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Stereoselective synthesis of *cis*- and *trans*-2,3-disubstituted eight-membered medium-ring ethers based on Ireland–Claisen rearrangement of 3-alkoxy-2-propenyl glycolate esters and ring-closing olefin metathesis

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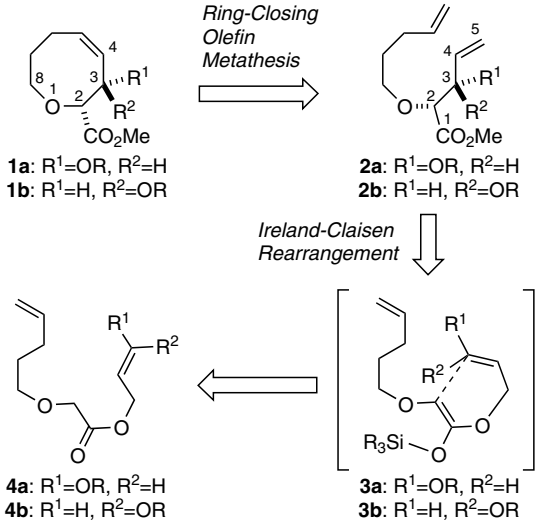
Abstract—A simple stereoselective synthesis of *cis*- and *trans*-2,3-disubstituted medium-sized cyclic ethers has been developed based on geometry-selective synthesis of 3-alkoxy-2-propenyl glycolate esters, Ireland–Claisen rearrangement of the glycolate esters, and ring-closing olefin metathesis.

Medium-ring ethers have attracted significant synthetic attention, because they are often seen in potent bioactive natural products,[1] such as ciguatoxin.[2] Among the many methods available for their synthesis,[3] a ring-closing olefin metathesis reaction (RCM) has now interested synthetic chemists, since it realizes efficient ring-closure under mild catalytic conditions and tolerates a wide variety of functional groups in its substrates.[4] On the other hand, the diene substrates of RCM for the synthesis of medium-ring ethers, which include an acyclic branched ether part, are still difficult to prepare. Therefore, stereoselective construction of these acyclic branched ethers has been a current crucial challenge in synthetic chemistry.[5] In this context, we have studied an application of Ireland–Claisen rearrangement[6] to the synthesis of branched ethers. Here, a simple stereoselective synthesis of medium-ring ethers based on the Ireland–Claisen rearrangement of 3-alkoxy-2-propenyl glycolates followed by RCM is described.[6d,e]

Our strategy for stereoselective synthesis of medium-ring ethers was represented by the retrosynthetic scheme of *cis*- and *trans*-3-alkoxy-2-carbomethoxy-2,3,6,7-tetrahydrooxocines (**1a** and **1b**) shown in Scheme 1, where Ireland–Claisen rearrangement[6] of 3-alkoxy-2-propenyl glycolate ester **4**[7] into 2,3-dialkoxy-4-pentenoate ester



Scheme 1.

2 and the subsequent RCM of **2** into **1** were the key steps. Since it was reported that a glycolate ester could be facilely transformed into a *Z*-ketene silyl acetal under the Ireland–Claisen conditions,[7a–e] *Z*-ketene silyl acetal **3** was thought to mediate the rearrangement of **4** into **2**. The stereochemistry of **2** could be predicted from the presumed chair-type conformation of **3** in the transition state.[6] Namely, *E*-3-alkoxy-2-propenyl derivative

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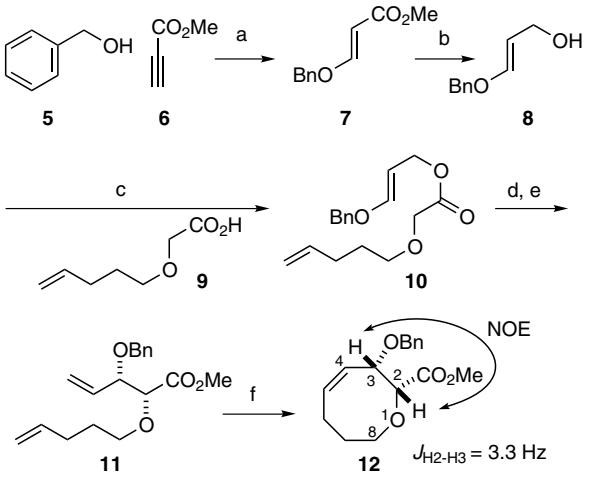
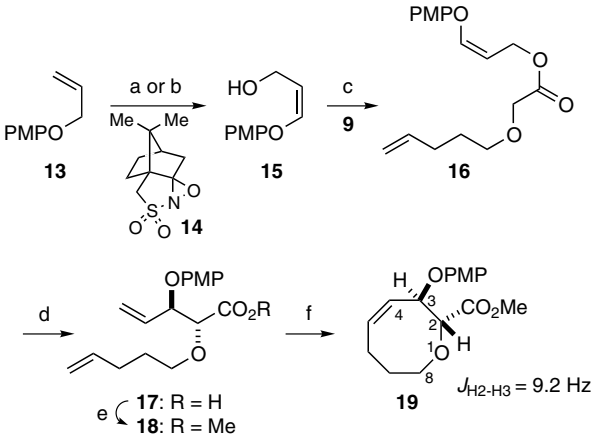


Scheme 2. Reagents and conditions: (a) Me_3P, CH_2Cl_2, 0 °C, 30 min, 96%; (b) DIBAH, CH_2Cl_2, −78 °C, 1 h, 93%; (c) DCC, DMAP, CH_2Cl_2, **8** (0.83 equiv), 0→23 °C, 93% from **8**; (d) KHMDS, THF, −78 °C, 1 min, then TMSCl, −78→23 °C, 35 min; (e) CH_2N_2, THF–Et_2O, 23 °C, 1 min, 79% from **10**; (f) $(PCy_3)_2Cl_2RuCHPh$ (0.1 equiv), CH_2Cl_2, reflux, 6.5 h, 87%.



Scheme 3. Reagents and conditions: (a) *s*-BuLi, TMEDA, THF, −78 °C, 1 h, then MoOPH, −78 °C, 1 h, then 25 °C, 30 min, 23%; (b) *s*-BuLi, TMEDA, THF, −78 ° C, 1 h, then **14**, −78→25 °C, 30 min, 29%; (c) **9** (2.7 equiv), EDCI·HCl, DMAP, CH_2Cl_2, 25 °C, 2 h; (d) KHMDS, TMSCl, THF, −78→25 °C, 1 h, 81% from **15**; (e) CH_2N_2, THF–Et_2O, 0 °C, 20 min, 81%; (f) $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (0.1 equiv), CH_2Cl_2, reflux, 5.5 h, 53%. PMP: 4-methoxyphenyl.

4a would give *syn*-2,3-dialkoxide **2a** via **3a**, and *Z*-derivative **4b** would provide *anti*-product **2b** via **3b**. Therefore, geometry-selective synthesis of the 3-alkoxy-2-propenyl group in **4** was important for the success of the strategy.

First, we examined the stereoselective preparation of *E*-3-benzyloxy-2-propenyl glycolate **10**, corresponding to **4a**, and its transformation into eight-membered cyclic ether **12** (Scheme 2). The glycolate ester **10** was prepared by condensation reaction of glycolic acid **9** with *E*-3-benzyloxy-2-propenol **8**[8] (93%). The geometry-selective synthesis of **8** employed Ireland's procedure[7g] with some modifications. Benzyl alcohol **5** reacted with methyl propiolate **6** in the presence of Me_3P[9] to give **7** exclusively (96%), which was reduced with DIBAH into **8** (93%). Deprotonation of **10** with KHMDS at −78 °C for 5 min followed by treatment with TMSCl and warming to ambient temperature induced Ireland–Claisen rearrangement to produce a 2,3-dialkoxy-4-pentenoic acid as a single diastereomer, which was converted with CH_2N_2 to methyl ester **11** in 79% overall yield. Ring closure of **11** with first-generation Grubbs' catalyst[10] gave eight-membered cyclic ether **12**[11] in 87% yield. The relative stereochemistry at C2 and C3 in **12** was confirmed as (2*R**,3*S**) by the presence of NOE between H2 and H3 as well as small $J_{H2–H3}$ (3.3 Hz). Thus, the Ireland–Claisen rearrangement of *E*-3-alkoxy-2-propenyl glycolate **10** gave exclusively *syn*-2,3-dialkoxy-4-pentenoate **11**, which was smoothly cyclized into eight-membered cyclic ether **12** by RCM.

Next, stereoselective synthesis of *Z*-3-(4-methoxyphenyloxy)-2-propenyl glycolate **16**, corresponding to **4b**, was examined (Scheme 3). Although several methods for preparing *Z*-3-alkoxy-2-propenyl alcohols were reported,[12] a more selective and simpler method was required for our synthesis. Therefore, we investigated a deprotonation–oxygenation process starting from an allyl ether. Deprotonation of allyl ether **13** with *s*-BuLi in the presence of TMEDA followed by treatment with MoOPH[13] gave the desired *Z*-type alcohol **15** as the sole geometrical isomer in 23% yield. From the fact of significant byproduction of 4-methoxyphenol, the modest yield of **15** was thought to result from decomposition of **13** caused by the oxygenation at the carbon adjacent to the PMPO group. In order to suppress the undesired oxygenation, Davis' reagent **14**[14] was then employed as a bulky oxidant that would improve the desired regioselectivity by its steric hindrance. The reaction was carried out in a similar way and produced **15** as the sole geometrical isomer in 29% yield. In this case, the byproduction of 4-methoxyphenol was reduced, but a significant amount of 4-methoxyphenyl-1-propenyl ether was given.[15] Although the problem of the modest yield remained to be solved, geometrically pure **15** was simply obtained. Treatment of **15** and **9** with EDCI·HCl followed by extractive workup gave almost pure ester **16**.

Then, the Ireland–Claisen rearrangement of **16** and the subsequent RCM were investigated. The ester **16** was deprotonated with KHMDS in the presence of TMSCl at −78 °C, and the resulting ketene silyl acetal was rearranged during warming to ambient temperature to produce **17** exclusively in 81% overall yield from **15**. The carboxylic acid **17** was transformed into **18** with CH_2N_2 (81%). The diene **18** was cyclized with second-generation Grubbs' catalyst[16] into eight-membered cyclic ether **19**[17] in 53% yield.[18] The *trans*-geometry of the substituents at C2 and C3 of **19** was determined by the large $J_{H2–H3}$ (9.2 Hz) and absence of NOE between H2 and H3. Thus, the process including Ireland–Claisen rearrangement and RCM starting from *Z*-3-alkoxy-2-propenyl glycolate ester **16** efficiently completed the construction of *trans*-disubstituted eight-membered cyclic ether **19** stereoselectively.

In conclusion, a simple stereoselective synthesis of *cis*- and *trans*-3-alkoxy-2-carbomethoxy-2,3,6,7-tetrahydrooxocines has been developed based on geometry-selective synthesis of *E*- and *Z*-3-alkoxy-2-propenyl glycolates, Ireland–Claisen rearrangement of the glycolate esters, and the subsequent ring-closing olefin metathesis. The next challenge toward the application of the method to natural product synthesis is asymmetric induction during the Ireland–Claisen rearrangement of the substrate having a cyclic ether group on the C2-oxygen of the glycolate part or on the C3-oxygen of the 2-propenyl part. The solution of the challenge will provide an efficient synthesis of a fused polycyclic ether system. Further studies on the issue are now in progress in our laboratory.

Acknowledgements

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11. Selected spectral data of **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (5H, m), 6.02 (1H, ddd, J = 7.7, 8.8, 11.0 Hz), 5.71 (1H, dd, J = 7.0, 11.0 Hz), 4.98 (1H, d, J = 12.1 Hz), 4.44 (1H, dd, J = 3.3, 7.0 Hz), 4.39 (1H, d, J = 12.1 Hz), 4.19 (1H, d, J = 3.3 Hz), 4.16 (1H, td, J = 3.9, 11.7 Hz), 3.73 (3H, s), 3.54–3.41 (1H, m), 2.88–2.70 (1H, m), 2.13–1.90 (2H, m), 1.63–1.45 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (c), 138.0 (C), 135.4 (CH), 128.2 (CH × 2), 127.73 (CH × 2), 127.54 (CH), 127.43(CH), 82.0 (CH), 75.5 (CH), 70.4 (CH_2 × 2), 52.1 (CH_3), 30.5 (CH_2), 24.5 (CH_2); IR (film) ν_{max} 3029, 2935, 1756, 1497, 1455, 1436, 1389, 1349, 1283, 1203, 1177, 1141, 1115, 1089, 1074, 1028, 736, 699 cm^{-1}; LR-FDMS, *m/z* 277 (22%, $[M+1]^+$), 276

(bp, $[M]^+$); HR-FDMS, calcd for $C_{16}H_{20}O_4$ $[M]^+$: 276.1362, found: 276.1337.

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15. The production of 4-methoxyphenyl-1-propenyl ether was probably due to the presence of the acidic protons in **15** and/or a sulfonyl imine, resulting from the deoxygenation of **15**. The allylic anion of **13** would absorb these protons rather than the oxygen atom of the oxaziridine in **14**. Further exploration of effective oxidants is currently underway.
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17. Selected spectral data of **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (4H, brs), 5.83 (1H, dddd, J = 11.2, 8.3, 6.6, 2.9 Hz), 5.70 (1H, dd, J = 11.2, 6.0 Hz), 5.05 (1H, ddd, J = 9.2, 6.0, 2.9 Hz), 4.13 (1H, ddd, J = 11.0, 4.7, 4.0 Hz), 4.01 (1H, d, J = 9.2 Hz), 3.75 (6H, s), 3.59 (1H, td, J = 11.0, 4.7 Hz), 2.52 (1H, tdd, J = 13.2, 9.9, 4.7 Hz), 2.19 (1H, dddd, J = 13.2, 7.3, 4.0, 3.3 Hz), 2.06 (1H, ddtd, J = 13.2, 11.0, 4.7, 3.3 Hz), 1.52 (1H, tq, J = 13.2, 4.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 154.4 (C), 151.5 (C), 132.2 (CH), 131.3 (CH), 117.0 (CH × 2), 114.5 (CH × 2), 83.1 (CH), 76.5 (CH), 69.8 (CH_2), 55.7 (CH_3), 52.2 (CH_3), 30.1 (CH_2), 24.2 (CH_2); IR (film) ν_{max} 3024, 2951, 2836, 1750, 1506, 1464, 1436, 1284, 1227, 1170, 1117, 1035, 996, 825, 733 cm^{-1}; LR-FDMS, *m/z* 293 (18%, $[M+1]^+$), 292 (bp, $[M]^+$); HR-FDMS, calcd for $C_{16}H_{20}O_5$ $[M]^+$: 292.1311, found: 292.1317.
18. When diene **18** was refluxed with first-generation Grubbs' catalyst in CH_2Cl_2, cyclic ether **19** was not produced and **18** was recovered almost quantitatively.