

An iterative approach to three fragments of ionomycin¹

Claude Spino and Martin Allan

Abstract: The S_N2' displacement of menthone-derived allylic carbonates with cuprate reagents occurs with high diastereoselectivity. This method can be used in an iterative fashion to construct stereocenters bearing a 1,3-relationship in a carbon chain. Each iteration provides the adduct in greater than 99% de. The synthesis of three fragments of the polyether ionophore ionomycin is disclosed.

Key words: menthone, chiral auxiliary, S_N2' displacement, cuprate, iteration, ionomycin.

Résumé : La substitution S_N2' de carbonates allyliques dérivés de la menthone avec des cuprates se produit avec une grande diastéréosélectivité. On peut utiliser cette méthode de façon itérative pour construire des stéréocentres ayant une relation 1,3 dans une chaîne carbonée. Chaque itération fournit l'adduit avec un excès diastéréomérique plus grand que 99 %. On a réalisé la synthèse de trois fragments du polyéther ionophore de l'ionomycine.

Mots clés : menthone, auxiliaire chiral, substitution S_N2' , cuprate, itération, ionomycine.

[Traduit par la Rédaction]

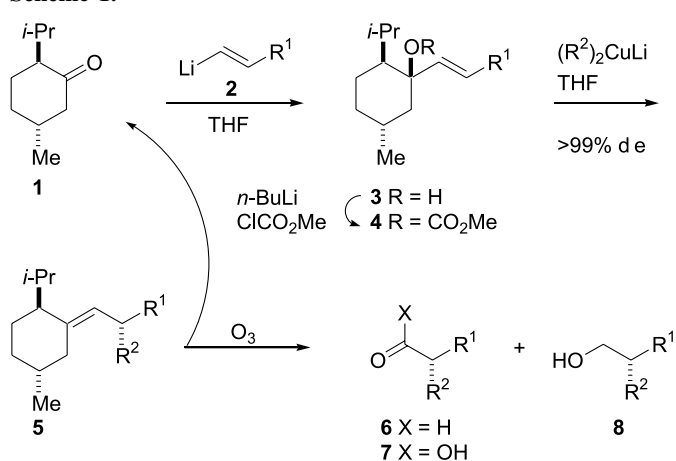
Introduction

We have developed in recent years a methodology equivalent to the alkylation of chiral enolates (1, 2). The key step in the strategy is the S_N2' displacement by cuprate reagents of a chiral allylic carbonate derived from (+)- or (-)-menthone **1** (Scheme 1). The transfer of chirality from carbonate **4** is generally high. Among the advantages of this strategy over the alkylation of chiral enolates is the higher diastereoselectivity generally achieved and the possible introduction of aryl and 2° or 3° alkyl groups.

Conceptually, the iterative alkylation of chiral enolates to form polyalkyl chains with a 1,3-relationship between the stereocenters is appealing. However, the relatively low reactivity of chiral enolates sometimes prohibits their reaction with β -branched alkyl halides or often requires that the electrophile be used in large excess. In addition, to be useful, any method used iteratively must provide products of high stereochemical purity at each iteration. For these reasons, examples of the use of enolates in an iterative approach to synthesis are scarce (3). The high diastereoselectivities and increased reactivity provided by our system prompted us to verify its usefulness in an iterative approach to three fragments of the polyether ionophore ionomycin (Fig. 1) (4, 5).

We prepared a large quantity of **3** ($R^1 = \text{Me}$), the addition product of *trans*-propenyllithium to (-)-menthone (Scheme 1). The alcohol was isolated as a single diastereomer (1). We also prepared *ent*-**3** ($R^1 = \text{Me}$) starting from (+)-menthone. The corresponding carbonate **4** ($R^1 = \text{Me}$) was prepared im-

Scheme 1.



mediately before its reaction with the cyanocuprate derived from *tert*-butyl methyl ether (**6**). Compound **9a** was then isolated in 92% yield (Scheme 2). Analysis by GC revealed the presence of essentially one diastereomer. For analysis purposes, the diastereomer **9b** was prepared from the same menthone, by addition of the cuprate derived from methyl-lithium on the carbonate of **13**, bearing the $\text{CH}_2\text{O}(t\text{-Bu})$ moiety (Scheme 3).

Ozonolysis of **9a** with a reductive work-up (NaBH_4) and conversion of the resulting alcohol **10** to the iodide **11** was achieved in high yield. In addition, some quantity of **10** was

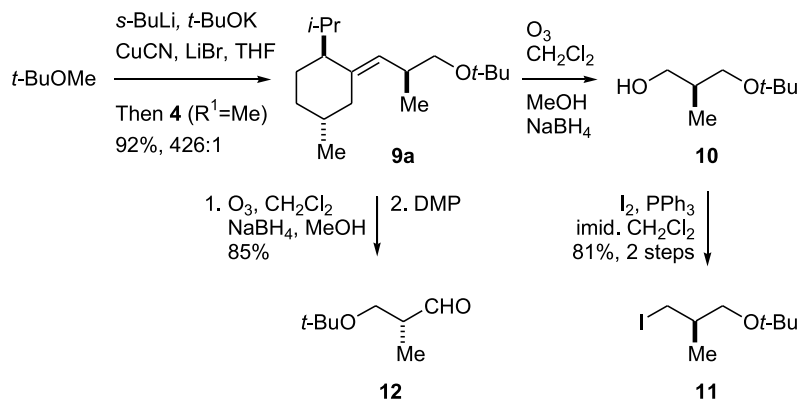
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Scheme 2.



Scheme 3.

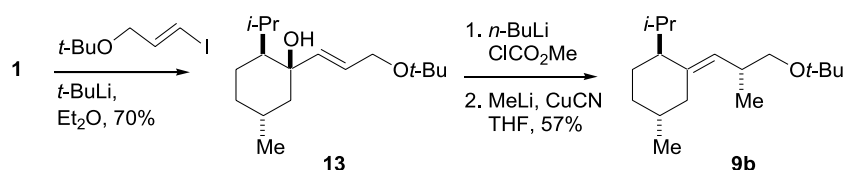
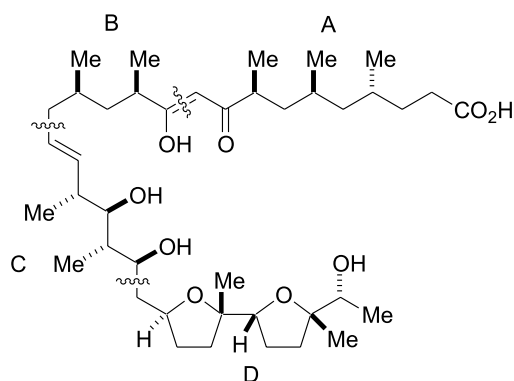


Fig. 1. Structure of ionomycin showing the three retrosynthetic disconnections.



oxidized to the aldehyde **12**, which is an intermediate to fragment C of ionomycin. This two-steps procedure for **12** was more efficient than the direct ozonolysis of **9a** in terms of yield and purity of the aldehyde, which was then used crude in the next step (vide infra).

The first iteration was tested with iodide **11**. Exchange of the iodine for lithium was accomplished with *t*-BuLi in diethyl ether and the monoalkylcyanocuprate derived from the resulting alkyllithium was added to carbonate **4** ($R^1 = \text{Me}$) with high diastereoselectivity to give **14** in 93% isolated yield (Scheme 4). Ozonolysis of **14** furnished syn alcohol **15**, which was shown to be >99% diastereomerically pure by comparison with an authentic sample of the diastereomeric *anti*-**15**, obtained by the same series of reaction starting from racemic **11**. A sufficient amount of **15** (precursor to fragment B of ionomycin) was set aside for its eventual coupling with fragments A and C. For that purpose, the free alcohol will be oxidized while the protected one will be converted to a primary iodide. The remainder of alcohol **15** was converted to iodide **16**, uneventfully. The latter suffered a lithium–iodine exchange under the same conditions as per

11 and further reaction with copper cyanide afforded the corresponding monoalkylcyanocuprate. Adding *ent*-**4** ($R^1 = \text{Me}$) to this mixture gave adduct **17a** in 87% yield. Ozonolysis gave alcohol **18a** as a 218:1 ratio of diastereomers, as shown by comparison with an authentic sample of its diastereomer **18b** (GC analysis). Alcohol **18b** was obtained by adding the same cyanocuprate made from **16** to carbonate **4** ($R^1 = \text{Me}$) followed by oxidative cleavage. Alcohol **18b** was also formed in >99% de. Any of the diastereomers of **18** can be prepared simply by choosing the appropriate carbonate (**4** or *ent*-**4** ($R^1 = \text{Me}$)) during the synthesis.

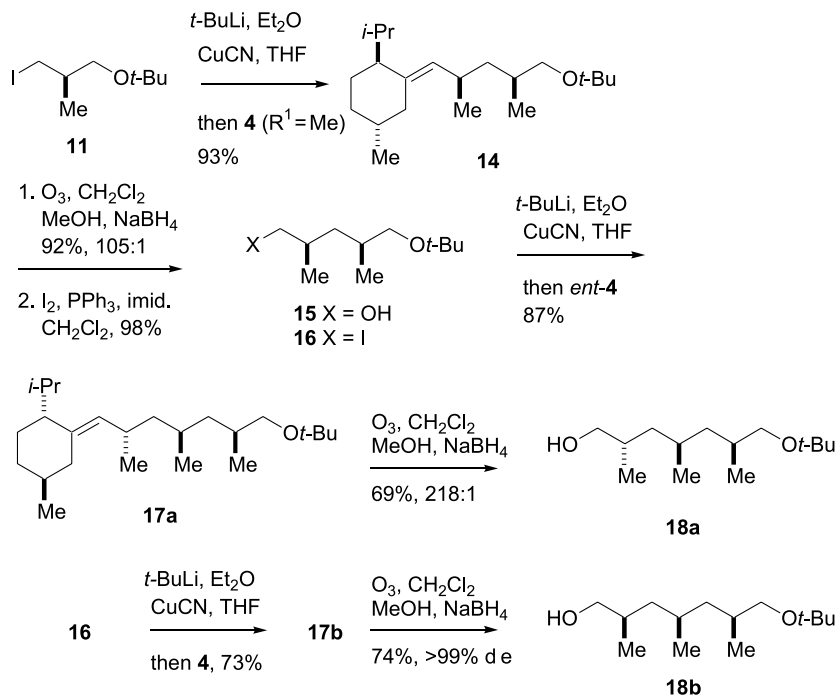
Fragment A of ionomycin was completed by a series of straightforward steps (Scheme 5). The auxiliary in **17a** was cleaved by ozonolysis and reductive work-up with triphenylphosphine gave an aldehyde. The latter was converted to the α,β -unsaturated methyl ester by a Wadsworth–Emmons reaction, which was further hydrogenated to give **19** in good overall yield. Deprotection of the *tert*-butyl ether with bromocatecholborane (**7**) gave the alcohol quantitatively, which was oxidized to aldehyde **20**. Conversion to fragment A (**21**) was performed using standard steps (**4a**).

With fragments A and a precursor to fragment B in hand, we set out to prepare fragment C. Unpurified aldehyde **12** was reacted with Roush's (*E*)-crotyl boronate (**8**) to give alcohol **22** in 71% yield as a 82:18 ratio of diastereomers as determined by GC analysis (Scheme 6). The mixture was easily separated by column chromatography to yield 57% of pure alcohol **22**. Although the ratio was slightly lower than that obtained using the Brown protocol (**9**), the Roush method proved easier to use and provided a higher yield of pure **22**. After protection of the alcohol as its triethylsilyl ether, the terminal double bond was cleaved to fragment C (**24**).

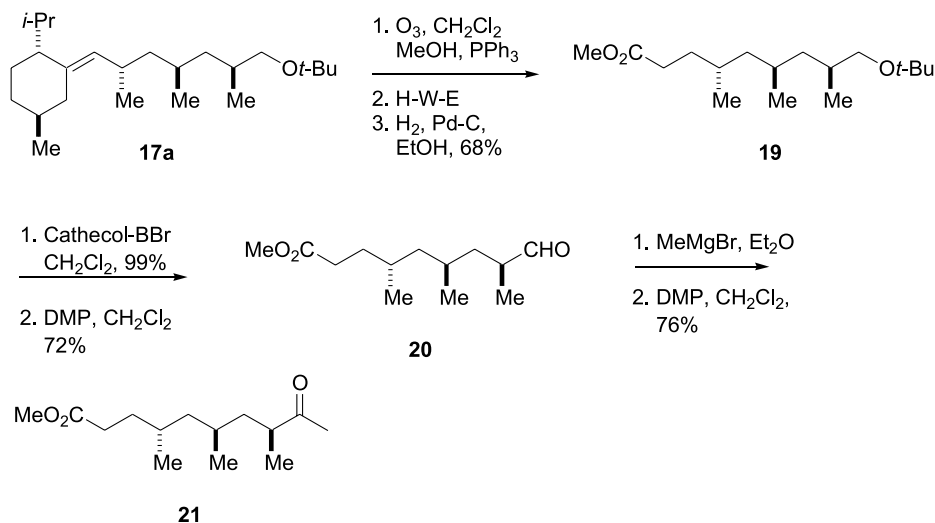
Conclusion

We have demonstrated the power of cyanoalkylcuprate displacement on menthone-derived carbonates as a synthetic

Scheme 4.



Scheme 5.



technology for the iterative preparation of 1,3-polymethyl-substituted carbon chains. Each iteration proceeded with >100:1 selectivity. A single intermediate **9** served to make fragments A, B, and C in **13**, five, and five steps, respectively. It was itself prepared in three steps from (–)-menthone. This highly efficient strategy allowed us to make large quantities of each of these three fragments of ionomycin. The synthesis of fragment D is underway and the total synthesis of ionomycin will be reported in due course.

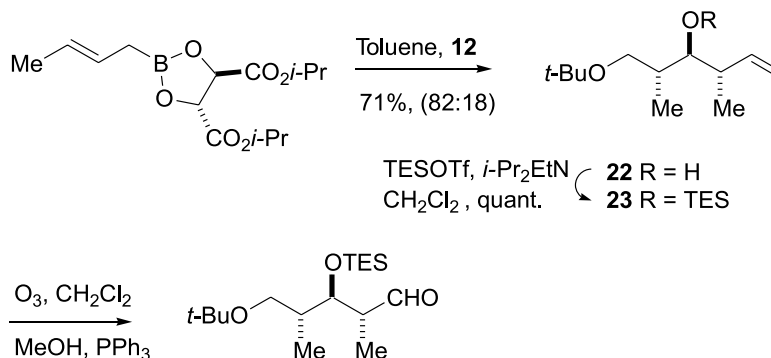
Experimental section

All reactions were carried out under an atmosphere of argon. Ethyl ether, toluene, and benzene were dried over metallic sodium using benzophenone as an indicator, while

tetrahydrofuran was dried over both sodium and potassium using the same indicator. Methanol was distilled from magnesium. Dichloromethane, triethylamine, imidazole, diisopropylethylamine, and diisopropylamine were distilled over calcium hydride. Hexanes was purchased anhydrous from Aldrich. Copper cyanide was purchased from Aldrich and used as is. Thin layer chromatography was performed using 0.25 mm Silica Gel 60 F254 (EM Science-Merck) and flash chromatography using silica gel Kieselgel 60 (230–400 mesh ASTM).

All NMR spectra were taken in deuterated chloroform on a Bruker AC-300 (1H (300 MHz), ^{13}C (75 MHz)). Chemical shifts are reported in parts per million (PPM) (δ) downfield from tetramethylsilane. The splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), qi (quintet),

Scheme 6.



sx (sextet), sp (septet), oc (octuplet), m (multiplet). The IR spectra were determined on a PerkinElmer 1600 Fourier transform spectrometer. The IR spectra were determined neat, unless otherwise stated. The melting points were performed on a Mettler Toledo model 62. High- and low-resolution mass spectra (HR-MS and LR-MS) were obtained with a micromass spectrometer ZAB-1F model VG. GC analysis was performed using an Agilent series 6890 on a HP5 column (5% phenyl methyl siloxane) 30 m \times 0.25 μm . All compounds were separated using a 100 $^\circ\text{C}$ for 2 min and 10 $^\circ\text{C}/\text{min}$ to 200 $^\circ\text{C}$ temperature program.

Alkene 9a

A solution of *tert*-butyl methyl ether (600 mL) and potassium *tert*-butoxide (18.33 g, 163 mmol) was cooled to -78 $^\circ\text{C}$, then *s*-BuLi (117 mL of a 1.4 mol L^{-1} solution in hexanes, 163 mmol) was added dropwise. The resulting mixture was stirred for 2.5 h. In another flask, a solution of CuCN (14.63 g, 327 mmol) and LiBr (28.36 g, 327 mmol) in THF (130 mL) was cooled to -78 $^\circ\text{C}$. This solution was added dropwise to the first one by cannula, and stirring was continued for 1 h. The carbonate was dissolved in a minimum amount of THF, then added to the mixture dropwise. The mixture was allowed to warm gradually to room temperature while stirring for 18 h. The reaction was quenched by adding a satd. aq. NH_4Cl and NH_4OH (9:1) solution. The aqueous layer was separated and extracted with Et_2O three times. The combined organic extracts were washed with brine, then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes) afforded the cuprate adduct (10.61 g, 92%) as a colourless oil. GC analysis showed a (426:1) diastereoisomer ratio. $[\alpha]_{\text{D}} = -2.82^\circ$ (CHCl_3 , $c = 1.44$). IR (cm^{-1}): 2970, 1461. ^1H NMR (CDCl_3) δ : 4.85 (d, 1H, $J = 9.4$ Hz), 3.23 (dd, 1H, $J = 8.3$ and 5.5 Hz), 3.03 (t, 1H, $J = 8.5$ Hz), 2.65–2.31 (m, 1H), 2.35 (dm, 1H, $J = 16.5$ Hz), 1.90 (sx, 1H, $J = 6.8$ Hz), 1.81–1.65 (m, 4H), 1.58–1.51 (m, 1H), 1.33–1.04 (m, 2H), 1.17 (s, 9H), 0.95–0.83 (m, 12H). ^{13}C NMR (CDCl_3) δ : 139.8 (s), 125.0 (d), 72.3 (s), 67.0 (t), 51.1 (d), 35.6 (t), 32.8 (d), 32.4 (d), 31.9 (t), 27.6 (q), 26.9 (t), 26.5 (d), 22.1 (q), 20.6 (q), 19.8 (q), 18.6 (q). LR-MS (m/z (relative intensity)): 266 (M^+ , 5), 210 (35), 109 (100). HR-MS calcd. for $\text{C}_{18}\text{H}_{34}\text{O}$: 266.2610; found: 266.2614.

Alkene 9b

A solution of alcohol **13** (451 mg, 1.68 mmol) in THF (17 mL) was cooled to -78 $^\circ\text{C}$. *n*-BuLi (1.26 mL of a

1.87 mol L^{-1} solution in hexanes, 2.36 mmol) was added dropwise, then stirring continued for 2 h. ClCO_2Me (0.20 mL, 2.53 mmol) was added. The mixture was stirred for 2 h at -78 $^\circ\text{C}$, then for 1 h while letting the reaction warm to 0 $^\circ\text{C}$, and 1 h at 0 $^\circ\text{C}$. The reaction was quenched by adding a satd. aq. NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O three times. The combined organic extracts were washed with brine, then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. The crude carbonate was used in the next step without further purification.

To a solution of CuCN (603 mg, 6.73 mmol) in THF (28 mL) cooled to -78 $^\circ\text{C}$, MeLi (4.21 mL of a 1.6 mol L^{-1} solution in Et_2O , 6.73 mmol) was added slowly. This mixture was stirred for 1.5 h. The carbonate was dissolved in a minimum of THF, then added to the reaction mixture at -60 $^\circ\text{C}$. Stirring was continued for 17 h, while the reaction was allowed to reach room temperature. The reaction was quenched by adding a satd. aq. NH_4Cl and NH_4OH (9:1) solution. The aqueous layer was separated and extracted with Et_2O three times. The combined organic extracts were washed with brine, then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes) afforded cuprate adduct **9b** (256 mg, 57%) as a colourless oil. $[\alpha]_{\text{D}} = -48.9^\circ$ (CHCl_3 , $c = 1.34$). ^1H NMR (CDCl_3) δ : 4.83 (d, 1H, $J = 9.4$ Hz), 3.15 (dd, 1H, $J = 8.8$ and 6.1 Hz), 3.03 (t, 1H, $J = 8.3$ Hz), 2.66–2.54 (m, 1H), 2.35–2.29 (m, 1H), 1.91 (sx, 1H, $J = 7.1$ Hz), 1.81–1.64 (m, 4H), 1.58–1.52 (m, 1H), 1.33–1.24 (m, 1H), 1.16 (s, 9H), 1.14–1.06 (m, 1H), 0.95 (d, 3H, $J = 6.6$ Hz), 0.90 (d, 3H, $J = 6.1$ Hz), 0.87 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 3H, $J = 6.9$ Hz). LR-MS (m/z (relative intensity)): 266 (M^+ , 5), 210 (35), 123 (100). HR-MS calcd. for $\text{C}_{18}\text{H}_{34}\text{O}$: 266.2610; found: 266.2614.

General procedure for the ozonolysis of cuprate adducts to the corresponding alcohols

O_3 was bubbled through a stirred solution of cuprate adduct in CH_2Cl_2 and MeOH (4:1, 0.1 mol L^{-1}) at -78 $^\circ\text{C}$ until the appearance of a blue colour. Then argon was bubbled through this solution until the blue colour disappeared. NaBH_4 (5.0 equiv.) was added portion-wise. The mixture was allowed to warm to room temperature slowly while stirring for 16 h. The reaction was quenched by adding a satd. aq. NH_4Cl solution. The aqueous layer was separated and extracted with CH_2Cl_2 three times. The combined organic

extracts were washed with brine, then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo.

Alcohol 10

Prepared from **9a** (1.0 g, 3.75 mmol) according to the general procedure for the ozonolysis of cuprate adducts. Purified by flash chromatography on silica gel (hexanes–AcOEt, 30%) gave 467 mg of **10** (85%) as a colourless oil. $[\alpha]_{\text{D}} = -16.8^\circ$ (CHCl_3 , $c = 1.84$). IR (cm^{-1}): 3384. ^1H NMR (CDCl_3) δ : 3.66–3.50 (m, 3H), 3.28 (t, 1H, $J = 8.8$ Hz), 2.00 (m, 1H), 1.21 (s, 9H), 0.85 (d, 3H, $J = 7.15$ Hz). LR-MS (m/z (relative intensity)): 131 ($\text{M}^+ - \text{Me}$, 80), 89 (100), 87 (10). HR-MS calcd. for $\text{C}_7\text{H}_{14}\text{O}_2$: 131.1072; found: 131.1076.

Iodide 11

(A higher overall yield of iodide **11** from **9a** was obtained using crude alcohol **10**). To a solution of alcohol **10** (1.21 g, 8.30 mmol) in CH_2Cl_2 (165 mL) was added imidazole (3.39 g, 50.0 mmol), then Ph_3P (8.71 g, 33.3 mmol). After complete dissolution of PPh_3 , the solution was protected from light, cooled to 0°C , and I_2 (8.45 g, 33.3 mmol) was added. The mixture was warmed to room temperature and stirring was continued for 16 h. The reaction was quenched by adding a satd. aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution. The aqueous layer was separated and extracted with EtOAc three times. The combined organic extracts were dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. The crude extract was triturated twice with hexanes to remove the remaining PPh_3 . Purification by flash chromatography on silica gel (hexanes–EtOAc, 2%) afforded iodide **11** (1.71 g, 81% for two steps) as a slightly yellow oil. $[\alpha]_{\text{D}} = -12.4^\circ$ (CHCl_3 , $c = 1.46$). IR (cm^{-1}): 2973, 1479. ^1H NMR (CDCl_3) δ : 3.31 (d, 2H, $J = 4.4$ Hz), 3.23 (dd, 1H, $J = 9.4, 5.5$ Hz), 3.13 (t, 1H, $J = 8.0$ Hz), 1.66–1.55 (m, 1H), 1.18 (s, 9H), 0.96 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (CDCl_3) δ : 72.6 (s), 65.4 (t), 35.3 (t), 27.6 (s), 17.8 (q), 15.1 (q). LR-MS (m/z (relative intensity)): 256 (M^+ , 10), 241 (25), 87 (100). HR-MS calcd. for $\text{C}_8\text{H}_{17}\text{OI}$: 256.0324; found: 256.0318.

Aldehyde 12

To a solution of alcohol (467 mg, 3.20 mmol) in wet CH_2Cl_2 (8.5 mL) was added Dess–Martin periodinane (1.628 g, 3.84 mmol). The mixture was stirred for 30 min. The reaction solution was evaporated in vacuo, then diluted with Et_2O , washed with a solution of satd. aq. $\text{Na}_2\text{S}_2\text{O}_3$, washed with a solution of satd. aq. NaHCO_3 , and washed with brine. The combined aqueous extracts were extracted with Et_2O three times. The combined organic extracts were dried over anhyd MgSO_4 , filtered, and concentrated in vacuo to afford crude aldehyde, which was used without further purification in the next step.

Alcohol 13

A solution of 3-*tert*-butyloxy-1-iodo-1-propene (914 mg, 3.78 mmol) in Et_2O (11 mL) was cooled to -78°C , then *t*-BuLi (6.05 mL of a 1.25 mol L^{-1} solution in Et_2O , 7.56 mmol) was added dropwise. The mixture was stirred for 1.6 h at -78°C and 1.5 h at 0°C , then cooled again at -78°C . (–)-Menthone (0.44 mL, 2.52 mmol) was dissolved in a minimum of Et_2O , then added to the reaction. Stirring

was continued for 21 h and the reaction was allowed to reach room temperature slowly during this time. The reaction was quenched by adding a satd. aq. NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O three times. The combined organic extracts were washed with brine, then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded alcohol **13** (472 mg, 70%) as a colourless oil. $[\alpha]_{\text{D}} = -19.1^\circ$ (CHCl_3 , $c = 1.98$). IR (cm^{-1}): 3466, 1468. ^1H NMR (CDCl_3) δ : 5.77 (dt, 1H, $J = 15.9$ and 5.0 Hz), 5.68 (d, 1H, $J = 15.9$ Hz), 3.95 (dd, 2H, $J = 5.0$ and 2.2 Hz), 2.02–1.90 (m, 1H), 1.80–1.67 (m, 2H), 1.54–1.43 (m, 4H), 1.21 (s, 9H), 1.23–1.11 (m, 2H), 0.94–0.83 (m, 10H). LR-MS (m/z (relative intensity)): 268 (M^+ , 5), 212 (55), 127 (100). HR-MS calcd. for $\text{C}_{18}\text{H}_{34}\text{O}$: 268.2402; found: 268.2393.

General procedure for the addition of cuprates to allylic carbonates

A solution of the iodide (1.5 equiv.) in Et_2O (0.1 mol L^{-1}) was cooled to -78°C . *t*-BuLi (3.0 equiv. of a solution in Et_2O) was added dropwise. The mixture was stirred for 30 min, then warmed to 0°C for 1 h, and cooled again to -78°C . In a different round-bottomed flask, CuCN (1.5 equiv.) in THF (0.2 mol L^{-1}) was degassed and purged with argon twice before being cooled to -78°C . The organolithium solution was cannulated dropwise into the CuCN solution. The reaction was stirred for 2 h. The carbonate was dissolved in a minimum of THF, then added to the cuprate reaction mixture at -50°C . While stirring, the temperature was allowed to reach 0°C slowly over a 1 h period, then room temperature over a 16 h period. The reaction was quenched by adding a satd. aq. NH_4Cl and NH_4OH (9:1) solution. The aqueous layer was separated and extracted with Et_2O three times. The combined organic extracts were washed with brine, then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo.

Alkene 14

Prepared from **11** (6.40 g, 25.0 mmol) following the general procedure for the addition of cuprates to allylic carbonates. Flash column chromatography (hexanes) gave 4.77 g (93%) of **14** as a colourless oil. $[\alpha]_{\text{D}} = -30.8^\circ$ (CHCl_3 , $c = 2.37$). IR (cm^{-1}): 2864, 1478. ^1H NMR (CDCl_3) δ : 4.81 (d, 1H, $J = 9.4$ Hz), 3.19 (dd, 1H, $J = 8.3$ and 5.5 Hz), 3.02 (t, 2H, $J = 7.7$ Hz), 2.59–2.47 (m, 1H), 2.39–2.31 (m, 1H), 1.91 (sx, 1H, $J = 7.1$ Hz), 1.80–1.50 (m, 6H), 1.37–1.19 (m, 2H), 1.17 (s, 9H), 1.13–0.95 (m, 2H), 0.92–0.83 (m, 15H). ^{13}C NMR (CDCl_3) δ : 138.2 (s), 128.4 (d), 72.1 (s), 67.7 (q), 50.7 (t), 42.3 (t), 35.7 (t), 32.6 (d), 32.2 (t), 31.9 (d), 29.0 (d), 27.6 (q), 26.8 (t), 26.5 (d), 22.7 (q), 22.1 (q), 20.9 (q), 19.7 (q), 17.3 (q). LR-MS (m/z (relative intensity)): 308 (M^+ , 5), 252 (70), 137 (100). $[\alpha]_{\text{D}} = -31.3^\circ$ (CHCl_3 , $c = 1.33$). IR (cm^{-1}): 2955, 1461. HR-MS calcd. for $\text{C}_{21}\text{H}_{40}\text{O}$: 308.3079; found: 308.3086. Minor isomer of alkene **14** made by starting from racemic **11**): ^1H NMR (CDCl_3) δ : 4.87 (d, 1H, $J = 9.1$ Hz), 3.22 (dd, 1H, $J = 8.1$ and 5.2 Hz), 3.00 (t, 1H, $J = 8.0$ Hz), 2.55–2.48 (m, 1H), 2.37–2.32 (m, 1H), 1.91 (sx, 1H, $J = 6.8$ Hz), 1.80–1.50 (m, 6H), 1.37–1.19 (m, 2H), 1.17 (s, 9H), 1.14–0.96 (m, 2H), 0.92–0.83 (m, 15H). LR-MS (m/z (relative intensity)): 252 ($\text{M}^+ - \text{C}_4\text{H}_9$, 45), 177 (10), 99

(100). HR-MS calcd. for $C_{17}H_{31}O$: 252.2453; found: 252.2458.

Alcohol 15

Prepared from **14** (4.77 g, 15.5 mmol) according to the general procedure for the ozonolysis of cuprate adducts. Flash column chromatography on silica gel (hexanes–AcOEt, 30%) gave 2.68 g (92%) of **15** as a colourless oil. GC analysis showed a (105:1) diastereomer ratio. **15**: $[\alpha]_D = -0.2^\circ$ ($CHCl_3$, $c = 1.73$). IR (cm^{-1}): 3341, 1479. 1H NMR ($CDCl_3$) δ : 3.48 (d, 2H, $J = 5.5$ Hz), 3.18–3.09 (m, 2H), 1.72 (oc, 2H, $J = 6.6$ Hz), 1.50–1.40 (m, 1H), 1.18 (s, 9H), 1.00–0.90 (m, 1H), 0.93 (d, 3H, $J = 6.6$ Hz), 0.91 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$) δ : 72.5 (s), 67.8 (t), 67.2 (t), 38.0 (d), 33.5 (d), 31.4 (t), 27.4 (q), 18.4 (q), 18.0 (q). LR-MS (m/z (relative intensity)): 173 ($M^+ - Me$, 10), 143 (20), 97 (100). HR-MS calcd. for $C_{10}H_{21}O_2$: 173.1541; found: 173.1535. Minor isomer of alcohol **15** (made from the ozonolysis of the minor isomer of alkene **14**): $[\alpha]_D = +10.1^\circ$ ($CHCl_3$, $c = 1.43$). IR (cm^{-1}): 3318, 1479. 1H NMR ($CDCl_3$) δ : 3.45 (d, 2H, $J = 6.6$ Hz), 3.18–3.09 (m, 2H), 1.79 (oc, 2H, $J = 6.6$ Hz), 1.34–1.25 (m, 1H), 1.18 (s, 9H), 1.20–1.10 (m, 1H), 0.88 (d, 6H, $J = 7.2$ Hz). LR-MS (m/z (relative intensity)): 173 ($M^+ - Me$, 10), 143 (25), 83 (100). HR-MS calcd. for $C_{10}H_{21}O_2$: 173.1541; found: 173.1546.

Iodide 16

Prepared from **15** (2.68 g, 14.2 mmol) according to the same procedure as per iodide **11**. Flash chromatography on silica gel (hexanes–EtOAc, 10%) afforded iodide **16** (4.17 g, 98%) as a colourless oil. $[\alpha]_D = -1.4^\circ$ ($CHCl_3$, $c = 1.28$). IR (cm^{-1}): 2974, 1479. 1H NMR ($CDCl_3$) δ : 3.26 (dd, 1H, $J = 9.9$ and 4.4 Hz), 3.20 (dd, 1H, $J = 8.3$ and 5.0 Hz), 3.12 (dd, 1H, $J = 9.4$ and 6.0 Hz), 3.05 (dd, 1H, $J = 8.3$ and 6.6 Hz), 1.74–1.51 (m, 2H), 1.44–1.35 (m, 1H), 1.17 (s, 9H), 1.05–0.95 (m, 1H), 0.99 (d, 3H, $J = 6.6$ Hz), 0.90 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$) δ : 72.3 (s), 67.0 (t), 41.0 (t), 32.0 (d), 31.5 (d), 27.5 (t), 21.5 (q), 18.1 (q), 17.7 (q). LR-MS (m/z (relative intensity)): 283 ($M^+ - Me$, 20), 225 (30), 115 (100). HR-MS calcd. for $C_{10}H_{21}O_2$: 283.0559; found: 283.0563.

Alkene 17a

Prepared from **16** (1.12 g, 3.75 mmol) and carbonate *ent*-**8** following the general procedure for the addition of cuprates to allyl carbonates. Flash column chromatography (hexanes) gave 762 mg (87%) of **17a** as a colourless oil. $[\alpha]_D = +18.9^\circ$ ($CHCl_3$, $c = 2.07$). IR (cm^{-1}): 2955, 1478. 1H NMR ($CDCl_3$) δ : 4.85 (d, 1H, $J = 9.1$ Hz), 3.22 (dd, 1H, $J = 8.7$ and 4.7 Hz), 2.92 (t, 1H, $J = 8.5$ Hz), 2.53–2.43 (m, 1H), 2.39–2.31 (m, 1H), 1.91 (sx, 1H, $J = 6.7$ Hz), 1.80–1.47 (m, 6H), 1.28–1.17 (m, 2H), 1.16 (s, 9H), 1.15–0.96 (m, 3H), 0.92 (d, 3H, $J = 6.3$ Hz), 0.89 (d, 3H, $J = 5.6$ Hz), 0.87 (d, 6H, $J = 5.8$ Hz), 0.85 (d, 6H, $J = 5.9$ Hz). ^{13}C NMR ($CDCl_3$) δ : 137.4 (s), 129.0 (d), 72.1 (s), 67.2 (t), 50.9 (d), 45.4 (t), 42.1 (t), 35.9 (t), 32.7 (d), 32.3 (t), 31.3 (d), 28.9 (d), 27.9 (d), 27.6 (q), 27.1 (t), 26.5 (d), 22.1 (q), 21.3 (q), 21.0 (q), 20.7 (q), 19.7 (q), 18.3 (q). LR-MS (m/z (relative intensity)): 350 (M^+ , 5), 294 (40), 99 (100). HR-MS calcd. for $C_{24}H_{36}O$: 350.3548; found: 350.3557.

Alkene 17b

Prepared from **16** (447 mg, 1.50 mmol) and carbonate **8** following the general procedure for the addition of cuprates to allyl carbonates. Flash column chromatography (hexanes) gave 255 mg (73%) of **17b** as a colourless oil. $[\alpha]_D = -28.8^\circ$ ($CHCl_3$, $c = 1.57$). 1H NMR ($CDCl_3$) δ : 4.77 (d, 1H, $J = 9.4$ Hz), 3.20 (dd, 1H, $J = 8.8$ and 5.5 Hz), 3.00 (t, 1H, $J = 7.7$ Hz), 2.56–2.46 (m, 1H), 2.40–2.32 (m, 1H), 1.89 (sx, 1H, $J = 7.2$ Hz), 1.80–1.61 (m, 5H), 1.54–1.43 (m, 1H), 1.31–1.06 (m, 4H), 1.16 (s, 9H), 0.99–0.88 (m, 3H), 0.92 (d, 3H, $J = 6.1$ Hz), 0.87 (d, 6H, $J = 6.6$ Hz), 0.85 (d, 6H, $J = 6.1$ Hz), 0.82 (d, 3H, $J = 6.6$ Hz). LR-MS (m/z (relative intensity)): 350 (M^+ , 5), 293 (50), 141 (100). HR-MS calcd. for $C_{24}H_{46}O$: 350.3548; found: 350.3553.

Alcohol 18a

Prepared from **17a** (150 mg, 0.43 mmol) according to the general procedure for the ozonolysis of cuprate adducts. Flash chromatography on silica gel (hexanes–AcOEt, 20%) afforded 67 mg (69%) of alcohol **18a** as a colourless oil. GC analysis showed a (218:1) diastereoisomer ratio. $[\alpha]_D = -22.5^\circ$ ($CHCl_3$, $c = 1.13$). IR (cm^{-1}): 3334, 1462. 1H NMR ($CDCl_3$) δ : 3.48 (dd, 1H, $J = 10.7$ and 6.2 Hz), 3.40 (dd, 1H, $J = 10.7$ and 6.4 Hz), 3.18 (dd, 1H, $J = 8.3$ and 5.3 Hz), 3.04 (t, 1H, $J = 8.4$ Hz), 1.78–1.58 (m, 2H), 1.33–1.24 (m, 2H), 1.17 (s, 9H), 1.11–1.06 (m, 2H), 0.99–0.92 (m, 1H), 0.88 (d, 6H, $J = 6.5$ Hz), 0.86 (d, 3H, $J = 6.4$ Hz). LR-MS (m/z (relative intensity)): 230 (M^+ , 5), 215 (10), 83 (100). HR-MS calcd. for $C_{13}H_{27}O_2$: 215.2011; found: 215.2003.

Alcohol 18b

Prepared from **17b** (234 mg, 0.67 mmol) according to the general procedure for the ozonolysis of cuprate adducts. The alcohol was purified by flash chromatography on silica gel (hexanes–AcOEt, 20%) to afford 113 mg (74%) of **18b** as a colourless oil. $[\alpha]_D = +8.7^\circ$ ($CHCl_3$, $c = 1.33$). IR (cm^{-1}): 3351, 1480. 1H NMR ($CDCl_3$) δ : 3.54 (dd, 1H, $J = 11.0$ and 5.5 Hz), 3.36 (dd, 1H, $J = 10.5$ and 6.6 Hz), 3.21 (dd, 1H, $J = 8.8$ and 5.0 Hz), 3.02 (t, 1H, $J = 7.2$ Hz), 1.79–1.54 (m, 2H), 1.31 (m, 2H), 1.16 (s, 9H), 0.93 (d, 3H, $J = 6.6$ Hz), 0.90–0.81 (m, 3H), 0.89 (d, 6H, $J = 6.6$ Hz). LR-MS (m/z (relative intensity)): 215 ($M^+ - Me$, 10), 173 (30), 83 (100). HR-MS calcd. for $C_{13}H_{27}O_2$: 215.2011; found: 215.2007.

Ester 19

Through a stirred solution of **17a** (800 mg, 2.28 mmol) in CH_2Cl_2 (19 mL) and MeOH (4 mL) at $-78^\circ C$ was bubbled O_3 until the appearance of a blue colour. Then, argon gas was bubbled through the solution until the blue colour disappeared and Ph_3P (720 mg, 2.74 mmol) was added. The mixture was warmed to room temperature and stirred for 4 h. The reaction was concentrated in vacuo, then triturated twice with hexanes. The crude aldehyde was used in the next step without further purification. The crude aldehyde was dissolved in CH_2Cl_2 (27 mL), then $MeO_2CCH=PPh_3$ (1.723 g, 5.154 mmol) was added. The mixture was stirred and heated to reflux for 17.5 h. The reaction was cooled to room temperature, then concentrated in vacuo. Two triturations, first with Et_2O then with hexanes, were performed. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded only the trans alkene (490 mg, 76%) as a

colourless oil. $[\alpha]_D = +22.0^\circ$ (CHCl_3 , $c = 1.82$). IR (cm^{-1}): 1725, 1658. ^1H NMR (CDCl_3) δ : 6.88 (dd, 1H, $J = 15.4$ and 8.3 Hz), 5.78 (d, 1H $J = 15.4$ Hz), 3.72 (s, 3H), 3.18 (dd, 1H, $J = 8.3$ and 5.0 Hz), 2.99 (t, 1H, $J = 8.0$ Hz), 2.40 (sp, 1H, $J = 7.2$ Hz), 1.68 (oc, 1H, $J = 5.5$ Hz), 1.56 (oc, 1H, $J = 6.6$ Hz), 1.36–1.25 (m, 2H), 1.22–1.10 (m, 1H), 1.15 (s, 9H), 1.00 (d, 3H, $J = 6.6$ Hz), 0.94–0.85 (m, 1H), 0.88 (d, 3H, $J = 6.6$ Hz), 0.86 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR (CDCl_3) δ : 167.1 (s), 155.2 (d), 118.7 (d), 72.0 (s), 66.7 (t), 51.1 (q), 43.3 (t), 41.6 (t), 33.8 (d), 31.1 (d), 27.6 (d), 27.3 (q), 20.3 (q), 19.0 (q), 18.2 (q). LR-MS (m/z (relative intensity)): 269 ($\text{M}^+ - \text{Me}$, 10), 227 (15), 127 (100). HR-MS calcd. for $\text{C}_{16}\text{H}_{29}\text{O}_3$: 269.2117; found: 269.2119.

To the α,β -unsaturated ester (426 mg, 1.50 mmol) dissolved in EtOH (15 mL) was added 5% Pd/C (75 mg). The reaction was degassed and flushed with argon 3 times, before being stirred for 2 h under 1 atm of H_2 (1 atm = 101.325 kPa). The mixture was filtered over a pad of Celite, then concentrated in vacuo. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) afforded ester **19** (388 mg, 90%) as a colourless oil. $[\alpha]_D = -17.9^\circ$ (CHCl_3 , $c = 0.88$). IR (cm^{-1}): 1744, 1462. ^1H NMR (CDCl_3) δ : 3.66 (s, 3H), 3.19 (dd, 1H $J = 8.8$ and 5.5 Hz), 3.02 (t, 1H, $J = 7.7$ Hz), 2.37–2.25 (m, 2H), 1.69 (oc, 1H, $J = 6.1$ Hz), 1.62–1.42 (m, 4H), 1.37–1.18 (m, 1H), 1.17 (s, 9H), 1.16–1.06 (m, 1H), 1.02–0.90 (m, 2H), 0.87 (d, 3H, $J = 6.6$ Hz), 0.83 (d, 3H, $J = 6.1$ Hz), 0.82 (d, 3H, $J = 6.6$ Hz). LR-MS (m/z (relative intensity)): 271 ($\text{M}^+ - \text{Me}$, 5), 229 (20), 87 (100). HR-MS calcd. for $\text{C}_{16}\text{H}_{31}\text{O}_3$: 271.2273; found: 271.2265.

Aldehyde 20

To a solution of ester **19** (120 mg, 0.42 mmol) in CH_2Cl_2 (1.7 mL) was added slowly a solution of *B*-bromocatecholborane (167 mg, 0.84 mmol) in CH_2Cl_2 (2.0 mL). The reaction was stirred for 15 min, then H_2O (5 mL) was added. Stirring continued for 30 min. The aqueous layer was separated and extracted with CH_2Cl_2 3 times. The combined organic extracts were washed 3 times with a solution of satd. aq. Na_2CO_3 , then dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (20% EtOAc in hexanes) afforded a primary alcohol (95 mg, 99%) as a colourless oil. $[\alpha]_D = -22.6^\circ$ (CHCl_3 , $c = 1.46$). IR (cm^{-1}): 3347, 1744, 1462. ^1H NMR (CDCl_3) δ : 3.66 (s, 3H), 3.50–3.39 (m, 2H), 2.38–2.24 (m, 2H), 1.77–1.36 (m, 6H), 1.34–1.25 (m, 1H), 1.15–0.87 (m, 3H), 0.92 (d, 3H, $J = 6.6$ Hz), 0.84 (d, 6H, $J = 6.1$ Hz). LR-MS (m/z (relative intensity)): 200 ($\text{M}^+ - \text{CH}_2\text{O}$, 20), 157 (20), 83 (100). HR-MS calcd. for $\text{C}_{12}\text{H}_{24}\text{O}_2$: 200.1776; found: 200.1782.

To a solution of this alcohol (157 mg, 0.69 mmol) in wet CH_2Cl_2 (3 mL) was added Dess–Martin's periodinane (349 mg, 0.82 mmol). The mixture was stirred for 30 min. The solution was then concentrated in vacuo, diluted with Et_2O , washed with a solution of satd. aq. $\text{Na}_2\text{S}_2\text{O}_3$, satd. aq. NaHCO_3 , and with brine. The combined aqueous extracts were extracted with Et_2O 3 times. The combined organic extracts were dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc in hexanes) afforded aldehyde **20** (113 mg, 72%) as a colourless oil. ^1H NMR (CDCl_3) δ : 9.59 (d, 1H, $J = 2.2$ Hz), 3.67 (s, 3H), 2.44 (dq, 1H, $J = 7.2$ and

2.8 Hz), 2.38–2.24 (m, 2H), 1.71–1.40 (m, 6H), 1.20–1.10 (m, 2H), 1.08 (d, 3H, $J = 6.6$ Hz), 0.86 (d, 3H, $J = 6.0$ Hz), 0.84 (d, 3H, $J = 6.1$ Hz). LR-MS (m/z (relative intensity)): 200 ($\text{M}^+ - \text{CO}$, 5), 197 (5), 87 (100). HR-MS calcd. for $\text{C}_{12}\text{H}_{24}\text{O}_2$: 200.1776; found: 200.1784.

Ketone 21

$[\alpha]_D = -14.1^\circ$ (CHCl_3 , $c = 1.74$) (lit. (4b) value -14.5° , CH_2Cl_2 , $c = 1.22$). ^1H NMR (CDCl_3) δ : 3.66 (s, 3H), 2.61 (sx, 1H, $J = 7.1$ Hz), 2.40–2.23 (m, 2H), 2.13 (s, 3H), 1.66–1.39 (m, 5H), 1.15–1.02 (m, 5H), 1.07 (d, 3H, $J = 6.6$ Hz), 0.83 (d, 6H, $J = 6.6$ Hz). ^{13}C NMR (CDCl_3) δ : 212.9 (s), 174.4 (s), 51.4 (q), 44.7 (d), 44.1 (t), 41.1 (t), 32.7 (t), 31.8 (t), 29.6 (d), 27.9 (d), 19.5 (q), 18.8 (q), 16.9 (q). LR-MS (m/z (relative intensity)): 243 (MH^+ , 5), 211 (20), 97 (100). HR-MS calcd. for $\text{C}_{14}\text{H}_{27}\text{O}_3$: 243.1960; found: 243.1953.

Alcohol 22

To a solution of Roush's crotyl borane (9.5 mL of a 0.51 mol L^{-1} solution in toluene, 4.81 mmol) was added 4 Å molecular sieves (60 mg). This mixture was stirred for 10 min, then cooled to -78°C . Crude aldehyde **12** in toluene (2.5 mL) was added dropwise, then stirred for 4 h. NaBH_4 (40 mg, 1.05 mmol) in EtOH (1 mL) was added dropwise, then the reaction was warmed to 0°C . NaOH (4 mL of a 2 N aqueous solution) was added and stirred for 1.5 h. The aqueous layer was separated and extracted with Et_2O 3 times. The combined organic extracts were dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. GC analysis of the crude product gave a (82:18) diastereoisomer ratio. Purification by flash chromatography on silica gel (2% EtOAc in hexanes) afforded the desired pure alcohol **22** (363 mg, 57%) as a colourless oil, and its diastereomer (88 mg, 14%) as a colourless oil. **22**: $[\alpha]_D = -29.3^\circ$ (CHCl_3 , $c = 2.09$). ^1H NMR (CDCl_3) δ : 6.01–5.89 (m, 1H), 5.07–5.02 (m, 2H), 4.37 (s, 1H), 3.49 (dd, 1H, $J = 8.8$ and 3.9 Hz), 3.37–3.31 (m, 2H), 2.37–2.31 (m, 1H), 1.89–1.77 (m, 1H), 1.20 (s, 9H), 1.10 (d, 3H, $J = 6.6$ Hz), 0.82 (d, 6H, $J = 7.2$ Hz). ^{13}C NMR (CDCl_3) δ : 139.9 (d), 114.7 (t), 80.8 (d), 76.5 (s), 67.7 (t), 41.1 (d), 36.2 (d), 27.2 (q), 17.8 (q), 13.5 (q). LR-MS (m/z (relative intensity)): 185 ($\text{M}^+ - \text{Me}$, 5), 145 (30), 84 (100). HR-MS calcd. for $\text{C}_{11}\text{H}_{21}\text{O}_2$: 185.1541; found: 185.1546. Minor isomer of alcohol **22**: $[\alpha]_D = +6.6^\circ$ (CHCl_3 , $c = 3.72$). ^1H NMR (CDCl_3) δ : 5.89–5.77 (m, 1H), 5.13–5.05 (m, 2H), 3.52–3.44 (m, 3H), 3.21 (d, 1H, $J = 1.7$ Hz), 2.26 (sx, 1H, $J = 6.6$ Hz), 1.90–1.80 (m, 1H), 1.18 (s, 9H), 0.97 (d, 3H, $J = 7.2$ Hz), 0.94 (d, 3H, $J = 6.6$ Hz). LR-MS (m/z (relative intensity)): 201 (MH^+ , 100), 145 (50). HR-MS calcd. for $\text{C}_{12}\text{H}_{25}\text{O}_2$: 201.1854; found: 201.1858.

Silyl ether 23

To a solution of alcohol **22** (500 mg, 2.5 mmol) in CH_2Cl_2 (50 mL) at 0°C was added *i*-Pr₂EtN (0.61 mL, 3.5 mmol) and TESOTf (0.68 mL, 3.0 mmol). The reaction was stirred for 30 min. The reaction was quenched by adding a satd. aq. NaHCO_3 solution. The aqueous layer was separated and extracted with Et_2O 3 times. The combined organic extracts were dried over anhyd MgSO_4 , filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (2% EtOAc in hexanes) afforded the silyl ether **23** (784 mg, quantitative) as a colourless oil. $[\alpha]_D = +16.8^\circ$ (CHCl_3 , $c =$

1.98). ^1H NMR (CDCl_3) δ : 5.88 (ddd, 1H, $J = 17.6, 10.4,$ and 8.2 Hz), 5.00–4.94 (m, 2H), 3.49–3.44 (m, 2H), 3.09 (t, 1H, $J = 8.3$ Hz), 2.43–2.31 (m, 1H), 1.84–1.71 (m, 1H), 1.16 (s, 9H), 1.02 (d, 3H, $J = 7.2$ Hz), 0.97 (t, 9H, $J = 8.3$ Hz), 0.89 (d, 3H, $J = 6.6$ Hz), 0.62 (q, 6H, $J = 8.3$ Hz). LR-MS (m/z (relative intensity)): 259 ($\text{M}^+ - \text{C}_4\text{H}_7$, 40), 229 (45), 173 (100). HR-MS calcd. for $\text{C}_{14}\text{H}_{31}\text{O}_2\text{Si}$: 259.2093; found: 259.2097.

Aldehyde 24

Through a stirred solution of silyl ether **23** (784 mg, 2.5 mmol) in CH_2Cl_2 (20 mL) and MeOH (5 mL) at -78°C was bubbled O_3 until the appearance of a blue colour. Then argon was bubbled through the solution until the blue colour disappeared. Ph_3P (981 mg, 3.75 mmol) was added. The mixture was warmed to room temperature and stirred for 4 h. The reaction was concentrated in vacuo, then triturated twice with hexanes. The crude aldehyde was not purified further. ^1H NMR (CDCl_3) δ : 9.78 (d, 1H, $J = 2.2$ Hz), 3.95 (dd, 1H, $J = 5.0$ and 3.9 Hz), 3.38 (dd, 1H, $J = 8.8$ and 6.1 Hz), 3.17 (dd, 1H, $J = 8.8$ and 6.6 Hz), 2.63–.54 (m, 1H), 1.93 (sp, 1H, $J = 6.1$ Hz), 1.16 (s, 9H), 1.11 (d, 1H, $J = 7.2$ Hz), 0.96 (t, 9H, $J = 7.7$ Hz), 0.90 (d, 3H, $J = 6.6$ Hz), 0.62 (q, 6H, $J = 7.7$ Hz).³

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³Supplementary data may be purchased from the Directory of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically).