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Stereoselective construction of an *anti*-β-alkoxy ether by Ireland–Claisen rearrangement for medium-ring ether synthesis

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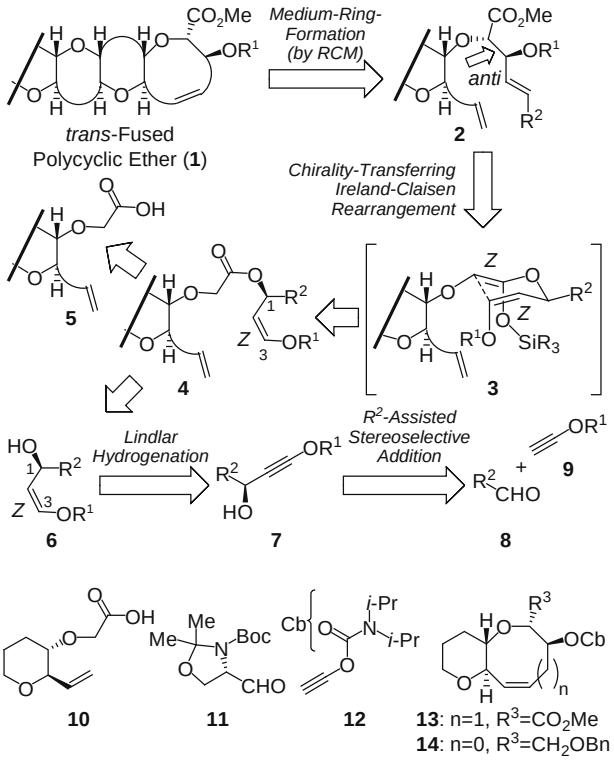
ABSTRACT

The asymmetric synthesis of an acyclic *anti*-β-alkoxy ether was achieved by the Ireland–Claisen rearrangement of *Z*-3-alkoxy-2-propenyl glycolate ester, prepared from Garner's aldehyde, a glycolic acid derivative, and ethynyl *N*,*N*-diisopropylcarbamate. The resulting acyclic ether was facilely converted to seven- and eight-membered cyclic ethers via processes involving ring-closing olefin metatheses.

Natural medium ring ether compounds, which are often bioactive, have attracted synthetic interest due to their particular structural features, such as medium-sized ring systems or stereochemical complexity around the ether linkage.[1] While a large number of synthetic methods have been developed by many research groups,[2] ring-closing olefin metathesis (RCM)[3] based approaches have been extensively explored,[4,5] because RCM realizes efficient ring-closure under mild catalytic conditions and tolerates a wide variety of functional groups in its substrates. However, the construction of the stereochemically complex ether linkage in the diene substrates of RCM for medium ring ethers is still difficult.[6] Therefore, approaches toward these systems have focused on the establishment of an efficient method for the stereoselective synthesis of acyclic ethers.

In our recent studies on the construction of medium ring ethers using RCM,[7] we found that the Ireland–Claisen rearrangement of an acyclic *Z*-3-alkoxy-2-propenyl glycolate ester stereoselectively produced an acyclic *anti*-β-alkoxy ether, corresponding to an ether moiety of a natural *trans*-fused polycyclic ether.[7a] Here, we describe the development of an improved variant of this rearrangement, which accomplishes the asymmetric synthesis of an acyclic *anti*-β-alkoxy ether from easily available starting materials for efficient medium ring ether synthesis.

The goal of this project was to devise a facile method to construct a terminal medium ring in a *trans*-fused polycyclic ether system (**1**) (Scheme 1). Toward this goal, a synthetic route was



Scheme 1.

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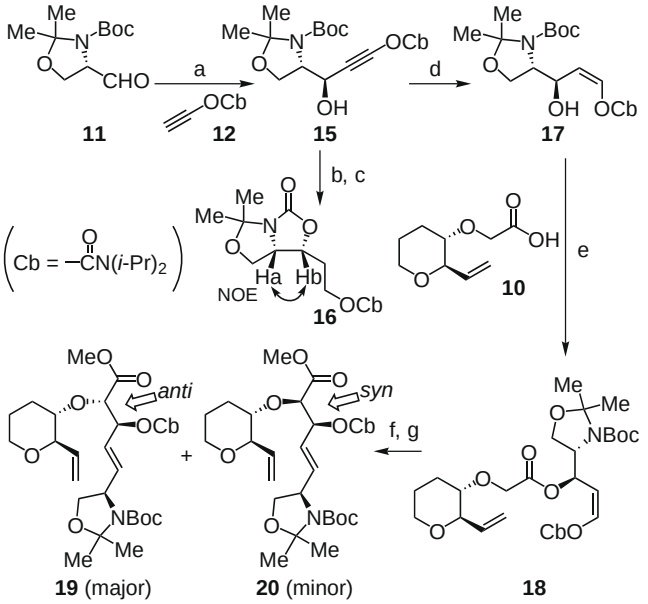
designed that relied on RCM for the ring closure of the terminal medium ring of **1** and chirality-transferring Ireland–Claisen rearrangement for setting up the *anti*-β-alkoxy ether substrate (**2**) stereoselectively. Based on our previous study that showed exclusive *anti* selectivity in the rearrangement of a simple *Z*-3-alkoxy-2-propenyl glycolate ester,[7a] 1-substituted *Z*-3-alkoxy-2-propenyl ester **4** was employed as a precursor of **2**. We also expected that the chirality at C1 of the propenyl group of **4** would be efficiently transferred to the newly formed stereocenters of **2** via putative transition state **3**.[8] Ester **4** would be prepared from polycyclic ether **5**, having a glycolic acid moiety, and chiral *Z*-3-alkoxy-2-propenol **6**. We chose to synthesize **6** by stereoselective addition of protected ynol **9** to aldehyde **8** with the assistance of the R^2 group as a chiral auxiliary, followed by Lindlar hydrogenation. Thus, the proposed synthetic route was demonstrated by the model synthesis of oxane-fused medium ring ethers **13** and **14** from oxane-connected glycolic acid **10**[9] corresponding to **5**, Garner's aldehyde (**11**),[10] reported to be efficient for stereoselective addition reactions,[11] and ethynyl *N*,*N*-diisopropylcarbamate (**12**),[12] a stable ynol derivative.

First, chiral *Z*-3-carbamoyloxy-2-propenol **17**, corresponding to **6**, was selectively synthesized (Scheme 2). The addition reaction of **11** with the acetylide derived from **12** in the presence of LiBr[13] produced alcohol **15**[14] (70%) with almost complete diastereoselectivity. The configuration of the newly generated stereocenter of **15** was determined by the presence of an NOE between Ha and Hb of **16**, derived from **15** by hydrogenation and subsequent basic treatment. Lindlar hydrogenation of **15**, followed by simple filtration, quantitatively gave **17**[14] in an almost pure form.

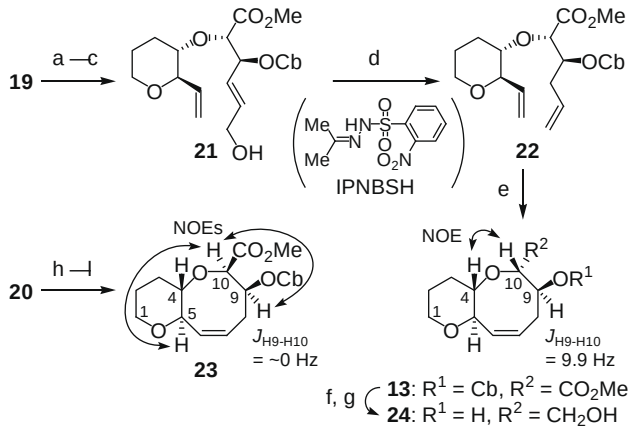
The chirality-transferring Ireland–Claisen rearrangement of ester **18**,[14] prepared by the condensation of **10** and **17** with EDCI·HCl (74%), was found to proceed successfully under the following conditions. After ester **18** was deprotonated with KHMDS (5 equiv)[15] in THF at −78 °C for 30 min, the resulting enolate was treated successively with TMSCl (5 equiv) and diethyl malonate (5 equiv). Subsequent warming of the reaction mixture to ambient temperature produced rearrangement products, which were methylated with $TMSCHN_2$[16] to afford a separable mixture of *anti*- and *syn*-ethers having an *E*-olefin (**19** and **20**, respectively) in a combined yield of 70% with 3.4:1 *anti*-selectivity. Diethyl malonate was added as a scavenger of the excess base to avoid elimination of the carbamoyloxy group from the rearrangement products. The moderate *anti*-selectivity was attributed to the moderate *Z*-preference in the ketene silyl acetal formation step from **18** under either kinetic or thermodynamic conditions. Since neither the extended time (1 h) for the deprotonation nor the addition of HMPA as a co-solvent affected the diastereoselectivity, the equilibrium thermodynamic ratio of *Z*/*E* ketene silyl acetals in this reaction is suggested to be 3.4:1. On the other hand, the kinetic formation of the ketene silyl acetal of **18** by treatment with TMSCl prior to deprotonation with KHMDS showed a somewhat decreased *anti*-selectivity (2.2:1). Thus, thanks to the thermodynamic equilibration, *anti*-ether **19** was obtained in 55% isolated yield and was available for the medium ring formation.

Next, oxane-fused eight-membered ring ethers **13** and **23** were synthesized from **19** and **20**, respectively (Scheme 3). The conversion of the 3-Boc-2,2-dimethyl-1,3-oxazoline-4-yl group of **19** to a hydroxymethyl group was first performed. A three-step process, including acidic methanolysis of **19**, oxidative cleavage of the resulting 1,2-aminoalcohol, and Luche reduction[17] produced **21** in good yield (85% from **19**). Allyl alcohol **21** was transformed to terminal alkene **22** (89%) by a modified Movassaghi's procedure,[18] in which an excess amount of 1-hexene was used as a scavenger of free diimide generated during the reaction. Treatment of **22** with a catalytic amount of second-generation Grubbs' catalyst[19] in refluxing CH_2Cl_2 promoted RCM to furnish **13**[20] in high yield (80%). The same five-step process from **20** also provided bicyclic ether **23**[20] facilely. Thus, a process for the construction of an eight-membered ether ring in five steps after the Ireland–Claisen rearrangement step was established. The *N*,*N*-diisopropylcarbamoyl (Cb) group of **13** could also be removed by stepwise treatment with $LiAlH_4$ and MeLi to produce **24** in an acceptable yield (57%).

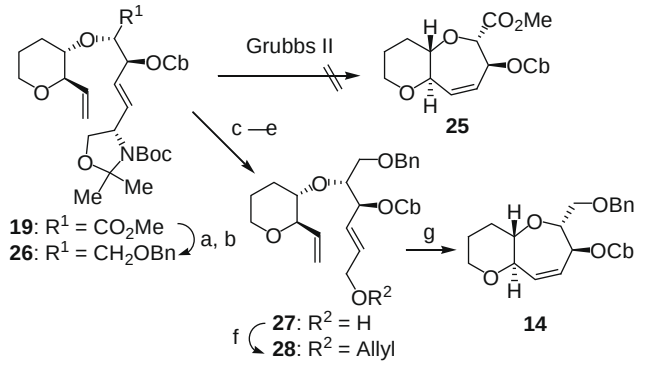
The stereochemistries of **13** and **23** were determined by NMR analysis, in which an NOE correlation H4/H10 and a large J_{H9-H10} (9.9 Hz) were detected in **13,** and NOE correlations H5/H10 and H9/H10 as well as a small J_{H9-H10} (~0 Hz) were observed in **23**,



Scheme 2. Reagents and conditions: (a) *i*-Pr_2NH, MeLi (including LiBr), **12**, THF, −78 °C, 30 min, then **11**, −78 °C, 12 h, 70%; (b) H_2, 10% Pd/C (cat.), EtOH, 24 °C, 1.5 h; (c) NaH, DMF, 24 °C, 12.5 h, 59% from **15**; (d) H_2, Lindlar's cat., PhH, 25 °C, 7.5 h, ~100%; (e) **10**, EDCI·HCl, DMAP, CH_2Cl_2, 1 h, 74% from **17**; (f) KHMDS (5 equiv), −78 °C, 30 min, then TMSCl (5 equiv), 30 min, then diethyl malonate (5 equiv), 30 min, then 24 °C, 1 h; (g) $TMSCHN_2$, MeOH, 24 °C, 10 min, 70% (**19**+**20**; **19**:**20** = 3.4:1) from **18**.



Scheme 3. Reagents and conditions: (a) 1 M HCl in MeOH, 23 °C, 3 h; (b) $NaIO_4$, 1,4-dioxane–pH 7 buffer (1:1), 25 °C, 1 h; (c) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, −78 °C, 10 min, 85% from **19**. (d) IPNBSH, Ph_3P, DEAD, THF–1-hexene (5:1), 0 °C→25 °C, 2 h, then CF_3CH_2OH–H_2O (1:1), 25 °C, 9 h, 89%; (e) $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (cat.), CH_2Cl_2, reflux, 3.5 h, 80%; (f) $LiAlH_4$, THF, 0 °C→23 °C, 1.5 h; (g) MeLi, THF, 0 °C, 1.5 h, 57% from **13**; (h) TFA–CH_2Cl_2 (1:2), 25 °C, 10 min; (i) $NaIO_4$, 1,4-dioxane–pH 7 buffer (1:1), 25 °C, 2 h; (j) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, −78 °C, 10 min, 44% from **20**; (k) IPNBSH, Ph_3P, DEAD, THF–1-hexene (5:1), 0 °C→25 °C, 2 h, then CF_3CH_2OH–H_2O (1:1), 25 °C, 9 h, 45%; (l) $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (cat.), CH_2Cl_2, reflux, 3.5 h, 92%.



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, THF, −20 °C, 1 h; (b) NaH, BnBr, Bu_4NI, THF, 0 °C→25 °C, 14 h, 87% from **19**; (c) TFA–CH_2Cl_2 (1:2), 25 °C, 10 min; (d) $NaIO_4$, 1,4-dioxane–pH 7 buffer (1:1), 25 °C, 2 h; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 10 min, 65% from **26**; (f) NaH, allyl bromide, Bu_4NI, THF, 0 °C→25 °C, 18 h, 87%; (g) $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (cat.), CH_2Cl_2, reflux, 12 h, 96%.

thereby confirming the configurations of rearrangement products **19** and **20**.

Construction of an oxane-fused seven-membered ring ether from **19** was also carried out (Scheme 4). The immediate treatment of **19** with second-generation Grubbs' catalyst[19] did not afford RCM product **25** but gave only recovered starting material. This suggested that steric congestion of the CbO- and the 3-Boc-2,2-dimethyl-1,3-oxazoline-4-yl groups would inhibit the access of any active ruthenium species to the internal olefin. Therefore, a stepwise route from **19** including the removal of the oxazolinyl group and a relay-RCM process,[21] an effective method for the RCM of sterically hindered substrates, was undertaken for the assembly of seven-membered ring ether **14**. After methyl ester **19** was converted to benzyl ether **26** by reduction and subsequent benzylation (87%), the 3-Boc-2,2-dimethyl-1,3-oxazoline-4-yl group of **26** was transformed to an allyl alcohol group by the same three-step process as described above (65%). The resulting alcohol **27** was allylated under Williamson conditions to provide **28** (87%), which was cyclized with second-generation Grubbs' catalyst[19] to furnish **14**[20] in high yield (96%). Thus, a simple procedure was set up for the seven-membered ring ether synthesis subsequent to the Ireland–Claisen step.

In conclusion, the asymmetric synthesis of an acyclic *anti*-β-alkoxy ether was achieved by the Ireland–Claisen rearrangement of *Z*-3-alkoxy-2-propenyl glycolate ester, prepared from Garner's aldehyde, a glycolic acid derivative, and ethynyl *N*,*N*-diisopropylcarbamate. The resulting acyclic ether was facilely converted to seven- and eight-membered cyclic ethers via processes involving ring-closing olefin metatheses. Further improvement of the diastereoselectivity of the rearrangement step and applications to the synthesis of natural medium ring ethers are now in progress.

Acknowledgments

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9. Acid **10** was prepared from known (2*R*,3*S*)-2-vinyltetrahydropyran-3-ol by a two-step process [(i) *tert*-butyl bromoacetate, Bu_4NHSO_4, 50% NaOH–CH_2Cl_2 (2:1), 22 °C, 1.5 h, 54%; (ii) TFA–CH_2Cl_2 (1:2), 24 °C, 1.5 h, ~100%]. The synthesis of (2*R*,3*S*)-2-vinyltetrahydropyran-3-ol, see: (a) Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carrol, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040–3054; (b) Alvarez, E.; Delgado, M.; Diaz, M. T.; Hanxing, L.; Perez, R.; Martin, J. D. *Tetrahedron Lett.* **1996**, *37*, 2865.
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13. The presence of LiBr enhanced the yield of **12**. In order to include LiBr in the reaction solution conveniently, acetylene **11** was deprotonated with LDA prepared from *i*-Pr_2NH and a commercially available ether solution of MeLi containing LiBr (Kanto Chemical Co. Ltd).
14. The compounds **15**, **17**, and **18** were stable enough to be purified by silica gel column chromatography with 5% Et_3N containing eluent.
15. An excess amount of KHMDS was required to obtain reproducible yields of the products. When **18** was treated with LDA, the terminal vinylic proton adjacent to the carbamoyloxy group was selectively deprotonated and substituted by a TMS group. LHMDS was unreactive to **18**.
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20. *Selected spectral data*: **13**: $[\alpha]_D^{25}$ +46 (*c* 0.035, $CHCl_3$); IR (neat) ν_{max} 3030, 2965, 2933, 2873, 2853, 1754, 1693, 1439, 1369, 1344, 1286, 1218, 1118, 1094, 1062, 1025, 769 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.07 (6H, d, *J* = 6.8 Hz), 1.08 (6H, d, *J* = 6.8 Hz), 1.19–1.38 (3H, m), 1.94–2.01 (1H, m), 2.52 (1H, ddd, *J* = 2.8, 6.7, 14.1 Hz), 2.67 (1H, dddd, *J* = 1.1, 3.5, 9.9, 14.1 Hz), 2.82–2.90 (1H, m), 3.12–3.20 (1H, m), 3.27–3.65 (1H, m), 3.40 (3H, s), 3.56–3.62 (1H, m), 3.71 (1H, br ddd, *J* = 1.7, 5.0, 8.6 Hz), 3.80–4.20 (1H, m), 4.27 (1H, d, *J* = 9.9 Hz), 5.60–5.69 (1H, m), 5.74 (1H, br td, *J* = 3.1, 9.9 Hz), 5.92 (1H, br dd, *J* = 5.0, 11.3 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 20.8 ($CH_3 \times 2$), 21.3 ($CH_3 \times 2$), 25.7 (CH_2), 30.1 (CH_2), 31.5 (CH_2), 45.6 (CH), 46.5 (CH), 51.6 (CH_3), 67.0 (CH_2), 73.7 (CH), 79.6 (CH), 79.9 (CH), 81.8 (CH), 125.1 (CH), 136.5 (CH), 154.2 (C), 171.2 (C); HR-EIMS calcd for $C_{19}H_{31}NO_6$ [M^+]: 369.2151, found: 369.2169. Compound **23**: $[\alpha]_D^{25}$ +139 (*c* 0.050, $CHCl_3$); IR (neat) ν_{max} 3030, 2957, 2927, 2850, 1760, 1736, 1686, 1440, 1369, 1290, 1210, 1147, 1121, 1075, 1030, 949, 769 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.00–1.42 (15H, m), 1.78–1.86 (1H, m), 1.92 (1H, tdd, *J* = 1.7, 7.3, 14.8 Hz), 2.81 (1H, ddd, *J* = 5.9, 8.2, 14.8 Hz), 2.92 (1H, br dt, *J* = 2.3, 12.0 Hz), 3.40–3.65 (4H, m), 3.45 (3H, s), 3.87 (1H, br s), 4.05–4.35 (1H, m), 5.67 (1H, br d, *J* = 5.7 Hz), 5.69–5.77 (1H, m), 5.89 (1H, ddd, *J* = 1.7, 7.2, 10.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 ($CH_3 \times 2$), 21.3 ($CH_3 \times 2$), 26.0 (CH_2), 27.3 (CH_2), 31.0 (CH_2), 45.3 (CH), 46.6 (CH), 52.4 (CH_3), 67.9 (CH_2), 74.6 (CH), 74.7 (CH), 76.4

(CH), 78.1 (CH), 126.5 (CH), 132.0 (CH), 154.7 (C), 171.0 (C); HR-EIMS calcd for $C_{19}H_{31}NO_6$ [M^+]: 369.2151, found: 369.2163. Compound **14**: $[\alpha]_D^{25}$ +15.8 (*c* 0.120, $CHCl_3$); IR (neat) ν_{max} 3089, 3064, 3031, 2970, 2929, 2867, 1693, 1439, 1369, 1335, 1287, 1263, 1215, 1133, 1097, 1048, 1031, 959, 769, 737, 699 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.86–1.26 (13H, m), 1.26–1.43 (2H, m), 1.93–2.00 (1H, m), 2.87–2.95 (1H, m), 3.21–3.29 (1H, m), 3.54–3.90 (4H, m), 3.64 (1H, dd, *J* = 6.5, 10.5 Hz), 3.73 (1H, dd, *J* = 2.3, 10.5 Hz), 3.94 (1H, ddd, *J* = 2.3, 6.5, 9.5 Hz), 4.41 (1H, d, *J* = 12.3 Hz), 4.50 (1H, d, *J* = 12.3 Hz), 5.72 (1H, br td, *J* = 2.5, 12.8 Hz), 5.84 (1H, br td, *J* = 2.1, 12.8 Hz), 5.87 (1H, br qd, *J* = 2.4, 9.5 Hz), 7.05–7.11 (1H, m), 7.14–7.21 (2H, m), 7.31–7.36 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 ($CH_3 \times 2$), 21.6 ($CH_3 \times 2$), 25.5 (CH_2), 31.0 (CH_2), 45.4 (CH), 46.5 (CH), 67.6 (CH_2), 71.0 (CH_2), 72.2 (CH_2), 73.5 (CH), 80.4 (CH), 81.0 (CH), 82.7 (CH), 127.5 (CH), 127.6 ($CH \times 2$), 128.3 ($CH \times 2$), 130.5 (CH), 132.2 (CH), 138.4 (C), 154.2 (C); HR-EIMS calcd for C24H35NO5 [M^+]: 417.2515, found: 417.2502.

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