from the first-generation process. The amounts of residual Pd and Mg in the API were lower than

20 ppm and 0.1%, respectively. The quality of API from the improved procedure without chromatographic purification was satisfactory. This new process is more practical and effective than the previous one because it requires no chromatographic purification and affords the target compound **7** in higher yield. This process is amenable to large-scale production; it was used to prepare several kilograms of compound **7** for clinical trials and commercial supply.

In summary, a practical multikilogram-scale synthesis process was developed for Doripenem hydrate (**7**) by deprotection of compound **25c**, which was prepared from enol phosphate **8b** and *N*-PNZ-protected aminomethylpyrrolidine **9c**. Effective extraction conditions were identified to remove *p*-toluidine and most other organic impurities using THF/water and $MgCl_2$. This process requires no chromatographic purification and affords compound **7** in good yield. This process is practical and efficient and has been scaled up to an over the 25 kg level at a commercial plant to manufacture Doripenem hydrate **7** for commercial supply.

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4. (a) A portion of this study was patented. Nishino, Y.; Yuasa, T.; Komurasaki, T.; Kakinuma, M.; Masui, T.; Kobayashi, M. Patent Application No. JP 2001-140782. (b) Nishino, Y.; Komurasaki, T.; Yuasa, T.; Kakinuma, M.; Izumi, K.; Kobayashi, M.; Fujiie, S.; Gotoh, T.; Masui, Y.; Hajima, M.; Takahira, M.; Okuyama, A.; Kataoka, T. *Org. Process Res. Dev.* **2003**, *7*, 649.
5. Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
6. (a) There are many efficient approaches to compound **8b**: Berks, A. H. *Tetrahedron* **1996**, *52*, 331. (b) This is commercially available from Takasago, Kaneka, and Nisso companies.
7. Brands, K. M. J.; Jobson, R. B.; Conrad, K. M.; Williams, J. M.; Pipik, B.; Cameron, M.; Davies, A. J.; Houghton, P. G.; Ashwood, M. S.; Cottrell, I. F.; Reamer, R. A.; Kennedy, D. J.; Dolling, U.-H.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 4771.
8. The solubility of compound **7** with 0.23 g of $MgCl_2$ in the aqueous layer was larger than that with 0.11 g of $MgCl_2$. Thus, $MgCl_2$ increased solubility of compound **7** in the aqueous layer.

Experimental Section

(2*S*,4*S*)-1-*tert*-Butoxycarbonyl-2-(*N*-*tert*-butoxycarbonyl-*N*-sulfamoylaminomethyl)-4-mercaptopyrrolidine (24b). To a solution of (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-acetylthio-2-(*N*-*tert*-butoxycarbonyl-*N*-sulfamoylaminomethyl)pyrrolidine (**9b**) (1.62 g, 32.8 mmol) in toluene (95 mL), 4.92 M sodium methoxide in MeOH (20 mL, 98.4 mmol) was added at -35 °C, and the mixture was stirred for 30 min. After adding water, the aqueous layer was acidified with conc. HCl (10 mL) under ice cooling and extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel chromatography, and the colorless oil obtained was cryatallized from a toluene-hexane mixture to give **24b** (9.32 g, 69%).

mp 92-93 °C; ^{1}H NMR ($CDCl_3$): δ 1.2-1.5 (m, 1H), 1.42 (s, 9H), 1.54 (s, 9H), 1.82 (d, J = 6.2 Hz, 1H), 2.5-2.7 (m, 1H), 4.09, 3.05 (ABX, J_1 = 12.0, 7.4, 3.2 Hz, 2H), 4.06, 3.62 (ABX, J_1 = 15.0, 10.8, 3.2 Hz, 2H), 4.2-4.6 (m,1H), 6.08 (s, 2H); IR ($CHCl_3$, cm^{-1}): 3380, 3220, 1718, 1680.

Diphenylmethyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-3-[[(3*S*,5*S*)-1-(*tert*-butoxycarbonyl)-5-[*N*-sulfamoyl-*N*-(*tert*-butoxycarbonyl)aminomethyl]pyrrolidin-3-yl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (25b). To a solution of (1*R*,5*S*,6*S*)-2-diphenoxyphosphonyloxy-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid diphenylmethyl ester (**8a**) (6.88 g, 11 mmol) in MeCN (70 mL), **24b** (5.43 g, 13.2 mmol) and diisopropylethylamine (13.2 mmol) were added under ice cooling. After the mixture was stirred for 4.5 h, EtOAc and ice water were added. The organic layer was washed with water and saturated brine, dried over $MgSO_4$

and concentrated under vaccum. The residue was purified by silica gel chromatography to give **25b** (8.65 g, 87%).

mp 163-164 °C; ^{1}H NMR ($CDCl_3$): δ 1.27 (d, *J* = 7.21 Hz, 3H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.39 (s, 9H), 1.42 (s, 9H), 1.78-1.87 (m, 1H), 2.45-2.65 (m, 1H), 3.1-3.35 (m, 2H), 3.28 (dd, *J* = 7.2, 2.6 Hz, 1H), 3.5-3.77 (m, 2H), 3.9-4.15 (m, 2H), 4.26 (dd, *J* = 7.0, 2.6 Hz, 1H), 4.2-4.37 (m, 1H), 4.45-4.66 (m, 1H), 6.07 (br, 2H), 6.95 (s, 1H), 7.2-7.6 (m, 10H); IR ($CHCl_3$, cm^{-1}): 3385, 3230, 1778, 1715, 1685.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[[(3*S*,5*S*)-5-(sulfamoylaminom-ethyl)pyrrolidin-3-yl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrate (Doripenem hydrate: 7) by deprotection of compound 25b. To a solution of $AlCl_3$ (11.2 kg) in anisole (110 L), a mixture of compound **25b** (11.0 kg, 14.0 mol) in CH_2Cl_2 (160 L) was added dropwise at 2 °C. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was cooled to -10 °C, and then was added dropwise to a solution of $NaHCO_3$ (4.4 kg) in water (154 L) at 2 °C. After the organic layer was separated, acetylacetone (33.6 kg) was added to the aqueous layer. Aqueous 15% Na_2CO_3 (ca.100 kg) was added dropwise to the aqueous extract at 3 °C to adjust the pH to 5.0. After stirring at 3 °C for 30 min, the mixture was washed with CH_2Cl_2 (122 L). After addition of acetylacetone (27.5 kg), the mixture was washed with CH_2Cl_2 (61 L x 2). Aqueous 15% Na_2CO_3 was added dropwise to the aqueous extract at 3 °C to adjust the pH to 5.5. After degassing *in vacuo* at 5 °C for 50 min, the solution (ca. 300 kg) was chromatographed on a Diaion HP-20 column. Eluent (ca. 1400 kg) of 7% EtOH was collected and concentrated by filtration through an RO (reverse osmosis) membrane to give the filtrate (190 kg). The filtrate was concentrated to 50 kg and was

decolorized with activated carbon (0.18 kg). The filtrate was sent through an ultrafiltration membrane to remove endotoxin. MeOH (25 L) and seed crystals (16 g) were added to the filtrate (50 kg) at 7 °C. After the mixture was stirred at 15 °C for 20 min, MeOH (125 L) was added dropwise at 10 °C over 1 h. The precipitates were collected by filtration, washed with 95% MeOH and dried to give **7**[1,2] (2.98 kg, 49%).

^{1}H NMR: (500 MHz, D_2O): δ 1.23 (d, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.77 (ddd, *J* = 6.6, 9.2, 14.9 Hz, 1H), 2.75 (dt, *J* = 14.3, 8.0 Hz, 1H), 3.38 (dq, *J* = 7.2, 9.3 Hz, 1H), 3.44 (dd, *J* = 4.2, 12.4 Hz, 1H), 3.44 (dd, *J* = 8.3, 15.0 Hz, 1H), 3.48 (dd, *J* = 2.5, 6.1 Hz, 1H), 3.55 (dd, *J* = 4.8, 15.0 Hz, 1H), 3.72 (dd, *J* = 7.0, 12.4 Hz, 1H), 3.95 (qd, *J* = 4.8, 8.5 Hz, 1H), 4.06 (qd, *J* = 7.4, 4.2 Hz, 1H), 4.24 (dd, *J* = 2.5, 9.3 Hz, 1H), 4.26 (m, 1H).

Screening of Inorganic Salts as Additives in a Model System for Extraction after Deprotection of Compound 25c. An inorganic salt (1.2 g) was dissolved in a solution of compound **7** (1.0 g) in THF (15.6 mL)-water (10.4 mL). The aqueous layer was separated and washed with THF (38 mL) until its weight was less than 5.5 g. Because a smaller amount of the aqueous extract gives a smaller crystallizing volume and leads to higher through-put. If an inorganic salt precipitated from the solution, it was removed by filtration. MeOH (20 mL) was added to the aqueous extract. The precipitates were collected by filtration, and dried to recover compound **7**. The results are summarized in Table 1.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-3-[[(3*S*,5*S*)-1-(4-nitrobenzyloxycarbonyl)-5-(sulfamoylaminomethyl)pyrrolidin-3-yl]thio]-7-oxo-1-aza

bicyclo[3.2.0]hept-2-ene-2-carboxylate (25c). A mixture of **9c**[4b] (33.6 kg, 63.1 mol) and 98% H_2SO_4 (15.8 kg) in MeOH (140 kg) was stirred at 65 °C for 2.5 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was cooled to below 25 °C and was concentrated to 110 L under reduced pressure. The resultant concentrate was poured into a mixture of EtOAc (225 kg) and water (250 kg). The organic layer was separated and was washed with an aqueous 5% NaCl (175 kg x 3). Each aqueous layer was back-extracted with EtOAc (90 kg). The combined extracts were concentrated to ca. 70 kg, then EtOAc (180 kg) was added to the residue. The mixture was concentrated again to give the concentrate (ca. 70 kg) containing **24c**. Enol phosphate **8b** (30.0 kg, 50.5 mol) and DMF (143 kg) were added to the concentrate. After cooling the mixture to 0 °C, diisopropylethylamine (9.1 kg) was added. The reaction mixture was stirred at 5 °C for 18 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was poured into a mixture of EtOAc (200 kg) and water (225 L). The organic layer was separated and washed with aqueous 0.7% HCl (153 kg), 5% $NaHCO_3$ (63 kg) and 5% NaCl (90 kg x 2). Each aqueous layer was back-extracted with EtOAc (90 kg). The combined extracts were concentrated to ca. 104 L, and then EtOAc (180 kg x 2) was added to the residue. The mixture was concentrated again under reduced pressure to remove water. Toluene (365 kg) was added dropwise to the residue (155 L) over 0.5 h. The precipitates were collected by filtration and dried to give **25c** (32.5 kg, 88%).

mp 160-180 °C (decomp); In the ^1H and ^{13}C NMR spectra, a 3:2 mixture of C–N rotamers was established. ^1H NMR (500 MHz, CD_3CN): δ 1.21 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 7.5 Hz, 3H), 1.81 (m, 1H, major isomer), 1.91 (m, 1H, minor isomer), 2.54 (m, 1H), 3.17 (m, 1H, minor isomer), 3.26 (m, 1H, minor isomer), 3.26 (m, 1H, major

isomer), 3.30 (m, 1H), 3.31 (m, 1H, major isomer), 3.49 (m, 1H), 3.76 (m, 1H, minor isomer), 3.80 (m, 1H, major isomer), 4.05 (m, 2H), 4.11 (m, 1H), 4.11 (m, 1H), 4.25 (m, 1H), 5.22 (s, 2H), 5.26 (d, J = 14.3 Hz, 1H), 5.43 (t, J = 6.5 Hz, 1H, minor isomer), 5.45 (d, J = 14.3 Hz, 1H), 5.65 (t, J = 6.5 Hz, 1H, major isomer), 7.61 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 8.22 (d, J = 8.5 Hz, 4H); ^{13}C NMR (125 MHz, CD_3CN) δ 17.7, 21.9 (minor), 22.0 (major), 35.1 (major), 35.5 (minor), 40.4 (minor), 40.9 (major), 44.4, 46.7 (minor), 46.9 (major), 55.9 (major), 56.3 (minor), 56.5, 57.5 (minor), 58.3 (major), 60.7, 65.7, 66.1, 66.4 (major), 66.5 (minor), 124.6, 124.7, 125.1 (minor), 128.9 (major), 129.1 (minor), 129.2, 129.3 (minor), 144.7, 145.6, 148.5, 148.6, 151.9 (major), 152.1 (minor), 155.0, 155.8, 161.5, 175.1; IR (KBr cm^{-1}) 1769, 1698, 1521, 1345; FAB-MS (m/z): 735 $(M + H)^+$; Anal. calcd. for $C_{30}H_{34}N_6O_{12}S_2$: C, 49.04; H, 4.66; N, 11.44; S, 8.73. Found: C, 48.77; H, 4.79; N, 11.19; S, 8.63.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[[(3*S*,5*S*)-5-(sulfamoylaminomethyl)pyrrolidin-3-yl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid hydrate (Doripenem hydrate: 7) by deprotection of compound 25c. To a solution of compound **25c** (8.8 kg, 12.0 mol) in THF (60 L), deionized water (40 L), 10 wt% Pd/C (5.0 kg) and $MgCl_2 \cdot 6H_2O$ (1.4 kg) were added. The suspension was stirred at temperatures ranging from 26 to 38 °C for 2 h under a hydrogen atmosphere (0.5 MPa). After completion of the reaction had been confirmed by HPLC analysis, the used Pd/C was removed by filtration and washed with a mixture of THF (18 L) and deionized water (12 L). $MgCl_2 \cdot 6H_2O$ (0.7 kg) was dissolved in the combined filtrates. After addition of THF (300 L) to the mixture, the aqueous layer was separated at 26 °C. After cooling of the extract to 0 °C, MeOH (40 L) and seed crystals (10 g) were added to the

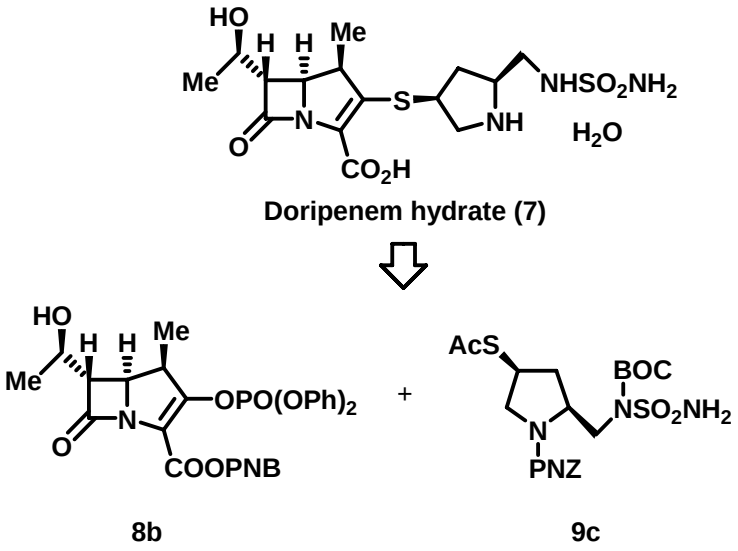
extract to obtain a suspension. After $MgCl_2 \cdot 6H_2O$ (0.7 kg x 2) was added to the organic layer, the resulting aqueous layer was separated and added to the previous aqueous suspension of **7**. MeOH (75 L) was added dropwise to the suspension. The mixture was stirred at -10 °C for 1 h. The precipitates were collected by filtration, washed with MeOH and dried to give **7**[1,2] (3.84 kg, 73%) as crude nonsterile crystals.

Purification, sterilization and crystallization to give 7 as a sterile API. Crude **7** (3.30 kg, 7.53 mol) was dissolved in water (66 L) at 55 °C. The solution was filtered sequentially through a funnel precoated with activated carbon (0.10 kg), a membrane filter (0.45 μm), an ultra filter for de-pyrogen and a membrane filter for the sterilization. The filtrate was cooled to room temperature. After stirring at room temperature for 0.5 h, the mixture was stirred at 2 °C for 2 h. 2-Propanol (26.1 kg), sterilized with filtration prior to use, was added dropwise over 80 min. After stirring at -5 °C for 4 h, the mixture was stirred at -10 °C overnight. The precipitates were collected by filtration, washed with sterilized aqueous 80% 2-propanol and dried to give **7**[1,2] (2.89 kg, 88%) as a sterile API. *p*-Toluidine and the other organic impurities were determined by HPLC; each was less than 0.1% by area. Residual Pd: less than 20 ppm. Residual Mg: less than 0.1%.

2-2. Practical Large-scale Synthesis of the 2-Aminomethylpyrrolidin-4-ylthio-containing Side Chain of Doripenem Hydrate

As described in the previous section, Doripenem can be assembled from *p*-nitrobenzyl-protected 1*β*-methylcarbapenem enol phosphate **8b** and the 2-aminomethylpyrrolidin-4-ylthio-containing side chain **9c** (Scheme 5).

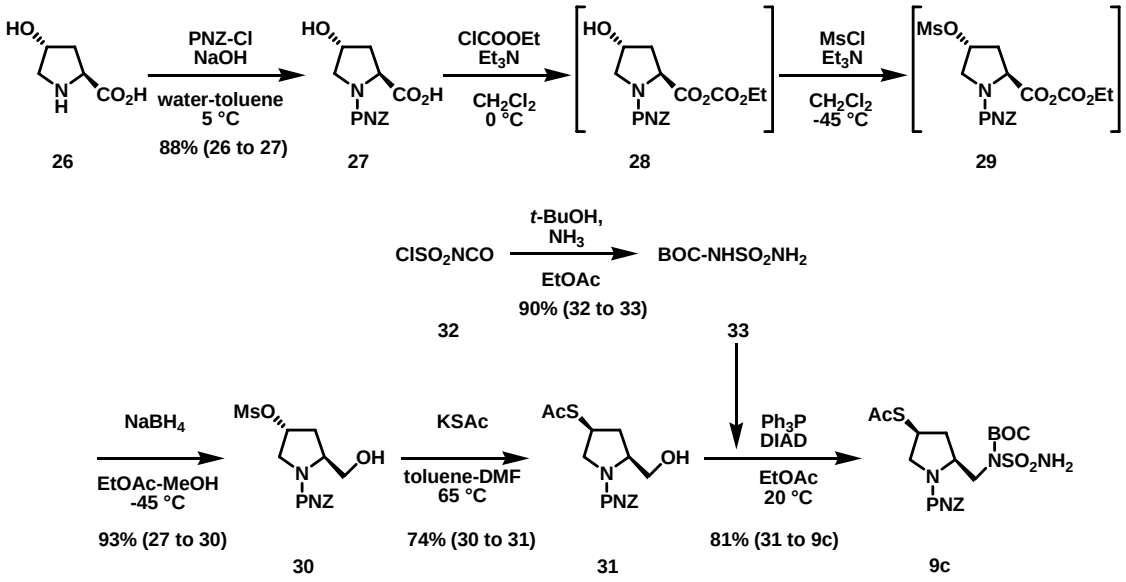
Scheme 5



With our first-generation process (Scheme 6), which was a modification of our previously reported procedure,[9] *N*-PNZ-protected aminomethylpyrrolidine **9c** was prepared by a sequence of six reaction steps from *trans*-4-hydroxy-*L*-proline (**26**) in 49% overall yield. The average yield per reaction was 89%. However, the first generation process for the synthesis of aminomethylpyrrolidine **9c** included several

undesirable conditions, for instance, cryogenic reaction temperature, use of haloalkane solvent and long operating periods of time. In order to reduce the cost or the

Scheme 6 First-generation Process



processing periods and to make the process more enviromentally suitable, we have developed an improved process which does not require cryogenic temperatures or haloalkane solvents and has shorter processing periods than the first-generation process. We describe an efficient and practical synthesis of aminomethylpyrrolidine **9c** that is amenable to large-scale production.[10]

The First-generation Process

N-PNZ-protected aminomethylpyrrolidine **9c** was prepared via a sequence of six reactions from hydroxyproline **26** as shown in Scheme 6. This is the first successful process of the synthesis of aminomethylpyrrolidine **9c**. This first-generation process

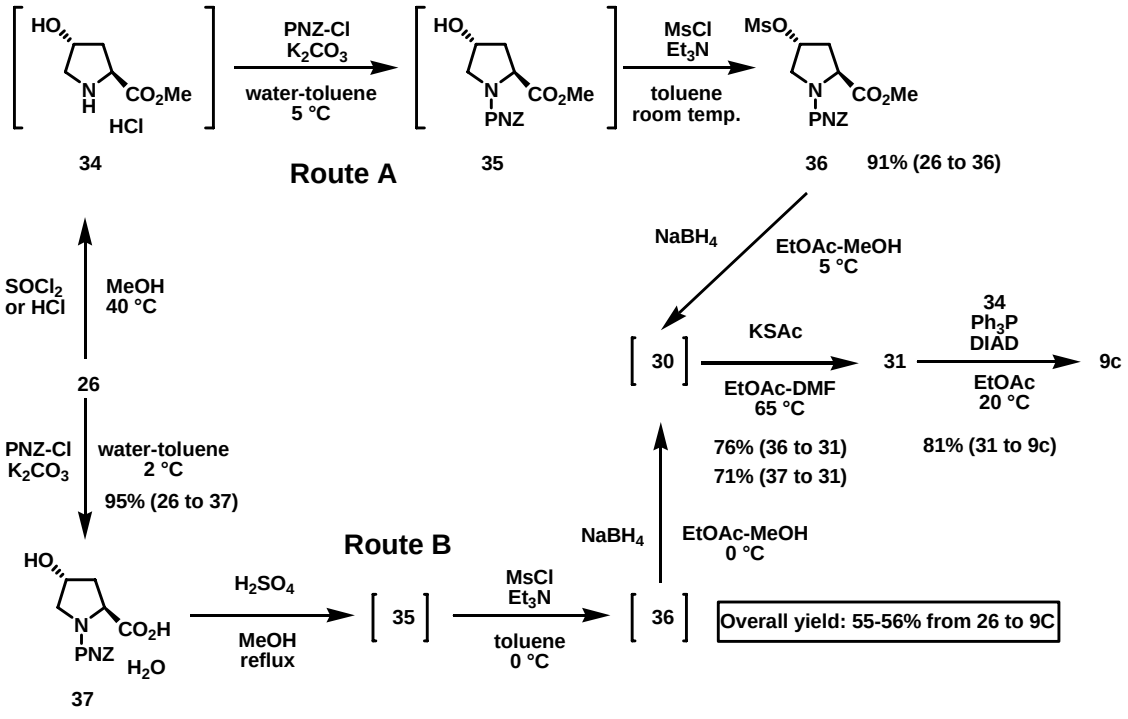
was a modification of our previously reported procedure,[9] which we described as a medicinal chemical process for the synthesis of another *N*-BOC-protected aminomethylpyrrolidine derivative. Hydroxyproline **26** was treated with *p*-nitrobenzyl chloroformate (PNZ-Cl) in toluene–water to give *N*-protected 4-hydroxyproline **27**[11] in 88% yield. Hydroxyproline **27** was converted into hydroxymethylpyrrolidine **30** in a one-pot procedure in 93% overall yield via a sequence of three reactions, namely the formation of mixed anhydride **28**, generated from hydroxyproline **27** with ethyl chloroformate and triethylamine (Et_3N), the *O*-mesylation of mixed anhydride **28** with methanesulfonyl chloride (MsCl) and Et_3N, and the reduction of the mixed anhydride **29** with sodium borohydride ($NaBH_4$). Hydroxymethylpyrrolidine **30** was treated with potassium thioacetate (KSAc) in DMF–toluene to afford acetylthiopyrrolidine **31** in 74% yield with the inversion of the C-4 configuration. The conversion of the hydroxyl group of acetylthiopyrrolidine **31** into the *N*-BOC-sulfamoyl group was successfully carried out by the Mitsunobu reaction to give the target compound **9c** in 81% yield. The overall yield of aminomethylpyrrolidine **9c** from hydroxyproline **26** was 49%. The average yield per reaction was 89%. This first-generation process required no chromatographic purification. We manufactured over 50 kg of aminomethylpyrrolidine **9c** by this first-generation process on a pilot scale. However, this process for the synthesis of aminomethylpyrrolidine **9c** included some undesirable conditions, for instance, cryogenic reaction temperature (two reactions being carried out at -45 °C), use of CH_2Cl_2 as a solvent (for the mixed anhydride formation) and long operating periods of time (numerous separations of biphasic layers in extractions and four isolation steps of the crystalline intermediates **27**, **30**, **31** and the product **9c**). A cryogenic reaction temperature restricts equipment and significantly increases the cost of production. As

for CH_2Cl_2, it is difficult to recover completely, mainly due to its low boiling point, and can have an adverse effect on the environment. The longer operating periods of time lead to lower productivity and higher manufacturing cost. In order to overcome these problems, an improved process was developed which does not require cryogenic temperature or haloalkane solvent and has shorter operating periods of time.

The Improved Process

A more efficient process for the synthesis of aminomethylpyrrolidine **9c** is shown in Scheme 7. There are two alternative routes to afford **35**. In Route A, hydroxyproline

Scheme 7 Improved Process



26 was converted into mesylate **36**[12] in 91% yield by a sequence of three reactions, namely esterification with MeOH in the presence of HCl or $SOCl_2$ to give methyl ester

hydrochloride **34**, *N*-protection with PNZ-Cl to give methyl ester **35**, and *O*-mesylation with MsCl and Et_3N without isolation of the two intermediates **34** and **35**. Acetylthiopyrrolidine **31** was prepared from mesylate **36** in 76% yield without isolation of hydroxymethylpyrrolidine **30**. The target compound **9c** was prepared from acetylthiopyrrolidine **31** in 81% yield. The overall yield of **9c** from **26** by Route A was 56%. In Route B, hydroxyproline **26** was treated with PNZ-Cl in toluene-water to give *N*-PNZ-protected carboxylic acid hydrate **37** in 95% yield. The carboxylic acid hydrate **37** was converted into acetylthiopyrrolidine **31** in 71% overall yield by a sequence of four reactions, namely esterification of **37** with MeOH in the presence of H_2SO_4, *O*-mesylation with MsCl and Et_3N, reduction of the methyl ester with $NaBH_4$, and substitution of the C-4 position with KSAc without isolation of the three intermediates **35**, **36** and **30**. The target compound **9c** was prepared from acetylthiopyrrolidine **31** in 81% yield. The overall yield of **9c** from **26** by Route B was 55%, which was similar to that by Route A (56%). The improved process offers better yields than the first-generation process by 6-7% and a choice of two routes to **35**. The average yield per reaction in each route was 91%. Route A is preferable because although PNZ-Cl is an expensive reagent, its use in a later step can actually help reduce manufacturing cost. However, if PNZ-Cl can be inexpensively produced, Route B can be chosen.

The three problems of the first-generation process were solved as follows. The first-generation process required a low temperature of -45 °C because of the instability of intermediates **28** and **29**. In the improved process, they were replaced by the stable intermediates **35** and **36**. The problematic use of CH_2Cl_2 was avoided by employing toluene as the reaction solvent. The third problem of processing periods was solved with a 3-fold higher process throughput (product produced per unit time)[12]. The total

production periods are the sum of the operation time for the reactions, extractions, concentrations, crystallizations, drying, equipment cleaning, quality control and other procedures. The operating periods of time was shortened by reducing the number of phase cuts in the extractions from 18 times to 5 times, by reducing the number of isolated crystalline products from four (**27**, **30**, **31** and **9c**) to three (**36** or **37**, **31** and **9c**), and by reducing the amounts of solvent concentrated during the work-up after the reactions or extractions. For example, the weight of solvent for the Mitsunobu reaction was reduced from 18-fold to 7-fold of the weight of **9c**. According to our simulation, the total production periods for 1 ton of **9c** from **26** by the improved process on a commercial scale would be almost one-third of that required by the first-generation process.

Since the improved process does not require chromatographic purification, cryogenic temperature or haloalkane solvent and has shorter operating periods of time, it is a practical, efficient and environmentally friendly process. This new process has been scaled up to over the 400 kg level in a commercial plant to produce compound **9c**.

In summary, this is the first example of the synthesis of (2*S*,4*S*)-4-acetylthio-2-(*N*-sulfamoyl-*tert*-butoxycarbonylaminomethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (**9c**), which is the side chain of the new parenteral carbapenem antibiotic Doripenem hydrate (**7**). A process was also developed offering two alternative routes to intermediate **35,** and its use for commercial-scale synthesis of **9c** was demonstrated. The improved process can provide **9c** from **26** in overall yield of 55-56% (by six reactions with an average of yield of 91%), and requires no chromatographic purification, no cryogenic temperature, no haloalkane solvent, and relatively short operating periods of time. This makes it practical, efficient, and industrially useful.

References and Notes

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Experimental Section

The First-generation Process

(2*S*,4*R*)-4-Hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-2-carboxylic acid (27). To a solution of *trans*-4-hydroxy-*L*-proline (**26**) (36.0 kg, 275 mol) and NaOH (24.2 kg) in water (240 L), a 50% solution of PNZ-Cl (130.0 kg, 1.1 equiv) in toluene was added dropwise at 5 °C. The reaction mixture was stirred at 5 °C for 1 h. After completion of the reaction had been confirmed by HPLC analysis, toluene (100 L) was added to the reaction mixture and the layers were separated. The aqueous layer was washed with toluene (90 L). Each organic layer was back-extracted with aqueous 2% NaOH (67.5 kg). EtOAc (360 L) was added to the combined aqueous extracts. The pH was adjusted to 2.0 by slow addition of conc. HCl (ca. 36 kg). Extraction with EtOAc (144 L) followed by crystallization from toluene gave *N*-protected proline **27**[13] (75.06 kg, 88%) as a colorless crystalline powder.

mp 182-183 °C (lit. 181.6-182.6 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.85-2.25 (m, 2H), 3.30 (br s, 1H), 3.40 (m, 2H), 4.28 (m, 2H), 5.20 (m, 2H), 7.60 (m, 2H), 8.20 (m, 2H), 12.65 (br s, 1H).

(2*S*,4*R*)-2-Hydroxymethyl-4-methylsulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (30). To a solution of *N*-protected proline **27** (31.0 kg, 99.9 mol) in CH_2Cl_2 (250 L), ethyl chloroformate (11.9 kg, 110 mol) and Et_3N (12.1 kg, 120 mol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was cooled to -45 °C. MsCl (12.6 kg, 110 mol) and Et_3N (12.1 kg, 120 mol) were added dropwise to

the reaction mixture at -45 °C. After stirring the reaction mixture at -45 °C for 0.5 h, the completion of the reaction was confirmed by HPLC analysis and then 2-propanol (78 kg) was added dropwise at -45 °C. A solution of $NaBH_4$ (5.7 kg, 151 mol) in water (23 L) was added to the reaction mixture at -45 °C and the reaction mixture was stirred at -45 °C for 0.5 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was poured into an aqueous 2.4% HCl (234 kg). After the layers were separated, the organic layer was washed with aqueous 2% $NaHCO_3$ and 3% NaCl. Each aqueous layer was back-extracted with CH_2Cl_2. The combined extracts were concentrated to 50 L. EtOAc (250 L) was added to the concentrate, and the mixture was concentrated to 110 L. Crystallization by addition of hexane (62 L) to the concentrate gave **30** (34.9 kg, 93%) as a colorless crystalline powder.

mp 113-116 °C; In the ^1H and ^{13}C NMR spectra, a 5:2 mixture of C–N rotamers was established. ^1H NMR (600 MHz, $CDCl_3$): δ 2.05 (m, 1H), 2.42 (m, 1H), 3.07 (minor isomer) and 3.09 (major isomer) (s, 3H), 3.60 (minor isomer) and 3.64 (major isomer) (m, 1H), 3.65 (minor isomer) and 3.72 (major isomer) (m, 1H), 3.89 (major isomer) and 3.95 (minor isomer) (m, 1H), 3.90-4.10 (br, 1H), 4.04 (m, 1H), 4.21 (m, 1H), 5.23 (d, *J* = 13.7 Hz, 1H, minor isomer), 5.26 (s, 2H, major isomer), 5.27 (major isomer) and 5.30 (minor isomer) (m, 1H), 5.30 (d, *J* = 13.7 Hz, 1H, minor isomer), 7.54 (minor isomer) and 7.67 (major isomer) (d, *J* = 9.1 Hz, 2H), 8.24 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 35.1 (major isomer) and 35.4 (minor isomer), 38.8 (minor isomer) and 38.9 (major isomer), 53.7 (minor isomer) and 53.8 (major isomer), 57.5 (minor isomer) and 59.3 (major isomer), 63.2 (minor isomer) and 65.1 (major isomer), 66.3 (major isomer) and 67.2 (minor isomer), 78.3 (major isomer) and 79.0 (minor isomer), 124.1, 128.3 (major isomer) and 128.4 (minor isomer), 143.6 (major isomer) and 143.7 (minor

isomer), 147.7, 155.9; IR (KBr cm^{-1}): 3439, 1699, 1684, 1523, 1342, 1169; FAB-MS (m/z): 375 $(M + H)^+$, 749 $(2M + H)^+$; Anal. calcd. for $C_{14}H_{18}N_2O_8S$: C, 44.92; H, 4.85; N, 7.48; S, 8.57. Found: C, 44.82; H, 4.68; N, 7.50; S, 8.40.

(2*S*,4*S*)-4-Acetylthio-2-hydroxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (31). A mixture of **30** (40.0 kg, 107 mol), KSAc (16.0 kg, 139 mol), DMF (80 L) and toluene (120 L) was stirred at 65 °C for 4 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was added to a mixure of EtOAc (600 L) and water (300 L). The layers were separated and the organic layer was washed with aqueous 5% NaCl (200 kg x 2). Each aqueous layer was back-extracted with EtOAc (120 L). The combined organic extracts were concentrated to 290 L. Toluene (340 L) was added to the concentrate. The mixture was concentrated to 290 L. The mixture was stored at room temperature overnight. The resultant precipitates were collected by filtration, washed with EtOAc-toluene, and dried to give **31** (27.9 kg, 74%) as a slightly yellow crystalline powder.

mp 132-133 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.66 (m, 1H), 2.33 (s, 3H), 2.50 (m, 1H), 3.26 (dd, 1H, *J* = 7.6, 11.2 Hz), 3.74 (m, 2H), 3.88 (m, 1H), 4.07 (m, 1H), 4.14 (dd, 1H, *J* = 8.8, 11.2 Hz), 4.42 (dd, 1H, *J* = 3.5, 8.6 Hz), 5.22 (s, 2H), 7.53 (d, 2H, *J* = 9.1 Hz), 8.28 (d, 2H, *J* = 9.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 30.8, 34.0, 38.5, 52.9, 60.9, 66.2, 66.5, 124.0, 128.4, 143.5, 147.6, 156.2, 195.5; IR (KBr, cm^{-1}): 3419, 1693, 1670, 1604, 1519, 1429, 1340, 1126: FAB-MS (m/z): 355 $(M + H)^+$, 709 $(2M + H)^+$; Anal. calcd. for $C_{15}H_{18}N_2O_6S$: C, 50.84; H, 5.12; N, 7.90; S, 9.05. Found: C, 50.88; H, 4.82; N, 7.97; S, 8.87.

***N*-*tert*-Butoxycarbonylsulfamide (33)**. To a solution of *tert*-butyl alcohol (32.7 kg) in EtOAc (626 L), chlorosulfonyl isocyanate **32** (62.5 kg, 442 mol) was added at -40 °C. The reaction mixture was stirred at -40 °C for 40 min, and then was cooled to -65 °C. After dry liquid ammonia (45.1 kg) had been added dropwise to the reaction mixture at -60 °C, the reaction mixture was warmed to 15 °C. Aqueous 22% H_2SO_4 (ca. 150 kg) was added to the reaction mixture with cooling to adjust the pH to 9.5. Water (100 L) was added to the mixture and the layers were separated. The aqueous layer was washed with EtOAc (230 L) and then was acidified with aqueous 22% H_2SO_4 (ca. 170 kg) to adjust the pH to 2.0. The resulting precipitates were collected by filtration, washed with water, and dried to give **33**[11] (78.4 kg, 90%) as a colorless crystalline powder.

mp 131-133 °C (lit. 130-131 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.43 (s, 9H), 7.27 (s, 2H).

(2*S*,4*S*)-4-Acetylthio-2-(*N*-sulfamoyl-*tert*-butoxycarbonylaminomethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9c). To a mixture of **31** (24.3 kg, 68.6 mol), triphenylphosphine (21.9 kg, 82.3 mol), *N*-BOC-sulfamide **33** (20.2 kg, 103 mol) in EtOAc (560 L), a solution of diisopropyl azodicarboxylate (DIAD) (16.7 kg, 82.3 mol) in EtOAc (24 L) was added dropwise at 20 °C. The reaction mixture was stirred at 20 °C for 2 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was concentrated to 110 L and the residual EtOAc was exchanged for MeOH by evaporation to give the concentrate (160 L). Water (19 L) was added to the concentrate at 65 °C. After addition of seed crystals (40 g), the mixture was stirred at 50 °C for 2 h and then was stored at room temperature overnight. The resulting precipitates

were collected by filtration, washed with 85% aqueous MeOH, and dried to give **9c** (29.6 kg, 81%) as a slightly yellow crystalline powder.

mp 139-142 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.57-1.61 (ddd, *J* = 14.1, 5.4, 3.6 Hz, 1H), 2.35 (s, 3H), 2.59 (dt, *J* = 14.1, 8.6 Hz, 1H), 3.27 (dd, *J* = 12.1, 6.5 Hz, 1H), 3.62 (dd, *J* = 14.9, 2.7 Hz, 1H), 3.96 (m, 1H), 4.02 (dd, *J* = 14.9, 8.5 Hz, 1H), 4.27 (dd, *J* = 12.1, 7.8 Hz, 1H), 4.55 (m, 1H), 5.18 (ABq, *J* = 13.4 Hz, 2H), 5.86 (br, 2H), 7.49 (A_2B_2, *J* = 8.7 Hz, 2H), 8.24 (A_2B_2, *J* = 8.7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 28.1, 30.5, 34.5, 39.2, 49.9, 52.2, 56.7, 66.1, 84.2, 123.9, 128.2, 143.1, 147.8, 151.8, 155.1, 194.9; IR (KBr, cm^{-1}) 3361, 3226, 2978, 1708, 1692, 1523, 1381, 1336, 1187,1149; FAB-MS (m/z): 533 $(M + H)^+$, 555 $(M + Na)^+$; Anal. calcd. for $C_{20}H_{28}N_4O_9S_2$: C, 45.10; H, 5.30; N, 10.52; S, 12.04. Found: C, 45.00; H, 5.27; N, 10.52; S, 11.99.

The Improved Process

Methyl (2*S*,4*R*)-4-methylsulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-2-carboxylate (36). To a mixture of hydroxyproline **26** (10.0 g, 76.3 mmol) in MeOH (50 mL), $SOCl_2$ (10.0 g, 76.3 mmol) was added dropwise at 0 °C. The reaction mixture was then stirred at 40 °C for 2 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was cooled to 0 °C and a 48% aqueous solution of NaOH (7.0 g) was added dropwise at 0 °C. After addition of water (30 mL), K_2CO_3 (15.8 g) was added slowly at below 20 °C by controlling the amount of gaseous CO_2 evolution. A solution of PNZ-Cl (16.4 g, 76.3 mmol) in toluene (17 mL) was added dropwise to the mixture at 5 °C. The reaction mixture was stirred at 2 °C for 1 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was concentrated to remove MeOH. After addition of EtOAc (100 mL) and water (60

mL) to the concentrate, the layers were separated. The organic layer was concentrated to replace EtOAc with toluene. After most of the EtOAc had been removed by concentration, Et_3N (9.3 g, 91.6 mmol) was added to the residue. MsCl (9.6 g, 83.9 mmol) was added dropwise to the mixture at room temperature. After stirring the reaction mixture at room temperature for 20 min, the completion of the reaction was confirmed by HPLC analysis and water (60 mL) was added. The precipitates were collected and dried to give **36**[14] (27.8 g, 91%) as a colorless crystalline powder.

mp 87-90 °C (lit. 78.0-80.0 °C); In the ^1H and ^{13}C NMR spectra, a 1:1 mixture of C–N rotamers was established. ^1H NMR (600 MHz, $CDCl_3$): δ 2.30 and 2.35 (m, 1H), 2.67 and 2.76 (m, 1H), 3.10 (s, 3H), 3.68 and 3.79 (s, 3H), 3.83 (m, 1H), 3.88 (m, 1H), 4.55 and 4.57 (t, J = 8.1 Hz, 1H), 5.14-5.35 (s and d, J = 13.7 Hz, 2H), 5.31 and 5.33 (m, 1H), 7.48 and 7.54 (d, J = 9.0 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 36.4 and 37.7, 38.8 and 38.9, 52.8 and 53.2, 52.9 and 53.1, 57.3 and 57.6, 66.2, 77.7 and 78.1, 124.0, 128.1 and 128.3, 143.6, 147.6 and 147.7, 153.6 and 154.2, 172.2 and 172.4; IR (KBr, cm^{-1}) 1745, 1707, 1523, 1440, 1345; FAB-MS (m/z): 403 $(M + H)^+$, 805 $(2M + H)^+$; Anal. calcd. for $C_{15}H_{18}N_2O_9S$: C, 44.77; H, 4.51; N, 6.96; S, 7.97. Found: C, 44.79; H, 4.34; N, 7.05; S, 7.78.

Hydroxymethylpyrrolidine 31 from 36. After dissolving **36** (27.6 g, 68.6 mmol) in a mixture of EtOAc (120 mL) and MeOH (16.5 mL) at 34 °C, the solution was cooled to 0 °C. $NaBH_4$ (13.2 g, 350 mmol) was added slowly to the solution with maintaining the temperature at 5 °C. The reaction mixture was stirred at 5 °C for 3 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was poured into aqueous 5% H_2SO_4 (138 mL). The layers were separated. The organic

layer was washed with aqueous 5% NaCl (55 mL x 2) and then was concentrated. KSAc (10.2 g, 89.3 mmol), DMF (50 mL) and EtOAc (66 mL) were added to the residue. The mixture was stirred at 65 °C for 8 h. After completion of the reaction had been confirmed by HPLC analysis, the mixture was cooled to below 30 °C and water (44 mL) and aqueous 5% H_2SO_4 (11 mL) were added to the mixture. After removal of the EtOAc, the precipitates were collected and dried to give **31** (18.4 g, 76%) as a slightly yellow crystalline powder.

(2*S*,4*R*)-4-Hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-2-carboxylic acid hydrate (37). To a solution of hydroxyproline **26** (10.0 g, 76.3 mmol) and K_2CO_3 (19.0 g) in water (50 mL), a solution of PNZ-Cl (16.4 g, 76.3 mmol) in toluene (17 mL) was added dropwise at 5 °C. After stirring the reaction mixture at 2 °C for 1 h, the completion of the reaction was confirmed by HPLC analysis and the layers were separated. Conc. HCl (15.4 g) was added to the aqueous layer. After stirring the mixture at 10 °C for 0.5 h, conc. HCl (4.6 g) was added to the suspension. Filtration followed by drying gave **37**[15] (23.8 g, 95%) as a colorless crystalline powder.

mp 136-138 °C (lit. 133-135 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.85-2.25 (m, 2H), 3.30 (br s, 1H), 3.40 (m, 2H), 4.28 (m, 2H), 5.20 (m, 2H), 7.60 (m, 2H), 8.20 (m, 2H), 12.65 (br s, 1H).

Hydroxymethylpyrrolidine 31 from 37. To a solution of **37** (10.0 g, 30.4 mmol) in MeOH (50 mL), 98% H_2SO_4 (0.6 g) was added. The reaction mixture was stirred at 60 °C for 7 h. After completion of the reaction had been confirmed by HPLC analysis, the mixture was cooled below 10 °C. The reaction mixture was neutralized with aqueous

5% NaOH to adjust the pH to 5 and then was concentrated. The residue (17.8 g) was poured into a mixture of EtOAc (50 mL) and aqueous 10% NaCl (50 mL). The layers were separated. The organic layer was concentrated to remove water. After cooling the residual organic solution to 0 °C, MsCl (3.8 g, 33.4 mmol) and Et_3N (3.7 g, 36.5 mmol) were added to the solution. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was washed with aqueous 5% H_2SO_4 and water. The organic layer was concentrated to remove water. EtOAc (48 mL) and MeOH (7.5 mL) were added to the residue (14.5 g). $NaBH_4$ (0.46 g x 5, 60.8 mmol) was added slowly to the solution at 0 °C. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was washed with aqueous 5% H_2SO_4 and water. The organic layer was concentrated. DMF (23 mL), EtOAc (34 mL) and KSAc (4.5 g, 39.4 mmol) were added to the residue (11.8 g). The reaction mixture was stirred at 65 °C for 7 h. After completion of the reaction had been confirmed by HPLC analysis, the mixture was cooled below 40 °C and aqueous 1% H_2SO_4 (24 mL) was added. After removal of the EtOAc, the aqueous mixture (60.0 g) was stirred at room temperature for 1 h. The precipitates were collected and dried to give **31** (7.62 g, 71%) as a slightly yellow crystalline powder.

Aminomethylpyrrolidine 9c. To a mixture of **31** (100.0 g, 282 mmol), triphenylphosphine (90.2 g, 338 mmol) and **33** (83.0 g, 423 mmol) in EtOAc (1 L), DIAD (68.3 g, 338 mmol) was added dropwise at 20 °C. The reaction mixture was stirred at 20 °C for 7 h. After completion of the reaction had been confirmed by HPLC analysis, the reaction mixture was concentrated by evaporation and most of the residual EtOAc was removed to give the concentrate (700 g). Water (75 mL) was added to the

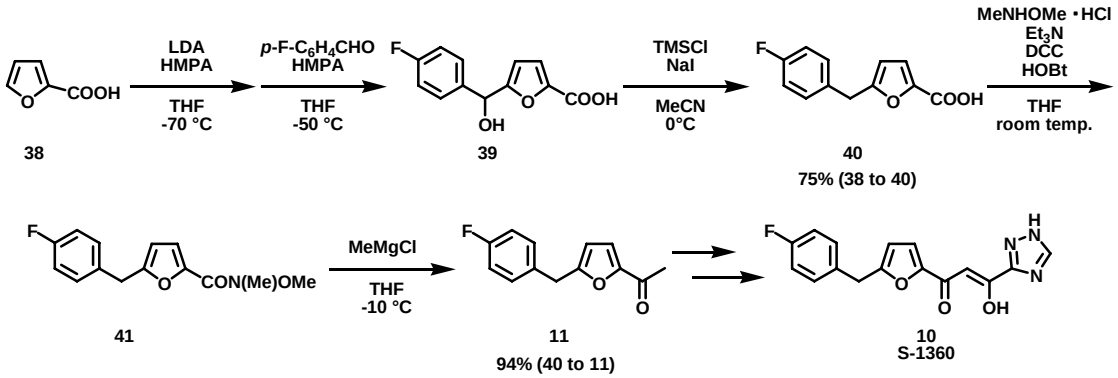
concentrate at 65 °C. The mixture was stirred at 50 °C for 2 h. After cooling, it was stored at room temperature overnight. The resultant precipitates were collected by filtration, washed with 85% aqueous MeOH, and dried to give **9c** (121.7 g, 81%) as a slightly yellow crystalline powder.

2-3. One-step Synthesis of 5-(4-Fluorobenzyl)-2-furyl Methyl Ketone: a Key Intermediate of HIV-integrase Inhibitor S-1360

5-(4-Fluorobenzyl)-2-furyl methyl ketone (**11**) is a key intermediate in the synthesis of HIV-integrase inhibitor S-1360, which was found by the Discovery Research Laboratory, Shionogi & Co., Ltd., Osaka, Japan.[13] HIV integrase has been considered an attractive therapeutic target, as HIV cannot replicate without integration with a host chromosome.[14] To develop S-1360, we needed a low-cost and reliable synthetic method by which S-1360 could be prepared on a large scale.[15] Described here are two procedures for the one-step synthesis of **11** via Friedel-Crafts benzylation.

The synthetic route employed in the medicinal research of S-1360 is shown in Scheme 8. A few kilograms of ketone **11** were synthesized by this route for nonclinical

Scheme 8 Medicinal Chemistry Route to S-1360



use. 2-Furoic acid (**38**) was lithiated with 2 molar equiv of LDA in the presence of HMPA, and the obtained dilithio derivative was allowed to react with 4-fluorobenzaldehyde to give alcohol **39**. This alcohol was reduced by TMSCl/NaI[16] to

afford 5-(4-fluorobenzyl)-2-furoic acid (**40**), which could be purified by crystallization. Acid **40** was converted into the corresponding Weinreb's amide[17] **41** and allowed to react with methylmagnesium chloride to give ketone **11**.

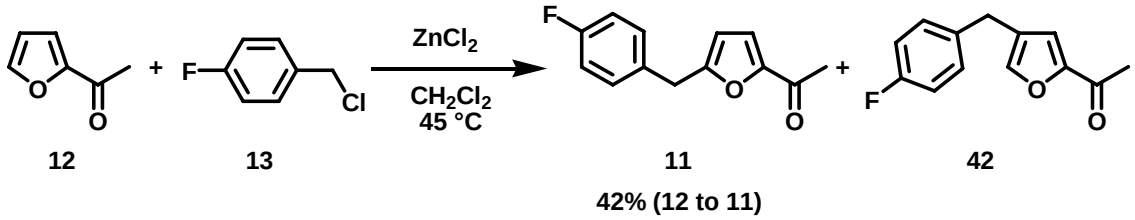
This route presented the following problems for industrial manufacturing of **11**: (1) toxic HMPA is needed to dissolve the generated dilithio derivatives; (2) iodine has to be recovered in order to protect the environment; and (3) LDA, MeNHOMe·HCl, HOBt and MeMgCl are expensive. To eliminate these scale-up issues, we investigated other synthetic methods. Friedel-Crafts-type reactions of electron-rich furans[18] and electron-deficient furans[19] are both well known,[20] but there are only a few examples of Friedel-Crafts reaction of furyl ketones. The exception is the Friedel-Crafts alkylation of 2-furyl methyl ketone (**12**),[21] which led us to examine the Friedel-Crafts benzylation of **12**.

Method A: We developed an excellent synthetic method of **11**, which involved the Friedel-Crafts reaction of **12** with 4-fluorobenzyl chloride (**13**) in the presence of anhydrous $ZnCl_2$ in CH_2Cl_2 to afford **11** in 53%[22] accompanied by 1%[22] of 4-(4-fluorobenzyl)-2-furyl methyl ketone (**42**) (Scheme 9). This one-step synthesis presents the following advantages. The starting materials **12** and **13** are inexpensive, and the isolation procedure of **11** is convenient. Namely, a mixture of **12**, 2 molar equiv of **13**, 1.5 molar equiv of anhydrous $ZnCl_2$ powder and CH_2Cl_2 was stirred at 45 °C. As the reaction proceeded, a complex of **11** with $ZnCl_2$ precipitated out of CH_2Cl_2. The precipitates were collected by filtration to remove **42** and other impurities and then were washed with water to obtain free **11** in 42%[22] yield. The obtained **11** could be used for the subsequent reactions without further purification.

Although a few kilograms of **11** were synthesized by this procedure for nonclinical

use, a problem remains that this procedure used CH_2Cl_2 as a reaction solvent, which could be harmful to the environment. We therefore searched for another procedure for the Friedel-Crafts reaction.

Scheme 9 Method A

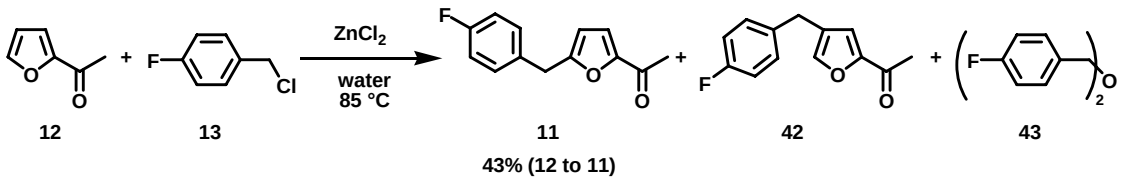


At first, we tried the reaction in the absence of a solvent. Friedel-Crafts reaction of **12** with benzyl chloride **13** without solvent also gave ketone **11** but posed two problems: (1) the reaction mixture easily solidified and was not suitable for large-scale synthesis and (2) on a 20-L scale, the three materials, **12**, **13** and $ZnCl_2$ were stirred and heated to start the reaction, but this could not be controlled. A reaction calorimeter study of this reaction revealed a large heat evolution of 327 kJ/mol and an adiabatic temperature rise of 355 degrees. In order to control the reaction, **12** was added gradually into a mixture of **13** and $ZnCl_2$, but this procedure gave **11** in poor yield.

Method B: Other solvents to replace CH_2Cl_2 were tested, and water was found to be the best (Scheme 10). The Friedel-Crafts reaction in the presence of water was a two-layer system, which contained a layer of organic compounds and aqueous $ZnCl_2$ solution. Namely the mixture of **12**, 2 molar equiv of **13** and 1.05 molar equiv of $ZnCl_2$ in 2 vol of water was stirred at 85 °C for 6 h. The Friedel-Crafts reaction gave 70%[22] of **11** accompanied by 5%[22] of ketone **42** and 5%[22] of di-4-fluorobenzyl ether (**43**). In

order to remove the isomer **42** and the ether **43**, the isolation procedure of **11** required distillation under reduced pressure and then crystallization under -10 °C from mixed solvents of 2-propanol and hexane.

Scheme 10 Method B



The desired ketone **11** was isolated in 43% yield from **12**. The calorimeter study revealed the total energy given off during this reaction with water to be 23.7 kJ/mol, which corresponded to an adiabatic temperature rise of 14 degrees. These conditions were adopted for large-scale synthesis, and ca. 500 kg/lot of ketone **11** was obtained.

In summary, a convenient and economical one-step synthesis of **11** was developed starting from the easily available compounds **12** and **13**. This procedure includes two different conditions. For small-scale synthesis in a laboratory, the reaction by anhydrous $ZnCl_2$ in CH_2Cl_2 can be recommended. On the other hand, for large-scale synthesis, the reaction with water should be adopted to protect the environment and reduce the safety risk. Modification of these procedures should be useful for synthesizing 5-substituted-2-furyl ketones.

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22. The reaction mixture was quenched with water and extracted with CH_2Cl_2 or EtOAc. The yield was estimated by HPLC analysis of the extract.

Experimental Section

5-(4-Fluorobenzyl)-2-furyl methyl ketone (11)

Method A: To a solution of **12** (19.71 g, 0.18 mol) in CH_2Cl_2 (120 mL), **13** (42.9 mL, 0.36 mol) and $ZnCl_2$ (36.6 g, 0.27 mol) were added and the mixture was stirred at 45 °C. After 12 h, the precipitated complexes of **11** with $ZnCl_2$ were collected, washed with CH_2Cl_2. Water was added to the complexes and then the mixture was extracted with EtOAc and the organic layer was washed with water and aqueous $NaHCO_3$ and then dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. Hexane was added to the residue and the precipitates were collected by filtration and dried to give **11** (16.4 g, 42 %).

mp 28 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 4.01 (s, 2H), 6.09 (d, J = 3.5 Hz, 1H), 6.96-7.26 (m, 5H).

Method B: The mixture of **12** (187.2 g, 1.7 mol), **13** (491.6 g, 3.4 mol), aqueous 50% $ZnCl_2$ (486.6 g, 1.785 mol) and water (131 mL) was vigorously stirred at 85 °C for 6 h. After completion of the reaction had been confirmed by HPLC analysis, EtOAc (1,498 ml) was added to the reaction mixture. The organic layer was washed with 3.65% aqueous HCl (936 mL × 3), 5% aqueous $NaHCO_3$ (936 mL) and water (936 mL). Each aqueous layer was back-extracted with EtOAc (374 mL). The combined organic layer was condensed *in vacuo* and then distilled under reduced pressure at 115-144 °C (370-210 Pa). A mixture of the distillate and 2-propanol (144.4 mL) was allowed to cool at 0 °C with stirring and then seed crystals were added. After 0.5 h hexane (288.7 mL) was added and then the mixture was allowed to cool at -10 °C with stirring. After 2 h the obtained crystals were filtered, washed with chilled hexane and dried to give **11**

(161.2 g 43 %).

List of Publications

1. Highly Diastereoselective and Enantioselective Synthesis of Enantiopure C_2-Symmetrical Vicinal Diamines by Reductive Homocoupling of Chiral *N*-*tert*-Butanesulfinyl Imines

   Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747.

2. A Highly Efficient and Direct Approach for Synthesis of Enantiopure *β*-Amino Alcohols by Reductive Cross-Coupling of Chiral *N*-*tert*-Butanesulfinyl Imines with Aldehydes

   Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956

3. Practical Large-Scale Synthesis of Doripenem: A Novel 1*β*-Methylcarbapenem Antibiotic

   Nishino, Y.; Kobayashi, M.; Shinno, T.; Izumi, K.; Yonezawa, H.; Masui,Y.; Takahira, M. *Org. Process Res. Dev.* **2003**, *7*, 846.

4. Practical Large-Scale Synthesis of the 2-Aminomethylpyrrolidin-4-ylthio-Containing Side Chain of the Novel Carbapenem Antibiotic Doripenem

   Nishino, Y.; Komurasaki, T.; Yuasa, T.; Kakinuma, M.; Izumi, K.; Kobayashi, M.; Fujiie, S.; Gotoh, T.; Masui, Y.; Hajima, M.; Takahira, M.; Okuyama, A.; Kataoka, T. *Org. Process Res. Dev.* **2003**, *7*, 649.

5. One-Step Synthesis of 5-(4-Fluorobenzyl)-2-furyl Methyl Ketone: A Key Intermediate of HIV-Integrase Inhibitor S-1360

Izumi, K.; Kabaki, M.; Uenaka, M.; Shimizu, S. *Org. Process Res. Dev.* **2007**, *11*, 1059.

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