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

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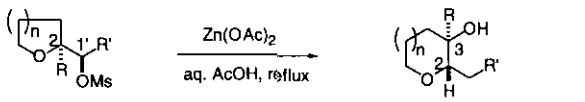
Abstract - Rearrangements of tetrahyrofurans and tetrahydropyrans having a C1'-mesyloxy group on the C2-side chain with zinc acetate in aq. AcOH were investigated. Rearrangement-ring expansion and/or rearrangement-ring opening reactions took place depending on the stereostructure of the substrates.

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 $Zn(OAc)_2$ treatment of 2-methyl-tetrahydrofuran (**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 $Zn(OAc)_2$-mediated rearrangement reaction of the cyclic ethers (**1b**; n=1, 2) having no C2-methyl group.

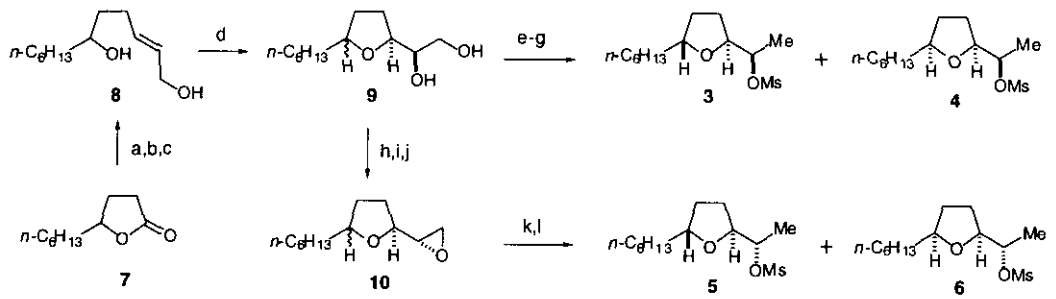


1a: R=Me
1b: R=H
n=1 or 2

2a: R=Me
2b: R=H
n=1 or 2

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 Ph_3P=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**)

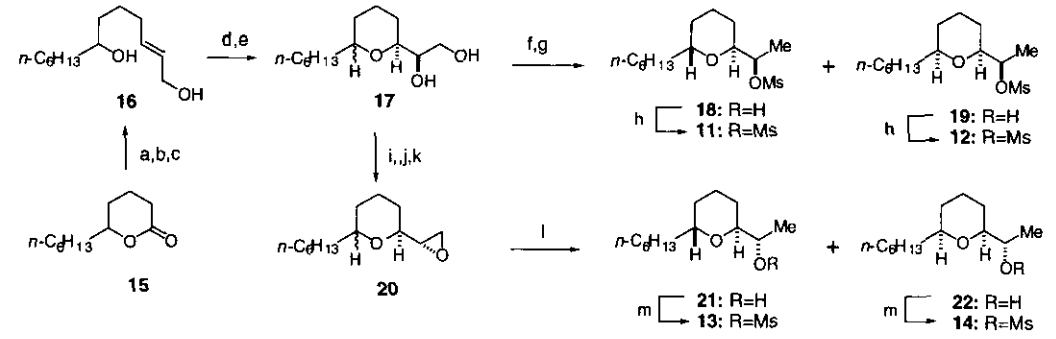


[a]Reagents and conditions: a) DIBALH, toluene, -78 °C (100%); b) $Ph_3P{=}CHCO_2Me$, toluene, 100 °C (93%); c) DIBALH, toluene, -78 °C (71%); d) *m*-CPBA, CH_2Cl_2, 0 °C (95%); e) *p*-TsCl, pyridine, 0 °C (89%); f) $LiAlH_4$, THF, 0 °C-rt (83%); g) MsCl, Et_3N, CH_2Cl_2, 0 °C (97%); HPLC separation; 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-undecanolactone (**15**) as shown in Scheme 2,[3] by following a similar route to that of the tetrahydrofurans (**3**-**6**).

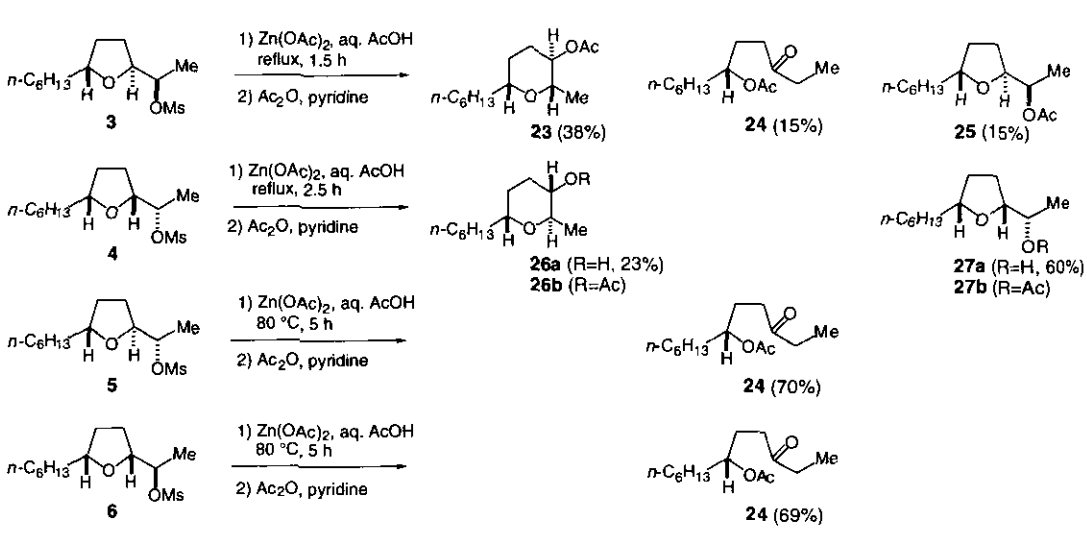
Scheme 2.[a] Synthesis of Tetrahydropyrans (**11**, **12**, **13**, and **14**)



[a]Reagents and conditions: a) DIBALH, toluene, -78 °C (100%); b) $Ph_3P{=}CHCO_2Me$, 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 $Zn(OAc)_2$ 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 $Zn(OAc)_2$



(**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.

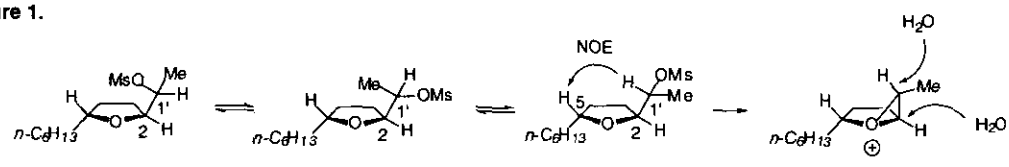


Figure 2.

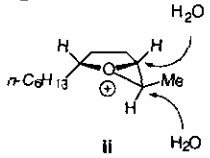


Figure 3.

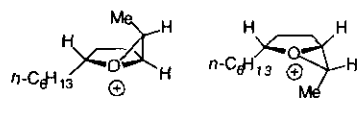
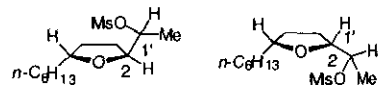


Figure 4.



1',2-*syn*-2,5-*syn*-tetrahydrofurans (**5** and **6**) with $Zn(OAc)_2$ 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 $Zn(OAc)_2$ 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-H_2 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-H_2 in **12** having two equatorial substituents.[5] The observed ROEs by selective PFG-1D-ROESY experiments[6] 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 $Zn(OAc)_2$

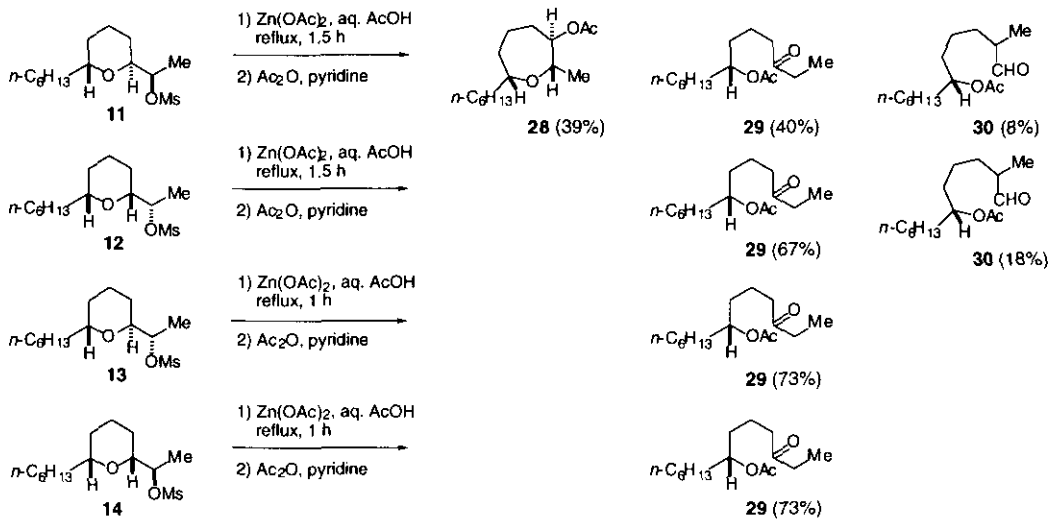


Figure 5.

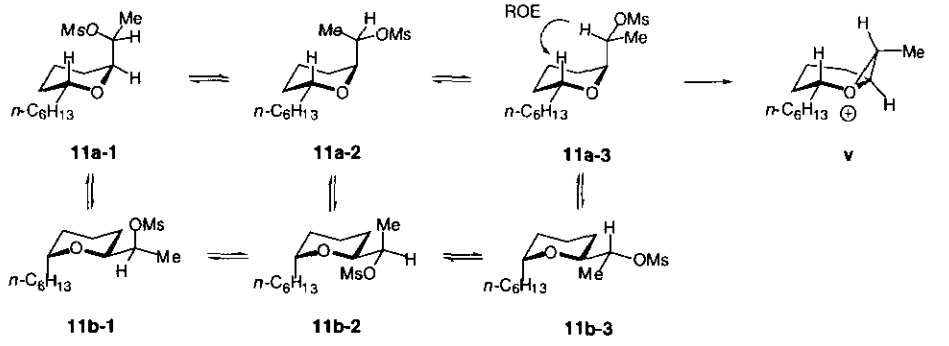


Figure 6.

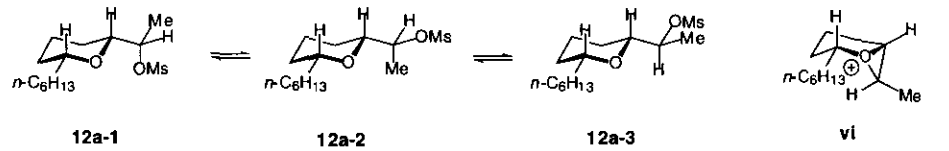


Figure 7.

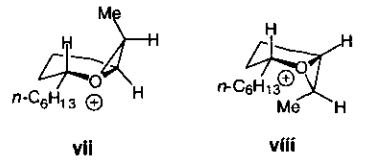


Figure 8.

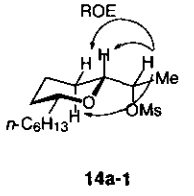
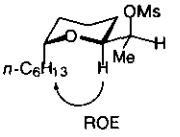


Figure 9.



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 H_2O 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 ($J_{2,3\text{-}syn}$ = 3.3 and $J_{2,3\text{-}anti}$ = 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 H_2O.

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 stereostructue of the substrates.

EXPERIMENTAL

IR spectra were measured with a JASCO VALOR-III FT-IR spectrophotometer. ^1H and ^{13}C 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 Me_4Si (0 ppm) for ^1H NMR and to $CDCl_3$ (77.0 ppm) for ^{13}C 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 H_2O (1 ml) were added to the mixture at -78 °C and the mixture was allowed to warm to rt. After $MgSO_4$, SiO_2 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 $Ph_3P{=}CHCO_2Me$ (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 H_2O (1 mL) were added to the mixture at -78 °C and the mixture was allowed to warm to rt. After $MgSO_4$, SiO_2 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, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 ($M+H^+$).

(2*S,5*R***S**)-2-[(1*R**)-1,2-Dihydroxyethyl]-5-hexyltetrahydrofuran (9).** To a solution of **8** (1.65 g, 8.33 mmol) in CH_2Cl_2 (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. $NaHCO_3$, the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ 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, $CDCl_3$) δ 3.92 (m, 4H), 3.73 (m, 6H), 0.88 (t, J = 6.9 Hz, 6H); MS (FAB) m/z 217 ($M+H^+$).

(2*S,5*R**)- and (2*S**,5*S**)-2-[(1*R**)-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 ℃ and the mixture was stirred for 3 h. After addition of H_2O, the mixture was extracted with ether. The organic layer was washed with 10% HCl, saturated aq. $NaHCO_3$, and brine, dried over $MgSO_4$ 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 $LiAlH_4$ (18 mg, 0.48 mmol) at 0 ℃ under argon and the mixture was stirred at rt for 1 h. After the mixture was diluted with ether, H_2O (0.1 mL), 15% NaOH (0.1 mL), and H_2O (0.1 mL) were added at 0 ℃. The mixture was dried over $MgSO_4$, 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 CH_2Cl_2 (2 mL) was added Et_3N (0.22 mL, 1.42 mmol) and MsCl (0.10 mL, 1.29 mmol) at 0 ℃ under argon and the mixture was stirred for 30 min. The mixture was diluted with EtOAc, washed with H_2O, saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, 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, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{13}H_{26}O_4SNa$ ($M+Na^+$) 301.1450, found 301.1438. **4:** oil; IR (neat) 1356 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{13}H_{26}O_4SNa$ ($M+Na^+$) 301.1450, found 301.1450.

(2*S,5*R***S**)-2-[(1*S**)-1,2-Epoxyethyl]-5-hexyltetrahydrofuran (10).** To a solution of **9** (478 mg, 2.23 mmol) in CH_2Cl_2 (10 mL) was added 2,4,6-collidine (0.87 mL, 6.62 mmol) and AcCl (0.25 mL, 3.31 mmol) at -78 ℃ under argon and the mixture was stirred for 35 min. After addition of H_2O at -78 ℃, the mixture was allowed to warm to rt. The mixture was extracted with EtOAc, washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated to give acetate. To a solution of the acetate in CH_2Cl_2 (10 mL) was added Et_3N (1.22 mL, 8.84 mmol) and MsCl (0.34 mL, 4.42 mmol) at 0 ℃ under argon and the mixture was stirred at 0 ℃ for 30 min. The mixture was diluted with EtOAc, washed with H_2O, 10% HCl, saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated to give mesylate. To a solution of the mesylate in MeOH (10 mL) was added K_2CO_3 (366 mg, 2.65 mmol) at 0 ℃ under argon and the mixture was stirred at rt for 3.5 h. After MeOH was evaporated, the mixture was diluted with Et_2O, washed with saturated aq. NH_4Cl, brine, dried over $MgSO_4$, 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, $CDCl_3$) 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 ($M+H^+$).

(2*S,5*R**)- and (2*S**,5*S**)-2-[(1*S**)-1-Mesyloxyethyl]-5-hexyltetrahydrofurans (5 and 6).** To a solution of **10** (384 mg, 1.94 mmol) in THF (10 mL) was added $LiAlH_4$ (147 mg, 3.88 mmol) at 0 ℃ and the mixture was stirred at 0 ℃ for 30 min and at rt for 1 h. The mixture was diluted with Et_2O and

then H_2O (1 mL), 10% NaOH (1 mL), and H_2O (1 mL) were added. The mixture was dried over $MgSO_4$, filtrated through a Celite pad, and evaporated to give alcohol. To a solution of the alcohol in CH_2Cl_2 (10 mL) was added Et_3N (1.0 mL, 7.76 mmol) and MsCl (0.3 mL, 3.88 mmol) at 0 ℃ and the mixture was stirred for 30 min. The mixture was diluted with EtOAc, washed with H_2O, 10% HCl, saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, 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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{13}H_{26}O_4SNa$ ($M+Na^+$) 301.1450, found 301.1462. **6:** oil; IR (neat) 1355 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{13}H_{26}O_4NaS$ ($M+Na^+$) 301.1450, found 301.1464.

(*E*)-2-Tridecene-1,7-diol (16): oil; IR (neat) 3338 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 ($M+H^+$).

(2*S,6*R***S**)-2-[(1*R**)-1,2-Dihydroxyethyl]-6-hexyltetrahydropyran (17):** oil; IR (neat) 3403 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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 ($M+H^+$).

(2*S,6*R***S**)-2-[(1*S**)-1,2-Epoxyethyl]-6-hexyltetrahydropyran (20):** oil; IR (neat) 1263 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 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 $C_{13}H_{25}O_2$ ($M+H^+$) 213.1855, found 213.1862.

(2*S,6*R**)-2-[(1*R**)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (11):** oil; IR (neat) 1356 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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 ($M+Na^+$).

(2*S,6*S**)-2-[(1*R**)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (12):** oil; IR (neat) 1359 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (67.8 MHz, $CDCl_3$) 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 $C_{14}H_{29}O_4S$ ($M+H^+$) 293.1787, found 293.1874.

(2*S,6*R**)-2-[(1*S**)-1-Mesyloxyethyl]-6-hexyltetrahydropyran (13):** oil; IR (neat) 1358 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) 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); ^{13}C NMR (150 MHz, $CDCl_3$) 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.

(2*S,6*S**)-2-[(1*S**)-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 $Zn(OAc)_4$: (2*S,3*R**,6*R**)-3-Acetoxy-2-methyl-6-hexyltetrahydropyran (23), (6*R**)-5-Acetoxy-3-dodecanone (24), and (2*S**,5*R**)-2-[(1*R**)-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 azeotoropically 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 azeotoropically 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; R (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.

(2*R,3*S**,6*R**)-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, 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.

(2*R,5*R**)-2-[(1*S**)-1-Acetoxyethy]-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 $C_{14}H_{26}O_3$ Na ($M+Na^+$) 265.1780, found 265.1787.

(2*S,3*R**,7*R**)-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.

(7*R)-7-Acetoxy-3-tridecanone (29):** oil; IR (neat) 1735, 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (quintet like, J = *ca.* 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.

(6*R)-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 = *ca.* 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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