

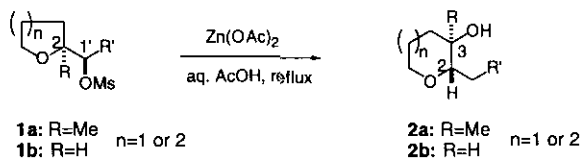
REARRANGEMENT REACTION OF TETRAHYDROFURANS AND TETRAHYDROPYRANS HAVING A C1'-MESYLOXY GROUP ON THE C2-SIDE CHAIN WITH ZINC ACETATE

Kazuo Nagasawa, Nobuyuki Hori, Hiroyuki Koshino, and Tadashi Nakata*

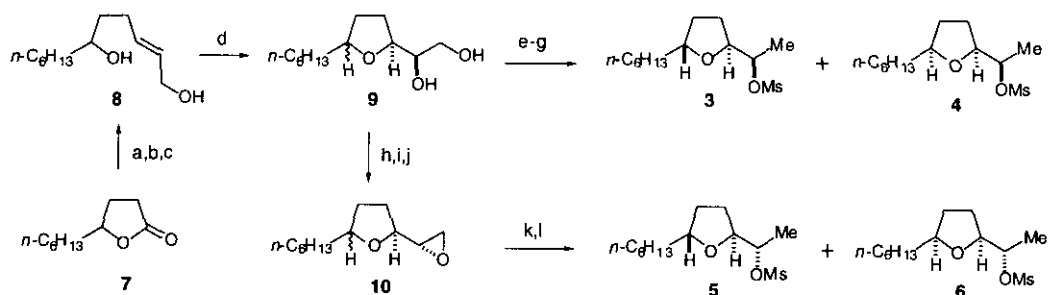
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Abstract - Rearrangements of tetrahydrofurans and tetrahydropyrans having a C1'-mesyloxy group on the C2-side chain with zinc acetate in aq. AcOH were investigated. Rearrangement-ring expansion and/or rearrangement-ring opening reactions took place depending on the stereostructure of the substrates.

In connection with the synthetic studies on marine polycyclic ethers, represented by brevetoxins,¹ we have recently developed an efficient rearrangement-ring expansion reaction of six- and seven-membered cyclic ethers having a mesylate on the C2-side chain.² Thus, upon $\text{Zn}(\text{OAc})_2$ treatment of 2-methyltetrahydrofuran (**1a**; $n=1$) and 2-methyltetrahydropyran (**1a**; $n=2$) having a C1'-mesyloxy group, the rearrangement-ring expansion stereoselectively took place giving the 2,3-*trans*-tetrahydropyran (**2a**; $n=1$) and tetrahydrooxepane (**2a**; $n=2$), respectively, in good yield.^{2a} The present reaction had been investigated so far using only cyclic ethers (**1a**; $n=1, 2$) having a methyl group at the C2-position. We now report further studies on the $\text{Zn}(\text{OAc})_2$ -mediated rearrangement reaction of the cyclic ethers (**1b**; $n=1, 2$) having no C2-methyl group.



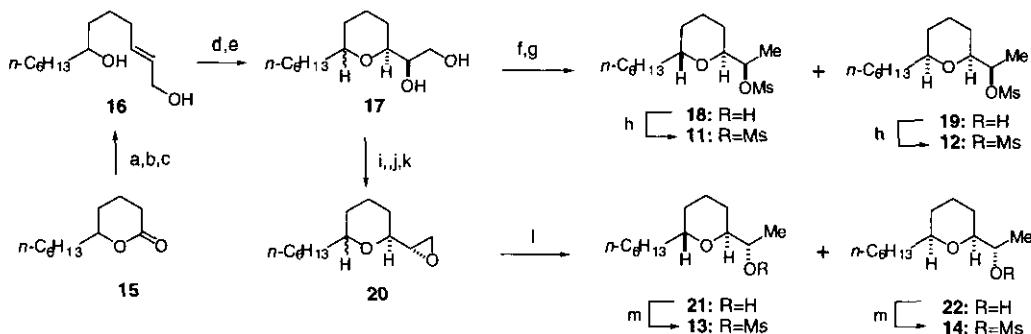
First, four possible stereoisomers of 2-(1'-mesyloxy)ethyl-5-hexyltetrahydrofurans (**3-6**) were synthesized as shown in Scheme 1.³ The reduction of γ -decanolactone (**7**) with DIBALH, the Wittig reaction using $\text{Ph}_3\text{P}=\text{CHCOOMe}$, and DIBALH reduction gave an allyl alcohol (**8**). Upon treatment of **8** with *m*-CPBA, epoxidation and successive 5-*exo*-cyclization took place to give the tetrahydrofuran (**9**). Selective tosylation of the primary hydroxyl group in **9** followed by LiAlH_4 reduction and mesylation provided a *ca.* 1:1 mixture of two isomeric mesylates (**3**) and (**4**), which were separated by HPLC. Then, the other two mesylates (**5**) and (**6**) were synthesized as follows. Selective acetylation of the primary hydroxyl group in **9** with AcCl -collidine,⁴ mesylation with MsCl - Et_3N , and successive K_2CO_3 treatment in MeOH gave an α -epoxide

Scheme 1.^a Synthesis of Tetrahydrofurans (**2**, **3**, **4**, and **5**)

^aReagents and conditions: a) DIBALH, toluene, -78 °C (100%); b) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, toluene, 100 °C (93%); c) DIBALH, toluene, -78 °C (71%); d) *m*-CPBA, CH_2Cl_2 , 0 °C (95%); e) *p*-TsCl, pyridine, 0 °C (89%); f) LiAlH_4 , THF, 0 °C-rt (83%); g) MsCl, Et_3N , CH_2Cl_2 , 0 °C (97%); HPLC separation; h) AcCl, 2,4,6-collidine, CH_2Cl_2 , -78 °C; i) MsCl, Et_3N , CH_2Cl_2 , 0 °C; j) K_2CO_3 , MeOH, 0 °C (88% from **9**); k) LiAlH_4 , THF, 0 °C-rt; l) MsCl, Et_3N , CH_2Cl_2 , 0 °C (91% from **10**); HPLC separation.

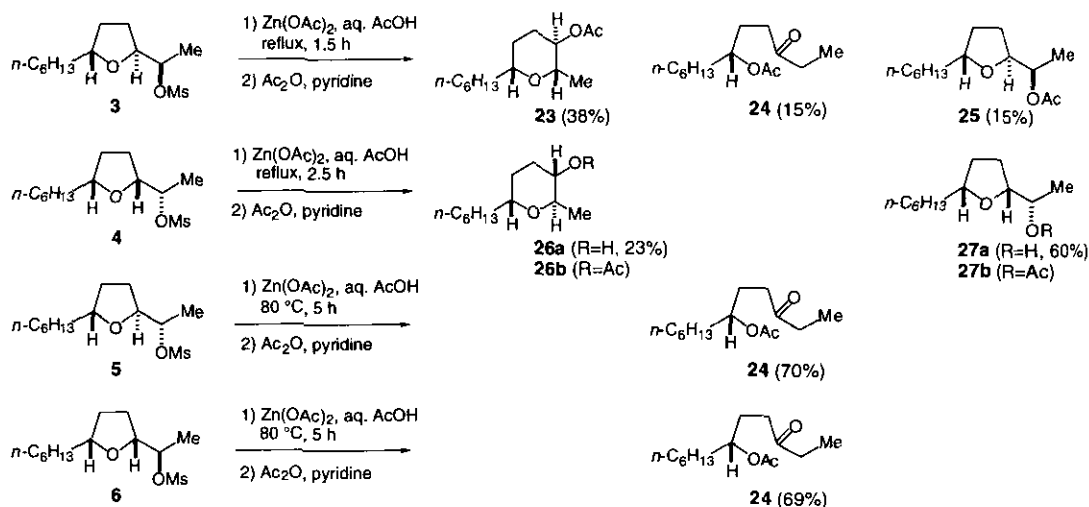
(**10**). The reduction of **10** with LiAlH_4 followed by mesylation gave a *ca.* 1:1 mixture of the desired **5** and **6**, which were also separated by HPLC. Thus, the required four stereoisomers (**3-6**) as the substrates for the rearrangement reaction were synthesized.

Next, the four possible stereoisomers of 2-(1'-mesyloxy)ethyl-6-hexyltetrahydropyrans (**11-14**) were synthesized from δ -undecan-10-ol-2-one (**15**) as shown in Scheme 2,³ by following a similar route to that of the tetrahydrofurans (**3-6**).

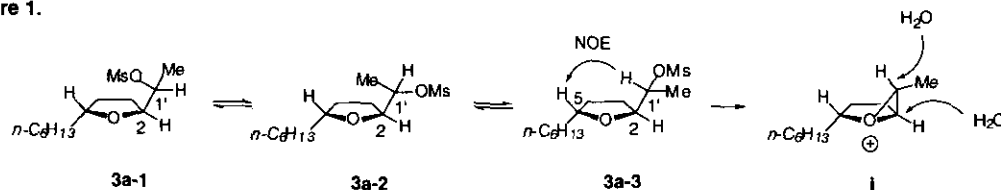
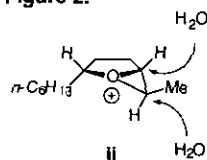
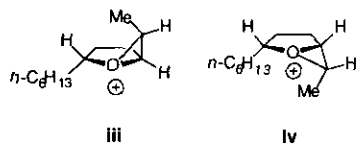
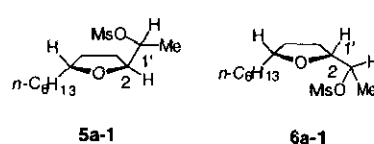
Scheme 2.^a Synthesis of Tetrahydropyrans (**11**, **12**, **13**, and **14**)

^aReagents and conditions: a) DIBALH, toluene, -78 °C (100%); b) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, toluene, 100 °C (100%); c) DIBALH, toluene, -78 °C (88%); d) *m*-CPBA, CH_2Cl_2 , 0 °C; e) CSA, CH_2Cl_2 , rt (91% from **16**); f) *p*-TsCl, pyridine, 0 °C (74%); g) LiAlH_4 , THF, 0 °C-rt (**18**, 43%; **19**, 42%); h) MsCl, Et_3N , CH_2Cl_2 , 0 °C (95% for **11**, 63% for **12**); i) AcCl, 2,4,6-collidine, CH_2Cl_2 , -78 °C; j) MsCl, Et_3N , 0 °C (82% from **17**); k) K_2CO_3 , MeOH, 50 °C (95%); l) LiAlH_4 , THF, 0 °C-rt (**21**, 52%, **22**, 31%); m) MsCl, Et_3N , CH_2Cl_2 , 0 °C (each 91% for **13** and **14**).

The rearrangement reaction of tetrahydrofurans (**3-6**) was then investigated as shown in Scheme 3.³ The 1',2-*anti*-2,5-*anti*-tetrahydrofuran (**3**) was treated with $\text{Zn}(\text{OAc})_2$ in aq. AcOH at reflux for 1.5 h and the product was acetylated with Ac_2O in pyridine to give the ring-expanded ether (**23**) in 38% yield, along with an ethyl ketone (**24**) (15%), and a tetrahydrofuran (**25**) (15%). The present ring expansion reaction would proceed stereoselectively *via* the oxonium ion (**i**) (Figure 1), which should be formed through a conformer

Scheme 3. Rearrangement of Tetrahydrofurans (**3**, **4**, **5**, and **6**) with $\text{Zn}(\text{OAc})_2$ 

(**3a-3**) having antiperiplanar relationship between the C2-O bond and the C1'-OMs group, and then addition of H_2O at the C2- and C1'-positions of **i** took place stereoselectively to give the tetrahydropyran (**23**) and the tetrahydrofuran (**25**), respectively, after acetylation. The observation of NOE between C1'-H and C5-H in **3** suggested the presence of the conformer (**3a-3**), although there are other conformers (**3a-1** and **3a-2**) due to rotation of the C2-side chain (Figure 1). The ethyl ketone (**24**) should be produced through another conformer (**3a-1**) which has antiperiplanar relationship between the C2-H and the C1'-OMs group; leaving of the C1'-OMs in **3a-1**, hydride-shift from the C2- to the C1'-position, and successive addition of H_2O at the C2-position concertedly took place to give the ketone (**24**), after acetylation. The 1',2-*anti*-2,5-*syn*-tetrahydrofuran (**4**) under the same reaction conditions produced the ring-expanded ether (**26a**) (23%) and a tetrahydrofuran (**27a**) (60%), which would be formed through the oxonium ion (**ii**) (Figure 2). The tetrahydropyran (**26a**) and tetrahydrofuran (**27a**) were acetylated to give the acetates (**26b**) and (**27b**), respectively. On the other hand, the treatment of 1',2-*syn*-2,5-*anti*- and

Figure 1.**Figure 2.****Figure 3.****Figure 4.**

1',2-*syn*-2,5-*syn*-tetrahydrofurans (**5** and **6**) with $\text{Zn}(\text{OAc})_2$ in aq. AcOH at 80 °C afforded the same ethyl ketone (**24**) in 70% and 69% yields, respectively, after acetylation. The formation of the oxonium ions (**iii**) and (**iv**) from **5** and **6** would be rather more difficult than that of **i** and **ii** from **3** and **4** because of the steric hindrance (Figure 3). Therefore, during the present reaction hydride-shift took place from the C2- to the C1'-position through the conformers (**5a-1**) and (**6a-1**) (Figure 4), respectively, which have antiperiplanar relationship between the C2-H and the C1'-OMs group, giving the ethyl ketone (**24**). Namely, in the case of 1',2-*syn*-tetrahydrofurans (**5** and **6**), rearrangement-ring opening reaction took place predominantly. The coupling constants of the C1'-H with C2-H in **3**, **4**, **5**, and **6** are 3.7, 3.8, 7.3 and 7.0 Hz, respectively, which suggested that the distribution of the rotamers due to the C2-side chain is almost the same as in **3** and **4**, and in **5** and **6**, respectively. These results also supported that the same type of reaction took place in **3** and **4**, and in **5** and **6**, respectively.

The rearrangement reaction of the tetrahydropyrans (**11-14**) was next investigated as shown in Scheme 4.³ The reaction of 1',2-*anti*-2,6-*anti*-tetrahydropyran (**11**) with $\text{Zn}(\text{OAc})_2$ afforded the ring-expanded ether, an oxepane (**28**), an ethyl ketone (**29**), and an aldehyde (**30**), in 39%, 40%, and 8% yields, respectively, after acetylation. The 1',2-*anti*-2,6-*syn*-tetrahydropyran (**12**) under the same reaction conditions yielded no ring-expanded ether, but produced the ketone (**29**) and the aldehyde (**30**) in 67% and 18% yields, respectively. The coupling constants ($J_{2,3\text{-syn}} = 2.9$ and $J_{2,3\text{-anti}} = 8.1$ Hz) of the C2-H with C3-H₂ in **11** suggested that **11** was present as a *ca.* 2:3 mixture of ring-flipped conformers (**11a**) and (**11b**) having the axial and equatorial C2-side chains, respectively (Figure 5); the ratio was deduced by comparison of the coupling constants ($J_{2,3\text{-syn}} = 2.1$ and $J_{2,3\text{-anti}} = 11.6$ Hz) of the axial C2-H with C3-H₂ in **12** having two equatorial substituents.⁵ The observed ROEs by selective PFG-1D-ROESY experiments⁶ between the C1'- and C6-protons, and C2-H and methylene protons of the C6-hexyl group in **11** also supported the presence of two conformers (**11a**) and (**11b**), respectively. The oxepane (**28**) obtained from **11** must be

Scheme 4. Rearrangement of Tetrahydropyrans with $\text{Zn}(\text{OAc})_2$

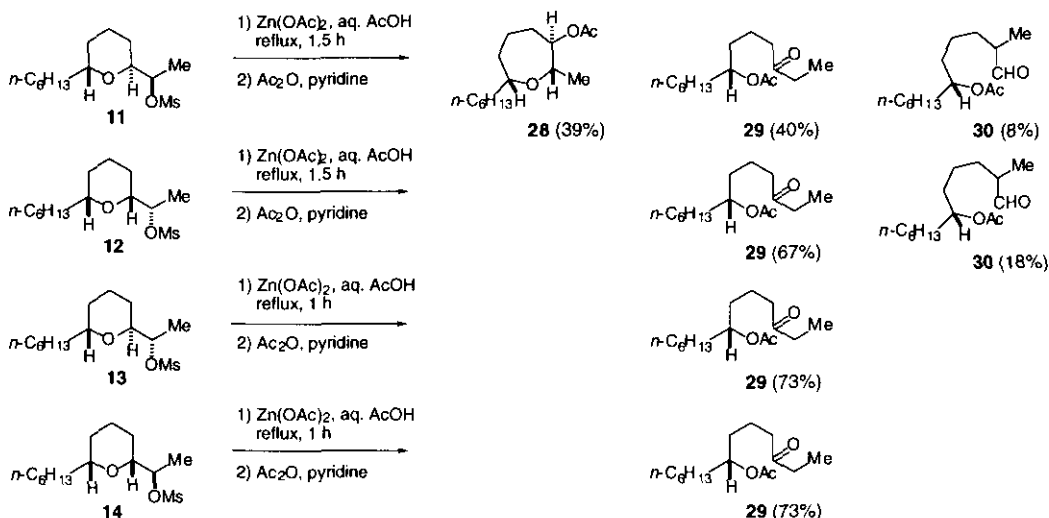


Figure 5.

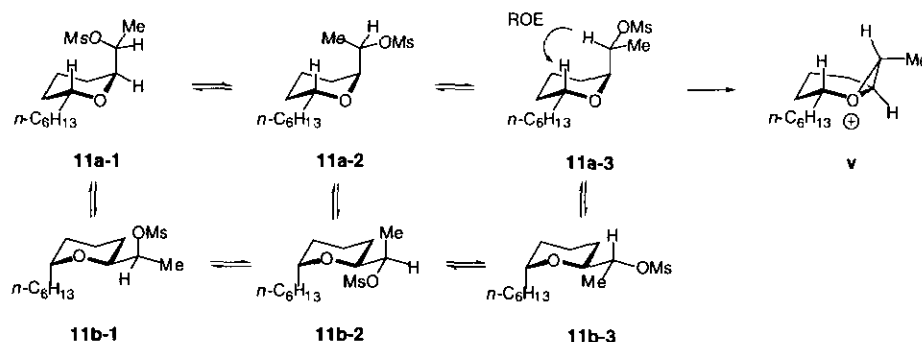


Figure 6.

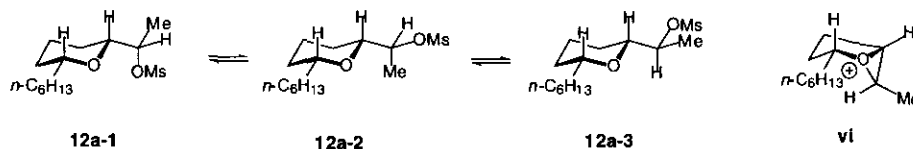


Figure 7.

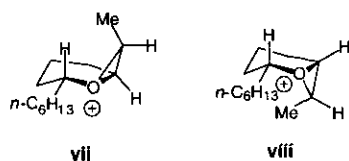


Figure 8.

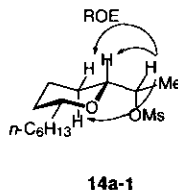
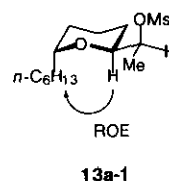


Figure 9.



produced *via* the oxonium ion (v) (Figure 5) formed through the conformer (11a-3). Formation of the oxonium ion (vi) (Figure 6) through 12a-3 would be rather more difficult than that of v, which resulted in no production of a ring-expanded ether from 12. The ketone (29) and aldehyde (30) from 11 and 12 should be produced by the C2-H and C2-3 bond migration to the C1'-position *via* conformers (11b-1, 12a-1) and (11b-2, 12a-2) (Figures 5 and 6), respectively, followed by addition of H₂O at the C2-position. On the other hand, 1',2-*syn*-2,6-*anti*- and 1',2-*syn*-2,6-*syn*-tetrahydropyrans (13) and (14) gave only the ethyl ketone (29), in both 73% yield. The non-production of a ring-expanded ether could be also explained by the difficulty of formation of the oxonium ions (vii) and (viii) (Figure 7) because of the steric hindrance. The ROE observation of 14 suggested the presence of the conformer (14a-1) (Figure 8), which led to the ketone (29) by hydride-shift. The coupling constant ($J_{2,3-syn} = 3.3$ and $J_{2,3-anti} = 9.9$ Hz) and ROE observation of 13 suggested that 13 would mainly take the conformation having an equatorial C2-side chain (Figure 9), although 13 is a mixture of ring-flipped conformers like 11; thus 13 would give the ketone (29) through 13a-1. The coupling constants of the C1'-H with C2-H in 11, 12, 13, and 14 are 6.2, 3.9, 6.6, and 6.8 Hz, respectively. The almost same coupling constants in 13 and 14 suggest almost the same distribution of rotamers due to the C2-side chain; thus, both reactions gave the same results. The different coupling constants in 11 and 12 would result from the difference in their conformers and

rotamers. Thus, only 1',2-*anti*-2,6-*anti*-tetrahydropyran (**11**), which forms the oxonium ion most easily among the four stereoisomers, produced the ring-expanded ether (**28**) although the yield is not so high. The other compounds (**12-14**) produced mainly the ethyl ketone (**29**) which resulted from hydride-shift followed by addition of H₂O.

In conclusion, in the Zn(OAc)₂-mediated reaction of 2-(1'-mesyloxy)ethyl-5-hexyltetrahydrofurans and 6-hexyltetrahydropyrans having no C2-Me group, rearrangement-ring expansion and/or rearrangement-ring opening reactions took place depending on the the stereostructure of the substrates.

EXPERIMENTAL

IR spectra were measured with a JASCO VALOR-III FT-IR spectrophotometer. ¹H and ¹³C NMR spectra were recorded on JEOL JNM-EX270, JNM-α-400, JNM-GSX500, and JNM-α-600. Chemical shifts are reported in ppm relative to Me₄Si (0 ppm) for ¹H NMR and to CDCl₃ (77.0 ppm) for ¹³C NMR as internal standard. MS spectra were recorded on JEOL JMS-HX110 spectrometers. Flash column chromatography was performed using Silica gel FL60D (Fuji Silysia Chemical Ltd.). HPLC was performed using PEGASIL SIL column (30φ x 250mm).

(E)-2-dodecene-1,6-diol (8). To a solution of γ-decanolactone (**7**) (790 mg, 4.64 mmol) in toluene (22 mL) was added DIBALH (0.98M/*n*-hexane, 5.68 mL, 5.56 mmol) at -78 °C under argon and the mixture was stirred for 1 h. Isopropyl alcohol (1 mL) and H₂O (1 mL) were added to the mixture at -78 °C and the mixture was allowed to warm to rt. After MgSO₄, SiO₂ and EtOAc were added, the mixture was stirred at rt for 1 h. The mixture was filtrated through a Celite pad, and the filtrate was evaporated. Flash column chromatography of the residue (*n*-hexane:EtOAc=3:1) gave 799 mg (100%) of lactol. To a solution of the lactol (799 mg, 4.64 mmol) in toluene (22 mL) was added Ph₃P=CHCO₂Me (1.86 g, 5.57 mmol) and the mixture was stirred at 100 °C for 1 h. After the solvent was evaporated, flash column chromatography (*n*-hexane:EtOAc=4:1) gave 988 mg (93%) of α,β-unsaturated ester. To a solution of the α,β-unsaturated ester (2.87 g, 11.8 mmol) in toluene (50 mL) was added DIBALH (0.98M/*n*-hexane, 29 mL, 28.5 mmol) at -78 °C and the mixture was stirred for 1 h. Isopropyl alcohol (2 mL) and H₂O (1 mL) were added to the mixture at -78 °C and the mixture was allowed to warm to rt. After MgSO₄, SiO₂ and EtOAc were added, the mixture was stirred at rt for 1 h. The mixture was filtrated through a Celite pad, and the filtrate was evaporated. Flash column chromatography (*n*-hexane:EtOAc=2:1) gave 1.65 g (71%) of allyl alcohol (**8**). oil; IR (neat) 3327, 1672 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 5.72 (dd, *J*=15.5, 5.4 Hz, 1H), 5.68 (dd, *J*=15.5, 4.8 Hz), 4.10 (d, *J*=4.3 Hz, 2H), 3.61 (m, 1H), 2.16 (m, 2H), 0.88 (t, *J*=6.3 Hz, 3H); ¹³C NMR (67.8 MHz, CDCl₃) δ 132.7, 129.3, 71.4, 63.6, 37.5, 36.6, 31.8, 29.3, 28.5, 25.6, 22.6, 14.1; MS (FAB) *m/z* 199 (M+H⁺).

(2S*,5R*S*)-2-[(1R*)-1,2-Dihydroxyethyl]-5-hexyltetrahydrofuran (9). To a solution of **8** (1.65 g, 8.33 mmol) in CH₂Cl₂ (30 mL) was added *m*-CPBA (2.16 g, 12.5 mmol) at 0 °C under argon and the mixture was stirred for 2.5 h. After addition of saturated aq. NaHCO₃, the mixture was extracted with ether. The organic layer was washed with brine, dried over MgSO₄ and evaporated. Flash column chromatography (*n*-hexane:EtOAc=2:1) gave 1.71 g (95%) of diol (**9**). oil; IR (neat) 3392 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 3.92 (m, 4H), 3.73 (m, 6H), 0.88 (t, *J*=6.9 Hz, 6H); MS (FAB) *m/z* 217 (M+H⁺).

(2S*,5R*)- and (2S*,5S*)-2-[(1R*)-1-Mesyloxyethyl]-5-hexyltetrahydrofurans (3 and 4). To a solution of **9** (718 mg, 3.32 mmol) in pyridine (10 mL) was added *p*-TsCl (760 mg, 3.99 mmol) at 0 °C and the mixture was stirred for 3 h. After addition of H₂O, the mixture was extracted with ether. The organic layer was washed with 10% HCl, saturated aq. NaHCO₃, and brine, dried over MgSO₄ and evaporated. Flash column chromatography (*n*-hexane:EtOAc=4:1) gave 1.10 g (89%) of tosylate. To a solution of the tosylate (45 mg, 0.12 mmol) in THF (2 mL) was added LiAlH₄ (18 mg, 0.48 mmol) at 0 °C under argon and the mixture was stirred at rt for 1 h. After the mixture was diluted with ether, H₂O (0.1 mL), 15% NaOH (0.1 mL), and H₂O (0.1 mL) were added at 0 °C. The mixture was dried over MgSO₄, filtrated through a Celite pad, and evaporated. Flash column chromatography (*n*-hexane:EtOAc=3:1) gave 22 mg (83%) of alcohol. To a solution of the alcohol (22 mg, 0.10 mmol) in CH₂Cl₂ (2 mL) was added Et₃N (0.22 mL, 1.42 mmol) and MsCl (0.10 mL, 1.29 mmol) at 0 °C under argon and the mixture was stirred for 30 min. The mixture was diluted with EtOAc, washed with H₂O, saturated aq. NaHCO₃, brine, dried over MgSO₄, and evaporated. Flash column chromatography (*n*-hexane:EtOAc=4:1) gave 27.2 mg (97%) of mesylates (**3** and **4**). The mesylates (**3** and **4**) were separated by HPLC (*n*-hexane:EtOAc=3:1, Flow rate; 14 mL/min). **3**: oil; IR (neat) 1356 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.89 (dq, *J* = 3.7, 6.7 Hz, 1H), 3.99 (ddd, *J* = 6.7, 3.7, 1.2 Hz, 1H), 3.92 (m, 1H), 3.03 (s, 3H), 1.38 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (67.8 MHz, CDCl₃) δ 80.8, 80.4, 80.1, 38.1, 35.7, 31.9, 31.7, 29.3, 26.3, 26.1, 22.5, 17.7, 14.0; HRMS (FAB) calcd for C₁₃H₂₆O₄SNa (M+Na⁺) 301.1450, found 301.1438. **4**: oil; IR (neat) 1356 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.77 (dq, *J* = 3.8, 6.4 Hz, 1H), 3.88 (ddd, *J* = 7.3, 7.3, 3.8 Hz, 1H), 3.83 (m, 1H), 3.03 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 3H); ¹³C NMR (67.8 MHz, CDCl₃) δ 80.34, 80.27, 80.2, 38.4, 35.6, 31.7, 30.9, 29.3, 26.2, 25.8, 22.5, 17.9, 14.0; HRMS (FAB) calcd for C₁₃H₂₆O₄SNa (M+Na⁺) 301.1450, found 301.1450.

(2S*,5R*)- and (2S*,5S*)-2-[(1S*)-1,2-Epoxyethyl]-5-hexyltetrahydrofuran (10). To a solution of **9** (478 mg, 2.23 mmol) in CH₂Cl₂ (10 mL) was added 2,4,6-collidine (0.87 mL, 6.62 mmol) and AcCl (0.25 mL, 3.31 mmol) at -78 °C under argon and the mixture was stirred for 35 min. After addition of H₂O at -78 °C, the mixture was allowed to warm to rt. The mixture was extracted with EtOAc, washed with saturated aq. NaHCO₃, brine, dried over MgSO₄, and evaporated to give acetate. To a solution of the acetate in CH₂Cl₂ (10 mL) was added Et₃N (1.22 mL, 8.84 mmol) and MsCl (0.34 mL, 4.42 mmol) at 0 °C under argon and the mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with H₂O, 10% HCl, saturated aq. NaHCO₃, brine, dried over MgSO₄, and evaporated to give mesylate. To a solution of the mesylate in MeOH (10 mL) was added K₂CO₃ (366 mg, 2.65 mmol) at 0 °C under argon and the mixture was stirred at rt for 3.5 h. After MeOH was evaporated, the mixture was diluted with Et₂O, washed with saturated aq. NH₄Cl, brine, dried over MgSO₄, and evaporated. Flash column chromatography (*n*-hexane:EtOAc=5:1) gave 385 mg (88%, 3 steps) of epoxide (**10**). oil; IR (neat) 1257 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 3.87 (m, 3H), 3.74 (m, 1H), 2.95 (m, 2H), 2.70 (m, 4H), 0.85 (t, *J* = 6.3 Hz, 6H); MS (FAB) *m/z* 199 (M+H⁺).

(2S*,5R*)- and (2S*,5S*)-2-[(1S*)-1-Mesyloxyethyl]-5-hexyltetrahydrofurans (5 and 6). To a solution of **10** (384 mg, 1.94 mmol) in THF (10 mL) was added LiAlH₄ (147 mg, 3.88 mmol) at 0 °C and the mixture was stirred at 0 °C for 30 min and at rt for 1 h. The mixture was diluted with Et₂O and

then H₂O (1 mL), 10% NaOH (1 mL), and H₂O (1 mL) were added. The mixture was dried over MgSO₄, filtrated through a Celite pad, and evaporated to give alcohol. To a solution of the alcohol in CH₂Cl₂ (10 mL) was added Et₃N (1.0 mL, 7.76 mmol) and MsCl (0.3 mL, 3.88 mmol) at 0 °C and the mixture was stirred for 30 min. The mixture was diluted with EtOAc, washed with H₂O, 10% HCl, saturated aq. NaHCO₃, brine, dried over MgSO₄, and evaporated. Flash column chromatography (*n*-hexane:EtOAc=4:1) gave 491 mg (91%, 2 steps) of mesylates (**5** and **6**). The mesylates were separated by HPLC (*n*-hexane:EtOAc=3:1, Flow rate; 14 mL/min). **5**: oil; IR (neat) 1354 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.61 (dq, *J* = 7.3, 6.4 Hz, 1H), 3.99 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1H), 3.93 (m, 1H), 3.09 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 82.7, 80.3, 79.8, 38.6, 35.6, 32.2, 31.8, 29.3, 28.8, 26.2, 22.6, 17.8, 14.0; HRMS (FAB) calcd for C₁₃H₂₆O₄SNa (M+Na⁺) 301.1450, found 301.1462. **6**: oil; IR (neat) 1355 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.61 (dq, *J* = 6.7, 6.7 Hz, 1H), 3.88 (q like, *J* = 7.0 Hz, 2H), 3.08 (s, 3H), 1.38 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 82.7, 80.6, 80.2, 38.5, 35.8, 31.8, 30.9, 29.3, 27.9, 26.2, 22.6, 18.1, 14.0; HRMS (FAB) calcd for C₁₃H₂₆O₄NaS (M+Na⁺) 301.1450, found 301.1464.

(E)-2-Tridecene-1,7-diol (16): oil; IR (neat) 3338 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 5.68 (dd, *J* = 15.2, 5.6 Hz, 1H), 5.59 (dd, *J* = 15.2, 5.3 Hz, 1H), 4.07 (d, *J* = 4.3 Hz, 2H), 3.58 (br s, 1H), 0.88 (t, *J* = 6.3 Hz, 3H); ¹³C NMR (67.8 MHz, CDCl₃) δ 132.8, 129.2, 71.7, 63.5, 37.4, 36.7, 32.1, 31.8, 29.3, 25.6, 25.1, 22.6, 14.0; MS (FAB) *m/z* 215 (M+H⁺).

(2S*,6R*S*)-2-[(1R*)-1,2-Dihydroxyethyl]-6-hexyltetrahydropyran (17): oil; IR (neat) 3403 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 3.72 (m, 7H), 3.52 (m, 2H), 3.28 (m, 1H), 0.88 (t, *J* = 6.3 Hz, 6H); MS (FAB) *m/z* 232 (M+H⁺).

(2S*,6R*S*)-2-[(1S*)-1,2-Epoxyethyl]-6-hexyltetrahydropyran (20): oil; IR (neat) 1263 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 3.80 (m, 1H), 3.47 (m, 1H), 3.20 (m, 2H), 3.07 (ddd, *J* = 5.3, 4.7, 2.6 Hz, 1H), 2.96 (ddd, *J* = 6.9, 4.3, 2.6 Hz, 1H), 2.73 (m, 2H), 2.63 (m, 2H), 0.91 (t, *J* = 6.3 Hz, 6H); HRMS (FAB) calcd for C₁₃H₂₅O₂ (M+H⁺) 213.1855, found 213.1862.

(2S*,6R*)-2-[(1R*)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (11): oil; IR (neat) 1356 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.82 (dq, *J* = 6.2, 6.4 Hz, 1H), 3.71 (m, 1H), 3.59 (ddd, *J* = 8.1, 6.2, 2.9 Hz, 1H), 3.04 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 79.7, 72.6, 72.0, 38.7, 32.1, 31.8, 29.2, 29.1, 25.8, 25.2, 22.6, 18.0, 17.5, 14.1; MS (FAB) *m/z* 316 (M+Na⁺).

(2S*,6S*)-2-[(1R*)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (12): oil; IR (neat) 1359 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.71 (dq, *J* = 3.9, 6.8 Hz, 1H), 3.33 (ddd, *J* = 11.2, 3.9, 2.4 Hz, 1H), 3.29 (m, 1H), 3.04 (s, 3H), 1.39 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H); ¹³C NMR (67.8 MHz, CDCl₃) δ 81.8, 78.9, 78.2, 38.4, 36.4, 31.7, 31.4, 29.2, 25.4, 25.1, 22.9, 22.5, 17.5, 14.0; HRMS (FAB) calcd for C₁₄H₂₉O₄S (M+H⁺) 293.1787, found 293.1874.

(2S*,6R*)-2-[(1S*)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (13): oil; IR (neat) 1358 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 4.69 (dq, *J* = 6.6, 6.6 Hz, 1H), 3.89 (m, 1H), 3.60 (ddd, *J* = 9.9, 6.6, 3.3 Hz, 1H), 3.05 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 81.7, 72.6, 71.6, 38.5, 31.8, 30.9, 29.2, 28.5, 26.9, 25.8, 22.6, 18.1, 17.9, 14.1; HRMS (FAB) calcd

for $C_{14}H_{29}O_4NaS$ ($M+Na^+$) 315.1606, found 315.1609.

(2S*,6S*)-2-[(1S*)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (14): oil; IR (neat) 1356 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 4.56 (dq, $J = 6.8, 6.8$ Hz, 1H), 3.27 (m, 1H), 3.38 (ddd, $J = 11.2, 6.8, 2.0$ Hz, 1H), 3.05 (s, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 82.2, 78.9, 77.9, 38.1, 36.1, 31.7, 30.8, 29.2, 26.8, 25.2, 23.0, 22.4, 17.5, 13.9; HRMS (FAB) calcd for $C_{14}H_{29}O_4NaS$ ($M+Na^+$) 315.1606, found 315.1609.

A typical procedure for the rearrangement reaction. Reaction of the tetrahydrofuran (3) with $Zn(OAc)_4$: (2S*,3R*,6R*)-3-Acetoxy-2-methyl-6-hexyltetrahydropyran (23), (6R*)-5-Acetoxy-3-dodecanone (24), and (2S*,5R*)-2-[(1R*)-1-Acetoxyethyl]-5-hexyltetrahydrofuran (25). To a solution of **3** (30 mg, 0.24 mmol) in $AcOH-H_2O$ (1:1, 2 mL) was added $Zn(OAc)_2$ (91 mg, 0.40 mmol) and the mixture was refluxed for 1.5 h. The mixture was extracted with $EtOAc$, and the organic layer was washed with H_2O , brine, dried over $MgSO_4$, evaporated, and azeotropically evaporated with toluene. To the residue was added pyridine (1 mL) and Ac_2O (1 mL) and the mixture was stirred at rt for 24 h. The mixture was azeotropically evaporated with toluene. Flash column chromatography (n -hexane: $EtOAc$ =4:1) gave 22 mg (38%, 2 steps) of **23**, 8 mg (15%) of **24**, and 8 mg (15%) of **25**. **23:** oil; IR (neat) 1740 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 4.40 (ddd, $J = 9.5, 9.5, 4.6$ Hz, 1H), 3.36 (dq, $J = 9.5, 6.3$ Hz, 1H), 3.27 (m, 1H), 2.03 (s, 3H), 1.16 (d, $J = 6.3$ Hz, 3H), 0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 77.6, 75.4, 74.0, 35.8, 31.8, 30.7, 29.4, 29.3, 25.7, 22.6, 21.2, 18.3, 14.0; MS (FAB) m/z 243 ($M+H^+$). **24:** oil; IR (neat) 1736, 1719 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 4.86 (m, 1H), 2.42 (m, 4H), 2.03 (s, 3H), 1.05 (t, $J = 7.6$ Hz, 3H), 0.87 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 170.9, 73.7, 38.1, 35.9, 34.3, 31.7, 29.1, 28.0, 25.2, 22.5, 21.2, 14.0, 7.8; HRMS (FAB) calcd for $C_{14}H_{26}O_3Na$ ($M+Na^+$) 265.1780, found 265.1779. **25:** oil; IR (neat) 1735 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 4.89 (dq, $J = 5.1, 6.2$ Hz, 1H), 3.98 (ddd, $J = 7.6, 7.6, 5.1$ Hz, 1H), 3.90 (m, 1H), 2.04 (s, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 80.20, 80.18, 72.5, 35.7, 31.8, 31.7, 29.4, 27.8, 26.1, 22.6, 21.4, 15.9, 14.1; HRMS (FAB) calcd for $C_{14}H_{26}O_3Na$ ($M+Na^+$) 265.1780, found 265.1769.

(2R*,3S*,6R*)-3-Acetoxy-2-methyl-6-hexyltetrahydropyran (26b): oil; IR (neat) 1740 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 4.57 (ddd, $J = 5.5, 4.0, 4.0$ Hz, 1H), 3.89 (dq, $J = 4.0, 6.8$ Hz, 1H), 3.67 (m, 1H), 2.08 (s, 3H), 1.23 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 71.9, 70.0, 69.8, 34.0, 31.8, 29.2, 26.8, 25.6, 23.7, 22.6, 21.4, 16.7, 14.1; HRMS (FAB) calcd for $C_{14}H_{27}O_3$ ($M+H^+$) 243.1960, found 243.1958.

(2R*,5R*)-2-[(1S*)-1-Acetoxyethyl]-5-hexyltetrahydrofuran (27b): oil; IR (neat) 1739 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 4.88 (dq, $J = 5.0, 6.3$ Hz, 1H), 3.87 (m, 2H), 2.04 (s, 3H), 1.21 (d, $J = 6.3$ Hz, 3H), 0.87 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.4, 80.5, 80.2, 72.1, 35.9, 31.9, 30.8, 29.5, 27.3, 26.1, 22.7, 21.4, 16.0, 14.2; HRMS (FAB) calcd for $C_{14}H_{26}O_3Na$ ($M+Na^+$) 265.1780, found 265.1787.

(2S*,3R*,7R*)-3-Acetoxy-2-methyl-7-hexyloxepane (28): oil; IR (neat) 1738 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 4.74 (ddd, $J = 6.8, 6.4, 3.7$ Hz, 1H), 3.51 (dq, $J = 6.4, 6.4$ Hz, 1H), 3.42 (m, 1H), 2.05 (s, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

170.3, 82.2, 79.1, 79.0, 37.1, 36.4, 31.9, 30.6, 29.2, 26.1, 22.6, 21.4, 20.3, 20.1, 14.1; HRMS (FAB) calcd for $C_{15}H_{28}O_3Na$ ($M+Na^+$) 279.1936, found 279.1946.

(7R*)-7-Acetoxy-3-tridecanone (29): oil; IR (neat) 1735, 1718 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 4.85 (quintet like, $J = \alpha$. 6 Hz, 1H), 2.41 (q like, $J = 7.3$ Hz, 4H), 2.04 (s, 3H), 1.05 (t, $J = 7.3$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 171.0, 73.8, 41.9, 35.9, 34.0, 33.5, 31.7, 29.1, 25.2, 22.6, 21.2, 19.4, 14.0, 7.8; HRMS (FAB) calcd for $C_{15}H_{28}O_3Na$ ($M+Na^+$) 279.1936, found 279.1947.

(6R*)-6-Acetoxy-2-methyl-1-dodecanal (30): oil; IR (neat) 1733 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 9.61 (d, $J = 1.7$ Hz, 1H), 4.87 (quintet like, $J = \alpha$. 6 Hz, 1H), 1.09 (d, $J = 6.9$ Hz, 3H), 0.88 (t, $J = 6.6$ Hz, 3H); HRMS (FAB) calcd for $C_{15}H_{28}O_3Na$ ($M+Na^+$) 279.1936, found 279.1932.

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