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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.

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 SiCl4 and BF3·Et2O 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 BF3·Et2O, the starting material 9 was only recovered. This is in good accordance with the literature. 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 BF3·OEt2 and SiCl4 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 with BF3·Et2O and SiCl4 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 SiBr4 was used in place of SiCl4 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 1H NMR and GC-MS, entry 11).

Table 1

<table>
<thead>
<tr>
<th>entry</th>
<th>Dihydrobenzofuran</th>
<th>Phenol (%)</th>
<th>Amine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>12a (0%)</td>
<td>13a (38%)</td>
</tr>
<tr>
<td>2</td>
<td>11b</td>
<td>12b (0%)</td>
<td>13b (48%)</td>
</tr>
<tr>
<td>3</td>
<td>11c</td>
<td>12c (0%)</td>
<td>11a (63%)</td>
</tr>
<tr>
<td>4</td>
<td>11d</td>
<td>12d (0%)</td>
<td>13b (0%)</td>
</tr>
<tr>
<td>5</td>
<td>11e</td>
<td>12e (0%)</td>
<td>13e (67%)</td>
</tr>
<tr>
<td>6</td>
<td>11f</td>
<td>12f (0%)</td>
<td>13f (43%)</td>
</tr>
</tbody>
</table>
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 quinocarin, which serves as its own reductant. As previously described, the optically active precursor 9 was prepared by Sonogashira coupling of the protected 4-ido-2,3-dihydrobenzofuran-3-amine (R)-11e with a propargylamine derivative, followed by Au(I)-catalyzed 6-endo-dig selective hydromethylation of the resulting phenol 10, and transesterification gave the optically active ethyl ester 15, whose spectral properties were identical to those reported for (±)-quinocarcinamide. 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-[(3-iodo[10-hydroxy-3-oxo-3,10b-dihydro-1H-oxazolo[4,3-a]isoquinolin-5-yl]methyl)(propargyl)amino]acetate, Pd(OAc)$_2$, n-Bu$_4$NOAc, DMF, 80 °C; b) IPr–AuCl, AgNTf$_2$, 1,2-DCE, 45 °C; c) Me$_2$SO$_4$, Cs$_2$CO$_3$, acetone, 0 °C; d) K$_2$CO$_3$, EtOH, 20 °C.

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 hydromethylation 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-oxazolo[4,3-a]isoquinolin-5-yl)methyl](methyl)amino]acetate (10) (Scheme 2). SiCl$_4$ (0.03 mL, 0.27 mmol) and BF$_3$: EtO$_2$ (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$_3$N (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). IR (neat, cm$^{-1}$): 3265 (OH), 1731 (C=O); H NMR (500 MHz, CD$_3$OD) $\delta$ 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); $^1$C NMR (125 MHz, CD$_3$OD) $\delta$ 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$_2$O$_5$: 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$_2$CO$_3$ (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$_2$SO$_4$ (0.1 mL, 1.07 mmol) was added at $-10$ °C, and the resulting mixture was stirred for 4 h at 0 °C. H$_2$O (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 gave the corresponding methyl ester as a yellow oil (0.34 g, 97%).

K$_2$CO$_3$ (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 NH₄Cl (2 mL) was added. The resulting mixture was extracted with EtOAc. The extract was washed with H₂O and brine, dried over MgSO₄, 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%): Rf = 0.47 (n-hexane–EtOAc 1:1); [α]D₂₆ −199.8 (c 0.87, CHCl₃); IR (neat, cm⁻¹): 1761 (C=O); 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) δ 14.3, 41.6, 54.7, 55.4, 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 C₈H₁₂N₂O₅ (MH+): 347.1607; found: 347.1609.

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References and notes


10. Less expensive N-methyl sarcosine methyl ester was used as the starting material instead of the ethyl ester, because at the beginning the compound 10 was prepared for model experiment in quinocarcin synthesis.