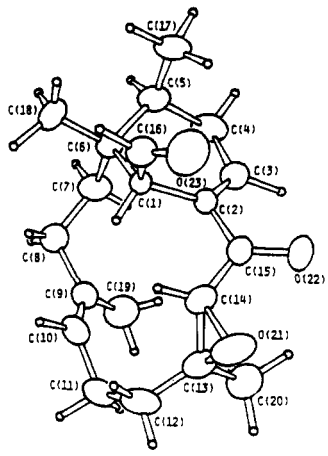

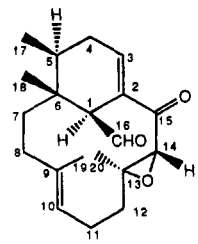

Sch 47918

Figure 2. ORTEP diagram showing the structure (relative stereochemistry) and solid-state conformation of Sch 47918; small circles represent hydrogen atoms.

fragments (1) and (2) should be connected through a two-site linkage to form a macrocyclic ring.

In order to verify the proposed structure and establish the overall stereochemistry of Sch 47918, X-ray diffraction analysis[7] was performed on a crystal obtained from a MeOH–$CHCl_3$ (1:2) solution. An ORTEP diagram showing the relative stereochemistry and solid-state conformation is provided in Figure 2. Sch 47918 is a new member of the rare cleomane class of diterpene, the only previous example being cleomeolide.[8]

Sch 47918 was tested in PAF-induced platelet aggregation assay[9] which was performed using freshly prepared human platelet rich plasma. The IC_{50} of this antagonist was found to be 6.96 μM in vitro. Sch 47918 was inactive against Gram-positive and Gram-negative bacteria and various fungi (*Candida* sp.) in agar diffusion assays (at 30 μg/disc). Additional details of the chemical and biological properties of Sch 47918 and related minor components will be reported elsewhere.[5]

Acknowledgment. We thank Dr. R. Bishop for biological data and Dr. P. Das for mass spectral data.

Supplementary Material Available: ^1H and ^{13}C NMR spectra and X-ray data for Sch 47918. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Crystallographic data for Sch 47918: $C_{20}H_{28}O_3$, M = 316.44, monoclinic, space group $P2_1$ (C^2_2) No. 4, a = 10.101 (1) Å, b = 11.538 (1) Å, c = 8.237 (1) Å, β = 112.93 (1)°, V = 884.1 (3) Å^3, Z = 2, D_{calcd} = 1.189 g cm^{-3}, μ (Cu Kα) = 5.8 cm^{-1}. Crystal dimensions 0.05 × 0.20 × 0.40 mm. Intensity data ($\pm h$,$-k$,$+l$, 1911 nonequivalent reflections, $\omega - 2\theta$ scans, θ_{max} = 75°) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, λ = 1.5418 Å graphite monochromator). The crystal structure was solved by direct methods (RANTAN). Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, O; fixed H contributions) converted (maximum shift:esd = 0.02σ) at R = 0.045 (R_w = 0.060, GOF = 1.24) over 1360 reflections with $I > 3.0\sigma(I)$. Crystallographic calculations were performed on PDP 11/44 and Micro VAX computers by use of the Enraf-Nonius Structure Determination Package (SDP).

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Articles

Synthesis of the Bis-spiroacetal Moiety of 17-Epi-20-deoxysalinomycin

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Received April 6, 1992

The synthesis of the bis-spiroacetal moiety of 17-epi-20-deoxysalinomycin (4) is reported in which the key step involves oxidative cyclization of the hydroxy spiroacetals 14 and 15 to the bis-spiroacetals 16 and 17 using (diacetoxyiodo)benzene and iodine under photolytic conditions.

The polyether antibiotic salinomycin (1),[1] isolated from the fermentation medium of *Streptomyces albus*, was found to exhibit marked activity against mycobacteria and fungi in addition to antibacterial and anticoccidial properties. Growth of *S. albus* in a different culture medium led to the isolation of both 17-epi-20-deoxysalinomycin (4) and 20-deoxysalinomycin (2) with the former antibiotic being present at much greater levels than the latter[2] while 4-methylsalinomycin or narasin A (3) was isolated from a culture of *S. aureofaciens*.[3] The interesting 1,6,8-tri-

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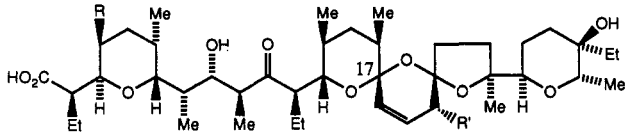
0022-3263/92/1957-5818$03.00/0

oxadispiro[4.1.5.3]pentadec-13-ene ring system is a key structural feature of salinomycin and has since been found in other polyether antibiotics, namely noboritomycin,[4] CP44,661,[5] and X-14766 A.[6]



salinomycin **1** R=H R'=OH
deoxy-(O-8)-salinomycin **2** R=R'=H
narasin A **3** R=Me R'=OH
epi-17-deoxy-(O-8)-salinomycin **4** R=R'=H, C 17 epimer

Total syntheses of salinomycin have been achieved by Kishi[7] and Yonemitsu[8] in which the bis-spiroacetal ring system was assembled by the addition of an acetylide ion to a δ-valerolactone assembly of a fully functionalized dihydroxy ketone, followed by acid-catalyzed cyclization. Elegant use of an oxidative rearrangement of 2-furyl ketones[9,10] has also resulted in formation of the ring system present in the salinomycin family of antibiotics; however, to date this approach has not been used to synthesize the natural products themselves. We now report the synthesis of the bis-spiroacetal moiety of 17-epi-20-deoxysalinomycin (**4**) in which the key step involves the oxidative cyclization of a hydroxy spiroacetal to a bis-spiroacetal. A similar strategy has also been used by Danishefsky et al.[11] in the total synthesis of avermectin A_{1a}.

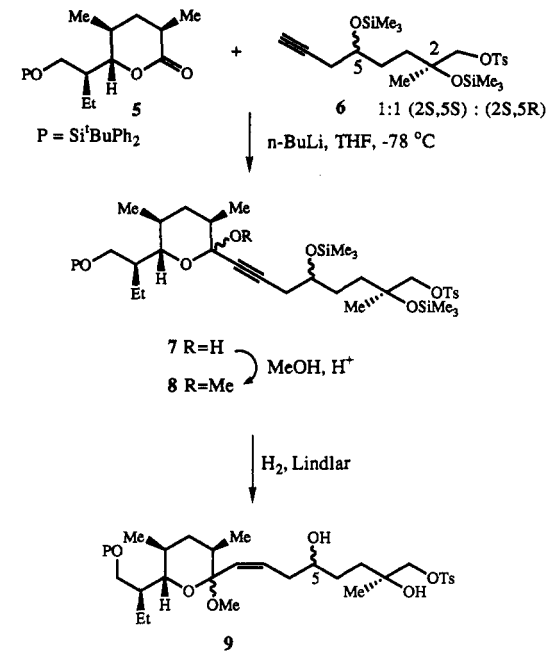
Results and Discussion

On the basis of our earlier model work,[12] iodides **14** and **15** were chosen as key cyclization precursors due to the compatibility of the iodide group to the oxidative cyclization conditions employed. Initial attention therefore focused on the synthesis of iodides **14** and **15** starting from optically active lactone **5** and the acetylene **6** with the required *S* configuration at C-2 (Schemes I and II).

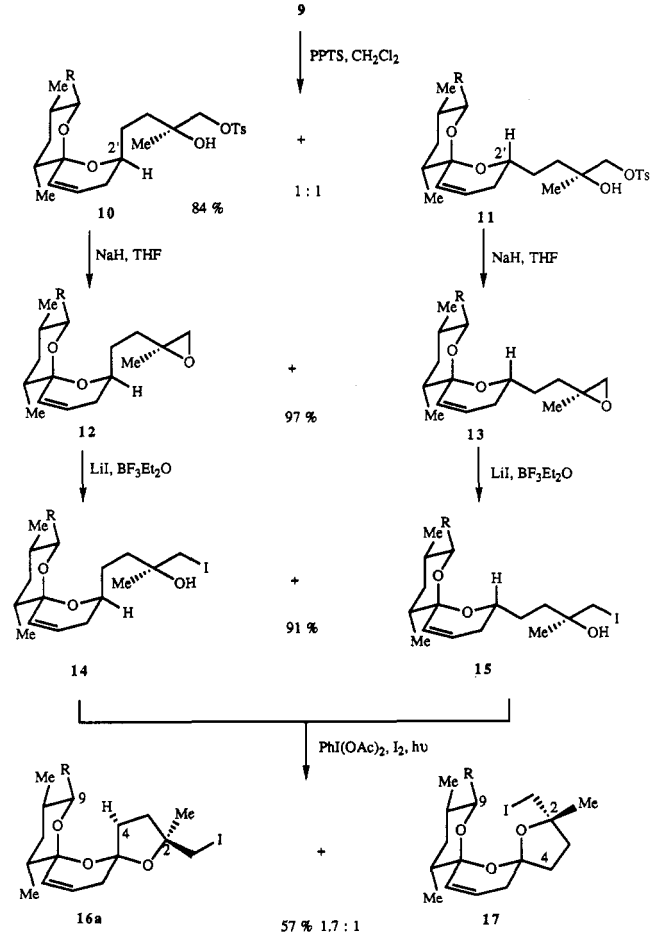
The methodology developed by Evans and Bartroli[13] in their synthesis of the structurally similar Prelog–Djerassi lactone has been successfully applied (with slight modification) to the synthesis of lactone **5**.[14] Acetylene **6** has been reported previously[12] without control of stereochemistry at C-2 starting from racemic lactonic acid. Thus in the present case incorporation of a resolution step into this procedure allowed the preparation of (2*S*)-acetylene **6** from (*S*)-(−)-lactonic acid.[15]

Treatment of acetylene **6** with *n*-BuLi at −78 °C for 0.5 h afforded the lithium acetylide which reacted with lactone **5** to give hemiacetal **7** (Scheme I), which was treated directly with Amberlite IR 120 resin in MeOH for 1 h to afford the methoxy acetal–diol **8**. Methoxy acetal–diol **8** was moderately unstable, therefore a solution of **8** in ethyl

Scheme I



Scheme II



10-16a,17 R = -CH(Et)$CH_2OSi^tBuPh_2$
16b R = -CH(Et)CH_2OH
16c R = -CH(Et)$CH_2OCOC(OCH_3)(CF_3)Ph$

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acetate/hexane was partially hydrogenated using Lindlar catalyst to afford the *cis*-olefin **9** which once again was not isolated but directly dissolved in dichloromethane and treated with a catalytic quantity of PPTS. This yielded a 1:1 mixture of the less polar spiroacetal–tosylate **10** and the more polar diastereomer **11** in 84% yield, which were separated by flash chromatography (Scheme II).

The structures of tosylates **10** and **11** were ascertained by considering both steric and anomeric effects. The favored conformation of the spiroacetal center of both isomers is that in which the C–O bonds adopt axial or pseudoaxial positions on their respective neighboring rings as dictated by the anomeric effect. The difference between the isomers arises from the unresolved C-5 of the cyclization precursor **9**. On spirocyclization 50% of the mixture will afford that isomer **10** with the relatively unfavorable pseudoaxial side chain at C-2′ and the remaining 50% that isomer **11** with the side chain placed in the pseudoequatorial position. Each isomer was distinguished by comparing the ^{1}H NMR spectra. Since 2′-H of **11** possesses a 1,3-diaxial relationship to a C–O bond, its resonance is therefore deshielded—occurring as a multiplet at δ 3.94–4.05—relative to the resonance for the same proton of isomer **10** which occurs upfield in the multiplet at δ 3.65–3.78. This effect is commonly recognized in spiroacetal chemistry.[16]

Having separated the diastereomeric tosylates **10** and **11**, the remainder of the synthetic procedure was conducted on the individual isomers, each being treated in precisely the same fashion.

Thus, tosylate **10** was converted to epoxide **12** in 97% yield using NaH in THF, and similarly the other diastereomeric epoxide **13** was obtained from **11** under identical conditions. The stereochemistry of each epoxide resembles that of the tosylate from which it is derived since a relatively deshielded resonance at δ 3.98–4.07 is observed in the ^{1}H NMR spectrum of **13** due to the pseudo-1,3-diaxial interaction of 2′-H with a C–O bond whereas the corresponding resonance for the other epoxide **12** occurs upfield at δ 3.65–3.71.

The iodohydrins **14** and **15** were then obtained in 91% yield by nucleophilic ring opening of the respective epoxides **12** and **13** by LiI in THF at −50 °C catalyzed by $BF_3{\cdot}Et_2O$. Hence each isomer, **14** and **15**, possessed stereochemistry analogous to the epoxide from which it was derived.

Having obtained the iodohydrins **14** and **15**, spirocyclization to the bis-spiroacetals was then undertaken using the same controlled photolytic conditions developed for model systems.[12] Irradiation of a solution of iodohydrin **14** in cyclohexane, containing iodine (2 equiv) and (diacetoxyiodo)benzene (2 equiv), under nitrogen, with a tungsten filament lamp afforded two less polar products. These could be separated by careful flash chromatography to afford the *trans*-bis-spiroacetal **16a** and the more polar *cis*-bis-spiroacetal **17** in a ratio of 1.7:1 in 57% overall yield. The yield of this cyclization step was somewhat lower than that obtained for the model system, which may be due in part to the steric influence of the chiral substituents during cyclization.

The ^{1}H NMR spectra readily distinguished the two isomers since the trans isomer **16a** exhibits the characteristic[12] resonance at δ 2.51–2.61 due to 4-H which is deshielded (owing to its close proximity to a ring oxygen) relative to 4-H of the cis isomer which resonates upfield at δ 2.02–2.11. The stereochemistry at C-2 is supported upon examination of the chemical shifts of the 2-Me group. Since C-2 of the cyclization precursor **14** possesses an *S* configuration, then after spirocyclization, the methyl group on the five-membered ring of the trans isomer **16a** adopts a 1,3-syn orientation to the C–O bond of the central ring and is therefore somewhat deshielded relative to the corresponding methyl group of the cis isomer **17** which is 1,3-anti to the same C–O bond. Thus, the spectrum of the trans isomer **16a** exhibits a singlet at δ 1.57 assigned to the methyl group at C-2 compared to δ 1.28 in the cis isomer **17**.

Subjecting the second iodohydrin **15** to the same photolytic conditions used above gave rise to the same ratio of products (**16a**:**17**, 1.7:1) in similar overall yield. This outcome may be explained by the proposed reaction mechanism[17] in that both diastereomeric precursors **14** and **15** form the same radical or carbocation intermediate which is subsequently trapped predominantly from the least hindered α-face to give *trans*-bis-spiroacetal **16a** as the major product.

Comparison of the ^{1}H and ^{13}C NMR data for *trans*-bis-spiroacetal **16a** with the natural product **4** clearly established that **16a** has the same trans stereochemistry as that present in 17-epi-20-deoxysalinomycin (**4**). The optical purity of **16a** was assessed by deprotection of the silyl ether on the side chain at C-9 to the alcohol **16b** using $Bu_4N^+F^-$ followed by conversion of the resultant alcohol to a Mosher ester derivative **16c** using (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Examination of the ^{1}H NMR spectrum indicated an enantiomeric excess greater than 96% since only one methoxy resonance was observed at δ_H 3.57. This was supported upon examination of the ^{19}F NMR spectrum which also exhibited a single peak at δ_F −104.1 relative to C_6F_6 at δ_F −163.0.

Conclusion

The successful synthesis of *trans*-bis-spiroacetal **16a** has been achieved. *trans*-Bis-spiroacetal **16a** is a key intermediate for the total synthesis of 17-epi-20-deoxysalinomycin (**4**) in that it not only possesses the correct stereochemistry for the bis-spiroacetal unit but it also contains functional groups at both ends of the molecule which provide "handles" for further synthetic elaboration to the natural product.

Experimental Section

General Details. Chemicals and reagents were purchased from the Aldrich Chemical Co. and used without further purification. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 270 and 67.8 MHz respectively. Mass spectra were recorded with an ionisation potential of 70 eV. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Analytical TLC was performed using precoated silica gel plates (Merck Kieselgel 60 F_{254}). THF was distilled from sodium benzophenone ketyl before use. (2*S*)-Acetylene **6** was prepared from (*S*)-(−)-lactonic acid[15] according to the procedure[12] reported previously starting from racemic lactonic acid. Lactone **5** was prepared according to the published procedure.[14]

(1″*S*,2*S*,2′*S*,6′*R*,8′*S*,9′*S*,11′*R*)- and (1″*S*,2*S*,2′*R*,6′*R*,8′*S*,9′*S*,11′*R*)-4-[8′-[1″-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]propyl]-9′,11′-dimethyl-1′,7′-dioxaspiro[5.5]undec-4′-en-2′-yl]-2-hydroxy-2-methylbutan-1-yl *p*-Toluenesulfonates (10 and 11). (2*S*)-Acetylene **6**[12] (71 mg, 0.15 mmol) was dissolved in dry THF (4 mL) and cooled to −75 °C under N_2. *n*-BuLi (0.09 mL of a 1.6 M solution in hexane, 0.15 mmol) was added and the reaction mixture stirred at this temperature for

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1 h, whereupon a solution of lactone **5**[14] (52 mg, 0.12 mmol) in dry THF (1 mL) was added dropwise. After being stirred for a further 0.5 h, the reaction mixture was quenched with 10% water in THF (0.5 mL), warmed to rt, and dried (K_2CO_3). The solvent was evaporated at reduced pressure and the residue filtered on Florisil to afford an oil which was dissolved in methanol and stirred with Amberlite IR 120 resin for 1 h. This solution was filtered and the methanol evaporated under reduced pressure to give a yellow residue which was purified by flash chromatography to afford the methoxy acetal–diol **8** (83 mg). This colorless, somewhat unstable oil was quickly dissolved in 1:1 hexane/ethyl acetyl (20 mL) and stirred vigorously with Lindlar catalyst (~2 mg) under H_2 for 5 h. The solution was filtered and the solvent evaporated to afford an oily residue which was dissolved in CH_2Cl_2 (10 mL) and stirred with a catalytic quantity of PPTS for 0.2 h. The solvent was removed and the resulting oil purified by flash chromatography using hexane/ethyl acetate (4:1) as eluant to afford the less polar tosylate **10** (30 mg, 42% from **5**) as a colorless oil: $[\alpha]^{22}_D$ −18.5° (*c* 1.09, Et_2O); IR (film) 3670–3290 (OH), 3035 (=CH), 2945, 2870 (CH), 1635 (C=C), 1362, 1175 (SO_2O) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.74 (3 H, t, *J* = 7.6 Hz, CH_2CH_3), 0.745 (3 H, d, *J* = 6.8 Hz, 9′-Me), 0.79 (3 H, d, *J* = 6.6 Hz, 11′-Me), 1.03 (3 H, s, 2-Me), 1.04 (9 H, s, *t*-Bu), 1.07–1.68 (11 H, m, C*H*Et, CH_2CH_3, 3 × CH_2, 2 × C*H*Me), 1.79–1.87 (2 H, m, =CCH_2), 2.43 (3 H, s, Ar-Me), 2.97 (1 H, s, OH), 3.59 (1 H, dd, $J_{8'ax,9'ax}$ = 10.4, $J_{8'ax,1''}$ = 1.3 Hz, $8'_{ax}$-H), 3.65–3.78 (5 H, m, 2 × CH_2O, 2′-H), 5.42 (1 H, ddd, $J_{5',4'}$ = 10.1, $J_{5',3'}$ = 2.8, $J_{5',3'}$ = 2.8 Hz, 5′-H), 5.87 (1 H, ddd, $J_{4',5'}$ = 10.1, $J_{4',3'}$ = 5.1, $J_{4',3'}$ = 2.4 Hz, 4′-H), 7.31–7.41 (8 H, m, Ar-H), 7.63–7.67 (4 H, m, Ar-H), 7.78 (2 H, d, *J* = 8.3 Hz, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.0 (q, C-3″), 16.0 (q, 9′-Me), 17.8 (q, 11′-Me), 18.1 (t, C-2″), 19.2 (s, CMe_3), 21.6 (q, Ar-Me), 24.3 (q, 2-Me), 27.0 (q, CMe_3), 29.8 (t, C-3′), 28.3, 33.0, 36.3 (t, C-3, C-4, C-10′), 31.7, 38.6, 43.7 (d, C-1″, C-9′ and C-11′), 65.4 (t, C-1‴), 66.3 (d, C-2′), 70.4 (s, C-2), 74.9 (d, C-8′), 75.7 (t, C-1), 96.8 (s, C-6′), 127.6 (d, C-4′), 127.5, 127.6, 128.0, 129.4, 129.8 (d, Ar), 129.9 (d, C-5′), 132.8, 134.0, 134.2, 144.8 (s, Ar), 135.5, 135.6 (d, Ar); MS (CI, NH_3) *m/z* 749 (M + H, 25), 730 (M − H_2O, 15), 691 (M − *t*-Bu, 9), 673 (M − *t*-Bu − H_2O, 16), 577 (M − OTs, 8), 559 (M − OTs − H_2O, 17), 519 (M − OTs − *t*-Bu, 12), 199 ($C_{12}H_{11}OSi$, 100); HRMS calcd for $C_{43}H_{60}O_7SSi$ (M + H) 749.3907, found 749.3900. Tosylate **11** (30 mg, 42% from **5**) was also produced as a colorless oil: $[\alpha]^{22}_D$ +38.8° (*c* 1.034, Et_2O); IR (film) 3670–3290 (OH), 3035 (=CH), 2945, 2870 (CH), 1634 (C=C), 1362, 1175 (SO_2O) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.75 (3 H, d, *J* = 6.4 Hz, 9′-Me), 0.76 (3 H, t, *J* = 7.4 Hz, CH_2CH_3), 0.81 (3 H, d, *J* = 6.4 Hz, 11′-Me), 1.02 (9 H, s, *t*-Bu), 1.14 (3 H, s, 2-Me), 1.07–1.85 (11 H, m, C*H*Et, CH_2CH_3, 3 × CH_2, 2 × C*H*Me), 1.89–1.95 (2 H, m, =CCH_2), 2.41 (3 H, s, Ar-Me), 2.43 (1 H, s, OH), 3.54–3.80 (5 H, m, 2 × CH_2O, $8'_{ax}$-H), 3.94–4.05 (1 H, m, 2′-H), 5.95 (1 H, ddd, $J_{4',5'}$ = 10.4, $J_{4',3'}$ = 3.6, $J_{4',3'}$ = 3.6 Hz, 4′-H), 6.08 (1 H, d, *J* = 10.4 Hz, 5′-H), 7.30–7.41 (8 H, m, Ar-H), 7.63–7.67 (4 H, m, Ar-H), 7.78 (2 H, d, *J* = 8.4 Hz, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.0 (q, C-3″), 15.7 (q, 9′-Me), 17.0 (t, C-2″), 17.1 (q, 11′-Me), 19.1 (s, CMe_3), 21.6 (q, Ar-Me), 23.6 (q, 2-Me), 26.8 (q, CMe_3), 31.2 (t, C-3′), 29.2, 34.6, 38.8 (t, C-3, C-4, C-10′), 31.6, 39.2, 43.8 (d, C-1″, C-9′, C-11′), 63.3 (t, C-1‴), 68.8 (d, C-2′), 70.4 (s, C-2), 76.3 (d, C-8′), 76.8 (t, C-1), 98.3 (s, C-6′), 123.8 (d, C-5′), 127.4, 127.5, 128.0, 129.4, 129.5, 129.8 (d, Ar), 128.7 (d, C-4′), 132.7, 134.0, 134.1, 144.7 (s, Ar), 135.5, 135.6 (d, Ar); MS (CI, NH_3) *m/z* 749 (M + H, 25), 730 (M − H_2O, 15), 691 (M − *t*-Bu, 9), 673 (M − *t*-Bu − H_2O, 16), 577 (M − OTs, 8), 559 (M − OTs − H_2O, 17), 519 (M − OTs − *t*-Bu, 12), 199 ($C_{12}H_{11}OSi$, 100); HRMS calcd for $C_{43}H_{60}O_7SSi$ (M + H) 749.3907, found 749.3901.

(1″*S*,2*S*,3′*S*,6*R*,8*S*,9*S*,11*R*)- and (1″*S*,2*R*,3′*S*,6*R*,8*S*,9*S*,11*R*)-8-[1″-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]propyl]-9,11-dimethyl-2-(3′,4′-epoxy-3′-methyl-1′-butyl)-1,7-dioxaspiro[5.5]undec-4-ene (12 and 13). To a solution of (−)-tosylate **10** (52 mg, 0.07 mmol) in dry THF (20 mL) was added NaH (15 mg of a 40% dispersion in oil, 0.25 mmol) and the suspension stirred overnight at rt. After the reaction was quenched with water (0.05 mL), the solvent was evaporated at reduced pressure and the oily solid residue purified by flash chromatography, using hexane/ethyl acetate (4:1) as eluant to afford epoxide **12** (39 mg, 97%) as a colorless oil: $[\alpha]^{22}_D$ −13.7° (*c* 0.766, Et_2O); IR (film) 3070 (Ar-H), 3039 (=CH), 2958, 2928, 2856 (CH), 1656 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.74 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 0.76 (3 H, d, *J* = 6.6 Hz, 9-Me), 0.80 (3 H, d, *J* = 6.4 Hz, 11-Me), 1.06 (9 H, s, *t*-Bu), 1.19 (3 H, s, 3′-Me), 1.05–1.70 (11 H, m, C*H*Et, CH_2CH_3, 3 × CH_2, 2 × C*H*Me), 1.80–1.85 (2 H, m, =CCH_2), 2.37 (1 H, d, *J* = 4.9 Hz, CH_AH_BO epoxide), 2.43 (1 H, d, *J* = 4.9 Hz, CH_AH_BO epoxide), 3.59 (1 H, dd, $J_{8ax,9ax}$ = 10.4, $J_{8ax,1''}$ = 1.5 Hz, 8_{ax}-H), 3.65–3.71 (3 H, m, CH_2OSi, 2-H), 5.43 (1 H, ddd, $J_{5,4}$ = 10.1, $J_{5,3}$ = 2.0, $J_{5,3}$ = 2.0 Hz, 5-H), 5.88 (1 H, ddd, $J_{4,5}$ = 10.1, $J_{4,3}$ = 4.5, $J_{4,3}$ = 3.0 Hz, 4-H), 7.34–7.42 (6 H, m, Ar-H), 7.64–7.69 (4 H, m, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.1 (q, C-3″), 16.1 (q, 9-Me), 17.9 (q, 11-Me), 18.2 (t, C-2″), 19.2 (s, CMe_3), 21.0 (q, 3′-Me), 27.0 (q, CMe_3), 30.3 (t, C-3), 38.7, 43.8 (d, C-1″, C-11), 53.7 (t, C-4′), 57.0 (s, C-3′), 65.6 (t, C-1‴), 66.1 (s, C-2), 74.8 (d, C-8), 96.2 (s, C-6), 127.6 (d, C-4), 127.5, 127.6, 129.5 (d, Ar), 130.2 (d, C-5), 134.1, 134.3 (s, Ar), 135.5, 135.7 (d, Ar); MS (EI) *m/z* 576 (M^+, 2), 519 (M − *t*-Bu, 23), 337 (6), 323 (5), 295 (7), 207 ($C_{14}H_{23}O$, 10), 199 ($C_{12}H_{11}OSi$, 100); HRMS calcd for $C_{36}H_{52}O_4Si$ (M^+) 576.3635, found 576.3640.

Repetition of this procedure using the corresponding (+)-tosylate **11** (52 mg, 0.07 mmol) afforded epoxide **13** (38 mg, 95%) also as a colorless oil: $[\alpha]^{22}_D$ +42.4° (*c* 0.752, Et_2O); IR (film) 3070 (Ar-H), 3039 (=CH), 2958, 2928, 2856 (CH), 1656 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.76 (3 H, d, *J* = 6.6 Hz, 9-Me), 0.79 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 0.83 (3 H, d, *J* = 6.4 Hz, 11-Me), 1.02 (9 H, s, *t*-Bu), 1.30 (3 H, s, 3′-Me), 0.97–1.80 (11 H, m, C*H*Et, CH_2CH_3, 3 × CH_2, 2 × C*H*Me), 1.89–1.95 (2 H, m, =CCH_2), 2.49 (1 H, d, *J* = 5.0 Hz, CH_AH_BO epoxide), 2.70 (1 H, d, *J* = 5.0 Hz, CH_AH_BO epoxide), 3.56–3.69 (3 H, m, CH_2OSi, 8_{ax}-H), 3.98–4.07 (1 H, m, 2-H), 5.94 (1 H, ddd, $J_{4,5}$ = 10.4, $J_{4,3}$ = 3.8, $J_{4,3}$ = 3.8 Hz, 4-H), 6.11 (1 H, ddd, $J_{5,4}$ = 10.1, $J_{5,3}$ = 1.8, $J_{5,3}$ = 1.8 Hz, 5-H), 7.33–7.43 (6 H, m, Ar-H), 7.64–7.70 (4 H, m, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.1 (q, C-3″), 15.9 (q, 9-Me), 17.2 (q, 11-Me), 17.3 (t, C-2″), 19.2 (s, CMe_3), 21.1 (q, 3′-Me), 26.8 (q, CMe_3), 31.1, 31.2, 31.9, 39.0 (t, C-1′, C-2′, C-3, C-10), 31.7, 39.2, 43.9 (d, C-1″, C-9, C-11), 53.9 (t, C-4′), 56.8 (s, C-3′), 63.3 (t, C-1‴), 67.0 (d, C-2), 76.1 (d, C-8), 98.1 (s, C-6), 124.4 (d, C-5), 128.5 (d, C-4), 127.4, 127.5, 129.4, 129.5 (d, Ar), 134.0, 134.2 (s, Ar), 135.5, 135.6 (d, Ar); MS (EI) *m/z* 576 (M^+, 2), 519 (M − *t*-Bu, 36), 477 ($C_{29}H_{37}O_4Si$, 7), 405 ($C_{26}H_{33}O_2Si$, 4), 337 (16), 323 (27), 295 (10), 207 ($C_{14}H_{23}O$, 35), 199 ($C_{12}H_{11}OSi$, 100); HRMS calcd for $C_{36}H_{52}O_4Si$ (M^+) 576.3635, found 576.3629.

(1″*S*,2*S*,2′*S*,6′*R*,8′*S*,9′*S*,11′*R*)- and (1″*S*,2*S*,2′*R*,6′*R*,8′*S*,9′*S*,11′*R*)-4-[8′-[1″-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]propyl]-9′,11′-dimethyl-1′,7′-dioxaspiro[5.5]undec-4′-en-2′-yl]-1-iodo-2-methyl-2-butanol (14 and 15). A solution of (−)-epoxide **12** (37 mg, 0.064 mmol) in dry THF (9 mL) was cooled to −50 °C under N_2. LiI (17 mg, 0.13 mmol) dissolved in dry THF (1 mL) was then added followed by BF_3·Et_2O (0.02 mL). The reaction mixture was stirred at this temperature for 1 h, quenched with 5% water in THF (0.5 mL), and warmed to rt. The solution was dried (K_2CO_3), the solvent was evaporated, and the residue was purified by flash chromatography using hexane/ethyl acetate (4:1) as eluant to afford iodohydrin **14** (41 mg, 91%) as a colorless oil: $[\alpha]^{22}_D$ −20.2° (*c* 0.6, Et_2O); IR (film) 3570–3200 (OH), 3069 (Ar-H), 3047 (=CH), 2958, 2923, 2856 (CH), 1653 (C=C); ^1H NMR (270 MHz, $CDCl_3$) δ 0.77 (3 H, d, *J* = 6.6 Hz, 9′-Me), 0.79 (3 H, t, *J* = 8.2 Hz, CH_2CH_3), 0.81 (3 H, d, *J* = 6.2 Hz, 11′-Me), 1.05 (9 H, s, *t*-Bu), 1.20 (3 H, s, 2-Me), 1.06–1.71 (11 H, m, C*H*Et, CH_2CH_3, 3 × CH_2, 2 × C*H*Me), 1.82–1.90 (2 H, m, =CCH_2), 2.25 (1 H, s, OH), 3.14 (2 H, s, CH_2I), 3.59 (1 H, dd, $J_{8'ax,9'ax}$ = 10.3, $J_{8'ax,1''}$ = 1.5 Hz, $8'_{ax}$-H), 3.71–3.74 (3 H, m, CH_2O, 2′-H), 5.45 (1 H, ddd, $J_{5',4'}$ = 10.0, $J_{5',3'}$ = 2.4, $J_{5',3'}$ = 1.5 Hz, 5′-H), 5.89 (1 H, ddd, $J_{4',5'}$ = 10.0, $J_{4',3'}$ = 4.8, $J_{4',3'}$ = 2.6 Hz, 4′-H), 7.32–7.45 (6 H, m, Ar-H), 7.65–7.70 (4 H, m, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.2 (q, C-3″), 16.1 (q, 9′-Me), 17.8 (q, 11′-Me), 18.3 (t, C-2″), 19.3 (s, CMe_3), 22.0 (t, C-1), 25.9 (q, 2-Me), 27.0 (q, CMe_3), 29.6 (t, C-3′), 30.0, 35.6, 36.4 (t, C-3, C-4, C-10′), 31.8, 38.7, 43.7 (d, C-1″, C-9′, C-11′), 65.8 (t, C-1‴), 66.2 (d, C-2′), 70.2 (s, C-2), 75.0 (d, C-8′), 96.6 (s, C-6′), 127.7 (d, C-4′), 127.5, 127.6, 129.5, 129.6 (d, Ar), 130.1 (d, C-5′), 134.2, 134.4 (s, Ar), 135.5, 135.7 (d, Ar); MS (EI) *m/z* 704 (M^+, 1), 647 (M − *t*-Bu, 34), 629 (M − *t*-Bu − H_2O, 7), 577 (M − I, 3), 519 (M − *t*-Bu − I, 7), 431 (9), 337 (21), 323 (12), 225 ($C_6H_{10}OI$, 37), 199 ($C_{12}H_{11}OSi$, 100); HRMS calcd for $C_{36}H_{53}O_4SiI$ (M^+) 704.2756, found 704.2744.

Repetition of this procedure, using the corresponding (+)-epoxide **13** (33 mg, 0.057 mmol) afforded iodohydrin **15** (37 mg, 92%) as a colorless oil: $[\alpha]^{22}_D$ +40.1° (*c* 0.51, Et_2O); IR (film) 3570–3200

(OH), 3069 (Ar-H), 3047 (=CH), 2958, 2923, 2856 (CH), 1653 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.77 (3 H, d, J = 6.6 Hz, 9'-Me), 0.78 (3 H, t, J = 8.4 Hz, CH_2CH_3), 0.82 (3 H, d, J = 6.6 Hz, 11'-Me), 1.02 (9 H, s, t-Bu), 1.33 (3 H, s, 2-Me), 1.08–1.80 (11 H, m, CHEt, CH_2CH_3, 3 × CH_2, 2 × CHMe), 1.92–1.98 (1 H, m, =CCH_2), 3.27 (1 H, s, OH), 3.32 (2 H, s, CH_2I), 3.54–3.78 (3 H, m, CH_2O, 8'$_{ax}$-H), 4.00–4.10 (1 H, m, 2'-H), 5.95 (1 H, ddd, $J_{4',5'}$ = 10.3, $J_{4',3'}$ = 3.3, $J_{4',3'}$ = 3.3 Hz, 4'-H), 6.10 (1 H, d, J = 10.3 Hz, 5'-H), 7.34–7.42 (6 H, m, Ar-H), 7.64–7.68 (4 H, m, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.0 (q, C-3''), 15.8 (q, 9'-Me), 17.1 (t, C-2''), 17.2 (q, 11'-Me), 19.2 (s, CMe_3), 22.7 (t, C-1), 26.2 (q, 2-Me), 26.8 (q, CMe_3), 31.1 (t, C-3'), 30.0, 36.5, 38.9 (t, C-3, C-4, C-10'), 31.6, 39.1, 43.9 (d, C-1'', C-9', C-11'), 63.3 (t, C-1'''), 68.5 (d, C-2'), 69.9 (s, C-2), 77.2 (d, C-8'), 98.3 (s, C-6'), 124.1 (d, C-5'), 127.4, 127.5, 129.4, 129.5 (d, Ar), 128.6 (d, C-4'), 134.0 (s, Ar), 135.5, 135.6 (d, Ar); MS (EI) m/z 704 (M^+, 1), 647 (M – t-Bu, 34), 629 (M – t-Bu – H_2O, 7), 577 (M – I, 3), 519 (M – t-Bu – I, 7), 431 (9), 337 (21), 323 (12), 225 ($C_6H_{10}OI$, 37), 199 ($C_{12}H_{11}OSi$, 100); HRMS calcd for $C_{36}H_{53}O_4SiI$ (M^+) 704.2756, found 704.2744.

***trans*-(1'*S*,2*S*,5*S*,7*S*,9*S*,10*S*,12*R*)- and *cis*-(1'*S*,2*S*,5*R*,7*S*,9*S*,10*S*,12*R*)-9-[1'-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]propyl]-2-(iodomethyl)-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes (16a and 17).** A solution of (–)-iodohydrin **14** (42 mg, 0.06 mmol), iodine (32 mg, 0.13 mmol), and (diacetoxyiodo)benzene (42 mg, 0.13 mmol) in cyclohexane (10 mL) was purged with nitrogen and irradiated with a 270-W tungsten filament lamp. After 1.5 h, during which time the temperature was maintained at about 18 °C, the solution was diluted with ether (50 mL), washed with 10% aqueous sodium thiosulfate (10 mL), water (10 mL), and brine (20 mL), and dried (K_2CO_3). The solvent was evaporated under reduced pressure and the resultant oil purified by flash chromatography using hexane/ethyl acetate (95:5) as eluant to afford *trans*-iodide **16a** (15.1 mg, 36%) as a colorless oil: $[\alpha]^{22}_D$ –10.5° (*c* 0.39, $CHCl_3$); IR (film) 3070 (Ar-H), 3040 (=CH), 2951, 2927, 2860 (CH), 1654 (C=C); ^1H NMR (270 MHz, $CDCl_3$) δ 0.66 (3 H, t, J = 7.5 Hz, CH_2CH_3), 0.77 (3 H, d, J = 6.2 Hz, 12-Me), 0.82 (3 H, d, J = 6.4 Hz, 10-Me), 1.06 (9 H, s, t-Bu), 1.57 (3 H, s, 2-Me), 1.17–1.88 (9 H, m, 3-H', 4-H', 2 × CHMe, CHEt, CH_2CH_3, 11$_{ax}$-H, 11$_{eq}$-H), 2.03–2.17 (2 H, m, 3-H, 15-H'), 2.36 (1 H, ddd, $J_{15,15'}$ = 16.8, $J_{15,14'}$ = 2.1, $J_{15,13'}$ = 2.4 Hz, 15-H), 2.51–2.61 (1 H, m, 4-H), 3.16 (1 H, d, J = 10.1 Hz, CH_AH_BI), 3.22 (1 H, d, J = 10.1 Hz, CH_AH_BI), 3.62 (2 H, d, J = 6.6 Hz, CH_2O), 3.72 (1 H, dd, $J_{9ax,10ax}$ = 10.1, $J_{9ax,1'}$ = 0.6 Hz, 9$_{ax}$-H), 5.40 (1 H, dd, $J_{13,14}$ = 10.1, $J_{13,15}$ = 2.4 Hz, 13-H), 5.86 (1 H, ddd, $J_{14,13}$ = 10.1, $J_{14,15}$ = 6.4, $J_{14,15}$ = 2.1 Hz, 14-H), 7.32–7.43 (6 H, m, Ar-H), 7.63–7.68 (4 H, m, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.9 (q, C-3'), 16.0 (q, 10-Me), 17.8 (t, C-2'), 18.2 (t, C-1'''), 18.3 (q, 12-Me), 19.1 (s, CMe_3), 27.0 (q, CMe_3), 28.4 (q, 2-Me), 33.9, 35.6, 35.9, 36.7 (t, C-3, C-4, C-11, C-15), 31.8, 39.4, 44.1 (d, C-1', C-10, C-12), 65.0 (t, C-1''), 75.6 (d, C-9), 82.8 (s, C-2), 99.1 (s, C-7), 107.4 (s, C-5), 125.2 (d, C-13), 127.5, 127.6 (d, Ar), 129.4, 129.5, 129.6 (d, Ar, C-14), 133.9, 134.2 (s, Ar), 135.5, 135.8 (d, Ar); HRMS calcd for $C_{36}H_{51}O_4SiI$ (M^+) 702.2601, found 702.2603 and the more polar *cis*-iodide **17** (8.9 mg, 21%) as a colorless oil: $[\alpha]^{22}_D$ –31.6° (*c* 0.215, $CHCl_3$); IR (film) 3070 (Ar-H), 3040 (=CH), 2951, 2927, 2860 (CH), 1654 (C=C); ^1H NMR (270 MHz, $CDCl_3$) δ 0.70 (3 H, d, J = 6.6 Hz, 12-Me), 0.84 (3 H, t, J = 7.3 Hz, CH_2CH_3), 0.86 (3 H, d, J = 6.5 Hz, 10-Me), 1.06 (9 H, s, t-Bu), 1.28 (3 H, s, 2-Me), 1.03–1.92 (9 H, m, 3-H', 4-H', 2 × CHMe, CHEt, CH_2CH_3, 11$_{ax}$-H, 11$_{eq}$-H), 2.02–2.11 (3 H, m, 3-H, 4-H, 15-H), 2.27 (1 H, ddd, $J_{15,15'}$ = 16.5, $J_{15,14'}$ = 5.1, $J_{15,13'}$ = 1.6 Hz, 15-H'), 3.15 (1 H, d, J = 9.3 Hz, CH_AH_BI), 3.29 (1 H, d, J = 9.3 Hz, CH_AH_BI), 3.55 (1 H, dd, $J_{9ax,10ax}$ = 10.4, $J_{9ax,1'}$ = 1.8 Hz, 9$_{ax}$-H), 5.61 (1 H, ddd, $J_{13,14}$ = 9.9, $J_{13,15}$ = 1.6, $J_{13,15}$ = 1.6 Hz, 13-H), 5.93 (1 H, ddd, $J_{14,13}$ = 9.9, $J_{14,15}$ = 5.1, $J_{14,15}$ = 3.7 Hz, 14-H), 7.32–7.43 (6 H, m, Ar-H), 7.63–7.68 (4 H, m, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.6 (q, C-3'), 15.8 (q, 10-Me), 17.4 (t, C-2'), 18.4 (q, 12-Me), 19.2 (s, CMe_3), 20.6 (t, C-1'''), 25.6 (q, 2-Me), 27.0 (q, CMe_3), 34.5, 36.0, 36.5, 39.1 (t, C-3, C-4, C-11, C-15), 32.5, 39.3, 45.6 (d, C-1', C-10, C-12), 64.9 (t, C-1''), 77.2 (d, C-9), 83.5 (s, C-2), 96.6 (s, C-7), 106.3 (s, C-5), 125.3 (d, C-13), 127.5, 127.6, 129.4 (d, Ar), 130.5 (d, C-14), 134.2 (s, Ar), 135.7, 135.8 (d, Ar); MS (EI) m/z 702 (M^+, 6), 645 (M – t-Bu, 100), 567 (7), 391 ($C_{16}H_{24}O_3I$, 12), 320 ($C_{20}H_{32}O_3$, 16), 303 (12), 200 (12), 199 ($C_{12}H_{11}OSi$, 66), 183 (18), 135 (26), 111 (12), 97 (12); HRMS calcd for $C_{36}H_{51}O_4SiI$ (M^+) 702.2601, found 702.2603. The procedure was repeated, irradiating a solution of the (+)-iodohydrin **15**, iodine, and (diacetoxyiodo)benzene in cyclohexane, to again form a diastereomeric mixture of bis-spiroketals **16a** (36%) and **17** (21%) which exhibited identical spectroscopic properties to those isomers already described.

(2*S*,2'*S*,5'*S*,7'*S*,9'*S*,10'*S*,12'*R*)-2-(2'-(Iodomethyl)-2',10',12'-trimethyl-1',6',8'-trioxadispiro[4.1.5.3]pentadec-13'-en-9'-yl)butan-1-ol (16b). To a solution of the *trans*-iodide **16a** (4 mg) in dry THF (1 mL) under nitrogen was added tetra-*n*-butylammonium fluoride (0.5 mL of a 1 M solution in THF, 0.5 mmol) and the mixture stirred overnight. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography, using hexane/ethyl acetate as eluant (2:1) to afford alcohol **16b** (~2.5 mg) as colorless prisms: mp 83–84.5 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 0.80 (3 H, d, J = 6.6 Hz, 10'-Me or 12'-Me), 0.81 (3 H, d, J = 6.6 Hz, 10'-Me or 12'-Me), 0.98 (3 H, t, J = 7.1 Hz, CH_2CH_3), 1.66 (3 H, s, 2'-Me), 1.25–1.79 (7 H, m, CHEt, 2 × CHMe, CH_2CH_3, 11'$_{ax}$-H, 11'$_{eq}$-H), 1.89 (1 H, dd, $J_{4',4'}$ = 12.6, $J_{4',3'}$ = 10, and $J_{4',3'}$ = 10 Hz, 4'-H'), 2.14–2.23 (3 H, m, 3'-H, 3'-H', 15'-H'), 2.41 (1 H, ddd, $J_{15',15'}$ = 16.8, $J_{15',14'}$ = 2.4, $J_{15',13'}$ = 3.0 Hz, 15'-H), 2.57 (1 H, ddd, $J_{4',4'}$ = 12.6, $J_{4',3'}$ = 5.1, $J_{4',3'}$ = 5.1 Hz, 4'-H), 2.85 (1 H, dd, $J_{HA,OH}$ = 10.5, $J_{HB,OH}$ = 1.7 Hz, OH), 3.27 (1 H, d, J = 10.3 Hz, CH_AH_BI), 3.32 (1 H, d, J = 10.3 Hz, CH_AH_BI), 3.67–3.78 (2 H, m, CH_2O), 3.83 (1 H, dd, $J_{9',10'}$ = 10.4, $J_{9',2}$ = 1.6 Hz, 9'-H), 5.48 (1 H, ddd, $J_{13',14'}$ = 10.1, $J_{13',15'}$ = 3.0, $J_{13',15'}$ = 0.8 Hz, 13'-H), 5.94 (1 H, ddd, $J_{14',13'}$ = 10.1, $J_{14',15'}$ = 6.2, $J_{14',15'}$ = 2.4 Hz, 14'-H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.3 (q, C-4), 15.9 (q, 10'-Me), 16.1 (t, C-1''), 17.5 (t, C-3), 17.6 (q, 12'-Me), 28.4 (q, 2'-Me), 31.8, 39.5, 41.7 (d, C-2, C-10', C-12'), 33.8 (t, C-15'), 35.5, 36.3, 37.0 (t, C-3', C-4', C-11'), 64.8 (t, C-1), 81.1 (d, C-9'), 82.8 (s, C-2'), 99.3 (s, C-7'), 107.5 (s, C-5'), 126.2 (d, C-13'), 128.7 (d, C-14'); MS (EI) m/z 464 (M^+, 22), 446 (M – H_2O, 6), 391 (M – C_4H_9OH, 29), 337 (M – I, 5), 320 (M – OH – I, 37), 309 (100), 308 (46), 291 (30), 224 ($C_{14}H_{24}O_2$, 19), 163 (26), 113 ($C_6H_9O_2$, 14), 99 ($C_5H_7O_2$, 8), 97 (25); HRMS calcd for $C_{20}H_{33}O_4I$ (M^+) 464.1424, found 464.1457.

Conversion of *trans*-alcohol **16b** to the Mosher ester derivative **16c** was performed as follows: To a solution of the alcohol **16b** (2 mg) and pyridine (0.1 mL) in CCl_4 (1 mL) under nitrogen was added a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (5 mg) in CCl_4 (0.5 mL), and the reaction was stirred overnight at room temperature. Water (1 mL) was added and the mixture extracted with ether (50 mL). The ether extract was washed with water (15 mL) and dried (K_2CO_3). Evaporation of the solvent under reduced pressure and purification of the residue by flash chromatography using hexane/ethyl acetate (9:1) as eluant afforded the Mosher ester **16c**: ^1H NMR (270 MHz, $CDCl_3$) δ 0.77 (3 H, d, J = 6.4 Hz, 10'-Me or 12'-Me), 0.80 (3 H, d, J = 6.4 Hz, 10'-Me or 12'-Me), 0.95 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.56 (3 H, s, 2'-Me), 1.17–2.02 (10 H, m, 2 × CHMe, CHEt, 3'-H', 3'-H, 4'-H', CH_2CH_3, 11'$_{ax}$-H, 11'$_{eq}$-H), 2.11 (1 H, dd, $J_{15',15'}$ = 16.7, $J_{15',14'}$ = 6.4 Hz, 15'-H'), 2.37 (1 H, ddd, $J_{15',15'}$ = 16.7, $J_{15',14'}$ = 2.6, $J_{15',13'}$ = 2.6 Hz, 15'-H), 2.45–2.52 (1 H, m, 4'-H), 3.17 (1 H, d, J = 10.3 Hz, CH_AH_BI), 3.25 (1 H, d, J = 10.3 Hz, CH_AH_BI), 3.57 (3 H, q, J = 1.3 Hz, OMe), 3.64 (1 H, dd, $J_{9'ax,10'ax}$ = 10.7, $J_{9'ax,2}$ = 1.2 Hz, 9'$_{ax}$-H), 4.10 (1 H, dd, $J_{HA,HB}$ = 10.8, $J_{HA,2}$ = 7.7 Hz, CH_AH_BO), 4.55 (1 H, dd, $J_{HB,HA}$ = 10.8, $J_{HB,2}$ = 5.5 Hz, CH_AH_BO), 5.43 (1 H, dd, $J_{13',14'}$ = 10.1, $J_{13',15'}$ = 2.6 Hz, 13'-H), 5.90 (1 H, ddd, $J_{14',13'}$ = 10.1, $J_{14',15'}$ = 6.4 Hz, $J_{14',15'}$ = 2.6 Hz, 14'-H); ^{19}F NMR δ –104.1 relative to C_6F_6 at δ –163.0.

Acknowledgment. We thank the Massey University Research Fund for financial support (to G.M.W.) and Professor R. Baker, MSD (Harlow), England for the gift of chemicals.

Supplementary Material Available: ^1H NMR spectra (270 MHz) for compounds **10–17** and ^{13}C NMR spectra (67.8 MHz) for compounds **16** and **17** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.