Graphical Abstract

Lewis-acid-mediated ring-exchange reaction of dihydrobenzofurans and its application to the formal total synthesis of (–)-quinocarcinamide

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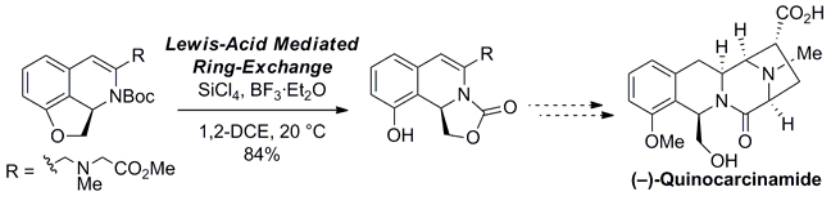

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Lewis-acid-mediated ring-exchange reaction of dihydrobenzofurans and its application to the formal total synthesis of (–)-quinocarcinamide

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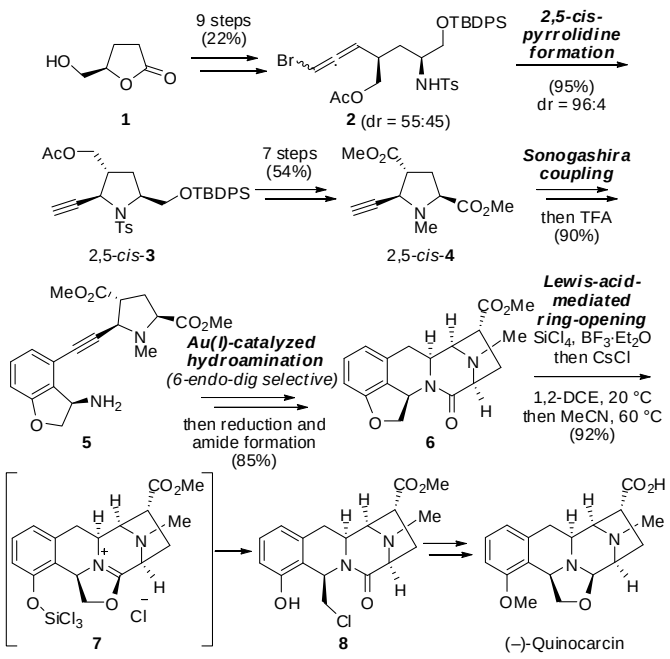
ABSTRACT

An unusual Lewis-acid-mediated ring-exchange reaction of dihydrobenzofurans is described. The fused tricyclic ring system is the key structural element for this reaction as it restricts C–N bond rotation and/or destabilizes the benzofuran ring. We achieved the formal total synthesis of (–)-quinocarcinamide using a combination of this reaction and the Au(I)-catalyzed 6-*endo-dig* hydroamination of an alkyne.

1. Introduction

Quinocarcin is a pentacyclic tetrahydroisoquinoline alkaloid, isolated by Takahashi and Tomita[1] in 1983. Its intricate polycyclic architecture and potent broad-spectrum antitumor activity[2,3] have attracted both synthetic and biological chemists, culminating in several efficient syntheses, reported by Fukuyama,[4] Garner, Terashima, Myers, Zhu, and Stoltz.[5] We recently reported the enantioselective total synthesis of (–)-quinocarcin using Au(I)-catalyzed intramolecular hydroamination of alkynes (Scheme 1).[6] In this synthesis, we had to overcome the challenging problem of cleaving the dihydrobenzofuran ring[7,8] in **6**, which was a key structural element for the 6-*endo-dig* over 5-*exo-dig* hydroamination. Based on the LiI-mediated ring-opening halogenation of benzofurans in the presence of $SiCl_4$ and BF_3·AcOH reported by Zewge et al.,[7] we attempted a ring-exchange strategy using neighboring group participation of the carbonyl oxygen of lactam **6** to afford an oxazolidinium intermediate **7**. Exposure of lactam **6** to BF_3·Et_2O and $SiCl_4$ in 1,2-dichloroethane (1,2-DCE) afforded a suspension, which possibly contained the expected oxazolidinium intermediate **7**. Addition of H_2O to the resulting suspension led to recovery of the starting material **6**, but work-up with CsCl afforded the desired chlorinated phenol **8** in 92% yield.

Based on these results, we thought that easier ring-opening of dihydrobenzofuran would be achieved by introduction of an appropriate nucleophilic functionality in the substrate. We embarked on an investigation to clarify the structural requirements which would accelerate the ring-opening reaction. Its synthetic application to the formal total synthesis of (–)-quinocarcinamide is also described.



Scheme 1. Total synthesis of (–)-quinocarcin.[6]

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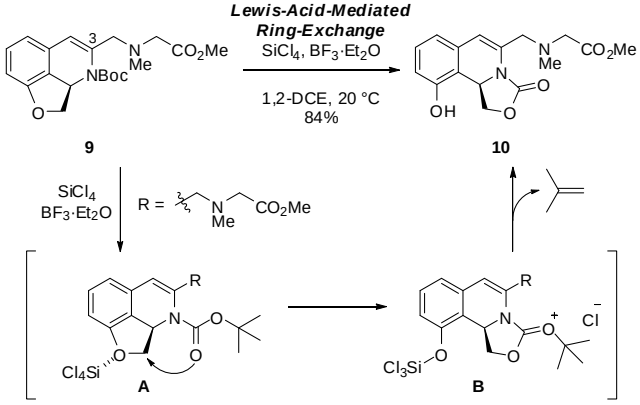
2. Results and discussion

We tested our theory using the reaction of *N*-Boc-dihydroisoquinoline **9** (Scheme 2). Treatment of **9** with $SiCl_4$ and $BF_3{\cdot}Et_2O$ in 1,2-DCE afforded oxazolidinone **10** in 84% yield. In this case, the reaction proceeded at room temperature and work-up with CsCl (to suppress the reverse reaction) was not necessary. When the reaction was performed in the absence of $BF_3{\cdot}Et_2O$, the starting material **9** was only recovered. This is in good accordance with the literature.[7] This ring-exchange reaction is interesting and unusual because the normally stable dihydrobenzofuran ring can be selectively converted into the oxazolidinone by simultaneous C–O bond cleavage of the dihydrobenzofuran and C–O bond formation of the oxazolidinone ring. We thought that the possible requirements for the ring-exchange reaction would be: (1) restricted C–N bond rotation to give the appropriate arrangement of the carbonyl oxygen at the back of the furan C-O bond as shown in **A**, and (2) slightly distorted tricyclic ring systems in **6** and **9** to destabilize the benzofuran ring. Restriction of the C–N bond in **9** can be achieved by the tricyclic ring system and/or an aminomethyl substituent at the C-3 position of dihydroisoquinoline.

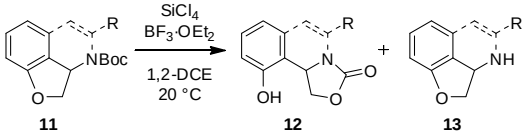


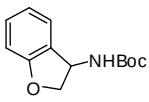
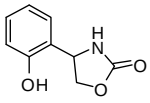
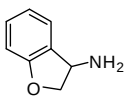
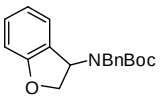
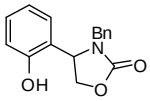
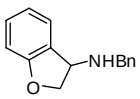
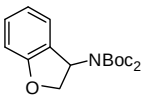
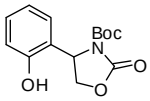
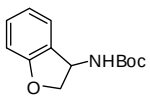
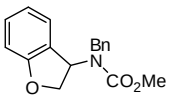
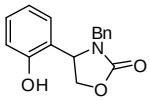
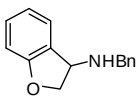
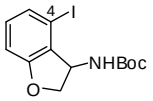
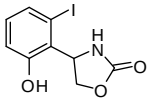
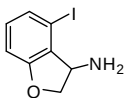
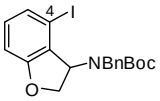
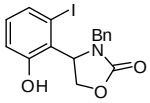
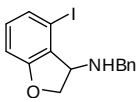
Scheme 2. Lewis-acid-mediated ring-exchange reaction of *N*-Boc-dihydroisoquinoline **9**.

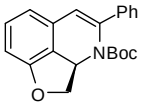
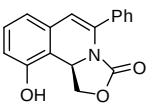
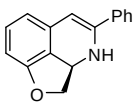
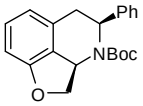
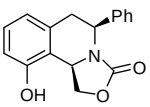
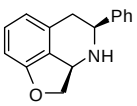
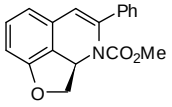
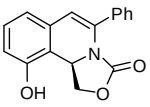
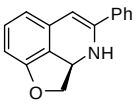
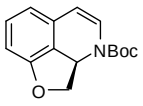
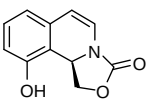
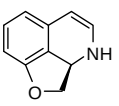
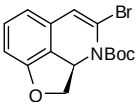
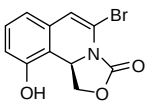
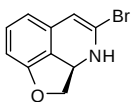
To clarify the structural requirements for the ring-exchange reaction, we investigated the reaction using *N*-Boc-3-aminodihydrobenzofurans **11a**–**c** (Table 1, entries 1–3). These substrates contain the minimum necessary functionalities for the reaction. Treatment of dihydrobenzofurans **11a**–**c** with $BF_3{\cdot}OEt_2$ and $SiCl_4$ in 1,2-DCE did not provide the oxazolidinones **12**. Instead, amines **13a**/**b** and **11a**, formed by removal of the Boc group, were obtained in modest yields. Similarly, methyl carbamate **11d** did not produce oxazolidinone **12b**, but underwent elimination of methyl benzylcarbamate (entry 4). These observations show that (1) restricted C–N bond rotation and/or (2) a distorted tricyclic ring system are important for a successful ring-exchange reaction.

We then investigated partial restriction of the C–N bond rotation by introduction of a substituent at the 4-position of the benzofuran ring. Treatment of 4-iododihydrobenzofurans **11e**/**f**[6] with $BF_3{\cdot}Et_2O$ and $SiCl_4$ only gave the corresponding amines **13e/f**, without promoting the ring-exchange reaction (entries 5 and 6). In sharp contrast, tricyclic dihydroisoquinoline **11g** (entry 7), which was prepared by Sonogashira coupling of aryl iodide **11e** with phenylacetylene, followed by Au(I)-catalyzed 6-*endo*-*dig* hydroamination of an alkyne, afforded the corresponding ring-exchange product **12g** in 95% yield upon exposure to identical reaction conditions. When the tricyclic tetrahydroisoquinoline-type substrate **11h** was used, the corresponding ring-exchange product **12h** was obtained in 45% yield along with 18% yield of the amine **13h**. These results showed that the appropriate fused ring structure, which would restrict the arrangement of the carbonyl oxygen and destabilize the benzofuran ring, is vital for this unusual ring-exchange reaction. Tricyclic dihydroisoquinoline substrate **11i**, *N*-methoxycarbonyl analogue of **11g**, was also converted into the same phenol **12g** albeit in lower yield (entry 9). Unfortunately, treatment of substrate **11j**, with no substituent at the C-3 position of dihydroisoquinoline, led to a complex mixture of unidentified products (entry 10). On the other hand, when using substrate **11k**, we obtained the resulting phenol **12k** in 75% yield bearing a bromo substituent, which is useful for further elaborations. It is noteworthy that in this case $SiBr_4$ was used in place of $SiCl_4$ because the reaction of the bromide **11k** under the standard conditions caused halogen-exchange to form a considerable amount of the corresponding chloride (ca. 50% yield, judged by ^{1}H NMR and GC-MS, entry 11).

Table 1
Investigation of dihydrobenzofuran ring-exchange reactions.

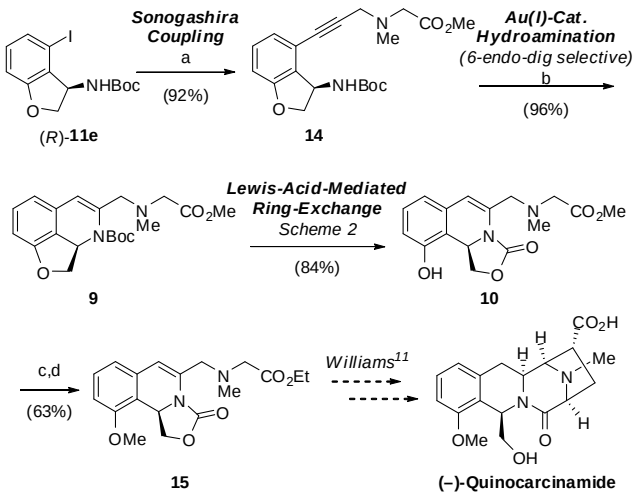


entry	Dihydrobenzofuran	Phenol (%)[a]	Amine (%)[a]
1	 **11a**	 **12a** (0%)	 **13a** (38%)
2	 **11b**	 **12b** (0%)	 **13b** (48%)
3	 **11c**	 **12c** (0%)	 **11a** (63%)
4[b]	 **11d**	 **12b** (0%)	 **13b** (0%)
5	 **11e**	 **12e** (0%)	 **13e** (67%)
6	 **11f**	 **12f** (0%)	 **13f** (43%)

7			
	11g	**12g** (95%)	**13g** (0%)
8			
	11h	**12h** (45%)	**13h** (18%)
9			
	11i	**12g** (42%)	**13g** (0%)
10			
	11j	**12j** (0%)	**13j** (0%)
11[c]			
	11k	**12k** (75%)	**13k** (0%)

[a]Isolated yields. No starting materials were recovered in all cases. [b]Methyl benzylcarbamate was formed in 59% yield. [c]$SiBr_4$ was used in place of $SiCl_4$.

Next, we applied this ring-exchange reaction to the formal total synthesis of quinocarcinamide. Quinocarcinamide is formed by a Cannizzaro-type self-redox disproportionation of quinocarcin, which serves as its own reductant.[9] As previously described,[6] the optically active precursor **9** was prepared by Sonogashira coupling of the protected 4-iodo-2,3-dihydrobenzofuran-3-amine (*R*)-**11e** with a propargylamine derivative, followed by Au(I)-catalyzed 6-*endo*-*dig* selective hydroamination of the corresponding alkyne **14** (Scheme 3). A Lewis-acid-mediated ring-exchange reaction of **9**, shown in Scheme 2, subsequent methylation of the resulting phenol **10**, and transesterification[10] gave the optically active ethyl ester **15**, whose spectral properties were identical to those reported for (±)-**15** by Flanagan and Williams in their total synthesis of (±)-quinocarcinamide.[11] This unusual Lewis-acid-mediated ring-exchange reaction of dihydrobenzofuran therefore provides easy access to the asymmetric synthesis of (–)-quinocarcinamide.



Scheme 3. Application to the formal total synthesis of (–)-quinocarcinamide. Reagents and conditions: a) methyl 2-[methyl(propargyl)amino]acetate, $Pd(OAc)_2$, *n*-Bu_4NOAc, DMF, 80 °C; b) IPr–AuCl, $AgNTf_2$, 1,2-DCE, 45 °C; c) Me_2SO_4, Cs_2CO_3, acetone, 0 °C; d) K_2CO_3, EtOH, 20 °C. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

3. Conclusions

In summary, we investigated the Lewis-acid-mediated ring-exchange reaction of dihydrobenzofurans. A tricyclic ring system for the restriction of the C–N bond rotation and/or destabilization of the benzofuran ring is the key structural element for the success of this ring-exchange reaction. A combination of this reaction with the Au(I)-catalyzed 6-*endo*-*dig* hydroamination of an alkyne was used to achieve the formal total synthesis of (–)-quinocarcinamide.

4. Experimental

4.1 Lewis-acid-mediated ring-exchange reaction

General procedure: synthesis of methyl (R)-2-{[(10-hydroxy-3-oxo-3,10b-dihydro-1H-oxazol[4,3-a]isoquinolin-5-yl)methyl](methyl)amino}acetate ***(10)*** *(Scheme 2).* $SiCl_4$ (0.03 mL, 0.27 mmol) and $BF_3 \cdot Et_2O$ (0.004 mL, 0.03 mmol) were added to a stirred solution of **9** (20.4 mg, 0.05 mmol) in 1,2-DCE (2 mL) under argon at room temperature. After stirring for 4 h, Et_3N (0.3 mL) and EtOH (2 mL) were added. An insoluble inorganic residue was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give **10** as a white solid (14.5 mg, 84% yield): R_f = 0.24 (*n*-hexane–EtOAc 1:1); mp 165–166 °C; $[\alpha]^{25}_D$ –164.7 (*c* 0.98, EtOH); IR (neat, cm^{-1}): 3265 (OH), 1731 (C=O); ^1H NMR (500 MHz, CD_3OD) δ 2.45 (s, 3H), 3.34 (d, *J* = 14.3 Hz, 1H), 3.41 (d, *J* = 16.6 Hz, 1H), 3.46 (d, *J* = 16.6 Hz, 1H), 3.67 (s, 3H), 4.34 (d, *J* = 14.3 Hz, 1H), 4.56 (dd, *J* = 10.9, 9.2 Hz, 1H), 5.04 (dd, *J* = 9.2, 8.0 Hz, 1H), 5.26 (dd, *J* = 10.9, 8.0 Hz, 1H), 6.03 (s, 1H), 6.63 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 7.07 (dd, *J* = 7.4, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 42.1, 51.9, 56.2, 57.3, 58.2, 71.1, 115.8, 116.0, 118.1, 119.1, 130.2, 133.3, 134.8, 154.4, 156.9, 173.0. Anal. calcd. for $C_{16}H_{18}N_2O_5$: C, 60.28; H, 5.85; N, 8.72. Found C, 60.37; H, 5.70; N, 8.80.

4.2 Formal synthesis of (–)-quinocarcinamide

Synthesis of ethyl (R)-2-{[(10-methoxy-3-oxo-3,10b-dihydro-1H-oxazolo[4,3-a]isoquinolin-5-yl)methyl](methyl)amino}acetate ***(15)*** *(Scheme 3).* Cs_2CO_3 (1.03 g, 3.16 mmol) was added to a stirred solution of **10** (0.33 g, 1.05 mmol) in acetone (50 mL) under argon at room temperature. After stirring the mixture for 30 min, Me_2SO_4 (0.1 mL, 1.07 mmol) was added at –10 °C, and the resulting mixture was stirred for 4 h at 0 °C. H_2O (50 mL) and EtOAc (50 mL) were added and the mixture was allowed to warm to room temperature. The organic phase was separated and washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave the corresponding methyl ether as a yellow oil (0.34 g, 97%).

K_2CO_3 (40.5 mg, 0.29 mmol) was added to a stirred solution of this methyl ether (19.5 mg, 0.06 mmol) in EtOH (2 mL) under argon at room temperature. After stirring the mixture for 9 h,

saturated aqueous NH_4Cl (2 mL) was added. The resulting mixture was extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure followed by purification by column chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give **15** as a yellow oil (12.9 mg, 63%): R_f = 0.47 (*n*-hexane–EtOAc 1:1); $[\alpha]^{26}_D$ –199.8 (*c* 0.87, $CHCl_3$); IR (neat, cm^{-1}): 1761 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.51 (s, 3H), 3.42 (d, *J* = 16.6 Hz, 1H), 3.52 (d, *J* = 16.6 Hz, 1H), 3.58 (d, *J* = 14.9 Hz, 1H), 3.81 (s, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.30 (d, *J* = 14.9 Hz, 1H), 4.50 (dd, *J* = 10.9, 9.2 Hz, 1H), 4.98 (dd, *J* = 9.2, 8.0 Hz, 1H), 5.27 (dd, *J* = 10.9, 8.0 Hz, 1H), 6.02 (s, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 41.6, 54.7, 55.4, 56.1, 57.6, 60.3, 69.4, 109.7, 112.7, 118.2, 119.1, 129.3, 132.4, 135.3, 154.6, 155.0, 171.2; HRMS (FAB) calcd for $C_{18}H_{23}N_2O_5$ (MH^+): 347.1607; found: 347.1609.

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