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A new approach to the synthesis of cyclic ethers via the intermolecular allylation of α-acetoxy ethers and ring-closing metathesis

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This paper is dedicated to Professor R. H. Grubbs on the occasion of his receipt of the 2003 Tetrahedron Prize

Abstract—A concise synthesis of the isolaurepinnacin skeleton **6** was achieved via the intermolecular allylation of the α-acetoxy ether **3** followed by ring-closing metathesis. This methodology was successfully applied to the convergent synthesis of the oxocene **15**, an advanced synthetic intermediate for the total synthesis of laurencin.

1. Introduction

Red algae and marine organisms which feed on *Laurencia* species have produced a variety of medium ring ethers such as isolaurepinnacin,[1] laurencin,[2] and obtusenyne[3] (Fig. 1). The unique structural features of these C15 metabolites have attracted the attention of synthetic chemists, and a number of strategies have been investigated.[4]

We recently developed a convergent method for the synthesis of polycyclic ether frameworks by the *intramolecular* allylation of α-acetoxy ether and ring-closing metathesis.[5] It was thought that the *intermolecular* version of this methodology would provide an efficient route to the construction of medium ring ethers. Crimmins et al. have reported similar approaches via asymmetric aldol- or alkylation followed by ring-closing metathesis.[6,7] In this paper, we wish to report concise syntheses of seven- and eight-membered ring ethers by the intermolecular allylation of α-acetoxy ethers and ring-closing metathesis.

2. Results and discussion

For an initial study, we examined the synthesis of the seven-membered cyclic ether **6** as shown in Scheme 1.[8] Reaction of the homoallylic alcohol **1**[9] with butyryl chloride and pyridine gave **2** in 99% yield. The ester **2** was then subjected to the Rychnovsky acetylation. Partial reduction of **2** with DIBAL-H followed by trapping of the resulting aluminium hemiacetal with acetic anhydride/pyridine/DMAP afforded the α-acetoxy ether **3** in 78% yield.[10] Treatment of **3** with allyltributyltin and $BF_3{\cdot}OEt_2$ gave the allylated product **4** as a 1:1 mixture of diastereoisomers in 85% yield.[11] Finally, the diene **4** obtained was subjected to ring-closing metathesis.[12] Thus, treatment of **4** with the first generation

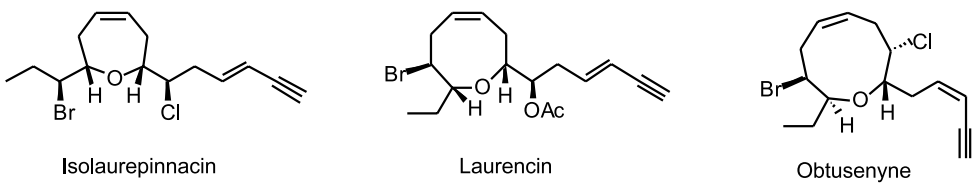

Figure 1. Representative marine medium ring ethers.

Keywords: Polycyclic ether; Allylation; RCM; Lewis acid; Marine natural product.
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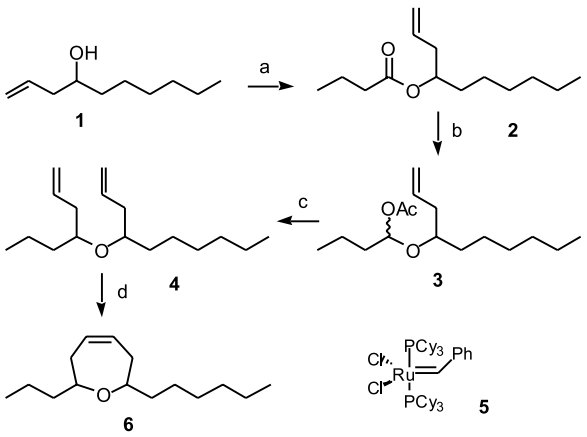
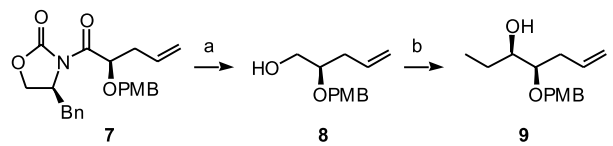


Scheme 1. Reagents and conditions: (a) C_3H_7COCl, pyridine, CH_2Cl_2, 0 °C, 99%; (b) DIBAL-H, CH_2Cl_2, −78 °C, then Ac_2O, pyridine, DMAP, −78 °C to rt, 78%; (c) allyltributyltin, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 85%; (d) **5**, CH_2Cl_2, 35 °C, 100%.

Grubbs catalyst **5**[13] provided the oxepene **6**, corresponding to the isolaurepinnacin skeleton, in quantitative yield. Although the target molecule **6** was obtained as a mixture of diastereoisomers, the methodology employed allowed us to construct the seven-membered cyclic ether **6** in only four steps from the known alcohol **1**.

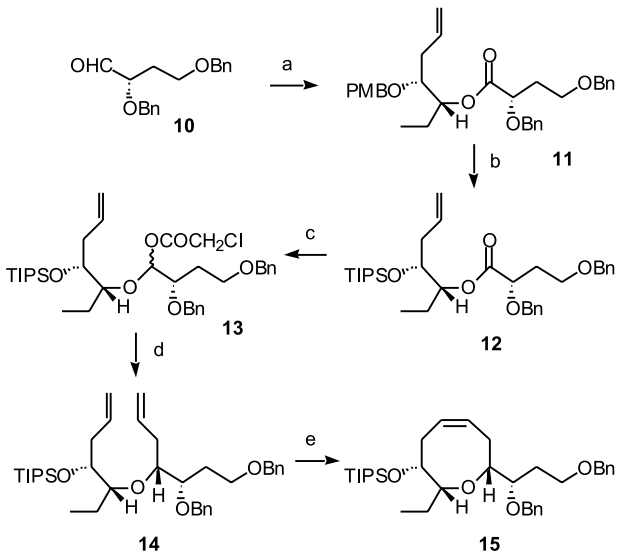
Encouraged by this result, we next examined the synthesis of eight-membered cyclic ether using the methodology described above. Scheme 2 illustrates the preparation of the alcohol segment **9**. Reduction of **7**[14] with $LiBH_4$ gave the alcohol **8** in 94% yield. Swern oxidation of **8** followed by Grignard reaction in the presence of $ZnBr_2$ afforded **9** as the sole product in 86% yield.[15]



Scheme 2. Reagents and conditions: (a) $LiBH_4$, MeOH, 0 °C, 94%; (b) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (ii) EtMgBr, $ZnBr_2$, ether, 0 °C, 86%.

Oxidation of the known aldehyde **10**[16] with Ag_2O generated from $AgNO_3$ and KOH in situ gave the corresponding carboxylic acid, which was subjected to the Yamaguchi esterification with the alcohol **9** obtained above, providing the ester **11** in 94% yield (Scheme 3).[17] Removal of the PMB group of **11** with DDQ followed by protection with TIPS group gave **12** in 81% overall yield.[18] The modified Rychnovsky acetylation afforded the α-chloroacetoxy ether **13** in 78% yield.[19] Allylation of **13** using allyltributyltin/$BF_3{\cdot}OEt_2$ gave **14** with high stereoselectivity (>95:5) in 64% yield.[20] Finally, the diene **14** was subjected to the ring-closing metathesis to provide **15** in 99% yield. The oxocene **15** is an advanced synthetic intermediate for the total synthesis of laurencin.

The α,α′-*cis* stereochemistry of **15** was unambiguously determined by NOE experiment on the acetate derivative **16** as shown in Figure 2.



Scheme 3. Reagents and conditions: (a) (i) $AgNO_3$, KOH, MeOH–H_2O, 0 °C; (ii) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, then **9** DMAP, toluene, rt, 94%; (b) (i) DDQ, $NaHCO_3$, CH_2–Cl_2–H_2O, 0 °C, 91%; (ii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt. 89%; (c) DIBAL-H, CH_2Cl_2, −78 °C, then $(CH_2ClCO)_2O$, pyridine, DMAP, −78 °C to rt, 78%; (d) allyltributyltin, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 64%; (e) **5**, CH_2Cl_2, 35 °C, 99%.

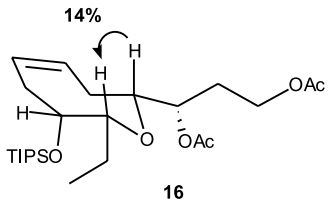


Figure 2. NOE experiment on the acetate **16**.

3. Conclusion

We have developed a new method for the construction of medium ring ethers via the intermolecular allylation of α-acetoxy ethers and ring-closing metathesis. The result described here demonstrates the efficiency and applicability of this methodology, and further studies towards the total synthesis of marine cyclic ethers having a medium ring are in progress.

4. Experimental

4.1. General

All reactions involving air- and/or moisture-sensitive materials were carried out under argon with dry solvents purchased from Wako or Kanto chemicals. On workup, extracts were dried over $MgSO_4$. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with Kanto Chemical silica gel (60N, spherical, neutral, particle size 0.100–0.210 mm). Yields refer to chromatographically and spectroscopically homogeneous materials.

4.1.1. Ester 2. To a solution of **1** (1.76 g, 11.2 mmol) in

CH_2Cl_2 (110 mL) at 0 °C were added pyridine (1.82 mL, 22.5 mmol) and butyryl chloride (1.39 mL, 13.4 mmol). After stirring for 1 h at the same temperature, the mixture was diluted with ether, then washed with saturated $NaHCO_3$ and brine. Concentration and chromatography (hexane/EtOAc, 20:1) gave **2** (2.49 g, 99%): oil; R_f=0.68 (hexane/EtOAc, 4:1); IR (neat) 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (dddd, J=17.1, 9.9, 7.2, 7.2 Hz, 1H), 5.10–5.00 (m, 2H), 4.93 (quint, J=6.3 Hz, 1H), 2.34–2.24 (m, 2H), 2.26 (t, J=7.3 Hz, 2H), 1.73–1.52 (m, 4H), 1.34–1.20 (m, 8H), 0.95 (t, J=7.3 Hz, 3H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 133.8, 117.4, 72.9, 38.6, 36.4, 33.5, 31.6, 29.0, 25.2, 22.5, 18.5, 13.9, 13.3. Anal. calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.60. Found: C, 73.90; H, 11.52.

4.1.2. α-Acetoxy ether 3. To a solution of **2** (0.57 g, 2.52 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added DIBAL-H (0.93 M in hexane, 5.0 mL, 5.04 mmol), and the mixture was stirred for 1 h at the same temperature. To the mixture, acetic anhydride (1.43 mL, 15.1 mmol), DMAP (0.61 g, 5.04 mmol) in CH_2Cl_2 (8 mL), and pyridine (0.62 mL, 7.5 mmol) were added. After stirring for 24 h at −78 °C, the mixture was allowed to warm to room temperature. The mixture was diluted with ether, then washed with saturated potassium sodium tatrate, saturated $NaHCO_3$, and brine. Concentration and chromatography (hexane/EtOAc, 40:1 containing 1% Et_3N) gave **3** (0.53 g, 78%) as a mixture of diastereomers: oil; R_f=0.57 (hexane/EtOAc 20:1); IR (neat) 1737 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.18–6.03 (m, 1H), 5.97–5.73 (m, 1H), 5.09–4.92 (m, 2H), 3.73–3.68 (m, 1H), 2.37–2.18 (m, 2H), 1.76 (s, 1.5H), 1.73 (s, 1.5H), 1.69–1.23 (m, 14H), 0.90–0.81 (m, 6H); HRMS (ESI), calcd for $C_{16}H_{29}O_3Na$ (M+Na): 293.2093. Found: 293.2043.

4.1.3. Diene 4. To a solution of **3** (0.19 g, 0.71 mmol) in CH_2Cl_2 (7 mL) at 0 °C were added allyltributyltin (0.45 mL, 1.42 mmol) and $BF_3{\cdot}OEt_2$ (1.0 M in CH_2Cl_2, 1.42 mL, 1.42 mmol). After stirring for 3 h at room temperature, the mixture was diluted with ether, then washed with saturated $NaHCO_3$ and brine. Concentration and chromatography (hexane/EtOAc, 20:1) gave **4** (2.49 g, 85%) as a 1:1 mixture of diastereoisomers: colorless oil; R_f=0.45 (hexane/EtOAc 10:1); IR (neat) 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80–5.68 (m, 2H), 5.03–4.82 (m, 4H), 3.40–3.22 (m, 2H), 2.22–2.00 (m, 4H), 1.54–1.00 (m, 14H), 0.89–0.78 (m, 6H); HRMS (EI), calcd for $C_{17}H_{32}O$ (M^+): 252.2453. Found: 252.2464.

4.1.4. Oxepene 6. To a solution of **4** (40 mg, 0.16 mmol) in CH_2Cl_2 (16 mL) was added **5** (26 mg, 32 μmol). After stirring for 4 h at 35 °C, the mixture was concentrated and purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give **6** (38 mg, 100%): colorless oil; R_f=0.56 (hexane/EtOAc 10:1); IR (neat) 2930, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74–5.64 (m, 2H), 3.98–3.94 (m, 1H), 3.30–3.25 (m, 1H), 2.37–2.03 (m, 4H), 1.60–1.28 (m, 14H), 0.93–0.87 (m, 6H); HRMS (EI), calcd for $C_{15}H_{28}O$ (M^+): 224.2140. Found: 224.2130.

4.1.5. Alcohol 8. To a solution of **7** (1.77 g, 4.47 mmol) and methanol (0.22 mL, 5.36 mmol) in ether (45 mL) at 0 °C was added $LiBH_4$ (0.12 g, 5.36 mmol), and the mixture was stirred for 1.5 h at the same temperature. The mixture was quenched with aqueous NaOH (10%, 40 mL) and extracted with EtOAc. The organic layer was washed with brine. Concentration and chromatography (hexane/AcOEt=2:1) gave **8** (0.94 g, 94%): oil; R_f=0.35 (hexane/AcOEt=2:1); $[\alpha]_D^{23}$=−14.1 (*c* 0.94, $CHCl_3$); IR (neat) 3600–3200, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=8.5 Hz, 2H), 6.89 (d, J=8.5 Hz, 2H), 5.81 (ddd, J=17.1, 7.1, 2.9 Hz, 1H), 5.14–5.07 (m, 2H), 4.59 (d, J=11.2 Hz, 1H), 4.47 (d, J=11.2 Hz, 1H), 3.81 (s, 3H), 3.68–3.50 (m, 3H), 2.41–2.26 (m, 2H), 1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 158.6, 133.5, 129.8, 128.8, 117.0, 113.4, 78.4, 70.9, 63.8, 55.1, 35.3.; HRMS (ESI), calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1148. Found: 245.1154.

4.1.6. Alcohol 9. To a solution of DMSO (0.95 mL, 13.4 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added $(COCl)_2$ (0.95 mL, 10.9 mmol), and the mixture was stirred for 15 min at the same temperature. A solution of **8** (1.35 g, 6.07 mmol) in CH_2Cl_2 (20 mL) was introduced to the resulting mixture. After stirring for additional 15 min, Et_3N (4.2 mL, 30.4 mmol) was added, and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with ether, then washed with water and brine. After concentration, the residual crude aldehyde was used for next reaction without purification.

To a stirring mixture of anhydrous zinc bromide (1.5 g, 6.70 mmol) in ether (30 mL) at 0 °C were added the alcohol obtained above in ether (30 mL) and EtMgBr (1.0 M in ether, 36 mL, 36 mmol). After stirring for 2 h at the same temperature, the mixture was quenched with saturated NH_4Cl and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ and brine. Concentration and chromatography (hexane/AcOEt=2:1) gave **9** (1.3 g, 86%): oil; R_f=0.57 (hexane/AcOEt=2:1); $[\alpha]_D^{21}$=−17.4 (*c* 0.99, $CHCl_3$); IR (neat) 3600–3200, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 5.85 (ddd, J=16.3, 10.0, 7.1 Hz, 1H), 5.15–5.06 (m, 2H), 4.62 (d, J=11.0 Hz, 1H), 4.41 (d, J=11.0 Hz, 1H), 3.79 (s, 3H), 3.44 (ddd, J=13.4, 5.1, 5.1 Hz, 1H), 3.32 (dd, J=11.1, 5.5 Hz, 1H), 2.49–2.29 (m, 3H), 1.60–1.38 (m, 2H), 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 159.1, 134.3, 130.4, 129.3, 117.2, 113.7, 80.8, 73.7, 71.8, 55.2, 34.9, 26.2, 10.1; HRMS (ESI), calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1461. Found: 273.1467.

4.1.7. Ester 11. To a solution of **10** (2.29 g, 8.06 mmol) in methanol (80 mL) at 0 °C were added KOH (6.78 g, 120 mmol) in water (40 mL) and $AgNO_3$ (13.7 g, 80.6 mmol) in water (40 mL). After stirring for 20 min at the same temperature, the insoluble material was filtered off through a Celite pad. The filtrate was acidified by 10% H_2SO_4 and extracted with EtOAc. The organic layer was washed with brine and concentrated to give the crude carboxylic acid which was used for next reaction without purification.

To a solution of the carboxylic acid obtained above in THF (80 mL) were added Et_3N (1.12 mL, 8.06 mmol) and 2,4,6-trichlorobenzoyl chloride (1.26 mL, 8.06 mmol). After stirring for overnight, the mixture was concentrated under

reduced pressures and diluted with toluene (80 mL). A solution of **9** (437 mg, 1.05 mmol) and DMAP (4.0 g, 32.2 mmol) in toluene (80 mL) was added, and the mixture was stirred for 3 h at room temperature. The mixture was diluted with ether, then washed with aqueous NH_4Cl, water, and brine. Concentration and chromatography (hexane/EtOAc, 10:1) gave **11** (2.76 g, 77%): oil; R_f=0.69 (hexane/AcOEt=2:1); $[\alpha]_D^{19}$=−17.4 (*c* 0.97, $CHCl_3$); IR (neat) 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.23 (m, 12H), 6.83 (d, *J*=8.8 Hz, 2H), 5.82 (dddd, *J*=17.1, 10.0, 7.1, 7.1 Hz, 1H), 5.11–4.95 (m, 2H), 4.68 (d, *J*=11.5 Hz, 1H), 4.58–4.40 (m, 4H), 4.32 (d, *J*=11.5 Hz), 4.16 (dd, *J*=10.7, 6.1 Hz, 1H), 3.75 (s, 3H), 3.66–3.54 (m, 3H), 3.50 (dd, *J*=10.7, 6.1 Hz, 1H), 2.29 (dd, *J*=6.8, 6.3 Hz, 2H), 2.18–1.95 (m, 2H), 1.74–1.53 (m, 2H), 0.86 (t, 3H)HH; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 159.0, 138.2, 137.4, 134.9, 134.3, 132.3, 130.2, 129.2, 128.2, 128.0, 127.9, 127.6, 127.4, 117.2, 113.6, 78.1, 75.9, 74.9, 72.9, 72.3, 71.6, 65.8, 55.2, 34.4, 33.2, 22.6, 10.1; HRMS (ESI), calcd for $C_{33}H_{40}O_6Na$ (M+Na): 555.2723. Found: 555.2705.

4.1.8. TIPS Ether 12. To a solution of **11** (16.8 mg, 38 μmol) in CH_2Cl_2 (0.4 mL) at 0 °C were added saturated $NaHCO_3$ (40 μL) and DDQ (31 mg, 0.13 mmol). After stirring for 5 h at the same temperature, the mixture was diluted with ether, then washed with saturated $NaHCO_3$ and brine. Concentration and chromatography (hexane/EtOAc, 4:1) gave the corresponding alcohol (11 mg, 91%).

To a solution of the alcohol obtained (9.3 mg, 29 μmol) in CH_2Cl_2 (1 mL) at 0 °C were added 2,6-lutidine (7 μL, 58 μmol) and TIPSOTf (11 μL, 41 μmol). After stirring for 4.5 h at room temperature, the mixture was quenched with MeOH, diluted with ether, then washed with water and brine. Concentration and chromatography (hexane/EtOAc, 10:1) gave **12** (12 mg, 89%): oil; R_f=0.63 (hexane/AcOEt=4:1); $[\alpha]_D^{24}$=−14.3 (*c* 1.43, $CHCl_3$); IR (neat) 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 10H), 5.85 (dddd, *J*=17.1, 10.0, 7.1, 7.1 Hz, 1H), 5.10–5.00 (m, 2H), 4.88 (ddd, *J*=9.3, 3.7, 3.7 Hz, 1H), 4.73 (d, *J*=11.5 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.42 (d, *J*=12.0 Hz, 1H), 4.37 (d, *J*=11.5 Hz, 1H), 4.15 (dd, *J*=9.0, 3.9 Hz, 1H), 3.97 (dd, *J*=10.3, 5.9 Hz, 1H), 3.69–3.54 (m, 2H), 2.38–1.94 (m, 3H), 1.80 (ddd, *J*=14.6, 7.6, 3.3 Hz, 1H), 1.75–1.50 (m, 2H), 1.16 (m, 21H), 0.89 (t, *J*=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 134.8, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 117.1, 78.2, 75.1, 73.0, 72.4, 72.2, 65.9, 37.7, 33.3, 21.7, 18.2, 15.4, 12.8, 10.4; HRMS (ESI), calcd for $C_{34}H_{52}O_5SiNa$ (M+Na): 591.3482. Found: 591.3476.

4.1.9. Diene 14. To a solution of **12** (345 mg, 0.61 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DIBAL-H (0.93 M in hexane, 1.30 mL, 1.21 mmol), and the mixture was stirred for 0.5 h at the same temperature. To the mixture, pyridine (0.15 mL, 1.83 mmol), DMAP (148 mg, 1.21 mmol) in CH_2Cl_2 (1.5 mL), and $(CH_2ClCO)_2O$ (626 mg, 3.66 mmol) in CH_2Cl_2 (1.5 mL) were added. After stirring for 1 h at −78 °C, the mixture was allowed to warm to room temperature. The mixture was diluted with ether, then washed with saturated potassium sodium tatrate, saturated $NaHCO_3$, and brine. Concentration gave the crude α-chloroacetoxy ether **13** which was used for next reaction without purification.

To a solution of **13** obtained above in CH_2Cl_2 (6 mL) at −78 °C were added allyltributyltin (0.96 mL, 3.10 mmol) and $BF_3{\cdot}OEt_2$ (1.0 M in CH_2Cl_2, 1.8 mL, 1.8 mmol). After stirring for 3 h at room temperature, the mixture was quenched with Et_3N, diluted with ether, then washed with saturated $NaHCO_3$ and brine. Concentration and chromathography (hexane/ether, 10:1) gave **14** (230 mg, 64%): oil; R_f=0.46 (hexane/AcOEt=10:1); $[\alpha]_D^{24}$=+1.0 (*c* 1.36, CH_3Cl); IR (neat) 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 10H), 5.96–5.79 (m, 2H), 5.10–4.99 (m, 4H), 4.69 (d, *J*=11.8 Hz, 1H), 4.49 (d, *J*=11.8 Hz, 1H), 4.45 (d, *J*=10.2 Hz, 1H), 4.42 (d, *J*=8.0 Hz, 1H), 3.95 (dt, *J*=8.3, 3.5 Hz, 1H), 3.71–3.67 (m, 1H), 3.62–3.55 (m, 3H), 3.47 (dt, *J*=9.3, 3.2 Hz, 1H), 2.47–2.06 (m, 4H), 1.93–1.70 (m, 5H), 1.43–1.35 (m, 2H), 1.07–1.00 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.4, 136.8, 135.4, 128.1, 128.0, 127.4, 127.3, 127.2, 117.0, 116.0, 84.2, 80.6, 72.7, 72.2, 67.1, 36.2, 36.0, 31.1, 21.8, 18.2, 12.8, 11.7; HRMS (ESI), calcd for $C_{37}H_{58}O_4SiNa$ (M+Na): 617.4002. Found: 617.3997.

4.1.10. Oxocene 15. To a mixture of **14** (179 mg, 0.303 mmol) in CH_2Cl_2 (60 mL) was added **5** (24 mg, 30 μmol). After stirring for 4 h at 35 °C, the mixture was concentrated and purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give **15** (170 mg, 99%): oil; R_f=0.33 (hexane/AcOEt, 10:1); $[\alpha]_D^{21}$=−15.7 (*c* 1.09, CH_3Cl); IR (neat) 3027, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 10H), 5.82–5.65 (m, 2H), 4.81 (d, *J*=11.5 Hz, 1H), 4.59 (d, *J*=11.5 Hz, 1H), 4.48 (d, *J*=11.9 Hz, 1H), 4.42 (d, *J*=11.9 Hz, 1H), 3.91 (ddd, *J*=8.8, 5.0, 2.0 Hz, 1H), 3.77–3.73 (m, 1H), 3.58 (t, *J*=7.2 Hz, 2H), 3.38–3.32 (m, 1H), 3.28 (dd, *J*=10.0, 2.6 Hz), 2.84–2.76 (m, 1H), 2.60–2.52 (m, 1H), 2.27–2.21 (m, 1H), 2.13 (dd, *J*=13.9, 8.3 Hz, 1H), 1.82 (q, *J*=6.2 Hz, 2H), 1.78–1.39 (m, 2H), 1.13–0.87 (m, 21H), 0.90 (t, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.5, 130.0, 129.2, 128.2, 128.1, 127.6, 127.4, 127.3, 84.7, 84.3, 79.3, 76.0, 73.0, 72.8, 67.4, 33.9, 32.9, 29.5, 26.1, 18.4, 18.3, 13.2, 12.8, 11.2; HRMS (ESI), calcd for $C_{35}H_{54}O_4SiNa$ (M+Na): 589.3689. Found: 589.3684.

4.1.11. Acetate 16. Lithium wire (2.3 mg, 330 μmol) was cut into small pieces and added to 10 mL of liquid ammonia at −78 °C, and the mixture was stirried for 10 min at the same temperature. To the resulting deep blue mixture, a solution of **15** (19 mg, 33 μmol) was introduced. After stirring for 20 min, the mixture was quenched with a 1:1 mixture of methanol and saturated NH_4Cl. The mixture was extracted with ether, and the organic layer was washed with brine. Concentration and chromathography (hexane/EtOAc, 2:1) gave the corresponding diol (12.8 mg, 100%).

To a solution of the diol obtained (7.5 mg, 19.4 μmol) in CH_2Cl_2 (0.5 mL) were added Ac_2O (11 μL, 116 μmol), pyridine (9.4 μL, 116 μmol), and DMAP (a catalytic amount). After stirring for 16 h, the mixture was concentrated and subjected to a column chromatography (hexane/EtOAc, 10:1 to 4:1) to give **16** (9 mg, 100%): oil; R_f=0.77 (hexane/AcOEt, 2:1); $[\alpha]_D^{25}$=−12.0 (*c* 0.40, CH_3Cl); IR

(neat) 2925, 1742 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.61–5.50 (m, 2H), 5.02 (ddd, J=9.5, 3.4 Hz, 1H), 4.21–4.01 (m, 2H), 3.79 (ddd, J=11.0, 4.9, 2.4 Hz, 1H), 3.34 (dd, J=10.5, 3.4 Hz), 3.26–3.22 (m, 1H), 2.84–2.76 (m, 2H), 2.37–1.65 (m, 6H), 1.74 (s, 3H), 1.69 (s, 3H), 1.12–0.94 (m, 21H), 0.96 (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 129.6, 129.3, 84.2, 82.5, 76.7, 73.9, 61.0, 34.2, 28.8, 26.5, 20.8, 18.7, 18.6, 18.5, 13.6, 11.1; HRMS (ESI), calcd for $C_{25}H_{46}O_6SiNa$ (M+Na): 493.2961. Found: 493.2991.

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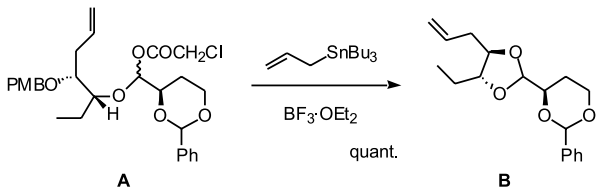
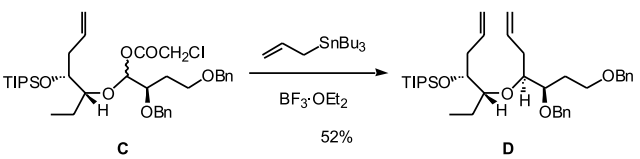
18. In a preliminary experiment, compound A, having a PMB protective group, was treated with allyltributyltin and $BF_3{\cdot}OEt_2$. Unexpectedly, the acetal derivative B was produced via the intramolecular attack of the PMB ether moiety to the resulting oxocarbenium ion. To avoid this undesired reaction, the electron-donating PMB group was replaced by a TIPS group at this stage.



A B

19. Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893–11899.
20. The reaction of the epimeric substrate C gave the diastereoisomer D, selectively (ca. 4:1). These results suggest that the stereoselectivity of the allylation is controlled by the stereochemistry at the β-position.



C D