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Prins cyclization of α-bromoethers under basic conditions

Patrice Arpin, Bryan Hill, Robin Larouche-Gauthier, and Claude Spino

Abstract: α-Bromoethers have been found to undergo Prins-type cyclization under basic conditions and without the need to add a promoter. The products are those derived from a Markovnikov addition on the pendant alkene. However, the stereochemistry and even the structure of the products sometimes differ from those expected with the classical Lewis-acid-catalyzed Prins reaction of acetals.

Key words: Prins cyclization, bromoethers, tetrahydrofuran, tetrahydropyran.

Résumé : Il a été découvert que les α-bromoéthers peuvent subir une cyclization de Prins en conditions basiques sans la présence d'un promoteur. Les produits obtenus découlent d'une addition Markovnikov de l'alcène. Cependant, la stéréochimie et même la structure des produits obtenus diffèrent parfois de ceux obtenus dans les conditions classiques de la réaction de Prins catalysée par un acide de Lewis.

Mots-clés : cyclization de Prins, bromoéthers, tétrahydrofuranne, tétrahydropyranne.

Introduction

The Prins cyclization is a powerful synthetic tool to make carbo- or oxacycles of different ring sizes.[1] They have been divided into three types according to the substitution pattern and the relative position of the alkene with respect to the oxonium ion (Scheme 1).[1c] The path to the final Prins type III products may or may not involve prior equilibrium of two oxonia–Cope intermediates (**A** and **B**).[2]

Although this reaction has been known for a long time,[3] it is now receiving an increasing amount of attention from the research community.[1b] This delay may be due, in part, to the fact that the typically strongly Brønsted or Lewis acidic conditions required for this transformation have limited its use in the synthesis of complex natural products.[1] More recently, many research groups are creating new catalysts, developing new reaction conditions, or inventing new structural features in the substrate to generate the pivotal oxocarbenium ion under milder reaction conditions.[4]

Among strategies to generate the oxocarbenium ion, the Lewis-acid-promoted cleavage of an acetal precursor is frequently used.[1,5] On a few occasions, authors have reported the generation of α-chloro-[6a,6b] or α-bromoethers[6c] as intermediates between the starting acetal and the oxocarbenium ion under Lewis acid treatment.

We report herein that α-bromomethyl ethers do not need any promoter to cyclize.[7] In fact, they cyclize in the absence of Brønsted or Lewis acid and in the presence of excess base[8] and many cyclize at or lower than room temperature. Moreover, the product of such cyclization may differ from the same cyclization that is promoted by a Lewis acid starting from the corresponding aldehyde or acetal.

We first observed this phenomenon when we attempted the radical cyclization of α-bromoether **1b** (Scheme 2). Instead of the expected product **3**, resulting from a radical cyclization, we obtained only the Prins cyclization product **2**. Curious about this unexpected outcome, we resubmitted the α-bromoether **1b** to the same reaction conditions but omitting the AIBN initiator and obtained the same compound **2** in a similar yield. We noted that the presence of Ph_3SnH accelerated the Prins cyclization, as the conversion of α-bromoether **1b** to **2** in refluxing benzene without any additive was indeed slower (almost no conversion after 10 h, the time required for the tin-promoted reaction to complete).

Intrigued by these observations, we surveyed the behavior of a number of α-bromoethers with and without additives. α-Bromoether **5** was prepared from the corresponding methoxymethyl ether (MOM) acetal **4** by the method of Guindon[9] using Me_2BBr at low temperature (Scheme 3). With excess potassium carbonate or di-*t*-butylmethylpyridine (DTBMP), the sensitive α-bromoether **5** could be isolated.[10] We submitted it to various reaction conditions to effect its cyclization to tetrahydrofuran **6**. Simply letting α-bromoether **5** sit at room temperature for 7 h in dichloromethane effected its cyclization to bromide **6**, which, given its sensitive nature, was reduced with Ph_3SnH to the isopropyl analogue **7**, in this case obtained in 44% yield for the two steps. In refluxing benzene, the cyclization was complete in a matter of minutes and we obtained a similar yield of **7** after reduction with Ph_3SnH. Strong Lewis acids ($SnCl_4$, $TiCl_4$, and BCl_3) or HBr promoted the reaction, which could then be performed at –78 °C in these cases, and again, product **7** was obtained in yields varying from 30% to 52%. Weak Lewis acids such as Me_4Sn, $(TMS)_3SiH$, and Ph_3SnH somewhat accelerated the cyclization but did not increase the yield of product **7** and we began to wonder if a promoter was really necessary. We thus added excess base to see if the reaction would proceed under basic conditions: we found that the reaction proceeded indeed in higher yield. When potassium carbonate was used, the cyclization/reduction product **7** was isolated in 74% yield for the two steps. With DTBMP, the two alkenes **8a** and **8b** were isolated in 98% yield and a 2:1 ratio.

A one-pot procedure starting from the MOM acetal was found to be optimal: after treatment with Me_2BBr and excess potassium carbonate or DTBMP for 15 min, the remaining boron reagent and the dimethylboron methoxide formed were removed under high vacuum[11] and the sensitive α-bromoether **5** was unambiguously

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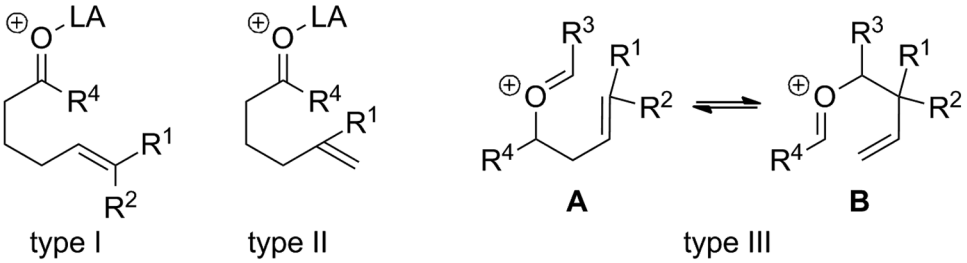
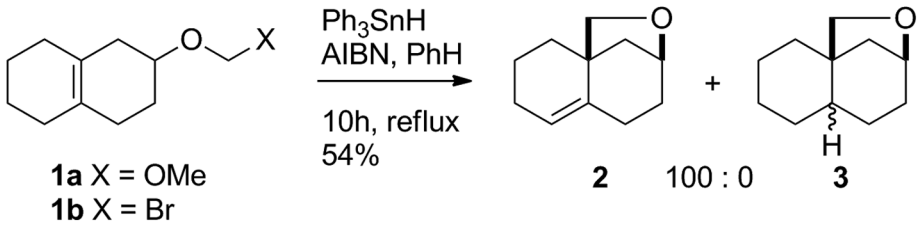
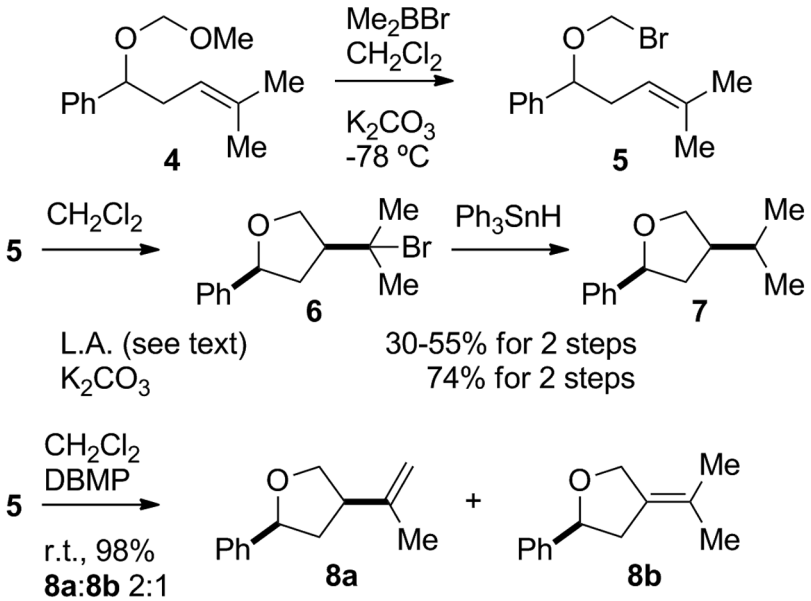
Scheme 1. Prins cyclizations.



Scheme 2. Prins cyclization of **1**.



Scheme 3. Prins cyclization of **5**.



assigned by ^{1}H NMR of an aliquot. Solvent was reintroduced and α-bromoether **5** in the presence of excess base cyclized (to **6** or **8a** and **8b** depending on the base) within 48 h at 25 °C.

Surprisingly, there are few reports of the utilization of the Prins cyclization to make tetrahydrofuran rings, none with the stereochemical relationship found in product **6** or **8**.[12] However, Rawal and co-workers cyclized the phenylselenide analogue of **5** (Br = SePh) under radical conditions and obtained **7** in 83% in a *syn*:*anti* ratio of 2.2:1.[13] The anionic cyclization of a similar compound gave mostly (15:1) the *syn* tetrahydrofuran analogous to **7** in 49% yield.[14]

We studied three more cases of the formation of five-membered rings using the procedure described above and potassium carbonate as the base (Fig. 1; Table 1, entries 1–3). Each time, only the tetrahydrofuran having the *syn* stereochemistry was obtained. Distinctively, cyclization of allylsilanes **13a** and **13b** was terminated by the bromide ion rather than by loss of the silyl group (Table 1, entry 3).[15] Elimination of trimethylsilyl bromide (TMSBr) occurred upon chromatography to give the terminal alkene **14c** (Fig. 1), although products **14a** and **14b** were unambiguously characterized in the crude mixture. The stereochemistry of **14c** was assigned by nOe experiments. The fact that the silyl group did not eliminate under such conditions suggests a fast delivery of the bromide ion onto the carbocation, perhaps via a tight ion pair. Rychnovsky and co-workers also argued an intimate ion pair to explain the unusual axially selective attack of bromide ion from the treatment of α-acetoxyethers with trimethylsilyl bromide.[6b,16] Indeed, axial attack of the bromide ion occurred in the cyclization of α-bromoethers **15a** and **15b** (Table 1, entry 4). Note that if the yield was higher using DTBMP, the ratio of **16a**:**16b** remained 8:1 when K_2CO_3 was used.

The 1,1-disubstituted alkene in **17** led to a 2:2:1 mixture of tetrahydropyrans **18a**, **18b**, and **18c** (Table 1, entry 5). This results stands in contrast with the axially selective Lewis-acid-catalyzed cyclization of a similar substrate by the group of Rychnovsky.[6b] However, preference for axial attack was shown to be sensitive to reaction conditions, and in neither case (Table 1, entries 4 and 5) could we ascertain whether an oxonia–Cope rearrangement was involved or not.[17]

Fig. 1. Structures of compounds in Table 1.

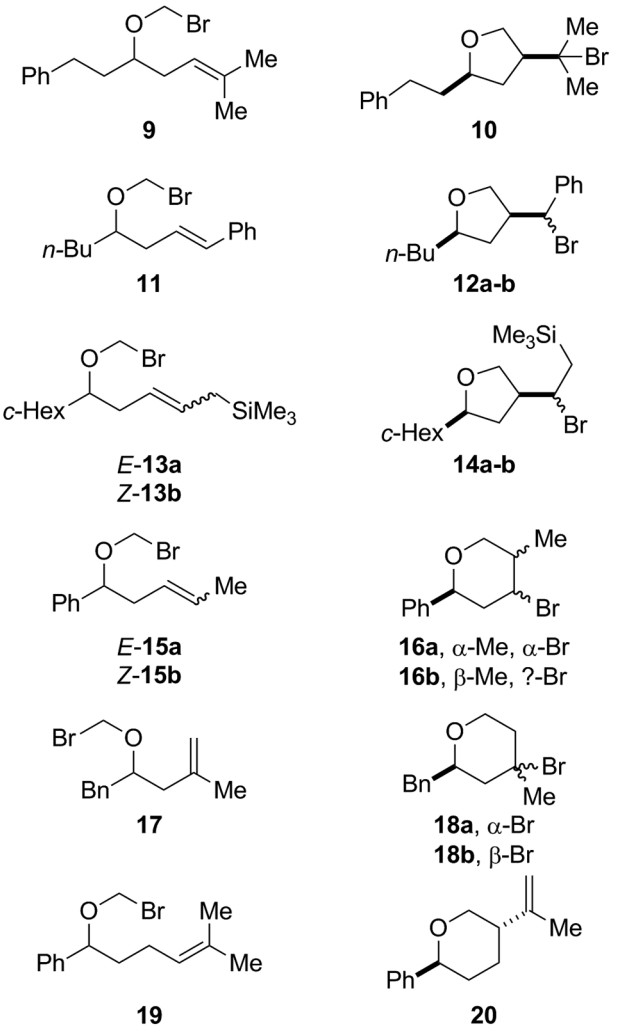


Table 1. Prins cyclization of α-bromoethers **9**, **11**, **13**, **15**, **17**, and **19** under basic conditions.

Entry	Base[a]	α-Bromoether	Product (yield)[b]
1	K_2CO_3	**9**	**10** (66%)[c]
2	K_2CO_3	**11**	**12a** and **12b** 89% (1:1)
3	K_2CO_3	*E*-**13a**[d] *Z*-**13b**	**14a** and **14b** (75%)[e]
4	DTMB	*E*-**15a** *Z*-**15b** (*E*:*Z* = 8:1)	**16a**, α-Me, α-Br **16b**, β-Me, ?-Br (84%, **a**:**b** = 8:1)
5	K_2CO_3	**17**	**18a**, α-Br **18b**, β-Br (68%, 1:1)[f]
6	DTMB	**19**	**20** (53%)

[a]See text for reaction conditions.
[b]Isolated yields.
[c]Best isolated after reduction of the bromide with *n*-Bu_3SnH.
[d]The α-bromoether could neither be isolated nor observed in this case.
[e]Yield of the product of elimination of Br-$SiMe_3$, alkene **14c** (Fig. 1), after chromatography.
[f]Accompanied by 17% of compound **18c** having an exocyclic double bond for a total yield of 85%.

The 6-exo-trig mode of cyclization led exclusively to the 2,5-*anti*-disubstituted tetrahydropyran **20** (entry 6). A purported tertiary bromide in the initial product presumably undergoes fast E1-type elimination under the reaction conditions.

The difference between the cyclization of α-bromoethers and the Lewis-acid-promoted cyclization of acetals is underscored in the cyclization of (*E*,*E*)- and (*Z*,*E*)-1,5-dienes **21a** and **21b** (Fig. 2). Polycyclization[18] is expected with such dienes and this is indeed the result we obtained using Lewis acids such as $SnCl_4$ and $BF_3{\cdot}Et_2O$ (Fig. 2; Table 2, entries 2 and 3). Strangely, the milder Lewis acid TMSBr led to a multitude of unidentifiable products (Table 2, entry 4) as did the stronger Lewis acid $TiCl_4$ (Table 2, entry 5). With our conditions, starting with (*E*)-**21a**, a 92% yield of a single diastereomer of monocyclization product **22a** was isolated, devoid of any trace of bis-cyclization products (Table 2, entry 1). When starting from the *Z* isomer, 70% of a 1:5 mixture of diastereomers **22a** and **22b** was isolated. The major diasteromer was now the *syn* isomer **22b**.

This initial study clearly shows that α-bromoethers cyclize under basic conditions and that the end product may be different from that obtained with the classic Lewis-acid-promoted cyclization of an acetal. We are now working to find a method to make α-bromoethers from alcohols under completely basic or neutral conditions.

Perhaps not surprisingly, when the alkoxide from alcohol **24** (Scheme 4) was mixed with different dihalomethanes or tosylhalomethanes in the presence of base, only a symmetrical acetal **25** was formed (Fig. 3).[19,20] Alcohol **24** reacted with Dolbier's salt[21] in DMF at reflux temperature to give products **8a** and **8b** in 58% combined yield and in a 4:1 ratio. The ammonium salt **26** was easily prepared from the alcohol **24** and Eschenmoser's salt. Heating it in refluxing DMF led to no reaction until lithium bromide was added. Then, compound **8b** was isolated in 67% yield. The high temperature is a drawback in these methods. Efforts to achieve acid-free Prins cyclization, including the use of bromomethyl carbene, are continuing.

We have shown that α-bromoethers can cyclize under basic conditions and need no promoter to do so. The cyclization products are often different, structurally or stereochemically, from the classic Lewis-acid-catalyzed reaction. Further efforts to discover strictly neutral or basic conditions to make the α-bromoethers from the corresponding alcohols are underway.

Experimental section

General considerations

All reactions were performed under an inert atmosphere of argon in glassware that had been flame dried. Solvents were distilled from calcium hydride (dichloromethane, triethylamine, and pyridine) and from potassium/benzophenone (tetrahydrofuran) prior to use.

n-Butyllithium (solution in hexanes) was titrated using the method of Love and Jones.[24] Reagents were purchased and used without purification. Flash chromatography was performed using silica gel (230–400 mesh) with solvents distilled prior to use. IR spectra were recorded as a neat film of oil on NaCl pellets. NMR spectra were recorded at 300 MHz for ^{1}H NMR and at 75.5 MHz for ^{13}C NMR. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR)). IR spectra were recorded on a thin layer of the product on a NaCl disk. GCMS analyses were performed on a 30 m lengh, 25 μ OD, DB-5ms MSD column coupled with a mass spectrometer.

2-(Methoxymethoxy)-1,2,3,4,5,6,7,8-octahydronaphthalene (1a)

To a stirred solution of 1,2,3,4,5,6,7,8-octahydronaphthalen-2-ol (prepared according to the method of Marshall and co-workers)[22] (420 mg, 2.75 mmol) and dimethoxymethane (14 mL) were added LiBr (240 mg, 2.76 mmol) and TsOH (53 mg, 0.28 mmol). After 2 days, both water and ethyl ether were added, the layers were separated, and the aqueous was extracted with ethyl ether (×3). The organics were dried over $MgSO_4$, filtered, and concentrated.

Fig. 2. Structures of compounds in Table 2.

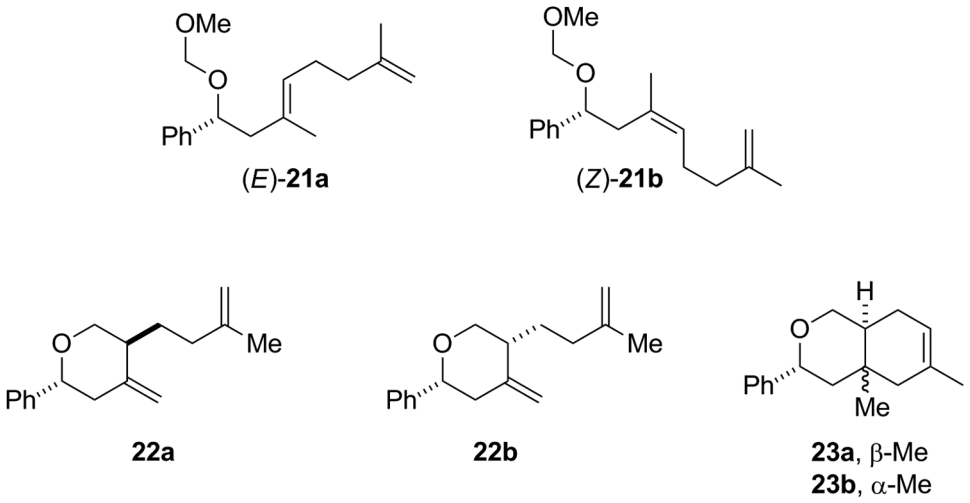


Table 2. Cyclization of diene-acetals **21a** and **21b**.

Entry	Reaction conditions	Yield from (*E*)-**21a**	Yield from (*Z*)-**21b**
1	Me_2BBr, DTBMP, –78 °C to room temperature	**22a** (92%)	**22b** (70%) (**21a**:**21b** = 1:5)
2	$SnCl_4$, CH_2Cl_2, 0 °C	**23a**, β-Me; **23b**, α-Me; 53% (**a**:**b** = 4:1)	**23a**, β-Me; **23b**, α-Me; 40% (1:1)
3	$BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C	**23a**, β-Me; **23b**, α-Me; 60% (**a**:**b** = 3:1)	**23a**, β-Me; **23b**, α-Me; 82% (1:1)
4	TMSBr	Complex mixture	Complex mixture
5	$TiCl_4$, –78 °C	Complex mixture	Complex mixture

Scheme 4. Attempted formation of α-bromoethers under strictly basic or neutral conditions.

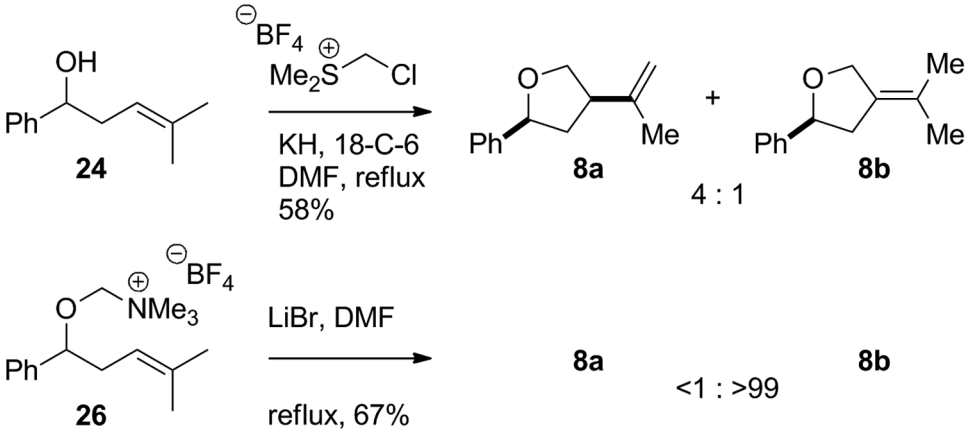
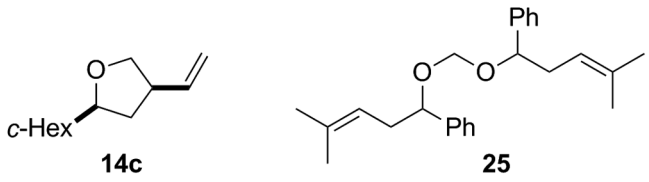


Fig. 3. Structure of **14c** and symmetrical acetal **25**.



Purification by flash chromatography (15:1 hexanes – ethyl acetate) yielded 461 mg (85%) of **1a** as a clear colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.70 (ABq, J = 9.6 Hz, 2H), 3.85–3.77 (m, 1H), 3.37 (s, 3H), 2.21–2.14 (m, 2H), 1.98–1.85 (m, 7H), 1.69–1.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 127.6 (s), 125.1 (s), 94.5 (t), 72.5 (d), 55.0 (q), 36.9 (t), 30.1 (t), 29.7 (t), 28.7 (t), 28.6 (t), 22.9 (t), 22.8 (t). IR (film, cm^{-1}): 2926, 2832, 1441, 1150, 1104, 1055, 1036. LRMS (*m*/*z*, relative intensity): 196 (M+, 3), 134 (100), 135 (95), 91 (85), 79 (70). HRMS calcd. for $C_{12}H_{20}O_2$: 196.1463; found: 196.1459.

2-(Bromomethoxy)-1,2,3,4,5,6,7,8-octahydronaphthalene (1b)

To a cooled –78 °C solution of methoxymethyl ether **1a** (75 mg, 0.382 mmol) and dichloromethane was added 1.33 mol L^{-1} Me_2BBr (373 μL, 0.5 mmol). The mixture was stirred at –78 °C for 1 h and then the solvent was evaporated under high vacuum while the bath was removed and the temperature slowly brought to room temperature. The resulting 93 mg of **1b** was then used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.79 (s, 2H), 4.04–3.95 (m, 1H), 2.24–2.17 (m, 2H), 1.99–1.83 (m, 7H), 1.73–1.50 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 127.8 (s), 124.5 (s), 75.9 (d), 74.8 (t), 35.3 (t), 30.0 (t), 29.6 (t), 28.1 (t), 27.1 (t), 22.7 (t). IR ($CHCl_3$) ν (cm^{-1}): 2925, 2831, 1442, 1103, 1056, 1029. LRMS (*m*/*z*, relative intensity): 246 (M+, 18), 244 (M+, 20). HRMS calcd. for $C_{11}H_{17}BrO$ (^{79}Br): 244.0463; found: 244.0466.

Oxatricyclo 2

To a refluxing solution of crude α-bromoether **1b** (93 mg, 0.379 mmol) and benzene (20 mL) was added Ph_3SnH (173 mg, 0.493 mmol) in benzene (2 mL) via syringe pump over 10 h. The solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (25:1 hexanes – ethyl acetate) yielding 34 mg (54%) of **2** as a volatile colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.35–5.31 (m, 1H), 4.45 (t, *J* = 5.0 Hz, 1H), 3.83 (d, *J* = 6.6 Hz, 1H), 3.47 (d, *J* = 6.6 Hz, 1H), 2.52–2.43 (m, 1H), 2.07 (dd, *J* = 14.4, 6.3 Hz, 1H), 1.97–1.81 (m, 2H), 1.78–1.50 (m, 6H), 1.40 (dt, *J* = 12.6, 6.5 207 Hz, 1H), 1.30–1.22 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 141.3 (s), 117.7 (d), 77.8 (t), 77.3 (d), 44.6 (t), 44.3 (s), 33.9 (t), 30.8 (t), 28.7 (t), 25.2 (t), 21.2 (t). IR ($CHCl_3$) *ν* (cm^{-1}): 2925, 1652. LRMS (*m*/*z*, relative intensity): 164 (M+, 3), 134 (100). HRMS calcd. for $C_{11}H_{16}O$: 164.1201; found: 164.1205.

General procedure A for the preparation of α-bromoethers

The acetal (1.0 equiv.) was dissolved in dichloromethane (0.2 mol L^{-1}). Anhydrous potassium carbonate (1.2–1.5 equiv.) was added and the solution was cooled to –78 °C. Dimethylbromoborane (1.1 equiv.) was then added and the solution was stirred for 15 min, after which time the reaction mixture was concentrated under reduced pressure for 3 h at –78 °C and then for an extra 3 h at room temperature to give the α-bromoether. Note that some bromoethers will cyclize completely or partially during this time.

General procedure B for the preparation of α-bromoethers

The acetal (1.0 equiv.) was dissolved in dichloromethane (0.2 mol L^{-1}). Anhydrous 2,6-di-*t*-butyl-4-methylpyridine (1.5 equiv.) was added and the solution was cooled to –78 °C. Dimethylbromoborane (1.1 equiv.) was then added and the solution was stirred for 15 min, after which time the reaction mixture was concentrated under reduced pressure for 3 h at –78 °C and then for an extra 3 h at room temperature to give the α-bromoether. Note that some bromoethers will cyclize completely or partially during this time.

1-(Bromomethylmethoxy)-4-methyl-1-phenylpent-3-ene (5)

The reaction was performed according to general procedure A with 1-(methoxymethoxy)-4-methyl-1-phenyl-3-pentene **4** (205 mg, 0.93 mmol), dichloromethane (5.0 mL, 0.2 mol L^{-1}), bromodimethylborane (0.10 mL, 1.02 mmol), and potassium carbonate (147 mg, 1.06 mmol) to give bromoether **5** as an oil containing some remaining potassium carbonate in suspension. The crude product was used in the next step (cyclization) without purification.

Alternatively, the reaction was performed according to general procedure B with 1-(methoxymethoxy)-4-methyl-1-phenyl-3-pentene **4** (147 mg, 0.67 mmol), dichloromethane (3.0 mL, 0.2 mol L^{-1}), bromodimethylborane (80 μL, 0.82 mmol), and 2,6-di-*t*-butyl-4-methylpyridine (230 mg, 1.12 mmol) to give bromoether **5** as a paste. The crude product was used in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35–7.30 (m, 5H), 5.78 (d, 1H, *J* = 3.6 Hz), 5.32 (d, 1H, *J* = 3.6), 5.07 (t, 1H, *J* = 7.2 Hz), 4.70 (t, 1H, *J* = 6.9 Hz), 2.64–2.55 (m, 1H), 2.48–2.38 (m, 1H), 1.67 (s, 3H), 1.51 (s, 3H). IR (film, cm^{-1}): 3020, 2916, 1452, 1105, 558. LRMS (*m*/*z*, relative intensity): 288 ($(MNH_4)^+$, 100), 286 ($(MNH_4)^+$, 100), 270 (MH^+, 25), 268 (M^+, 25), 206 (70), 189 (45), 171 (45). HRMS calcd. for $C_{13}H_{17}OBr$: 268.0463; found: 268.0468.

*4-(2-Bromoprop-2-yl)-2-phenyltetrahydrofuran (***rac***-6)*

To bromoether **5** (220 mg, 1.07 mmol), obtained from general procedure A or B, was added dichloromethane (5 mL) at room temperature. The solution was stirred at room temperature for 2 days and then was filtered and the filtrate was concentrated in vacuo to give bromide **6** as an oil. The crude product was characterized but unstable and thus was used in the next step (reduction) without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.41–7.28 (m, 5H), 4.89 (dd, 1H, *J* = 10.4, 5.5 Hz), 4.13–4.03 (m, 2H), 2.74–2.62 (m, 1H), 2.41 (ddd, 1H, *J* = 12.3, 7.7, 5.5 Hz), 1.89–177 (m, 1H), 1.77 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.9 (s), 128.4 (d), 127.9 (d), 127.6 (d), 125.8 (d), 81.9 (d), 70.9 (t), 68.7 (s), 53.8 (d), 39.0 (t), 33.2 (q), 32.3 (q). IR (film, cm^{-1}): 3026–2862, 1110, 570. LRMS (*m*/*z*, relative intensity): 270 (60), 268 (60), 189 (45), 159 (75), 105 (100). HRMS calcd. for $C_{13}H_{16}O$ (M-HBr$^+$): 188.1201; found: 188.1205.

*4-Isopropyl-2-phenyltetrahydrofuran (***rac***-7)*[23]

To bromide **6** (111 mg, 0.41 mmol), obtained from bromoether **5** via general procedure A, in benzene (2 mL, 0.2 mol L^{-1}) was added triphenyltin hydride (150 mg, 0.43 mmol) and the solution was heated to refluxing temperature for a 12 h period. Then, the solution was cooled and concentrated in vacuo to give a white paste. The crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–hexanes (50:50) to give tetrahydrofuran **7** as a colorless oil (58 mg, 74% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34–7.25 (m, 5H), 4.90 (dd, 1H, *J* = 10.4, 5.5 Hz), 4.11 (t, 1H, *J* = 8.3 Hz), 3.73 (t, 1H, *J* = 8.3 Hz), 2.46–2.38 (m, 1H), 2.21–2.07 (m, 1H), 1.60–1.26 (m, 4H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 6.6 Hz).

*cis-4-Isopropenyl-2-phenyltetrahydrofuran (***rac***-8a) and 4-isopropylidene-2-phenyltetrahydrofuran (***rac***-8b)*

Bromoether **6**, obtained from bromoether **5** via general procedure B, was dissolved in dichloromethane (3 mL) at room temperature. The solution was stirred for 2 days and then diethyl ether (5 mL) was added and the solution was filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc–hexanes (10:90) to give a mixture of **8a** and **8b** (123 mg, 98%, ratio 2:1). Isomer **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.38–7.23 (m, 5H), 4.96 (dd, 1H, *J* = 10.2, 6.1 Hz), 4.78 (2, 2H)), 4.13 (t, ^{1}H, *J* = 8.3 Hz), 3.87 (t, 1H, *J* = 8.3 Hz), 3.16–3.04 (m, 1H), 2.45 (ddd, 1H, *J* = 12.1, 6.1, 6.1 Hz), 1.84–1.73 (m, 1H), 1.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 144.4 (s), 142.8 (s), 128.4 (d), 127.3 (d), 125.7 (d), 110.6 (t), 81.6 (d), 72.1 (t), 47.3 (d), 40.4 (t), 20.7 (q). IR (film, cm^{-1}): 3026–2862, 1110, 570. LRMS (*m*/*z*, relative intensity): 188 (M^+, 15), 158 (20), 143 (100), 105 (50). HRMS calcd. for $C_{13}H_{16}O$: 188.1201; found: 188.1196. Isomer **8b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.24 (m, 5H), 4.94 (dd, 1H, *J* = 8.8, 6.6 Hz), 4.59 (br d, 1H, *J* = 12.7 Hz), 4.38 (br d, 1H, *J* = 12.7 Hz), 2.89 (dd, 1H, *J* = 15.4, 6.6 Hz), 2.46–2.38 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 142.2 (s), 131.7 (s), 128.3 (d), 127.4 (d), 125.9 (d), 121.4 (s), 81.3 (d), 70.3 (t), 39.0 (t), 21.5 (q), 20.6 (q). IR (film, cm^{-1}): 3030, 2910, 2854, 1451, 1053, 699. LRMS (*m*/*z*, relative intensity): 188 (M^+, 20), 128 (15), 104 (100), 82 (90). HRMS calcd. for $C_{13}H_{16}O$: 188.1201; found: 188.1198.

*4-(2-Bromoprop-2-yl)-2-phenethyltetrahydrofuran (***rac***-10)*

Bromoether **9** was prepared from the corresponding MOM acetal (29 mg, 0.12 mmol), potassium carbonate (30 mg, 0.22 mmol), and dimethylbromoborane (13 μL, 0.13 mmol) using general procedure A. It was then dissolved in dichloromethane (1 mL) and stirred for 2 days. The reaction mixture was concentred in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc–hexanes (5:95) to give bromide **10** as colorless oil (23 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32–7.16 (m, 5H), 3.91–3.82 (m, 3H), 2.82–2.62 (m, 2H), 2.50 (dddd, 1H, *J* = 9.9, 7.7, 7.7, 7.7 Hz), 2.10 (ddd, 1H, *J* = 12.1, 7.7, 5.0 Hz), 2.04–1.78 (m, 2H), 1.75 (s, 3H), 1.73 (s, 3H), 1.50 (dt, 1H, *J* = 9.9, 12.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.9 (s), 128.4 (d), 125.8 (d), 79.5 (d), 70.1 (d), 69.2 (q), 53.5 (d), 36.9 (t), 35.9 (t), 33.1 (q), 32.6

(t), 32.4 (q). IR (film, cm^{-1}): 3026–2862, 1453, 1110, 701, 570. LRMS (*m*/*z*, relative intensity): 298 and 296 (7), 218 (30), 117 (40), 91 (100). HRMS calcd. for $C_{15}H_{21}BrO$: 296.0776; found: 296.0772.

*4-(Bromobenz-1-yl)-2-*n*-butyltetrahydrofurans (*rac*-12a and* rac*-12b)*

Bromoether **11** was prepared from the corresponding MOM acetal (205 mg, 0.83 mmol), potassium carbonate (140 mg, 1.01 mmol), and dimethylbromoborane (0.09 mL, 0.9 mmol) using general procedure A. It was then dissolved in dichloromethane (5 mL) and the solution was stirred at room temperature for 14 h. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc–hexanes (10:90) to give **12a** as a colorless oil (109 mg 44%) and **12b** (111 mg, 45%). Bromoether **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.38–7.19 (m, 5H), 6.45 (d, 1H, *J* = 16.0 Hz), 6.19 (dt, 1H, *J* = 16.0, 7.1 Hz), 5.80 (s, 2H), 3.83 (qi, 1H, *J* = 6.0 Hz), 2.52–2.46 (m, 2H), 1.62–1.55 (m, 2H), 1.42–1.25 (m, 4H), 0.91 (t, 3H, *J* = 6.9 Hz). IR (film, cm^{-1}): 3027–2860, 1454, 1111. LRMS (*m*/*z*, relative intensity): 298 (M^+, 10), 296 (M^+, 10), 239 (M-$C_4H_9^+$, 20), 217 (M-Br^+, 60), 131 (100), 91 (95). HRMS calcd. for $C_{15}H_{21}OBr$: 296.0776; found: 296.0772. **12a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.28 (m, 5H), 4.81 (d, 1H, *J* = 11.0 Hz), 4.10 (dd, 1H, *J* = 9.1, 7.4 Hz), 3.95 (dd, 1H, *J* = 9.1, 6.3 Hz) 3.84 (dddd, 1H, *J* = 9.9, 5.8, 5.8, 5.8 Hz), 3.31–3.17 (m, 1H), 1.84 (ddd, 1H, *J* = 17.9, 8.0, 5.5 Hz), 1.63–1.54 (m, 1H), 1.46–1.14 (m, 5 H), 0.97 (dt, 1H, *J* = 12.6, 9.3 Hz), 0.86 (t, 3H, *J* = 6.9 Hz). **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.28 (m, 5H), 4.82 (d, 1H, *J* = 11.0 Hz), 3.92–3.82 (m, 1H), 3.56 (dd, 1H, *J* = 8.8, 8.8 Hz), 3.35 (dd, 1H, *J* = 8.8, 6.3 Hz), 3.28–3.15 (m, 1H), 2.47 (ddd, 1H, *J* = 18.1, 7.7, 5.5 Hz), 1.72–1.49 (m, 4H), 1.42–1.27 (m, 5H), 0.91 (t, 3H, *J* = 6.9 Hz).

*2-Cyclohexyl-4-(1-bromo-2-trimethylsilyleth-1-yl)tetrahydrofuran (*rac*-14) and 2-cyclohexyl-4-ethenyl)tetrahydrofuran (*rac*-14c)*

Bromoethers **13a** and **13b** were prepared from the corresponding MOM acetals (143 mg, 0.50 mmol), potassium carbonate (106 mg, 0.77 mmol), and bromodimethylborane (50 μL, 0.51 mmol) according to general procedure A to give tetrahydrofurans **14a** and **14b** as a paste (cyclization occurred instantaneously and bromoethers **13a** and **13b** could not be isolated or characterized). The crude product was used in the next step without purification. The crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–hexanes (30:70). Upon chromatography, elimination of TMSBr occurred to give **14c** as a colorless oil (68 mg, 75% for 2 steps). BromoTHF **14a** and **14b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.21–4.10 (m, 1H), 3.94–3.82 (m, 1H), 3.62–3.49 (m, 2H), 2.63–2.52 (m, 1H), 2.13–2.00 (m, 1H), 1.93 (br d, 1H, *J* = 12.7 Hz), 1.74–1.57 (m, 4H), 1.55–1.12 (m, 6H), 1.03–0.89 (m, 2H), 0.08 (s, 9H). IR (film, cm^{-1}): 2927, 2853, 1449, 1248, 1041, 850. LRMS (*m*/*z*, relative intensity): 317 ((M-CH_3)$^+$, 5), 253 (65), 185 (50), 169 (60), 139 (85), 97 (100). HRMS calcd. for $C_{14}H_{26}BrOSi$ ((M-CH_3)$^+$): 317.0936; found: 317.0951. Tetrahydrofuran **14c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.73 (ddd, 1H, *J* = 17.0, 10.2, 8.0 Hz), 5.06 (d, 1H, *J* = 17.0 Hz), 4.98 (dd, 1H, *J* = 10.2, 1.4 Hz), 3.90 (t, 1H, *J* = 8,2 Hz), 3.59 (ddd, 1H, *J* = 9.9, 7.8, 5.5 Hz), 3.48 (t, 1H, *J* = 8.2 Hz), 2.88 (dddd, 1H, *J* = 15.9, 8.8, 8.8, 8.8 Hz), 2.09 (ddd, 1H, *J* = 12.4, 7.8, 5.5 Hz), 1.94 (br d, 1H, *J* = 12.4 Hz), 1.76–1.59 (m, 4H), 1.44–1.07 (m, 5H), 0.97 (qd, 2H, *J* = 11.7, 3.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.2 (d), 114.8 (t), 84.7 (d), 72.2 (t), 44.3 (d), 43.2 (d), 36.9 (t), 30.0 (t), 29.0 (t), 26.5 (t), 26.0 (t), 25.8 (t). IR (film, cm^{-1}): 3077, 2924, 2852, 1642, 1079, 912. LRMS (*m*/*z*, relative intensity): 180 (M^+, 15), 98 (10), 97 (100). HRMS calcd. for $C_{12}H_{20}O$: 180.1514; found: 180.1509.

*4-Bromo-5-methyl-2-phenyltetrahydropyrane (*rac*-16a and* rac*-16b)*

Bromoethers **15a** and **15b** were prepared from the corresponding MOM acetals (149 mg, 0.72 mmol), 2,6-di-*t*-butyl-4-methylpyridine (256 mg, 1.24 mmol), and bromodimethylborane (85 μL, 0.87 mmol) according to general procedure B. Then dichloromethane (5 mL) was added at room temperature and the excess of 2,6-di-*t*-butyl-4-methylpyridine was left in the solution. The solution was stirred for 2 days, filtered, and concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–hexanes (0:100 to 50:50) to give an 8:1 mixture of the two epimers **16a** and **16b** (155 mg, 84%, 8:1). Bromoethers **15a** and **15b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36–7.30 (m, 5H), 5.77 (d, 1H, *J* = 3.8 Hz), 5.95–5.44 (m, 1H), 5.37–5.28 (m, 1H), 5.31 (d, 1H, *J* = 3.8 Hz), 4.71 (t, 1H, *J* = 6.6 Hz), 2.66–2.54 (m, 1H), 2.48–2.39 (m, 1H), 1.68 (d, 3H, *J* = 5.0, *trans* isomer), 1.62 (d, 3H, *J* = 6.1 Hz *cis* isomer). IR (film, cm^{-1}): 3029, 2917, 1451, 1106, 701, 561. LRMS (*m*/*z*, relative intensity): 254 (M^+, 5), 175 (60), 107 (55), 99 (80), 81 (100). HRMS calcd. for $C_{12}H_{15}OBr$: 254.0306; found: 254.0310. **16a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37–7.24 (m, 5H), 4.89 (dd, 1H, *J* = 10.4, 2.5 Hz), 4.65 (br d, 1H, *J* = 2.7 Hz), 3.79 (dd, 1H, *J* = 11.5, 4.1 Hz), 3.69 (t, 1H, *J* = 11.5 Hz), 2.33 (dt, 1H, *J* = 14.3, 2.7 Hz), 2.20 (ddd, 1H, *J* = 14.3, 10.4, 2.7 Hz), 2.02–1.90 (m, 1H), 0.96 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 141.6 (s), 128.4 (d), 127.6 (d), 126.0 (d), 73.8 (d), 68.8 (t), 59.4 (d), 42.6 (t), 35.4 (d), 16.3 (q). IR ($CHCl_3$, cm^{-1}): 3013, 2967, 2870, 1454, 1210, 554. LRMS (*m*/*z*, relative intensity): 254 (M^+, 2), 175 (100), 145 (60), 107 (90). HRMS calcd. for $C_{12}H_{15}BrO$: 254.0306; found: 254.0310. mp (°C): 58–61. **16b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32–7.23 (m, 5H), 4.35 (dd, 1H, *J* = 12.0, 2.19 Hz), 4.11 (dd, 1H, *J* = 11.6, 4.4 Hz), 3.96 (dt, 1H, *J* = 11.6, 4.4 Hz), 3.26 (t, 1H, *J* = 11.6 Hz), 2.52 (ddd, 1H, *J* = 13.2, 4.4, 2.2 Hz), 2.22 (t, 1H, *J* = 13.2 Hz), 2.15–1.24 (m, 1H), 1.06 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 140.9, 128.4, 127.9, 125.8, 80.4, 73.5, 56.1, 45.7, 40.6, 15.7. IR ($CHCl_3$, cm^{-1}): 3063, 3032, 2958, 2848, 1454, 1085, 1025, 700. LRMS (*m*/*z*, relative intensity): 254 (M^+, 2), 175 ((M-Br)$^+$, 100), 145 (45), 107 (80). HRMS calcd. for $C_{12}H_{15}OBr$: 254.0306; found: 254.0308.

*2-Benzyl-4-bromo-4-methyltetrahydropyrane (*rac*-18)*

Bromoether **17** was prepared from the corresponding MOM acetal (137 mg, 0.62 mmol), potassium carbonate (102 mg, 0.73 mmol), and dimethylbromoborane (68 μL, 0.69 mmol) according to general procedure A. Then dichloromethane (5 mL) was added at room temperature. The solution was stirred for 2 days, filtered, and concentrated in vacuo to give a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with CH_2Cl_2–hexanes (30:70 to 50:50) to give a mixture of the three compounds **18a**, **18b**, and **18c** (85%, 2:2:1). Compound **18a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.32–7.29 (m, 2H), 7.24–7.22 (m, 3H), 4.02 (dddd, 1H, *J* = 10.6, 7.3, 5.9, 5.9 Hz), 3.94 (dd, 1H, *J* = 11.7, 5.1 Hz), 3.86 (dt, 1H, *J* = 11.7, 2.2 Hz), 2.90 (dd, 1H, *J* = 13.9, 7.3 Hz), 2.70 (dd, 1H, *J* = 13.9, 5.9 Hz), 2.01 (d, 1H, *J* = 14.7 Hz), 1.93 (d, 1H, *J* = 14.7 Hz), 1.92 (s, 3H), 1.67 (ddd, 1H, *J* = 14.7, 11.7, 5.1 Hz), 1.37 (dd, 1H, *J* = 14.7, 10.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 137.8 (s), 129.3 (d), 128.4 (d), 126.4 (d), 75.8 (d), 65.1 (t), 62.7 (s), 49.4 (t), 43.9 (t), 42.5 (t), 29.2 (q). IR (film, cm^{-1}): 2959–2863, 1453, 1103, 699, 504. LRMS (*m*/*z*, relative intensity): 270 (M^+, 5), 268 (5), 205 (5), 177 (100), 97 (90). HRMS calcd. for $C_{13}H_{17}BrO$: 268.0463; found: 268.0465. **18b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.31–7.19 (m, 5H), 3.80 (ddd, 1H, *J* = 12.9, 5.1, 1.8 Hz), 3.61 (dddd, 1H, *J* = 12.8, 6.2, 6.2, 2.6 Hz), 3.51 (dt, 1H, *J* = 12.9, 2.2 Hz), 2.88 (dd, 1H, *J* = 13.9, 7.0 Hz), 2.66 (dd, 1H, *J* = 13.9, 6.2 Hz), 2.50 (dt, 1H, *J* = 12.8, 5.1 Hz), 2.21 (t, 1H, *J* = 13.2 Hz), 2.08 (ddd, 1H, *J* = 13.2, 3.7, 1.8 Hz), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.0 (s), 129.3 (d), 128.4 (d), 126.4 (d), 74.7 (d), 65.1 (t), 62.7 (s), 49.4 (t), 43.9 (t), 42.5 (t), 29.2 (q). IR (film, cm^{-1}): 2959–2863, 1453, 1103, 699, 504. LRMS (*m*/*z*, relative intensity): 270 (2), 268 (M^+, 2), 205 (15), 177 (95), 97 (100), 83 (20). HRMS calcd. for $C_{13}H_{17}BrO$: 268.0463; found: 268.0465. **18c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33–7.20 (m, 5H), 4.72 (d, 1H, *J* = 1.9 Hz), 4.67 (d, 1H, *J* = 1.9 Hz), 4.08 (ddd, 1H, *J* = 11.0, 5.8, 1.3 Hz), 3.50 (dddd, 1H, *J* = 12.6, 6.6, 6.6, 2.2 Hz), 3.37 (td, 1H, *J* = 11.0, 2.7 Hz), 2.94 (dd, 1H, *J* = 13.7, 6.6 Hz), 2.73 (dd, 1H, *J* = 13.7, 6.6 Hz) 2.32 (br dt, 1H, *J* = 12.6, 5.8 Hz), 2.25–1.99 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 144.4 (s), 138.3 (d), 129.3 (d), 128.2 (d), 126.2 (d), 108.6 (t), 79.5 (d), 68.7 (t), 42.8 (t), 40.6 (t), 35.1 (t). IR (film, cm^{-1}): 3067, 3027, 2939, 2846, 1654, 1093.

LRMS (*m*/*z*, relative intensity): 188 (1), 128 (5), 115 (5), 103 (5), 97 (100), 91 (60), 69 (30), 41 (20). HRMS calcd. for $C_{13}H_{16}O$: 188.1201; found: 188.1208.

***5-(Propen-1-yl)-2-phenyltetrahydropyrane* (rac-*20*)**

Bromoether **19** was prepared from the corresponding MOM acetal (153 mg, 0.653 mmol), 2,6-di-*t*-butyl-4-methylpyridine (246 mg, 1.12 mmol), and bromodimethylborane (80 μL, 0.82 mmol) in dichloromethane (3.5 mL) according to general procedure B. To bromoether **19** containing the excess potassium carbonate was added dichloromethane (2 mL) at room temperature. The solution was stirred for 2 days and then was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc–hexanes (6:94) to give **20** as a colorless oil (70 mg, 53%). Bromoether **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37–7.30 (m, 5H), 5.77 (d, 1H, *J* = 3.3 Hz), 5.30 (d, 1H, *J* = 3.3 Hz), 5.10 (t, 1H, *J* = 6.6 Hz), 4.70 (q, 1H, *J* = 6.4 Hz), 2.10–1.88 (m, 2H), 1.85–1.62 (m, 2H), 1.68 (s, 3H), 1.56 (s, 3H). IR (film, cm^{-1}): 3031, 2919, 1451, 1106, 701, 558. LRMS (*m*/*z*, relative intensity): 282 (M$^+$, 5), 254 (15), 199 (80), 173 (80), 145 (85), 105 (100). HRMS calcd. for $C_{14}H_{19}BrO$: 282.0619; found: 282.0622. **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37–7.25 (m, 5H), 4.82 (s, 1H), 4.74 (s, 1H), 4.31 (dd, 1H, *J* = 11.0, 2.2 Hz), 4.16 (ddd, 1H, *J* = 11.0. 3.8, 2.2 Hz), 3.43 (t, 1H, *J* = 11.0 Hz), 2.32 (broad dt, 1H, *J* = 11.0, 3.8 Hz), 2.05–1.91 (m, 2H), 1.77 (s, 3H), 1.70–1.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 146.1 (s), 142.9 (s), 128.3 (d), 127.3 (d), 125.8 (d), 110.1 (t), 80.0 (d), 72.7 (t), 43.2 (d), 33.9 (t), 29.4 (q), 21.7 (t). IR (film, cm^{-1}): 3028–2857, 1453, 1092, 700. LRMS (*m*/*z*, relative intensity): 202 (M$^+$, 15), 146 (10), 104 (100), 77 (15). HRMS calcd. for $C_{14}H_{18}O$: 202.1358; found: 202.1361.

***5-(3-Methylbut-3-enyl)-4-methylene-2-phenyltetrahydro-2H-pyran* (rac-*22a*)**

Bromoether **58** was prepared from acetal (*E*)-**21a** (51 mg, 0.19 mmol), di-*t*-butylmethylpyridine (52 mg, 0.25 mmol), and bromodimethylborane (20 μL, 0.20 mmol) according to general procedure B. It was then dissolved in dichloromethane (1 mL) at room temperature. The solution was stirred 15 h and diethyl ether was added. The solution was filtered and concentrated in vacuo to give a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with PhMe–hexanes (50:50) to give **22a** as a colorless oil (47 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39–7.28 (m, 5H), 4.89 (s, 1H), 4.79 (s, 1H), 4.76 (s, 1H), 4.74 (s, 1H), 4.33 (dd, 1H, *J* = 11.0, 2.8 Hz), 4.22 (dd, 1H, *J* = 11.0, 5.2 Hz), 3.20 (t, 1H, *J* = 11.0 Hz), 2.51 (dd, 1H, *J* = 13.2, 2.8 Hz), 2.35 (t, 1H, *J* = 12.4 Hz), 2.35–2.27 (m, 1H), 2.12 (t, 2H, *J* = 7.8 Hz), 1.89–1.75 (m, 1H), 1.76 (s, 3H), 1.38 (dq, 1H, *J* = 13.7, 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.1 (s), 145.6 (s), 142.2 (s), 128.4 (d), 127.6 (d), 125.8 (d), 110.2 (t), 106.4 (t), 81.6 (d), 73.6 (t), 44.5 (t), 41.6 (d), 35.1 (t), 25.5 (t), 22.4 (q). IR (film, cm^{-1}): 3081, 2940, 1649, 1452, 1099, 889, 698. LRMS (*m*/*z*, relative intensity): 242 (M$^+$, 15), 214 (20), 136 (60), 121 (65), 107 (100), 79 (90). HRMS calcd. for $C_{17}H_{22}O$: 242.1671; found: 242.1662.

***5-(3-Methylbut-3-enyl)-4-methylene-2-phenyltetrahydro-2H-pyran* (rac-*22b*)**

Bromoether **58** was prepared from acetal (*Z*)-**21b** (53 mg, 0.19 mmol), di-*t*-butylmethylpyridine (52 mg, 0.25 mmol), and bromodimethylborane (20 μL, 0.20 mmol) according to general procedure B. Then, it was dissolved in dichloromethane (1 mL) at room temperature. The solution was stirred for 15 h and diethyl ether was then added. The solution was filtered and concentrated in vacuo to give a yellow oil. The crude product was purified by flash column chromatography on silica gel eluting with PhMe–hexanes (50:50) to give **22a** and **22b** as a colorless oil (47 mg, 60%, 1:5). Compound **22b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.40–7.28 (m, 5H), 4.83 (s, 2H), 4.74 (s, 1H), 4.72 (s, 1H), 4.30 (dd, 1H, *J* = 11.3, 3.0 Hz), 4.06 (d, 1H, *J* = 11.6 Hz), 3.72 (dd, 1H, *J* = 11.3, 2.8 Hz), 2.49–2.39 (m, 1H), 2.32 (dd, 1H, *J* = 13.7, 2.8 Hz), 2.22–2.17 (m, 1H), 2.01 (t, 2H, *J* = 7.7 Hz), 1.96–1.79 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 146.7 (s), 145.6 (s), 142.4 (s), 128.4 (d), 127.6 (d), 125.8 (d), 109.7 (t), 106.4 (t), 81.2 (d), 72.9 (t), 43.5 (t), 39.5 (d), 35.5 (t), 28.6 (t), 22.5 (q). IR (film, cm^{-1}): 3069, 2940, 2847, 1649, 1452, 1096, 890, 699. LRMS (*m*/*z*, relative intensity): 242 (M$^+$, 10), 214 (15), 136 (40), 107 (75), 105 (75), 77 (100). HRMS calcd. for $C_{17}H_{22}O$: 242.1671; found: 242.1662. 121.

***4a,6-Dimethyl-3-phenyl–3,4,4a,5,8,8a-hexahydro-1H-isochromene* (rac-*23a and 23b*)**

Method A

To a solution of diene (*E*)-**21a** (15 mg, 0.055 mmol) and sodium carbonate (15 mg, 0.14 mmol) in dichloromethane (1 mL) at 0 °C was added $SnCl_4$ (10 μL, 0.13 mmol). Water was then added, the organic layer was separated, and the aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with PhMe–hexanes (50:50) to give bicyclic compounds **23a** and **23b** as a colorless oil (7 mg, 53%, 3.7:1).

Method B

To a solution of diene (*E*)-**21a** (15 mg, 0.055 mmol) in dichloromethane (1 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (10 μL, 0.12 mmol). Water was then added, the organic layer was separated, and the aqueous phase was extracted twice with dichloromethane. The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with PhMe–hexanes (50:50) to give bicyclic compound **23a** and **23b** as a colorless oil (8 mg, 60%, 2.9:1). Compound **23a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37–7.22 (m, 5H), 5.38 (br s, 1H), 4.63 (dd, 1H, *J* = 11.5, 2.7 Hz), 3.83 (dd, 1H, *J* = 11.5, 3.8 Hz), 3.50 (t, 1H, *J* = 11.5 Hz), 1.93–1.74 (m, 4H), 1.69–1.42 (m, 3H), 1.64 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 143.1 (s), 132.2 (s), 128.2 (d), 127.3 (d), 125.8 (d), 119.1 (d), 75.7 (d), 68.8 (t), 48.6 (t), 46.1 (t), 39.0 (d), 31.5 (s), 24.1 (t), 24.0 (q), 16.1 (q). IR (film, cm^{-1}): 3031, 2925, 1725, 1452, 1073, 700. LRMS (*m*/*z*, relative intensity): 242 (M$^+$, 100), 121 (50), 93 (70). HRMS calcd. for $C_{17}H_{22}O$: 242.1671; found: 242.1665.

Bis(4-methyl-1-phenylpent-3-enyloxy)methane (25)

To a solution of alcohol **24** (100 mg, 0.570 mmol) in THF (5 mL) was added a 30% suspension of sodium hydride in mineral oil (25 mg, 0.63 mmol). After 30 min, chloroiodomethane was added (0.25 mL, 3.4 mmol) and the reaction mixture was stirred overnight at room temperature. The solution was filtered, rinced with diethyl ether, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc–hexanes (5:95) to give mixture of diastereomers of **25** as a colorless oil (25 mg, 40%, 1:1). Separation of the two diastereomers for the purpose of characterization was possible upon further column chromatography, although the stereochemical assignment was not possible. Similar results were obtained with other dihalomethanes or halo(toluenesulfonyloxy) methanes. Diastereoisomer **25a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.34–7.22 (m, 10H), 5.23 (t, 2H, *J* = 7.1 Hz), 4.73 (dd, 2H, *J* = 7.1, 6.0 Hz), 4.40 (s, 2H), 2.61–2.51 (m, 2H), 2.44–2.35 (m, 2H), 1.72 (s, 6H), 1.57 (s, 6H). ^{13}C NMR (**75** MHz, $CDCl_3$) δ (ppm): 141.6 (s), 133.7 (s), 128.2 (d), 127.5 (d), 127.1 (d), 120.4 (d), 90.0 (t), 77.39 (d), 36.8 (t), 25.8 (q), 17.9 (q). IR (film, cm^{-1}): 3030, 2915, 1452, 1097, 1060, 1024, 701. LRMS (*m*/*z*, relative intensity) 295.1 ((M-C_5H_9)$^+$, 5), 189.1 (10), 159.1 (100), 117.1 (35). HRMS calcd. for $C_{20}H_{32}O_2$ ((M-C_5H_9)$^+$): 295.1698; found: 295.1695. **25b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36–7.17 (m, 10H), 4.94 (t, 2H, *J* = 7.1 Hz), 4.78 (d, 1H, *J* = 7.1 Hz), 4.50 (t, 3H, *J* = 7.1 Hz), 2.39–2.21 (m, 4H), 1.61 (s, 6H), 1.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 142.3 (s, 133.7 (s), 128.1 (d), 127.3 (d), 126.8 (d), 119.8

(d), 91.9 (t), 78.7 (d), 36.2 (t), 25.7 (q), 17.7 (q). IR (film, cm^{-1}): 3029, 2913, 2856, 1453, 1062, 1019, 700. LRMS (*m*/*z*, relative intensity): 295.1 ($(M-C_5H_9)^+$, 5), 189.1 (10), 159.1 (100), 117.1 (35). HRMS calcd. for $C_{20}H_{32}O_2$ ($(M-C_5H_9)^+$): 295.1698; found: 295.1704.

Formation of THF 8a and 8b via Dolbier's salt

To a solution of alcohol **24** (236 mg, 1.34 mmol) in DMF was added KH (80 mg, 2.0 mmol) and 18-C-6 (52 mg, 0.2 mmol). After stirring the suspension for 1 h at room temperature, Dolbier's salt (535 mg, 2.70 mmol) was added and the resulting solution was stirred at reflux temperature for 24 h. The reaction mixture was cooled to room temperature and poured into a mixture of diethyl ether and brine. The organic phase was separated and the aqueous phase was extracted thrice with diethyl ether. The combined organic phases were dried with anhydrous magnesium sulfate, evaporated in vacuo, and the residue was purified by flash column chromatography on silica gel eluting with EtOAc–hexanes (10:90) to give a mixture of **8a** and **8b** (146 mg, 58%, ratio 4:1).

Formation of THF 8b via the quaternary ammonium salt

To a mixture of NaH (30 mg (60% dispersion in oil, 0.738 mmol) in dry DMF (3 mL) was added alcohol **24** (100 mg, 0.567 mmol) at 0 °C under argon. The resulting mixture was then stirred for 1 h at room temperature and Eschenmoser's salt (157 mg, 0.815 mmol) was added. The reaction mixture was stirred 16 h at room temperature. After that, Me_3OBF_4 (109 mg, 0.738 mmol) was added and the mixture was stirred for 18 h at room temperature (monitored by ^{1}H NMR). LiBr (148 mg, 1.70 mmol) was then added to the reaction mixture and the resulting solution was stirred at 150 °C for 15 h (monitored by ^{1}H NMR). DMF was then removed in vacuo and the residue was mixed with EtOAc and water. The layers were separated and the aqueous phase was extracted twice with diethyl ether. The combined organic phases were dried over magnesium sulfate and evaporated in vacuo. The crude product was purified by silica gel column chromatography eluting with EtOAc–hexanes (0:100 to 2:98) to give **8b** as a colorless oil.

Supplementary material

Supplementary material is available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2013-0337.

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