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Regioselective Isomerisation of Highly Substituted 1-Methylenecyclohexenepoxides to the Corresponding Allylic Alcohols. Influence of the Base and of the Protecting Groups

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Summary. Highly substituted 1-methylenecyclohexenepoxides **3**, useful building blocks for a projected synthesis of wailupemycin A (**1**), were synthesized from (*R*)-carvone in eight synthetic steps in 23–40% overall yield. The regioselectivity of the subsequent isomerisation to the corresponding allylic alcohols was shown to depend on the basicity of the reagent and on the bulkiness of the protecting groups existing in **3**. With diethylaluminum 2,2,6,6-tetramethylpiperidid (*DATMP*), secondary allylic alcohols **5** were formed exclusively. With strong bases such as a mixture of lithium di-*iso*-propylamide and potassium *tert*-butoxide (*LIDAKOR*), the tertiary allylic alcohol **6** was obtained as predominant product.

Keywords. Epoxide rearrangement; Allylic alcohols; Regioselectivity.

Introduction

Recently, we became interested in wailupemycin A (**1**, Scheme 1) and its C7 epimer wailupemycin B, marine metabolites isolated from *Streptomyces maritimus* by *Davidson* and co-workers [1]. The wailupemycins are bacteriostatic polyketides possessing unprecedented carbon skeletons. Because of the limited supplies from natural sources, the potentially useful biological activity has not been fully evaluated. The biosynthesis of these compounds has attracted considerable attention

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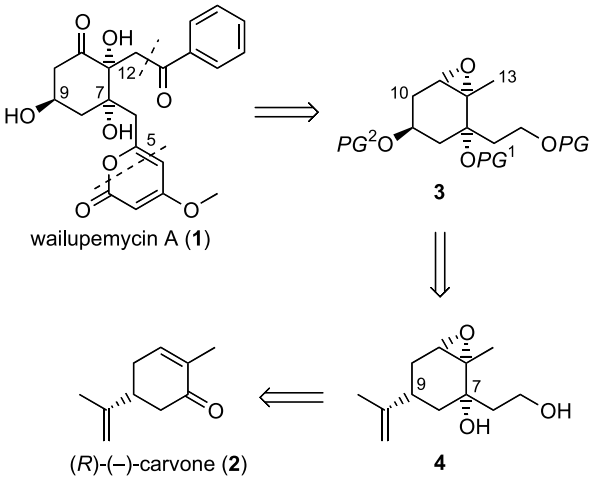
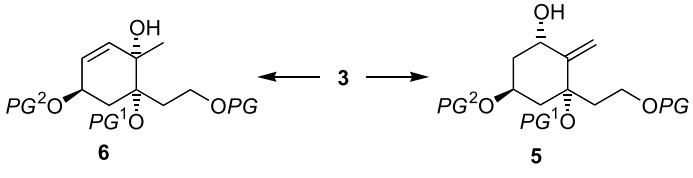


Scheme 1

[2]. Our efforts to develop a *de novo* synthesis of the wailupemycins have recently culminated in a total synthesis of wailupemycin B [3].

The most notable features of wailupemycin A (**1**) from the perspective of a synthetic chemist are the highly substituted cyclohexanone moiety and the 2-pyrone containing side chain. It was envisaged that the protected intermediate **3** could be used as a potential precursor (Scheme 1). Regioselective isomerisation of 1-methylenecyclohexenepoxide **3** to the corresponding secondary allylic alcohol should facilitate an entry to the target compound. We previously reported a methodology for the synthesis of 6-substituted 4-hydroxy-2-pyrones from aldehydes [4], which should allow for the introduction of the 2-pyrone moiety by formation of the C4–C5 bond. Key intermediate **3** could originate from precursor **4**. In a synthetic direction, oxidative transformation of the 2-propenyl group into a hydroxy group, followed by an inversion of the C9-hydroxy would complete the synthesis of key intermediate **3**. (*R*)-Carvone (**2**), which is readily available in enantiomerically pure form, was identified as an ideal inexpensive starting material for the projected synthesis. A C6–C7 bond formation by diastereoselective enolate addition followed by directed diastereoselective epoxidation would allow for conversion of (*R*)-carvone (**2**) into precursor **4**.

Rearrangement of epoxide **3** to the secondary allylic alcohol **5** (Scheme 2) turned out to be a critical step in the projected synthesis of wailupemycin A (**1**). Unlike compound **5**, tertiary allylic alcohol **6** cannot act as precursor for wailupemycin A (**1**). We therefore turned our attention to reagents able to lead selectively to compound **5**. Several reagents have been developed so far to carry out such transformations under mild conditions [5–10]. Amongst others, lithium dialkylamides [5], diethylaluminum



Scheme 2

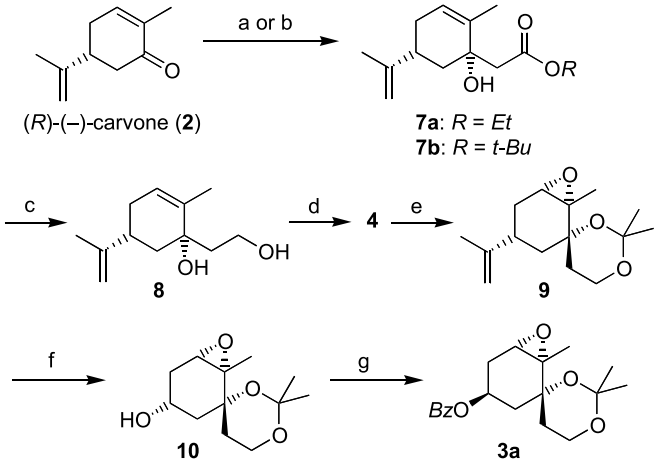
2,2,6,6-tetramethylpiperidide (*DATMP*) [6], and methylmagnesium *N*-cyclohexyl-*N*-*iso*-propylamide (*MICA*) [7] have frequently been used as reagents to achieve regioselective isomerisations. In addition, a mixture of lithium di-*iso*-propylamide and potassium *tert*-butoxide (*LIDAKOR*) is reported to promote the smooth ring opening of oxiranes to afford allylic alcohols [8]. Treatment of oxiranes with trimethylsilyl trifluoromethanesulfonate and 1,5-diazabicyclo[5.4.0]undec-5-ene (*DBU*) also gives the corresponding allylic alcohol protected as trimethylsilyl ether [10]. All these methods have in common that the ring opening takes place preferentially at the more substituted carbon [5–10], when an unsymmetrically trisubstituted oxirane is employed. To access the higher substituted alcohol a two-step procedure *via* an organoselenium reagent was developed [11].

This report details the synthesis of key intermediate **3** and its isomerisation to the corresponding allylic alcohols **5** and **6**. Influences of different bases as reagents and of the protecting groups in 1-methylenecyclohexenepoxide **3** on the regioselectivity of the epoxide opening by elimination have been studied.

Results and Discussion

Synthesis of Key Intermediate 3

Our synthesis of key epoxide **3** started from (*R*)-carvone (**2**) (Scheme 3). The stereoselective aldol addition of ethyl acetate to carvone promoted by stoichiometric amounts of cerium(III) chloride [12] as well as the diastereoselective addition of *tert*-butyl acetate in the presence of 0.25 equiv. of CeF_3 have been described [13]. We found that a complete conversion of carvone to tertiary alcohols **7a** and **7b** occurred even when using lithium enolates without cerium(III) salts as additives. The reaction of (*R*)-carvone (**2**) gave rise to a single isomer **7a**/**b**, presumably



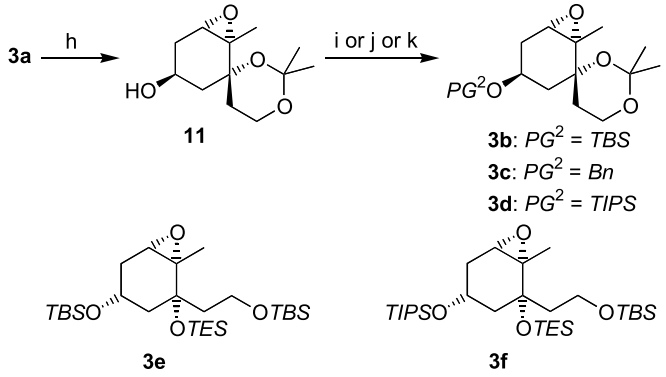
Scheme 3. (a) $LiCH_2CO_2Et$, −78°C (*THF*), d.r. > 95:5, 99%; (b) $LiCH_2CO_2t\text{-}Bu$, −78°C (*THF*), d.r. > 95:5, 85%; (c) *LAH*, rt (Et_2O), 98% for $R = Et$, 84% for $R = t\text{-}Bu$; (d) *MCPBA*, −40°C (CH_2Cl_2), d.r. > 95:5, 87%; (e) 2-methoxypropene, [*PPTS*], 0°C (CH_2Cl_2), 80%; (f) (i) O_3, $NaHCO_3$, −78°C (CH_2Cl_2, *Me*OH), (ii) Ac_2O, NEt_3, [*DMAP*], reflux (CH_2Cl_2), (iii) K_2CO_3, rt (*Me*OH), 74%; (g) *Ph*COOH, PPh_3, *DIAD*, 0°C (*THF*), 94%

as a result of the stereoelectronically favored axial addition to the carbonyl group. Subsequent reduction of the esters was conducted with lithiumaluminum hydride to give the 1,3-diol **8** in good yields. The regio- and stereoselective epoxidation of tertiary allylic alcohol **8** was achieved with *MCPBA* and the free hydroxy groups of the resulting epoxide **4** were protected as isopropylidene acetal. Oxidative degradation of the 2-propenyl group of compound **9** was carried out by ozonolysis in methanol to an α-methoxy hydroperoxide which upon treatment with acetic anhydride and triethylamine underwent *in situ Criegee* rearrangement affording epoxy alcohol **10** in 74% yield [14]. The rearrangement is known to occur with retention of configuration. It is worthy to note, that ozonolysis of **9** without sodium bicarbonate as an acid scavenger resulted in decomposition of the α-methoxy hydroperoxide. Our attempts to use a two-step C=C-cleavage/*Baeyer-Villiger* sequence failed. We were able to convert the 2-propenyl double bond to the corresponding ketone by oxidative C=C bond cleavage using OsO_4 and $NaIO_4$ [15]. Unexpectedly, the subsequent *Baeyer-Villiger* oxidation using different reagents in a variety of solvents was very slow producing a number of byproducts.

At this stage the configuration of the C9-hydroxy group had to be inverted in order to gain access to the correct configuration of the natural product. *Mitsunobu* reaction [16] of alcohol **10** with benzoic acid in the presence of diisopropyl azodicarboxylate (*DIAD*) and triphenylphosphine (*TPP*) occurred with inversion of configuration at C9 affording benzoate **3a**.

The success of the synthesis now hinged upon the selective isomerisation of epoxide **3a** to secondary allylic alcohol **5a**. Several methods known to effect the rearrangement of epoxides to allylic alcohols were tried [5–10]. Epoxide **3a** was exposed to the complex prepared *in situ* from Et_2AlCl and lithium 2,2,6,6-tetramethylpiperidide (*LTMP*) [6], but the method failed to give more than a trace of the desired product. Only cleavage of the isopropylidene acetal was observed under *Noyori*'s conditions with *TMSOTf/DBU* [10]. Next, we explored strong bases as lithium diethylamide [5] and *LIDAKOR* [8], and obtained the corresponding C9–C10 cyclohexene as sole product of benzoic acid elimination.

These results prompted us to prepare several epoxides **3b**–**3f**, which differ in the protecting groups *PG*, PG^1, and PG^2 (Scheme 4). Benzoate **3a** was saponified



Scheme 4. (h) NaOH, rt (*Me*OH), 93%; (i) *TBS*Cl, *im*, rt (*DMF*), 92%; (j) *Bn*Br, NaH, rt (*DMF*), 90%; (k) *TIPS*Cl, *im*, rt (*DMF*), 72%

with NaOH in methanol at room temperature yielding alcohol **11** in 93% yield. Silyl ethers **3b** and **3d** were obtained by protection of the C9 hydroxy group as its *tert*-butyldimethylsilyl (*TBS*) ether and its triisopropylsilyl (*TIPS*) ether, respectively. The C9 alcohol function was also protected as the benzyl ether using *Bn*Br, NaH in *DMF* to give **3c**. Silyl ethers **3e** and **3f** were prepared by standard protecting group conversions starting from benzoate **3a** [17].

*Isomerisation of Epoxide **3** to Allylic Alcohols*

The utility of the present substrates **3b**–**3f** is largely dependent on the success of the regioselective transformation of epoxide **3** into secondary allylic alcohol **5**. Several examples of this transformation are given in Table 1.

Surprisingly, the reaction of *TBS* ether **3b** with strong bases as lithium diethylamide, *LTMP*, and *LIDAKOR* gave tertiary alcohol **6b** as sole product (entry 1–3). Proton abstraction from the C10 methylene group is obviously greatly preferred over that from the C13 methyl group. This preference has to be attributed to the preferred geometry for proton abstraction. Notably, the reaction of *LIDAKOR* with epoxide **3b** (entry 3) afforded at −78°C exclusively product **6b** in 98% yield. The reaction of methylmagnesium *N*-cyclohexyl-*N-iso*-propylamide with epoxide **3b** (entry 4), however, led to a 2:1 mixture of the isomeric olefins **5b** and **6b** with the latter predominating as determined by ^{1}H NMR analysis. Next, we explored butylmagnesium *N*-cyclohexyl-*N-iso*-propylamide without affecting the ratio of regioisomers. The rearrangement proceeded slowly and incompletely at room temperature. Reaction of **3b** with methylmagnesium diethylamide gave no product of epoxide isomerisation (entry 6). However, treatment of **3b** with *DATMP* led to regioselective formation of secondary allylic alcohol **5b** in low and non-reproducible yields (entry 7–8). No isomerisation was observed with *TMSOTf*/*DBU* (entry 9) neither with Al(O*iPr*)$_3$ [9] (entry 10). Longer reaction times led to extensive decomposition, revealing the instability of **3b** towards Lewis-acidic conditions.

It seemed logical to expect that the steric bulk of the C9-hydroxy protecting group PG^2 plays a significant role in the selectivity of isomerisation. Bulkier protecting groups PG^2 should block the proton abstraction from the C10 methylene group. Indeed, reaction of *TIPS* ether **3d** with *MICA* under standard conditions gave a mixture of the isomeric olefins **5d** and **6d** with the former prevailing (63:37 ratio) (entry 13). Our observations are in line with what one would expect for a more hindered substrate. However, an enhancement of the selectivity for the desired isomer **5** in magnesium amide promoted rearrangements has not been successful. In contrast, the less sterically biased benzyl ether **3c** (entry 11–12) isomerized to the tertiary alcohol **6c** as the predominant product, showing enhanced selectivity and reactivity compared to *TBS* ether **3b**. Unlike acetonides **3b**–**3d**, the fully silyl protected epoxide **3e** was inert to the standard reaction conditions for *MICA* (entry 15). *TBS* Substrate **3f** did not react either (entry 17). The regioselectivity of the epoxide isomerisation using magnesium amides seems to be strongly dependent on the bulkiness of the protecting group PG^2. The proton abstraction from the C10 methylene group is the favoured reaction pathway in case of small protecting groups PG^2. The proton abstraction from C13 methyl group becomes the more predominant the bulkier the protecting group is. On the other hand, *LIDAKOR* and the other strong

Table 1. Formation of allylic alcohols **5** and **6**

Entry	# **3**	*PG*	*PG*[1]	*PG*[2]	Reagent
1	**b**	$-C(CH_3)_2-$		*TBS*	Li*N*Et_2
2	**b**	$-C(CH_3)_2-$		*TBS*	*LTMP*
3	**b**	$-C(CH_3)_2-$		*TBS*	*LIDAKOR*
4	**b**	$-C(CH_3)_2-$		*TBS*	*MICA*
5	**b**	$-C(CH_3)_2-$		*TBS*	*Bu*Mg-(*c-Hex*)(*i-Pr*)
6	**b**	$-C(CH_3)_2-$		*TBS*	*Me*Mg-NEt_2
7	**b**	$-C(CH_3)_2-$		*TBS*	*DATMP*
8	**b**	$-C(CH_3)_2-$		*TBS*	*DATMP*
9	**b**	$-C(CH_3)_2-$		*TBS*	Al(O*i-Pr*)$_3$
10	**b**	$-C(CH_3)_2-$		*TBS*	*TMSOTf*, *DBU*
11	**c**	$-C(CH_3)_2-$		*Bn*	*MICA*
12	**c**	$-C(CH_3)_2-$		*Bn*	*Me*Mg-NEt_2
13	**d**	$-C(CH_3)_2-$		*TIPS*	*MICA*
14	**d**	$-C(CH_3)_2-$		*TIPS*	*DATMP*
15	**e**	*TBS*	*TES*	*TIPS*	*MICA*
16	**e**	*TBS*	*TES*	*TIPS*	*DATMP*
17	**f**	*TBS*	*TES*	*TBS*	*MICA*
18	**f**	*TBS*	*TES*	*TBS*	*DATMP*

Entry	Reaction conditions	Ratio[a] **5**:**6**	Compound, yield/%
1	(4 eq), reflux (*Et*$_2$O)	0:100	**6b**, 62
2	(4 eq), 0°C (benzene)	0:100	**6b**, 87
3	(2 eq), −78°C → 0°C (*THF*)	0:100	**6b**, 98
4	(4 eq), 0°C → rt (*THF*)	33:67	**5b** + **6b**, 93
5	(4 eq), 0°C → rt (*THF*)	33:67	**5b** + **6b**, 62
6	(4 eq), 0°C → rt (*THF*)	/	n.r.[e]
7	(4 eq), 0°C (benzene)	100:0	**5b**, ∼16[b]
8	(4 eq), −78°C (toluene)	100:0	**5b**, 21
9	(10 eq), reflux (toluene)	/	decomposition[c]
10	(1 eq), rt (benzene)	/	decomposition[d]
11	(4 eq), 0°C → rt (*THF*)	25:75	**5c** + **6c**, 71
12	(4 eq), 0°C → rt (*THF*)	11:89	**5c** + **6c**, 42
13	(4 eq), 0°C → rt (*THF*)	63:37	**5d** + **6d**, 65
14	(4 eq), 0°C (benzene)	100:0	**5d**, 78
15	(4 eq), 0°C → rt (*THF*)	/	n.r.
16	(4 eq), 0°C (benzene)	/	n.r.
17	(4 eq), 0°C → rt (*THF*)	/	n.r.
18	(4 eq), 0°C (benzene)	100:0	**5f**, 48

[a] Ratio by ^{1}H NMR of crude product; [b] yield was not reproducible; [c] decomposition to not isolated products; [d] mainly acetal cleavage; [e] n.r. = no reaction

lithium bases favour epoxide isomerisation via an E2 elimination pathway abstracting exclusively the proton from the C10 methylene group. Possibly, the C–H bond is already stretched to a significant extent in the transition state of these eliminations. The steric environment at C9 is not important.

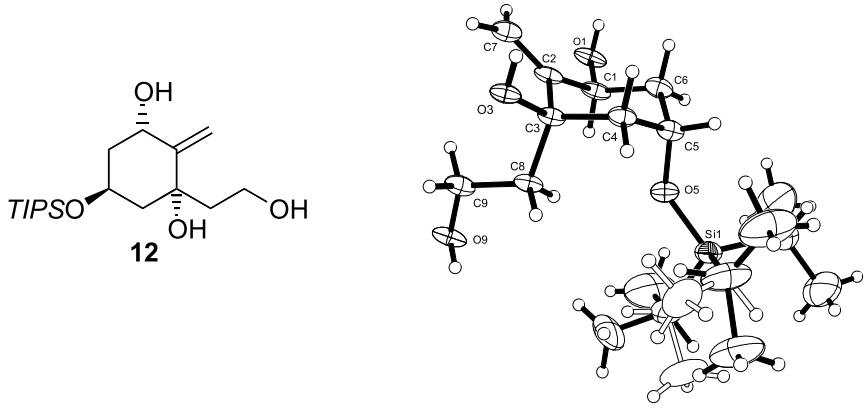


Fig. 1. A molecule of compound **12** in the crystal

Exposure of *TIPS* ether **3d** to *DATMP* gave rise to a single isomer **5d** in good yields (entry 14). In addition, *TBS* ether **3f** reacted with *DATMP* under standard conditions to give the secondary allylic alcohol **5f** in moderate yield. The high regioselectivity of reactions mediated by *DATMP* is in keeping with literature precedence [6]. The high affinity of aluminum to oxygen seems to be essential to ensure proton abstraction from the C13 methyl group. For steric reasons, *DATMP* coordinates to the exocyclic lone pair of the epoxide oxygen atom and facilitates a *syn*-elimination at the exocyclic methyl group. Apparently, *DATMP* is the reagent of choice for the conversion of epoxide **3d** to secondary allylic alcohol **5d**, and, therefore, was planned to be used in the envisioned total synthesis of wailupemycin A (**1**). It was subsequently found that aqueous work-up led to the partially hydrolysis of the isopropylidene acetal to give triol **12** as major byproduct. Since byproduct formation became even more substantial on scale-up, we performed the isomerisation of **3d** with *DATMP*, affording exclusively triol **12** after acidic work-up procedure (HCl). The configuration of **12** was additionally verified by X-ray analysis (Fig. 1).

Conclusion

In summary, we have shown that the success in the regioselective isomerisation of 1-methylenecyclohexenepoxide **3** depends on the basicity of the reagent in addition to the sterical demand of the protecting groups for the three hydroxyl groups present in **3**. Reaction of epoxide **3b** ($PG/PG^1 = -C(CH_3)_2-$, $PG^2 = TBS$) with *LIDAKOR* at $-78°C$ in *THF* gave tertiary allylic alcohol **6b** exclusively in 98% yield. On the other hand, treatment of **3d** ($PG/PG^1 = -C(CH_3)_2-$, $PG^2 = TIPS$) with *DATMP* at 0°C in benzene led to regioselective formation of secondary allylic alcohol **5d** in 78% yield. In view of all the results mentioned in the present study, the application of this strategy to the synthesis of the more complex wailupemycins is currently being pursued in our laboratory.

Experimental

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Tetrahydrofuran (*THF*) was distilled from sodium immediately prior to

use. *N,N*-Di-*iso*-propylamine was distilled from calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. Ozonolyses were conducted using a Fischer Ozone Generator 502. TLC: Merck glass sheets (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection by UV or coloration with cerium ammonium molybdate (*CAM*). Optical Rotation: Perkin-Elmer 241 MC. NMR: Bruker AV-360, AV-500. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature unless stated otherwise. Chemical shifts are reported relative to tetramethylsilane as internal standard. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically non-equivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. IR: Perkin-Elmer 1600 FT-IR. MS: Finnigan MAT 8200 (EI). Elemental Analysis: Elementar Vario EL. All reported compounds show satisfying elemental analyses. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (*ca.* 50 g for 1 g of material to be separated) with the indicated eluent. Common solvents for chromatography [pentane (*P*), cyclohexane (*CH*), ethyl acetate (*EA*)] were distilled prior to use. The crystal structure of compound **12** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 221991.

Ethyl 2-[(1S,5R)-1-Hydroxy-5-isopropenyl-2-methyl-2-cyclohexenyl]acetate
(**7a**, $C_{14}H_{22}O_3$) [12]

A *THF* (150 cm^3) solution of diisopropylamine (11 cm^3, 8.05 g, 80 mmol) was cooled to 0°C. Butyllithium, 2.5 *M* in hexanes (32 cm^3, 80 mmol), was added over 10 min, while maintaining the reaction temperature at 0°C. After stirring at that temperature for 5 min and then cooling to −78°C, ethyl acetate (7.8 cm^3, 7.0 g, 80 mmol) was added dropwise, while maintaining the reaction mixture below −70°C. After stirring at −78°C for 25 min, (*R*)-(−)-carvone (**2**) (10.4 cm^3, 10.0 g, 67 mmol) was added slowly. After stirring for 2 h at −78°C, TLC analysis indicated complete reaction. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (35 cm^3). After the exotherm has subsided, the cooling bath was removed, and the resulting thick suspension was diluted with diethylether (100 cm^3) and water (100 cm^3), and allowed to warm to ambient temperature. The mixture was extracted with diethylether (3 × 50 cm^3). The combined organic phases were washed sequentially with water (150 cm^3), and saturated aqueous NaCl solution (150 cm^3), dried over Na_2SO_4, filtered, and concentrated to dryness. Flash chromatography (*P*:*EA* = 90:10) gave 15.7 g (99%) of **7a** as a colorless oil (d.r. > 95:5). $R_f = 0.51$ (*P*:*EA* = 80:20); $[\alpha]_D^{20} = -35.8°$ cm^3 g^{-1} dm^{-1} ($c = 0.94$, $CHCl_3$); IR (film): $\bar{\nu} = 3504$ (m br), 3084 (w), 2978 (s), 2938 (s), 1712 (s), 1645 (m), 1371 (s), 1321 (s), 1203 (s), 1170 (s), 1043 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 220 (24) [M^+–H_2O], 180 (11), 151 (37), 132 (54), 109 (100), 82 (98), 43 (64); ^{1}H NMR (300 MHz): $\delta = 1.28$ (t, $J = 7.0$ Hz, CH_2CH_3), 1.65 (dd, $J = 12.5$, 1.5 Hz, C6H*H*), 1.73 (s, CH_3), 1.74 (s, CH_3), 1.89–2.14 (m, C4H_2, C6*H*H), 2.27–2.42 (m, H5), 2.58 (d, $J = 14.7$ Hz, CH*H*CO), 2.72 (d, $J = 14.7$ Hz, C*H*HCO), 3.86 (s, OH), 4.19–4.20 (m, OCH_2), 4.76–4.77 (m, C=CH_2), 5.46–5.48 (m, H3); ^{13}C NMR (75.5 MHz): $\delta = 14.5$ (q, OCH_2CH_3), 17.4 (q, CH_3), 20.8 (q, CH_3), 31.2 (t, C4), 40.0 (d, C5), 41.4 (t, C6), 42.3 (t, CH_2CO), 61.1 (t, OCH_2), 73.0 (s, C1), 109.5 (t, C=CH_2), 124.8 (d, C3), 137.3 (s, C2), 148.8 (s, C=CH_2), 173.3 (s, CO).

tert-Butyl 2-[(1S,5R)-1-Hydroxy-5-isopropenyl-2-methyl-2-cyclohexenyl]acetate
(**7b**, $C_{16}H_{26}O_3$) [13]

The same procedure as for the preparation of **7a** was used, starting with *tert*-butyl acetate (1.68 cm^3, 1.43 g, 12.5 mmol) and (*R*)-(−)-carvone (**2**) (1.56 g, 10.4 mmol). Yield: 2.35 g (85%) of **7b** as a colorless oil (d.r. > 95:5). $R_f = 0.60$ (*P*:*EA* = 80:20); $[\alpha]_D^{20} = -26.1°$ cm^3 g^{-1} dm^{-1} ($c = 0.74$, $CHCl_3$); IR (film): $\bar{\nu} = 3499$ (m br), 3082 (w), 2976 (s), 2934 (s), 1704 (s), 1369 (s), 1336 (s), 1250 (m), 1153 (s); MS (EI, 70 eV): m/z (%) = 248 (9) [M^+–H_2O], 210 (11), 192 (88), 151 (87), 132 (70), 109 (100), 57 (96) cm^{-1}; ^{1}HNMR (250 MHz): $\delta = 1.41$ [s, $C(CH_3)_3$], 1.57 (dd, $J = 13.1$, 1.5 Hz, C6H*H*), 1.68

(s, CH_3), 1.69 (s, CH_3), 1.69–1.71 (m, C6*H*H), 1.78–1.99 (m, C4H_2), 2.15–2.24 (m, H5), 2.48 (d, $J = 14.8$ Hz, CH*H*CO), 2.62 (dd, $J = 14.8$ Hz, $J = 1.2$ Hz, C*H*HCO), 4.00 (s, OH), 4.67–4.78 (m, C=CH_2), 5.38–5.40 (m, H3); ^{13}C NMR (62.9 MHz): $\delta = 17.5$ (q, CH_3), 20.8 (q, CH_3), 28.4 [q, C(CH_3)$_3$], 31.1 (t, C4), 40.1 (d, C5), 41.5 (t, C6), 43.3 (t, CH_2CO), 73.1 (s, C1), 82.1 [s, C(CH_3)$_3$], 109.5 (t, C=CH_2), 124.6 (d, C3), 137.5 (s, C2), 148.9 (s, C=CH_2), 172.9 (s, CO).

(1S,5R)-1-(2-Hydroxyethyl)-5-isopropenyl-2-methyl-2-cyclohexen-1-ol (**8**, $C_{12}H_{20}O_2$)

A solution of ester **7a** (15.3 g, 64 mmol) in diethylether (80 cm^3) was added to a suspension of $LiAlH_4$ (2.53 g, 64 mmol) in diethylether (40 cm^3) at 0°C. The mixture was stirred for 2 h at rt, and sequentially treated with water (2.5 cm^3), aqueous NaOH (15%) (2.5 cm^3), and water (7.5 cm^3). After stirring for 20 min at rt, the solid was removed by filtration and washed with diethylether (2×30 cm^3). The combined organic phases were washed, dried over Na_2SO_4, filtered, and concentrated to dryness. Flash chromatography (*P*:*EA* = 80:20) gave 12.3 g (98%) of **8** as a colorless solid. $R_f = 0.07$ (*P*:*EA* = 80:20); mp 86°C; $[\alpha]_D^{20} = -49.8°$ cm^3 g^{-1} dm^{-1} ($c = 0.51$, $CHCl_3$); IR (film): $\bar{\nu} = 3367$ (s br), 3088 (w), 2924 (s), 1647 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 196 (0.1) [M$^+$], 178 (13) [M$^+$–H_2O], 151 (74), 109 (100), 69 (25), 55 (25); ^{1}H NMR (300 MHz): $\delta = 1.66$–1.86 (m, C*H*HCH_2OH, C6*H*H), 1.85 (s, CH_3), 1.85 (s, CH_3), 1.87–2.09 (m, C4*H*H), 2.14–2.29 (m, CH*H*CH_2OH, C6H*H*, C4H*H*, H5), 3.38 (s, OH), 3.75 (s br, OH), 3.77–3.86 (m, C*H*HOH), 3.92–4.10 (m, CH*H*OH), 4.82–4.83 (m, C=CH_2), 5.50 (m, H3); ^{13}C NMR (75.5 MHz): $\delta = 17.4$ (q, CH_3), 20.9 (q, CH_3), 31.4 (t, C4), 38.4 (t, CH_2CH_2OH), 39.9 (d, C5), 40.3 (t, C6), 59.6 (t, CH_2OH), 75.7 (s, C1), 109.6 (t, C=CH_2), 123.7 (d, C3), 138.9 (s, C2), 149.2 (s, C=CH_2).

(1S,2S,3S,5R)-2,3-Epoxy-1-(2-hydroxyethyl)-5-isopropenyl-2-methylcyclohexan-1-ol
(**4**, $C_{12}H_{20}O_3$)

To a vigorously stirred solution of **8** (10.7 g, 54 mmol) in CH_2Cl_2 (100 cm^3) at −40°C was added MCPBA (70% purity, 9.32 g, 54 mmol) in three portions. The resulting mixture was stirred at −40°C for 1 h, then warmed up to −10°C over a period of 2 h. After stirring for additional 2 h at −10°C, TLC analysis indicated complete reaction. The solid was removed by filtration and washed with CH_2Cl_2 (2×60 cm^3). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (3×100 cm^3), water (100 cm^3), and brine (100 cm^3), and dried over Na_2SO_4, filtered, and concentrated to dryness. Flash chromatography (*P*:*EA* = 50:50) gave 10.6 g (87%, d.r. > 95:5) of **4** as a colorless solid. $R_f = 0.08$ (*P*:*EA* = 1:1); mp 92°C; $[\alpha]_D^{20} = -25.8°$ cm^3 g^{-1} dm^{-1} ($c = 0.99$, $CHCl_3$); IR (KBr): $\bar{\nu} = 3304$ (s br), 3079 (w), 2958 (s), 2934 (s), 1441 (s), 1437 (s), 1378 (s), 1193 (s), 1120 (s), 1050 (s), 959 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 212 (0.2) [M$^+$], 194 (1) [M$^+$–H_2O], 149 (7), 123 (22), 109 (42), 97 (37), 73 (60), 55 (20), 43 (100); ^{1}H NMR (360 MHz): $\delta = 1.39$ (s, C3CH_3), 1.53 (virt. dt, $J = 12.8$, 1.2 Hz, C6H*H*), 1.66 [s, C(=CH_2)CH_3], 1.71–1.81 (m, C4H*H*, CH_2CH_2OH), 1.91–2.15 (m, C6*H*H, C4*H*H, H5), 2.42 (s br, OH), 3.02 (s br, OH), 3.18 (d br, $J = 4.5$ Hz, H3), 3.70–3.82 (m, CH*H*OH), 3.87–3.95 (m, C*H*HOH), 4.67–4.68 (m, C=CH_2); ^{13}C NMR (62.9 MHz): $\delta = 17.1$ (q, CH_3), 20.4 (q, CH_3), 28.6 (t, C4), 35.5 (t, CH_2CH_2OH), 35.7 (t, C6), 38.9 (d, C5), 59.5 (t, CH_2OH), 62.9 (d, C3), 63.4 (s, C2), 75.7 (s, C1), 110.2 (t, C=CH_2), 147.8 (s, C=CH_2).

(6S,7S,8S,10R)-7,8-Epoxy-10-isopropenyl-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undecane
(**9**, $C_{15}H_{24}O_3$)

To a solution of diol **4** (7.5 g, 35.3 mmol) in CH_2Cl_2 (40 cm^3) at 0°C was added 2-methoxypropene (3.64 cm^3, 2.74 g, 38 mmol) and *PPTS* (~20 mg). The resulting yellow solution was stirred at 0°C for 30 min and quenched with triethylamine (1 cm^3). The mixture was diluted with saturated aqueous $NaHCO_3$ (200 cm^3), followed by extraction with diethylether (2×150 cm^3). The combined extracts were washed with water (200 cm^3) and brine (200 cm^3), and dried over Na_2SO_4, filtered, and con-

centrated to dryness. Flash chromatography (*P*:*EA* = 90:10) gave 7.12 g (80%) of **9** as a colorless oil. $R_f = 0.59$ (*P*:*EA* = 80:20); $[\alpha]_D^{20} = -44.1°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.97$, $CHCl_3$); IR (film): $\bar{\nu} = 3072$ (w), 2972 (s), 2934 (s), 1436 (s), 1377 (s), 1267 (m), 1193 (s), 1161 (s), 1102 (s), 1050 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 252 (5) [M^+], 237 (17) [M^+–CH_3], 177 (32), 119 (44), 68 (40), 43 (100); ^{1}H NMR (360 MHz): $\delta = 1.36$ (s, C7CH_3), 1.40 (s, C2CH_3), 1.43 (s, H_3CC2), 1.66 [s, C(=CH_2)CH_3], 1.63–2.08 (m, H9, H10, H11, H5), 3.02 (d br, $J = 4.9$ Hz, H8), 3.81 (ddd, $J = 10.0$, 5.5, 4.5 Hz, C4H*H*), 3.92 (ddd, $J = 10.0$, 9.5, 4.5 Hz, C4*H*H), 4.67 (s br, C=CH_2); ^{13}C NMR (62.9 MHz): $\delta = 17.8$ (q, C7*C*H_3), 20.3 (q, C(=CH_2)*C*H_3), 27.1 (q, C2*C*H_3), 28.3 (t, C9), 28.5 (t, C5), 30.1 (q, H_3*C*C2), 36.6 (t, C11), 39.1 (d, C10), 56.6 (t, C4), 60.9 (d, C8), 62.4 (s, C7), 75.9 (s, C6), 98.9 (s, C2), 110.2 (t, C=*C*H_2), 148.4 (s, *C*=CH_2).

(6R,7S,8S,10R)-7,8-Epoxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undecan-10-ol
(**10**, $C_{12}H_{20}O_4$)

To a solution of **9** (1.1 g, 4.4 mmol) in CH_2Cl_2 (30 cm^3) was added *Me*OH (6 cm^3) and sodium bicarbonate (2.6 g, 31 mmol). The reaction mixture was ozonized at −78°C until a pale blue color appeared. Nitrogen was bubbled through the mixture until it became colorless. After warming to room temperature, *Ac*$_2$O (8.5 cm^3, 9.2 g, 90 mmol), N*Et*$_3$ (6.3 cm^3, 4.5 g, 45 mmol), and a catalytic amount of *DMAP* (30 mg) was added. The reaction mixture was then refluxed overnight (12 h), cooled to room temperature, and poured into saturated aqueous NH_4Cl solution (40 cm^3). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 cm^3), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 cm^3) and brine (50 cm^3), dried over $MgSO_4$, filtered, and concentrated. The crude product was dissolved in *Me*OH (20 cm^3) and treated with K_2CO_3 (1.6 g, 12 mmol). The mixture was stirred for 2 h at room temperature, filtered, and concentrated. The resultant liquid was then dissolved in CH_2Cl_2 (30 cm^3), washed with water (20 cm^3) and brine (20 cm^3), and subsequently dried ($MgSO_4$). After filtration, the solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (*P*:*EA* = 90:10) to yield alcohol **10** as a colorless oil (743 mg, 74%). $R_f = 0.08$ (*P*:*EA* = 1:1); $[\alpha]_D^{20} = -45.1°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.52$, $CHCl_3$); IR (film): $\bar{\nu} = 3425$ (s br), 2984 (s), 2938 (s), 1435 (m), 1370 (s), 1226 (s), 1184 (s), 1159 (s), 1092 (s), 1020 (s), 975 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 213 (6) [M^+–CH_3], 153 (7), 109 (15), 99 (24), 93 (53), 82 (11), 71 (48), 43 (100); ^{1}H NMR (250 MHz): $\delta = 1.38$ (s, C7CH_3), 1.42 (s, C2CH_3), 1.47 (s, H_3CC2), 1.61 (virt. dt, $J \cong 4.0$, 13.7 Hz, C5H*H*), 1.77–1.89 (m, C11H*H*, C9H*H*), 2.05 (ddd, $J = 13.7$, 9.8, 5.5 Hz, C5*H*H), 2.22–2.33 (m, C11*H*H, C9*H*H), 2.52 (s br, OH), 2.99 (d br, $J = 4.5$ Hz, H8), 3.64–3.76 (m, H10), 3.84 (ddd, $J = 11.9$, 5.5, 4.0 Hz, C4H*H*), 4.01 (ddd, $J = 11.9$, 9.8, 4.0 Hz, C4*H*H); ^{13}C NMR (62.9 MHz): $\delta = 17.6$ (q, C7*C*H_3), 26.7 (q, C2*C*H_3), 29.0 (t, C5), 30.1 (q, H_3*C*C2), 32.9 (t, C9), 40.9 (t, C11), 56.5 (t, C4), 58.8 (d, C8), 62.5 (s, C7), 64.8 (d, C10), 75.2 (s, C6), 98.9 (s, C2).

(6R,7S,8S,10S)-10-Benzoyloxy-7,8-epoxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undecane
(**3a**, $C_{19}H_{24}O_5$)

Alcohol **10** (180 mg, 0.8 mmol), triphenylphosphine (210 mg, 0.8 mmol), and benzoic acid (97.6 mg, 0.8 mmol) were dissolved under argon in *THF* (5 cm^3) and cooled in ice. Then a solution of *DIAD* (0.15 cm^3, 161 mg, 0.8 mmol) in *THF* (1 cm^3) was added dropwise over 1 h at 0°C. Stirring was continued for 24 h at 0°C. The mixture was evaporated *in vacuo*. The residue was purified by flash chromatography (*P*:*EA* = 70:30) to yield benzoate **3a** as a colorless oil (250 mg, 94%). $R_f = 0.52$ (*P*:*EA* = 1:1); $[\alpha]_D^{20} = -27.4°\ cm^3\ g^{-1}\ dm^{-1}$ ($c = 0.80$, $CHCl_3$); IR (film): $\bar{\nu} = 3062$ (w), 2985 (s), 2938 (s), 1715 (s), 1370 (s), 1276 (s), 1225 (m), 1175 (m), 1107 (s), 1089 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 317 (6) [M^+–CH_3], 135 (65), 105 (100) [$PhCO^+$], 77 (30), 43 (62); ^{1}H NMR (500 MHz): $\delta = 1.39$ (s, C7CH_3), 1.40 (s, C2CH_3), 1.43 (s, H_3CC2), 1.90–2.19 (m, H5, H9), 2.42 (dd, $J = 14.6$, 2.1 Hz, C11H*H*), 2.52 (dd, $J = 14.6$, 7.7 Hz, C11*H*H), 3.04 (s br, H8), 3.83 (ddd, $J = 11.7$, 5.9,

3.3 Hz, C4H*H*), 3.95 (ddd, $J = 11.7$, 11.0, 4.1 Hz, C4*H*H), 5.23–5.25 (m, H10), 7.39 (dd, $J = 7.7$, 7.4 Hz, $2H_{Ar}$), 7.52 (t, $J = 7.4$ Hz, $1H_{Ar}$), 7.90 (d, $J = 7.7$ Hz, $2H_{Ar}$); ^{13}C NMR (62.9 MHz): $\delta = 17.6$ (q, C7*C*H_3), 27.3 (q, C2*C*H_3), 29.2 (t, C5), 30.0 (t, C9), 30.1 (q, H_3*C*C2), 35.8 (t, C11), 56.6 (t, C4), 58.9 (d, C8), 62.4 (s, C7), 68.9 (d, C10), 74.4 (s, C6), 98.8 (s, C2), 128.9 (d), 129.7 (d), 130.6 (s), 133.5 (d), 165.9 (s, C=O).

(6R,7S,8S,10S)-7,8-Epoxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undecan-10-ol (**11**, $C_{12}H_{20}O_4$)

Ester **3a** (4.0 g, 12 mmol) was dissolved in *Me*OH (150 cm^3). The solution was treated with NaOH (1 g), and stirred for 5 h at room temperature. The mixture was evaporated *in vacuo*. The residue was diluted with CH_2Cl_2 (100 cm^3), washed with water (60 cm^3), brine (100 cm^3), and dried over Na_2SO_4, filtered, and concentrated to dryness. Flash chromatography (*P*:*EA* = 90:10) gave 2.53 g (93%) of **11** as a colorless oil. $R_f = 0.20$ (*P*:*EA* = 50:50); IR (film): $\bar{\nu} = 3463$ (s br), 2986 (s), 1369 (s), 1230 (s), 1193 (s), 1166 (s), 1099 (vs), 1077 (vs), 864 (s) cm^{-1}; MS (EI, 70 eV): m/z (%) = 213 (20) [M^+–CH_3], 153 (38), 135 (36), 109 (28), 99 (50), 93 (74), 71 (72), 43 (100); ^{1}H NMR (250 MHz): $\delta = 1.27$ (s, 3H), 1.34 (s, 3H), 1.35 (s, 3H), 1.76–1.89 (m, 3H), 1.98–2.04 (m, 1H), 2.13–2.23 (m, 2H), 2.63 (ddd, $J = 14.0$, 4.6, 2.4 Hz, H9), 3.27 (d, $J = 5.2$ Hz, H8), 3.62 (ddd, $J = 12.2$, 6.1, 3.7 Hz, H4), 3.85 (dd, $J = 9.7$, 2.1 Hz, H10), 3.90–3.93 (m, H4′); ^{13}C NMR (62.9 MHz): $\delta = 18.1$ (q), 24.5 (q), 26.9 (q), 32.6 (t, C5), 38.3 (t), 40.0 (t), 57.6 (t, C4), 63.8 (d, C10), 66.7 (d, C8), 72.5 (s, C7), 76.9 (s, C6), 100.5 (s, C2).

(6R,7S,8S,10S)-10-tert-Butyldimethylsilyloxy-7,8-epoxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undecane (**3b**, $C_{18}H_{34}O_4Si$)

A solution of **11** (190 mg, 0.83 mmol), *tert*-butyldimethylsilyl chloride (0.34 cm^3, 1.0 mmol, 2.9 *M* solution in toluene), and imidazole (68 mg, 1.0 mmol) in *DMF* (4 cm^3) was stirred at 20°C for 24 h. Et_2O (30 cm^3) was added and the solution was washed with water (50 cm^3). The aqueous layer was extracted twice with Et_2O (30 cm^3). The combined organic phases were washed with water (50 cm^3) and brine (50 cm^3), dried (Na_2SO_4), filtered, and the solvent was evaporated. Flash chromatography (*P*:*EA* = 90:10) gave 262 mg (92%) of the protected alcohol **3b** as a colorless oil. $R_f = 0.74$ (*P*:*EA* = 50:50); IR (film): $\bar{\nu} = 3450$ (vs br), 2856 (s), 1368 (s), 1253 (vs), 1229 (s), 1120 (s), 1080 (vs), 1021 (s), 896 (s), 836 (vs), 775 (vs) cm^{-1}; MS (EI, 70 eV): m/z (%) = 344 (1) [M^+], 327 (15) [M^+–CH_3], 227 (26) [M^+–TBS], 197 (53), 157 (57), 135 (74), 107 (47), 93 (54), 75 (100) [$C_2H_7OSi^+$], 43 (83); ^{1}H NMR (250 MHz): $\delta = -0.01$ (s, 6H, $SiCH_3$), 0.81 [s, $SiC(CH_3)_3$], 1.37 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.70–1.86 (m, 2H), 1.71–1.81 (m, 1H), 1.84 (ddd, $J = 14.0$, 4.0, 0.9 Hz, 1H), 1.99 (ddd, $J = 13.4$, 5.8, 1.2 Hz, 1H), 2.05–2.16 (m, 2H), 2.24 (ddd, $J = 15.9$, 6.7, 0.9 Hz, 1H), 2.97 (d, $J = 3.0$ Hz, H8), 3.81 (ddd, $J = 11.6$, 5.8, 3.0 Hz, C4*H*H), 3.92–4.02 (m, C4H*H*, H10); ^{13}C NMR (62.9 MHz): $\delta = -4.6$ (q, $SiCH_3$), −4.6 (q, $SiCH_3$), 18.0 (q, C7CH_3), 18.3 [s, Si*C*$(CH_3)_3$], 26.1 (q), 27.1 (q), 29.9 (t), 30.4 (q, C2CH_3), 33.0 (t), 38.8 (t), 56.9 (t, C4), 59.4 (d, C8), 62.4 (s, C7), 65.7 (d, C10), 74.8 (s, C6), 98.5 (s, C2).

(6R,7S,8S,10S)-10-Benzyloxy-7,8-epoxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undecane (**3c**, $C_{19}H_{26}O_4$)

To a solution of **11** (547 mg, 2.4 mmol) in *DMF* (10 cm^3) was added NaH (60% in oil, 108 mg, 2.7 mmol) at 0°C. After 5 min stirring at 0°C, the mixture was warmed to room temperature, and a solution of benzyl bromide (0.32 cm^3, 461 mg, 2.7 mmol) in *THF* (10 cm^3) was added slowly. Stirring was continued for 2 h at room temperature. Et_2O (100 cm^3) was added and the solution was washed with water (100 cm^3). The aqueous layer was extracted twice with Et_2O (50 cm^3). The combined organic phases were washed with water (1000 cm^3) and brine (100 cm^3), dried (Na_2SO_4), filtered,

and the solvent was evaporated. Flash chromatography (*P*:*EA* = 90:10) gave 688 mg (90%) of the protected alcohol **3c** as a colorless oil. $R_f = 0.70$ (*P*:*EA* = 50:50); IR (film): $\bar{\nu} = 2985$ (m), 1368 (m), 1229 (m), 1193 (m), 1090 (s), 1028 (m), 738 (m) cm^{-1}; MS (EI, 70 eV): m/z (%) = 303 (6), 243 (3), 197 (6), 91 (100) [$C_7H_7^+$], 43 (24); ^{1}H NMR (250 MHz): $\delta = 1.40$ (s, C7CH_3), 1.41 (s, C2CH_3), 1.44 (s, H_3CC2), 1.86–1.92 (m, 1H), 1.92–1.95 (m, 1H), 1.95–2.08 (m, 2H), 2.25 (dd, $J = 7.0$, 1.2 Hz, C11*H*H), 2.30–2.37 (m, C11H*H*), 3.01 (d, $J = 2.4$ Hz, H8), 3.68–3.72 (m, C4*H*H), 3.81–3.89 (m, C4H*H*), 3.97–4.08 (m, H10), 4.43 (s, CH_2Ph), 7.24–7.35 (m, H_{Ar}); ^{13}C NMR (62.9 MHz): $\delta = 17.9$ (q, C7*C*H_3), 27.1 (q, C2*C*H_3), 29.3 (t, C5), 29.9 (t, C9), 30.3 (q, H_3*C*C2), 35.8 (t, C11), 57.0 (t, C4), 59.4 (d, C8), 62.5 (s, C7), 70.8 (t, *C*H_2Ph), 72.4 (d, C10), 74.8 (s, C6), 98.6 (s, C2), 127.6 (d), 127.8 (d), 127.9 (d), 128.8 (d), 128.8 (d), 138.8 (s).

(6R,7S,8S,10S)-7,8-Epoxy-2,2,7-trimethyl-10-tri-iso-propylsilyloxy-1,3-dioxaspiro[5.5]undecane (**3d**, $C_{21}H_{40}O_4Si$)

A solution of **11** (2.53 g, 11.1 mmol), triisopropylsilyl chloride (3.52 cm^3, 3.2 g, 16.6 mmol), and imidazole (1.13 g, 16.6 mmol) in *DMF* (10 cm^3) was stirred at 20°C for 14 h. Et_2O (100 cm^3) was added and the solution was washed with water (150 cm^3). The aqueous layer was extracted with Et_2O (2 × 50 cm^3). The combined organic phases were washed with water (150 cm^3) and brine (150 cm^3), dried (Na_2SO_4), filtered, and the solvent was evaporated. Flash chromatography (*P*:*EA* = 99:1) gave 3.09 g (72%) of the protected alcohol **3d** as a light yellow oil which was still contaminated with silyl side products. An analytical sample could not be obtained. $R_f = 0.82$ (*P*:*EA* = 90:10); ^{1}H NMR (250 MHz): $\delta = 1.02$ [s, 21H, SiC*H*(CH_3)$_2$], 1.37 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 1.67–2.08 (m, 4H), 2.18 (dd, $J = 13.7$, 3.0 Hz, 1H), 2.33 (dd, $J = 16.2$, 7.3 Hz, 1H), 2.99 (s, H8), 3.78–3.86 (m, 1H), 3.97–4.12 (m, 2H); ^{13}C NMR (90.6 MHz): $\delta = 12.5$ [d, Si*C*H(CH$_3$)$_2$], 12.6 [d, Si*C*H(CH$_3$)$_2$], 17.8 (q, C7CH$_3$), 18.4 [q, SiCH(*C*H$_3$)$_2$], 18.5 [q, SiCH(*C*H$_3$)$_2$], 26.8 (q, C2CH$_3$), 29.9 (t), 30.5 (q, C2CH$_3$), 33.4 (t), 39.6 (t), 57.0 (t, C4), 59.4 (d, C8), 62.5 (s, C7), 65.7 (d, C10), 74.9 (s, C6), 98.5 (s, C2).

*Isomerisation of Epoxide **3** with DATMP*

A solution of 2,2,6,6-tetramethylpiperidine (*TMP*, 0.38 cm^3, 318 mg, 2.25 mmol) in dry benzene (5 cm^3) was cooled to 0°C and a solution of *n*-butyl lithium in hexane (2.5 *M*, 0.9 cm^3, 2.25 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 10 min, a solution of Et_2AlCl in toluene (1.8 *M*, 1.27 cm^3, 2.3 mmol) was slowly added, and the reaction was stirred for 30 min. A solution of epoxide **3** (0.45 mmol) in benzene (1 cm^3) was added over 10 min at 0°C. The reaction mixture was stirred at 0°C for 30 min and then quenched by addition of saturated aqueous NH_4Cl (20 cm^3). The layers were separated and extracted with ethyl acetate (2 × 20 cm^3). The combined organic layers were washed with water (40 cm^3) and brine (40 cm^3), dried (Na_2SO_4), filtered, and concentrated. The ratio of regioisomers was determined by ^{1}H NMR of crude product. The residue was purified by flash chromatography.

*Isomerisation of Epoxide **3** with MICA*

N-Cyclohexylisopropylamine (0.25 cm^3, 212 mg, 1.5 mmol) was dissolved in *THF* (4 cm^3) and cooled to 0°C. Then a solution of *n*-butyllithium in hexane (2.5 *M*, 0.6 cm^3, 1.5 mmol) was added dropwise and stirring was continued for 15 min at 0°C. A solution of methylmagnesium bromide in diethyl ether (3 *M*, 0.5 cm^3, 1.5 mmol) was added dropwise and stirring continued for 15 min at 0°C. Finally, a solution of epoxide **3** (0.3 mmol) in *THF* (2 cm^3) was added at 0°C, the temperature was allowed to rise to room temperature, and stirring was continued at room temperature until TLC analysis indicated complete conversion. The reaction mixture was treated with saturated aqueous NaH_2PO_4 (10 cm^3). The layers were separated and extracted with ethyl acetate (2 × 10 cm^3). The combined organic layers were washed with water (20 cm^3) and brine (20 cm^3), dried (Na_2SO_4), filtered, and concentrated. The ratio of

regioisomers was determined by ^{1}H NMR of crude product. The residue was purified by flash chromatography.

(6R,8S,10S)-10-tert-Butyldimethylsilyloxy-2,2-dimethyl-7-methylene-1,3-dioxaspiro[5.5]undec-8-ol (**5b**, $C_{18}H_{34}O_4Si$)

Reaction with MICA: According to the procedure described above, a solution of compound **3b** (103 mg, 0.3 mmol) in *THF* was treated with *MICA* (1.5 mmol) for 3 h at room temperature. The crude product contained secondary alcohol **5b** and tertiary alcohol **6b** (**5b**:**6b** = 1:2). The compounds could not be separated by chromatography. Flash chromatography (*P*:*EA* = 90:10) yielded a (1:2)-mixture of isomers **5b**/**6b** as a colorless liquid (96 mg, 93%).

Reaction with DATMP: According to the procedure described above, a solution of compound **3b** (154 mg, 0.45 mmol) in benzene was treated with *DATMP* (2.25 mmol) for 30 min at 0°C. Flash chromatography (*P*:*EA* = 90:10) yielded the allylic alcohol **5b** as a colorless liquid (24.7 mg, 16%). $R_f = 0.41$ (*P*:*EA* = 80:20); IR (film, **5b**/**6b**): $\bar{\nu} = 3354$ (s br), 2954 (s), 2878 (s), 1471 (m), 1255 (s), 1089 (s), 836 (vs), 775 (s) cm^{-1}; MS (EI, 70 eV, **5b** pure): m/z (%) = 327 (3) [M^+–CH_3], 285 (3) [M^+–*t*Bu], 227 (10) [M^+–$C_6H_{15}Si$], 135 (39), 105 (30), 75 (100) [$C_2H_7OSi^+$]; ^{1}H NMR (250 MHz, **5b** pure): $\delta = 0.06$ (s, 6H, $SiCH_3$), 0.86 [s, $SiC(CH_3)_3$], 1.41 (s, C2CH_3), 1.45 (s, H_3CC2), 1.50–1.60 (m, 2H), 1.83–1.88 (m, 1H), 2.01–2.17 (m, 3H), 3.31 (d, $J = 9.1$ Hz, OH), 3.89–4.02 (m, 2H), 4.28–4.38 (m, 2H), 5.07 (d, $J = 0.6$ Hz, C=C*H*H), 5.11 (d, $J = 0.6$ Hz, C=CH*H*); ^{13}C NMR (62.9 MHz, **5b** pure): $\delta = -4.7$ (q, $SiCH_3$), −4.6 (q, $SiCH_3$), 18.1 [s, Si*C*$(CH_3)_3$], 25.8 (q, C2CH_3), 26.5 [q, SiC(*C*$H_3)_3$], 29.2 (q, C2CH_3), 32.3 (t, C5), 44.8 (t), 49.4 (t), 56.9 (t, C4), 63.9 (d, C10), 73.7 (d, C8), 75.8 (s, C6), 99.2 (s, C2), 109.8 (t, C=*C*H_2), 150.4 (s, C7).

(6R,7S,10R)-10-tert-Butyldimethylsilyloxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undec-8-en-7-ol (**6b**, $C_{18}H_{34}O_4Si$)

To a solution of diisopropylamine (0.08 cm^3, 58.7 mg, 0.58 mmol) and KO*t-Bu* (65.1 mg, 0.58 mmol) in *THF* (5 cm^3) was added a solution of *n*-butyllithium in hexane (2.5 *M*, 0.23 cm^3, 0.58 mmol) at −78°C. The yellow solution was stirred for 15 min at −78°C, then a solution of epoxide **3b** (188 mg, 0.55 mmol) in *THF* (3 cm^3) was added dropwise. After stirring for 15 min at −78°C, the solution was warmed up to 0°C, and stirring was continued at 0°C for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (20 cm^3) and diethyl ether (10 cm^3). The layers were separated and extracted with diethyl ether (2 × 15 cm^3). The combined organic layers were washed with water (20 cm^3) and brine (20 cm^3), dried (Na_2SO_4), filtered, and concentrated. The crude product contained tertiary alcohol **6b** as sole product. Flash chromatography (*P*:*EA* = 90:10) gave 185 mg (98%) of tertiary alcohol **6b** as a colorless oil. $R_f = 0.42$ (*P*:*EA* = 80:20); MS (EI, 70 eV): m/z (%) = 324 (3) [M^+–H_2O], 239 (10), 214 (100), 157 (40), 135 (30), 75 (87); ^{1}H NMR (250 MHz): $\delta = 0.06$ (s, 6H, $SiCH_3$), 0.87 [s, $SiC(CH_3)_3$], 1.15 (s, C7CH_3), 1.16–1.26 (m, 1H), 1.37 (s, C2CH_3), 1.50 (s, H_3CC2), 1.51–166 (m, 1H), 2.19 (dt, $J = 12.8$, 6.1 Hz, 1H), 2.54 (ddd, $J = 13.7$, 5.5, 1.5 Hz, 1H), 3.18 (s br, OH), 3.83 (ddd, $J = 12.2$, 5.8, 1.8 Hz, C4*H*H), 4.03 (dt, $J = 12.2$, 3.3 Hz, C4H*H*), 4.36–4.42 (m, H10), 5.43 (dd, $J = 10.6$, 1.5 Hz, 1H), 5.53 (d, $J = 10.6$ Hz, 1H); ^{13}C NMR (62.9 MHz): $\delta = -4.2$ (q, $SiCH_3$), −4.1 (q, $SiCH_3$), 18.5 [s, Si*C*$(CH_3)_3$], 23.3 (q, C2CH_3), 24.9 (q, C2CH_3), 26.2 [q, SiC(*C*$H_3)_3$], 27.3 (t, C5), 31.0 (q, C7*C*H_3), 39.8 (t, C11), 56.6 (t, C4), 66.8 (d, C10), 72.3 (s, C7), 76.9 (s, C6), 98.9 (s, C2), 130.3 (d, C8), 134.6 (d, C9).

(6R,8S,10S)-10-Benzyloxy-2,2-dimethyl-7-methylene-1,3-dioxaspiro[5.5]undec-8-ol (**5c**, $C_{19}H_{26}O_4$)/*(6R,7S,10S)-10-Benzyloxy-2,2,7-trimethyl-1,3-dioxaspiro[5.5]undec-8-en-7-ol* (**6c**, $C_{19}H_{26}O_4$)

According to the procedure described above, a solution of compound **3c** (95.5 mg, 0.3 mmol) in *THF* was treated with *MICA* (1.5 mmol) for 3 h at room temperature. The crude product contained second-

ary alcohol **5c** and tertiary alcohol **6c** (**5c**:**6c** = 1:3). The compounds could not be separated by chromatography. Flash chromatography (*P*:*EA* = 90:10) yielded a (1:3)-mixture of isomers **5c**/**6c** as a colorless liquid (68 mg, 71%). $R_f = 0.58$ (*P*:*EA* = 50:50); ^{1}H NMR (250 MHz): $\delta = 1.16$ (s, C7CH_3, **6c**), 1.15–1.27 (m, 3H, **5c**), 1.33–1.44 (m, C2CH_3, **6c**; CH_3, **5c**), 1.58–1.68 (m, 1H, **6c**; 1H, **5c**), 2.02–2.43 (m, 1H, **6c**; 1H, **5c**), 2.67 (ddd, $J = 13.6$, 5.2, 1.5 Hz, 1H, **6c**), 3.16 (s br, OH, **6c**), 3.54 (m br, OH, **5c**), 3.84–4.18 (m, 3H, **6c**; 3H, **5c**), 4.42–4.45 (m, 1H, **5c**), 4.56–4.58 (m, CH_2Ph, **6c**; CH_2Ph, **5c**), 5.07 (d, $J = 0.5$ Hz, C=C*H*H, **5c**), 5.14 (d, $J = 0.5$ Hz, C=CH*H*, **5c**), 5.53 (dd, $J = 4.4$ Hz, $J = 2.6$ Hz, 1H, **6c**), 5.74 (d, $J = 4.4$ Hz, 1H, **6c**), 7.23–7.31 (m, 5H_{Ar}, **5c**/**6c**); ^{13}C NMR (62.9 MHz): $\delta = 23.2$ (q, **6c**), 24.5 (q, **6c**), 26.8 (q, **5c**), 27.3 (t, **6c**), 29.4 (q, **5c**), 31.0 (q, **6c**), 32.4 (t, **5c**), 36.4 (t, **6c**), 41.8 (t, **5c**), 46.8 (**5c**), 56.6 (t, **6c**), 57.3 (t, **5c**), 70.6 (t, **6c**), 70.7 (t, **5c**), 72.6 (d, **6c**), 72.6 (s, **6c**), 74.7 (d, **5c**), 76.2 (d, **5c**), 76.9 (s, **6c**), 98.9 (s, **6c**), 99.7 (s, **5c**),111.1 (t, **5c** C=*C*H_2), 126.9 (d, **6c** = CH), 127.9 (d, **6c**), 127.9 (d, **5c**), 128.0 (d, **6c**), 128.1 (d, **5c**), 128.8 (d, **6c**), 128.8 (d, **5c**), 136.1 (d, **6c** = CH), 138.8 (s, **6c**), 138.9 (s, **5c**), 149.8 (s, **5c** *C*=CH_2).

(1S,3R,5R)-3-(2-tert-Butyldimethylsilyloxyethyl)-3-triethylsilyloxy-5-tert-butyldimethylsilyloxy-2-methylenecyclohexanol (**5f**, $C_{27}H_{58}O_4Si_3$)

According to the procedure described above, a solution of compound **3f** (239 mg, 0.45 mmol) in benzene was treated with *DATMP* (2.25 mmol) for 30 min at 0°C. Flash chromatography (*P*:*EA* = 95:5) yielded the allylic alcohol **5f** as a colorless liquid (115 mg, 48%) which was still contaminated with silyl side products. An analytical sample could not be obtained. $R_f = 0.35$ (*P*:*EA* = 80:20); IR (film): $\bar{\nu} = 3354$ (m br), 2954 (s), 1462 (m), 1255 (m), 1089 (s), 1061 (m), 836 (s), 775 (m) cm^{-1}; ^{1}H NMR (250 MHz): $\delta = 0.00$ [s, 12H, $(CH_3)_3CSi(CH_3)_2$], 0.60 [q, $J = 7.8$ Hz, $Si(CH_2CH_3)_3$], 0.85 [s, 18H, $(CH_3)_3CSi(CH_3)_2$], 0.95 [t, $J = 7.9$ Hz, $Si(CH_2CH_3)_3$], 1.20–1.36 (m, 2H), 1.62–1.80 (m, 2H), 2.01–2.08 (m, 1H), 2.25–2.30 (m, 1H), 3.46 (dt, $J = 9.9$, 5.8 Hz, C*H*HOTBS), 3.68 (dt, $J = 9.9$, 5.2 Hz, CH*H*OTBS), 3.78–3.88 (m, 1H), 4.05–4.10 (m, 1H), 5.09 (s, C=C*H*H), 5.18 (s, C=CH*H*); ^{13}C NMR (62.9 MHz): $\delta = -5.0$ [q, $(CH_3)_3CSi(CH_3)_2$], −4.9 [q, $(CH_3)_3CSi(CH_3)_2$], −4.3 [q, $(CH_3)_3CSi(CH_3)_2$], −4.2 [q, $(CH_3)_3CSi(CH_3)_2$], 7.4 [t, $Si(CH_2CH_3)_3$], 7.5 [q, $Si(CH_2CH_3)_3$], 18.5 [s, $(CH_3)_3CSi(CH_3)_2$], 18.7 [s, $(CH_3)_3CSi(CH_3)_2$], 26.0 [q, $(CH_3)_3CSi(CH_3)_2$], 26.4 [q, $(CH_3)_3CSi(CH_3)_2$], 43.5 (t), 46.5 (t), 50.9 (t), 59.4 (t, CH_2OTBS), 65.9 (d, C5), 68.0 (d, C1), 76.0 (s, C3), 105.1 (t, C2=CH_2), 153.5 (s, C2).

(1R,3S,5S)-1-(2-Hydroxyethyl)-5-tri-iso-propysilyloxy-2-methylenecyclohexan-1,3-diol (**12**, $C_{18}H_{36}O_4Si$)

According to the procedure described above, a solution of compound **3d** (1.74 g, 4.5 mmol) in benzene (40 cm^3) was treated with *DATMP* (15 mmol) for 45 min at 0°C. The reaction was quenched by addition of saturated aqueous NH_4Cl (40 cm^3). The mixture was acidified with aqueous HCl (1 *N*, 100 cm^3) and stirred for 1 h at room temperature. After dilution with diethyl ether (100 cm^3), the layers were separated and extracted with ethyl acetate (2 × 50 cm^3). The combined organic layers were washed with water (100 cm^3) and brine (100 cm^3), dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (*CH*:*EA* = 50:50) gave 945 mg (61%) of triol **12** as a colorless solid. $R_f = 0.13$ (*P*:*EA* = 50:50); mp 90–96°C; $[\alpha]_D^{20} = -84.6°$ cm^3 g^{-1} dm^{-1} ($c = 0.23$, CH_2Cl_2); IR (film): $\bar{\nu} = 3286$ (vs br), 2942 (vs), 2866 (s), 1384 (m), 1098 (m), 1058 (s), 914 (m) cm^{-1}; MS (EI, 70 eV): m/z (%) = 301 (43) [M$^+$–*i*Pr], 283 (56), 135 (100), 107 (87), 81 (64), 75 (83), 43 (44) [*i*Pr$^+$]; ^{1}H NMR (360 MHz): $\delta = 1.06$ [s, 21H, $SiCH(CH_3)_2$], 1.78–2.01 (m, 5H,), 2.21 (d, $J = 6.1$ Hz, C3OH), 2.27 (ddd, $J = 15.0$, 5.9, 3.9 Hz, C4HH_b), 2.41 (t, $J = 4.6$ Hz, CH_2OH), 3.74 (s, C1OH), 3.85–3.87 (m, CH_2OH), 4.40 (virt. quint, $J \cong 4.9$ Hz, H5), 4.43–4.49 (m, H3), 5.17 (s, C=C*H*H), 5.19 (s, C=CH*H*); ^{13}C NMR (90.6 MHz): $\delta = 12.2$ [d, $SiCH(CH_3)_2$], 18.1 [q, $SiCH(CH_3)_2$], 18.1 [q, $SiCH(CH_3)_2$], 40.5 (t, CH_2CH_2OH), 44.5 (t, C6), 47.8 (t, C4), 60.0 (t, CH_2OH), 65.4 (d, C5), 70.4 (d, C3), 76.8 (s, C1), 107.0 (t, C=CH_2), 153.0 (s, *C*=CH_2).

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