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Tetrahedron Letters 49 (2008) 1514–1517
Tetrahedron Letters

Concise stereoselective synthesis of *cis*-3-alkoxy-2-carbomethoxy medium-ring oxacycles from (*R*)-3-(3-butenyl)-4-propynoyloxazolidin-2-one

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Received 21 November 2007; revised 13 December 2007; accepted 20 December 2007
Available online 25 December 2007

Abstract

A concise process for the stereoselective synthesis of chiral *cis*-3-alkoxy-2-carbomethoxy medium-ring oxacycles from (*R*)-3-(3-butenyl)-4-propynoyloxazolidin-2-one (**1**) was developed. The process includes five major steps: (i) hetero-Michael reaction between an alcohol and **1**, (ii) stereoselective reduction of the resulting ketone, featuring stereochemical assistance of the neighboring oxazolidin-2-one group, (iii) esterification with an alkoxy acetic acid, (iv) chirality-transferring Ireland–Claisen rearrangement of the resulting 3-alkoxyallyl glycolate ester to provide a *syn*-2,3-dialkoxy carboxylate ester, and (v) relay ring-closing olefin metathesis to form a medium-ring ether along with the simultaneous removal of the oxazolidin-2-one moiety.

Keywords: Stereoselective synthesis; Cyclic ethers; Ireland–Claisen rearrangement; Relay ring-closing olefin metathesis

Medium-ring ethers, often occurring in potent bioactive natural products,[1] have attracted much attention among synthetic chemists due to the challenges in the stereoselective construction of the medium-rings and ether systems with adjacent oxygen-functionalities. To date, various synthetic methodologies have been reported by numerous research groups,[2] including our diastereoselective synthesis of racemic *cis*- and *trans*-3-alkoxy-2-carbomethoxy eight-membered oxacycles from 3-alkoxyallyl glycolates via Ireland–Claisen rearrangement[3] and ring-closing olefin metathesis (RCM).[4,5] As an extension of our methodology toward the construction of optically active cyclic ethers, the concise stereoselective synthesis of (2*S*,3*R*)-*cis*-3-alkoxy-2-carbomethoxy medium-ring oxacycles (**2**) from (*R*)-3-(3-butenyl)-4-propynoyloxazolidin-2-one (**1**) is described herein.

Our asymmetric synthesis of medium-ring ethers **2** from chiral *E*-3-alkoxyallyl alcohol **5** is shown in Scheme 1. Based on our previously reported synthetic methodology, **5** was transformed into glycolate ester **4**, which was subjected to a chirality-transferring Ireland–Claisen rearrangement to **3**, then cyclized to **2** via RCM. Because the preparation of **5** requires the stereoselective construction of an *E*-alkoxy alkene with a hydroxymethyne group, diastereoselective reduction of **6** to **5** was carried out with the assistance of a 3-(3-butenyl)oxazolidin-2-one-4-yl moiety (R^1) (as a chiral auxiliary),[6] following the *E*-selective hetero-Michael reaction of an alcohol to **1**, which was prepared from L-serine. Furthermore, the chiral auxiliary can be removed, as bicyclic **8,** during the final cyclization of **3** to **2** by a relay ring-closing olefin metathesis (RRCM) process[7] via intermediates **7** and **9**.

First, as shown in Scheme 2, chiral acetylene ketone **1**[8] was prepared from known oxazolidinone **10**[9,10] (available from L-serine) via Swern oxidation,[11] followed by the

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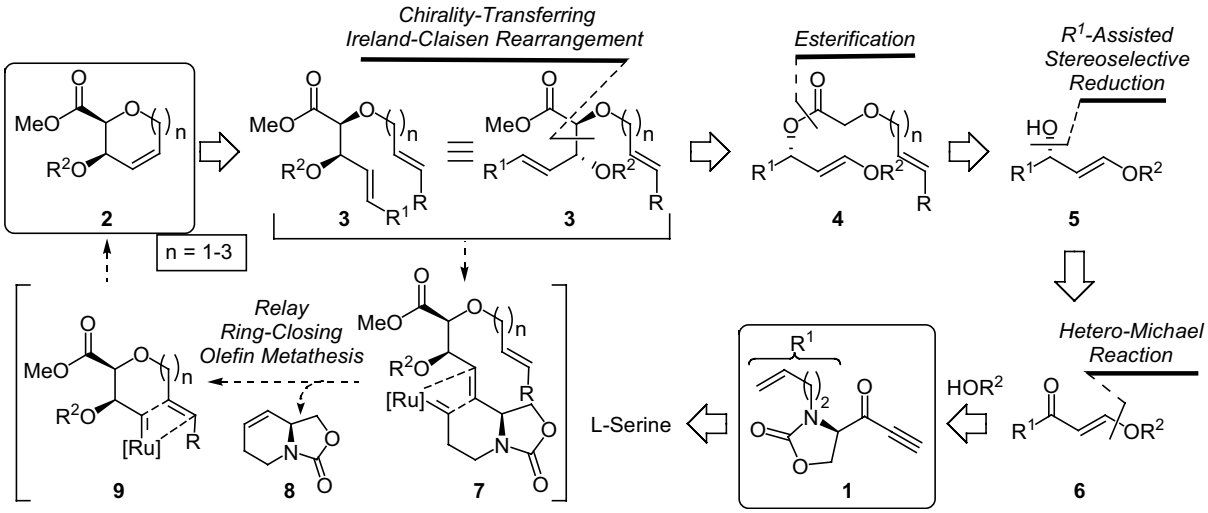
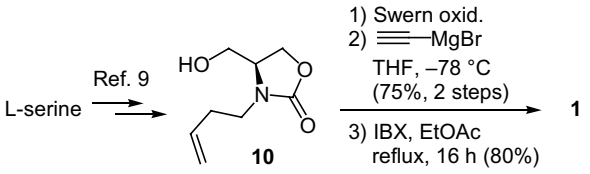
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.111



Scheme 1.

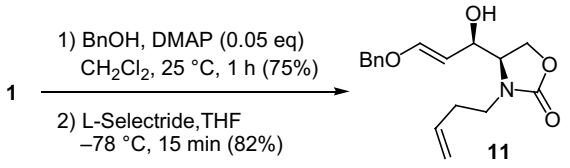


Scheme 2.

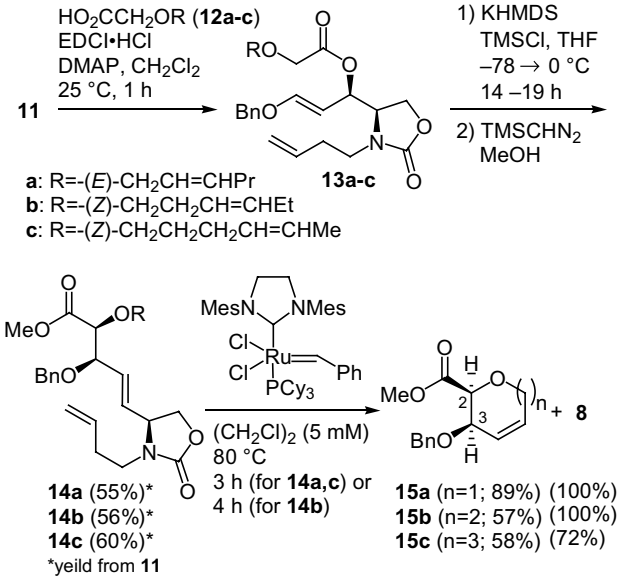
addition of ethynylmagnesium bromide and IBX oxidation[12] (overall 60%).

Next, to establish the geometry and stereocenter for the subsequent Ireland–Claisen rearrangement step, the hetero-Michael reaction between acetylene ketone **1** and an alcohol, followed by diastereoselective reduction was investigated (Scheme 3). In the presence of a catalytic amount of DMAP, the reaction between **1** and benzyl alcohol proceeded smoothly to selectively give an *E*-alkenyl ketone (75%),[13] which was reduced with L-Selectride to afford alcohol **11** as a single stereoisomer (82%).[6]

The second half of our synthetic route is shown in Scheme 4. Using EDCI/DMAP, alcohol **11** was esterified with alkenyloxyacetic acids **12a–c** to give corresponding esters **13a–c**, which are unstable under typical purification conditions but easily separable from impurities by simple extractive work up, and therefore, used without further purification. Upon deprotonation of esters **13a–c** using KHMDS in THF at −78 °C in the presence of TMSCl, the resulting ketene silyl acetals stereoselectively rearranged to the corresponding carboxylic acids while warming to

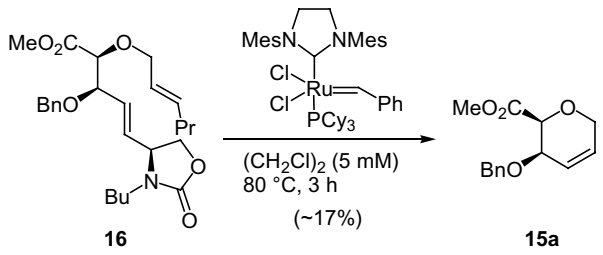


Scheme 3.



Scheme 4.

ambient temperature. Treatment of each carboxylic acid with $TMSCHN_2$ produced a stereochemically homogeneous methyl (*E*)-*syn*-2,3-dialkoxy-4-pentenoate (**14a**: 55%, **14b**: 56%, **14c**: 60%, from **11**). Trienes **14a–c** were then subjected to RRCM using a second-generation Grubbs' catalyst[14] to give the corresponding six-, seven-, and eight-membered cyclic ethers **15a–c**[15] (89%, 57%, and 58%, respectively) along with **8** (72–100%). The relative stereochemistry of **15a–c** was confirmed by the relatively small J_{H2-H3} values (**15a**: 2.8 Hz, **15b**: 1.8 Hz, **15c**: 3.3 Hz) and the presence of NOE between H2 and H3 in NMR analysis. To prove the efficiency of the chirality-transfer process from **1** to the oxocycle products, the absolute stereochemistry of **15a** was investigated as a representative example and determined to be a 2*S*,3*R*-configuration[16] with the same optical purity (>93% ee)[17] as that of **10**.[18]



Scheme 5.

Then, we examined RCM of 3-butyloxazolidin-2-on-4-yl derivative **16** instead of **14a** as a control experiment to clarify the efficiency of the *N*-(3-butenyl) group in RRCM process. As a result, a significant decrease in the yield of **15a** (~17%) was observed under identical cyclization conditions (Scheme 5).[19] This indicates that, during the initial step of RRCM, the metathesis of the *N*-(3-butenyl) group is required for high yields of the cyclic ethers.

In summary, a concise process for the stereoselective synthesis of chiral *cis*-3-alkoxy-2-carbomethoxy medium-ring oxacycles from (*R*)-3-(3-butenyl)-4-propynoyloxazolidin-2-one (**1**) was developed. The process includes major five steps: (i) hetero-Michael reaction between an alcohol and **1**, (ii) stereoselective reduction of the resulting ketone **6**, featuring the stereochemical assistance of the neighboring oxazolidin-2-one group, (iii) esterification with an alkoxy acetic acid, (iv) chirality-transferring Ireland–Claisen rearrangement of the resulting 3-alkoxyallyl glycolate ester **4** to provide *syn*-2,3-dialkoxy carboxylate ester **3**, and (v) relay ring-closing olefin metathesis to produce medium-ring ether **2** along with the simultaneous removal of the oxazolidin-2-one moiety. Further studies including the reutilization of **8** and the application of the process to natural product synthesis are currently underway in our laboratories.

Acknowledgments

We thank Mr. Kenji Watanabe and Dr. Eri Fukushi (GC–MS and NMR Laboratory, Graduate School of Agriculture, Hokkaido University) for the measurements of mass spectra. This work was supported by a Global COE Program (B01: Catalysis as the Basis for Innovation in Materials Science) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japanese Government.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.111.

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8. Selected spectral data of **1**: $[\alpha]_D^{10}$ +1.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, ddd, $J = 16.9$, 7.3, 6.9 Hz), 5.16–5.08 (2H, m), 4.50 (1H, t, $J = 10.6$ Hz), 4.42 (1H, dd, $J = 10.6$, 3.7 Hz), 4.39 (1H, dd, $J = 10.6$, 3.7 Hz), 3.75 (1H, dt, $J = 14.3$, 7.3 Hz), 3.52 (1H, s), 3.19 (1H, dt, $J = 14.3$, 6.6 Hz), 2.34 (2H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.3 (C), 157.3 (C), 134.1 (CH), 117.4 (CH_2), 84.7 (CH), 78.3 (C), 63.8 (CH), 63.1 (CH_2), 42.4 (CH_2), 31.4 (CH_2); IR (film) ν_{max} 3250, 3080, 2979, 2919, 2091, 1753, 1691, 1450, 1443, 1415, 1217, 1113, 1047, 916, 757; LR-EIMS *m*/*z* 194 (10.9%, $[M^+ + H]$), 55 (bp); HR-EIMS calcd for $C_{10}H_{12}O_3N$ $[M^+ + H]$: 194.08.
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15. Selected spectral data: **15a**: $[\alpha]_D^{23}$ −239.4 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (5H, m), 5.86 (1H, dd, $J = 10.8$, 3.3 Hz), 5.98 (1H, ddd, $J = 15.4$, 2.6, 1.5 Hz), 4.66 (1H, d, $J = 11.8$ Hz), 4.55 (1H, d, $J = 11.8$ Hz), 4.28 (1H, td, $J = 14.1$, 2.6 Hz), 4.25 (1H, d, $J = 2.8$ Hz), 4.19 (1H, dd, $J = 14.1$, 1.5 Hz), 4.15 (1H, dd $J = 3.3$, 2.8 Hz), 3.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (C), 138.2 (C), 131.2 (CH), 128.2 (CH × 2), 127.7 (CH × 2), 127.5 (CH), 122.8 (CH), 77.1 (CH), 70.5 (CH_2), 68.7 (CH), 65.8 (CH_2), 52.0 (CH_3); IR (film) ν_{max} 3032, 2950, 2869, 1764, 1735, 1496, 1454, 1437, 1393, 1352, 1322, 1292, 1260, 1209, 1189, 1096, 1068, 1041, 958, 938, 868, 739, 698; LR-EIMS; *m*/*z* 189 ($[M^+ - CO_2CH_3]$, 3.1%), 91 (bp); HR-EIMS calcd for $C_{12}H_{13}O_2$ $[M^+ - CO_2CH_3]$: 189.0916, found: 189.0879. **15b**: $[\alpha]_D^{23}$ −145.5 (*c* 0.73, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (5H, m), 6.09 (1H, ddd, $J = 11.3$, 6.9, 3.6 Hz), 5.89 (1H, ddd, $J = 11.3$, 6.6, 2.5 Hz), 4.68 (1H,

d, $J = 12.1$ Hz), 4.45 (1H, d, $J = 12.1$ Hz), 4.37 (1H, dd, $J = 6.6$, 1.8 Hz), 4.32 (1H, dd, $J = 9.5$, 2.9 Hz), 4.26 (1H, d, $J = 1.8$ Hz), 3.74 (3H, s), 3.65 (1H, td, $J = 9.5$, 2.5 Hz), 2.71 (1H, m), 2.30 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C), 138.2 (C), 135.7 (CH), 128.2 (CH × 2), 127.9 (CH × 2), 127.6 (CH), 127.3 (CH), 81.7 (CH), 75.6 (CH), 70.3 (CH_2), 69.7 (CH_2), 52.2 (CH_3), 31.9 (CH_2); IR (film) ν_{max} 3063, 3027, 2950, 2907, 1762, 1731, 1496, 1454, 1434, 1389, 1339, 1287, 1204, 1152, 1090, 1065, 1027, 921, 737, 698, 671; LR-FDMS m/z 262 ([M^+], bp); HR-FDMS calcd for $C_{15}H_{18}O_4$ [M^+]: 262.1205, found: 262.1205. **15c**: $[\alpha]_D^{23}$ −58.7 (c 0.60, $CHCl_3$); other spectral data were identical with those reported in Ref. 5.

16. Ester **15a** was converted to known (2*R*,3*R*)-3-benzyloxy-2-hydroxymethyloxane by reduction with $LiAlH_4$ followed by hydrogenation with Pt/C, and the sign of the optical rotation of the derivative agreed with that of the literature: $[\alpha]_D^{16}$ −51.5 (c 0.195, $CHCl_3$) {lit.: $[\alpha]_D^{25}$ −58.9 (c 2.1, $CHCl_3$)}: Carrillo, R.; Martín, V. S.; López, M.; Martín, T. *Tetrahedron* **2005**, *61*, 8177.
17. The precise optical purity of **15a** was determined by NMR analysis of the diastereomer ratio in the reaction mixture obtained from (*R*)- or (*S*)-MTPA with an alcohol derived from **15a** via $LiAlH_4$-reduction.
18. The absolute stereochemistry and optical purity of **15b**,**c** have not yet been determined due to the absence of appropriate literature for authentic data. They are now under investigation.
19. A significant amount of **16** was recovered (74%).