Avermectin–Milbemycin Synthetic Studies. Part 7. An Approach to the Southern Hemisphere of Milbemycin α_1

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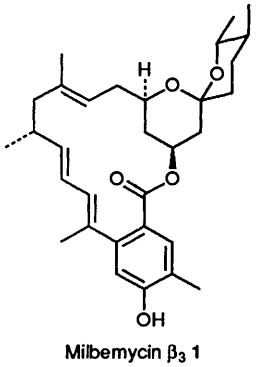
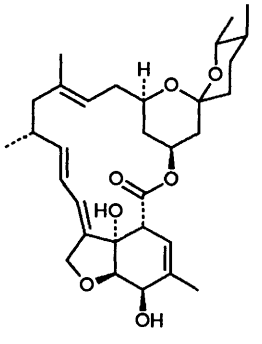
An asymmetric approach to oxahydrindene **5**, the southern hemisphere of the anthelmintic macrolide milbemycin α_1, **2**, is described. [2 + 2]-Photocycloaddition of the dihydrofuran chiral template (+)-**11** with cyclobutenoate **12** furnished the requisite *cis-anti-cis*, head-to-tail photoadduct (+)-**17** in 54% yield. de Mayo-type fragmentation then smoothly furnished hydrindane **21** α,β; further elaboration afforded the 3,4-dihydro-4-normethyl southern fragment **39**. Efforts to install the C(4) methyl group and C(3,4) unsaturation in several advanced intermediates related to **39** gave unsatisfactory results.

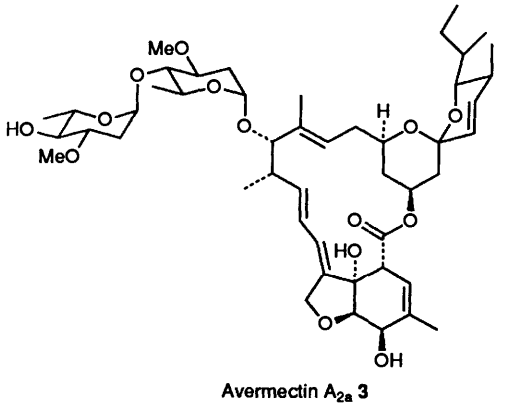
The milbemycins and avermectins comprise a sizeable class of architecturally complex, biologically significant antibiotics.[1] In 1975 Mishima *et al.* reported the isolation of the β milbemycins (*e.g.*, **1**) from a fermentation broth of *Streptomyces hygroscopicus*;[2a] in extensive follow-up studies they also characterized the more richly endowed α series, exemplified by milbemycin α_1 (**2**)[2b] as well as other congeners.[2c] At Merck a screen for new anthelmintic agents led to the independent discovery of the avermectins (*e.g.*, **3**), produced by a different *Streptomyces* strain obtained from Ōmura at the Kitasato Institute.[3] Key structural features of both the avermectins and milbemycins include 16-membered lactone rings, [6,6]spiroketal moieties, and, in many examples, highly functionalized oxahydrindene subunits. Moreover, these macrolides typically possess potent anthelmintic and insecticidal activity,[4] and they currently represent the treatment of choice for African river blindness, caused by the nematode *Onchocerca volvulus*.



Milbemycin β_3 **1**

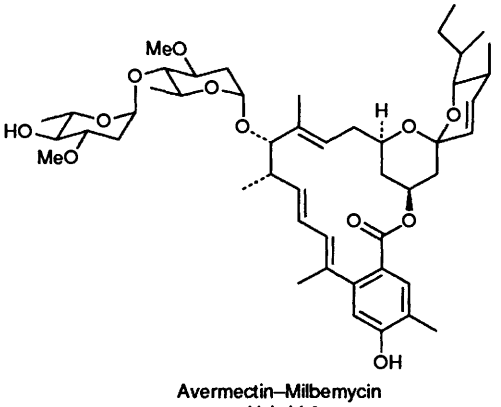


Milbemycin α_1 **2**



Avermectin A_{2a} **3**

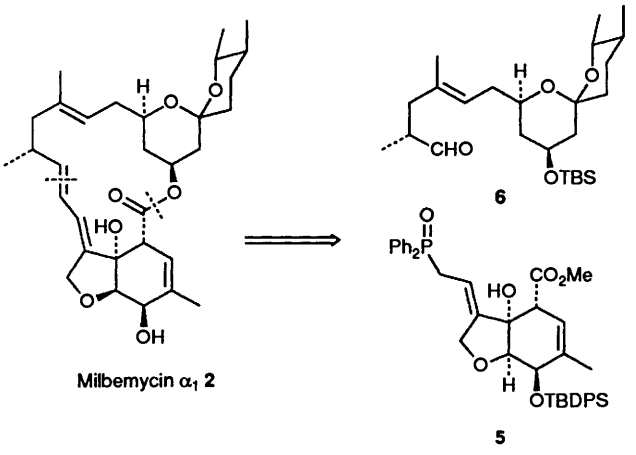
Notwithstanding the ready availability of the natural products *via* fermentation, the avermectins and milbemycins have stimulated intensive activity in the synthetic community, resulting to date in twelve total syntheses[5] as well as diverse approaches to the spiroketal[6] and oxahydrindene[7] fragments. In planning our own efforts in this area, we sought to devise a unified synthetic strategy which would yield not only known target structures, but also analogues of biological interest. Of particular relevance to the current venture, the preparation of simplified 4-normethyl and 4-normethyl-3,4-dihydro species would permit elucidation of the structure–activity relationships for this functionality. We have previously recorded the first total synthesis of a member of this family [*i.e.*, milbemycin β_3 (**1**)][8] and a relay synthesis of the novel avermectin–milbemycin hybrid **4**.[9] Our recent efforts have focused on the more complex α milbemycin problem; herein we describe experiments directed toward an asymmetric construction of oxahydrindene **5** (Scheme 1), a southern hemisphere building block for milbemycin α_1 **2**.[10]



Avermectin–Milbemycin Hybrid **4**

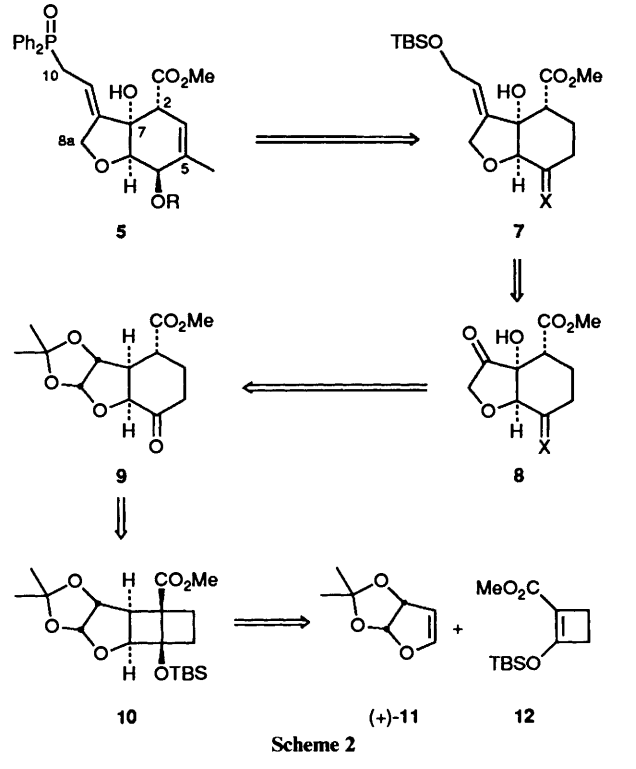
Retrosynthetic Analysis.—Our unified strategy, first outlined in 1982,[8] employs initial disconnection of the lactone and C(10,11) olefin linkages (Scheme 1). The corresponding endgame strategy would then entail Horner–Emmons olefination followed by macrolactonization, a sequence successfully exploited for the syntheses of both milbemycin β_3[8] and the avermectin–milbemycin hybrid.[9] Our earlier studies also furnished an efficient, stereoselective route to the northern-hemisphere fragment **6**.[8] Thus, the development of an approach

to the oxahydrindene subunit **5** that would be amenable to analogue preparation emerged as our primary objective.*



Scheme 1

The C(4) methyl group and C(3,4) unsaturation in **5** were envisioned to derive from ketone **7** (X=O) *via* standard alkylation and selenoxide elimination methods (Scheme 2). Introduction of the exocyclic trisubstituted olefin would then entail elaboration of furanone **8**; installation of the C(7) hydroxy

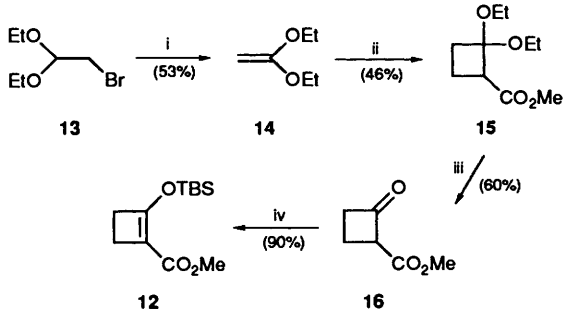


Scheme 2

would proceed as previously described.[5b,7f,q] This analysis sets the stage for the cornerstone of our synthetic design, an asymmetric [2 + 2]-photocycloaddition–cyclobutane fragmentation protocol.[11–13] Specifically, addition of the known[12,13] dihydrofuran chiral template (+)-**11** to cyclobutenoate **12** was expected to furnish the *cis-anti-cis* adduct **10**, whereupon cleavage of the central bond of the [2.2.0]bicyclohexane moiety would generate the requisite oxahydrindane skeleton in **9**.

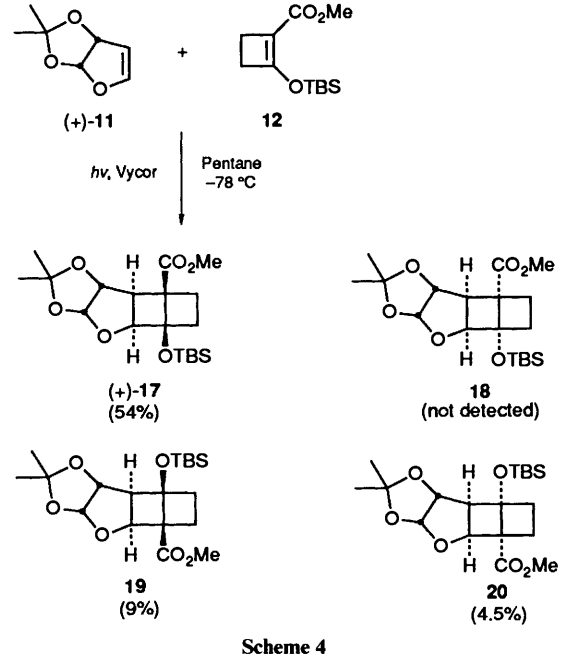
* The numbering system used throughout the Discussion section of this paper is that associated in the literature with the title compound; systematic names and numbering are used in the Experimental section.

[2 + 2]-*Photocycloaddition–Fragmentation: Cornerstone of the Synthetic Strategy.*—Efficient routes to both enantiomers of dihydrofuran acetonide **11** were previously developed in our laboratory.[12,13] The requisite cyclobutene **12** was readily prepared in four steps from bromo acetal **13** (Scheme 3). The latter was first converted into ketene acetal **14** *via* the procedure of McElvain.[14] Thermal [2 + 2]-cycloaddition of **14** with methyl acrylate[15] followed by hydrolysis of the resultant ketal **15** provided the known cyclobutanone **16**[15] (28% yield, two steps). Treatment with TBSOTf and 2,6-lutidine[16] then afforded cyclobutenoate **12** in 90% yield.



Scheme 3 *Reagents and conditions:* i, K°, Bu'OH; ii, CH_2CHCO_2Me, heat; iii, $HClO_4$, CH_2Cl_2, THF; iv, TBSOTf, 2,6-lutidine

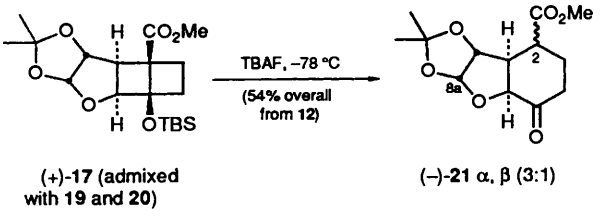
With ample quantities of (+)-**11** and **12** in hand, we began to explore the [2 + 2]-photocycloaddition. *Exo* addition to **11** could generate as many as four isomeric *cis*-fused photoadducts **17**–**20** (Scheme 4). Best results were obtained by irradiating a solution of cyclobutenoate **12** (0.03 M) and dihydrofuran (+)-**11** (5 equiv.) in pentane for 5 h at −78 °C with a medium-pressure Hanovia mercury lamp and Vycor filter. As expected,[17] the requisite *cis-anti-cis*, head-to-tail adduct (+)-**17** predominated (54% yield), accompanied by head-to-head isomers **19** and **20** (9 and 4.5%, respectively). Unreacted dihydrofuran **11** could be recovered in 40–60% yield. The selective formation of **17** reflects both the topology and polarization of **11**.



Scheme 4

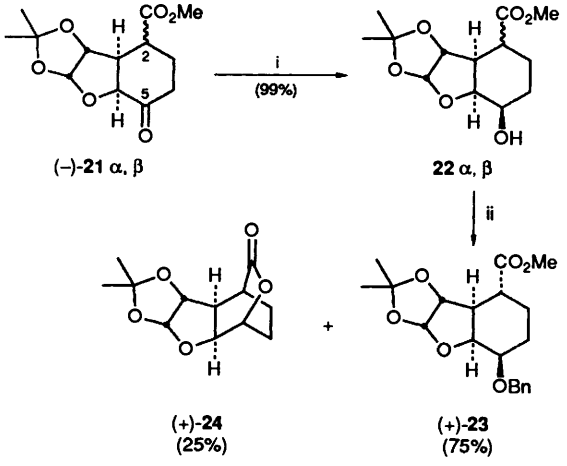
Fragmentation of the central bond of the bicyclohexane moiety in **17** was next envisioned to furnish **21**. In preparative experiments, treatment of the crude mixture of photoadducts with tetra-*N*-butylammonium fluoride at −78 °C effected both

desilylation and the desired fragmentation, affording (−)-**21** in 54% overall yield from **12** as a 3:1 mixture of α and β epimers (Scheme 5).* The cycloaddition–cyclobutane fragmentation protocol is related to the de Mayo fragmentation,[11] and apparently represents the first application of this tactic to the construction of a six-membered carbocyclic ring. Interestingly, isomeric keto esters derived from **19** and **20** were not detected.



Scheme 5

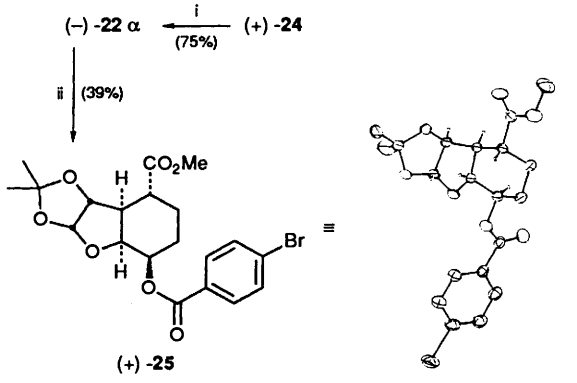
Further Elaboration of the Oxahydrindane Nucleus.—To accommodate the functionalization of the tetrahydrofuran ring, we elected to protect the C(5) ketone by conversion into a benzyl ether. To this end, reduction of **21**α,β [3:1 mixture of C(2) epimers] with $NaBH_4$ in MeOH–THF[18] provided the β alcohols **22**α,β exclusively in 99% yield (Scheme 6). Reaction



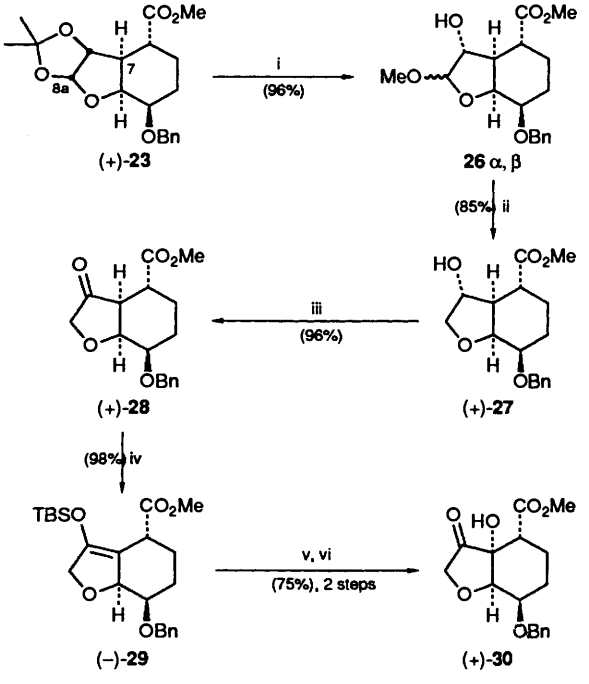
Scheme 6 *Reagents and conditions:* i, $NaBH_4$, MeOH, THF; ii, KH, BnBr, THF, 0 °C

with KH and benzyl bromide at 0 °C then furnished benzyl ether (+)-**23** (75% yield) and lactone (+)-**24** (25%). Whereas the *syn* hydroxy ester **22**β lactonized under these strongly basic conditions,[19] treatment of the resultant lactone **24** with K_2CO_3 in methanol furnished only the desired hydroxy ester (−)-**22**α in 75% yield (Scheme 7). The connectivity and relative stereochemistry of **22**α were confirmed by single-crystal X-ray analysis† of the derived *p*-bromobenzoate (−) **25**.

We next addressed the requisite deoxygenation at C(8a) and introduction of the C(7) tertiary hydroxy (Scheme 8). Methanolysis of acetonide **23** afforded a 3:1 mixture of hydroxy acetals **26**α,β in 96% yield, and reduction of the latter with a large excess of BF_3·Et_2O and Et_3SiH provided the desired methylene alcohol (+)-**27** (85%).[7j] The C(7) hydroxy was envisioned to derive from oxidation of an enol ether, as demonstrated by White[5b] in his synthesis of avermectin B_{1a}. Accordingly, furanone (+)-**28** was obtained in 96% yield from



Scheme 7 *Reagents:* i, K_2CO_3, MeOH; ii, *p*Br(C_6H_4)COCl, Et_3N



Scheme 8 *Reagents and Conditions:* i, MeOH, TsOH, heat; ii, EtSiH, BF_3·Et_2O; iii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; iv, TBSOTf, Et_3N, 2,6,-Lutidine, PhH, heat; v, *m*-CPBA, $NaHCO_3$, vi, TBAF

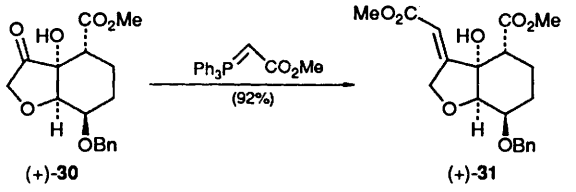
27 *via* the Swern procedure. Whereas **28** did not react with TMSOTf[16] and 2,6-lutidine, the use of Et_3N led to nearly quantitative generation of silyl enol ether (−)-**29**. Similar high regioselectivity had been observed by White.[5b] Rubottom oxidation[20] with *m*-CPBA followed by desilylation with TBAF then furnished the desired α-hydroxy ketone (−)-**30** (75% yield, two steps).

Installation of the exocyclic trisubstituted olefin at C(8) was then required to complete the elaboration of the furan ring. Whereas Crimmins[7i] and Williams[7n] successfully employed Wittig and Horner–Emmons reagents for this purpose, neither (triphenylphosphoranylidene)acetaldehyde[21] nor methylsiloxycarbonylmethanephosphonate [$Me_3SiO_2CCH_2P(O)(OEt)_2$][22] reacted satisfactorily with **30** under a variety of conditions. Exposure of **30** to methyl (triphenylphosphoranylidene)-acetate[23] did furnish (+)-**31** in 92% yield (Scheme 9). Unfortunately, this tactic also proved unproductive, as we could not effectively discriminate between the saturated and unsaturated esters.

As an alternative to direct olefination, we next explored the [1,3]-transposition of a tertiary allylic alcohol. To this end, vinylmagnesium bromide added to hydroxy ketone **30** exclusively from the convex face, affording (−)-**32** in 72% yield

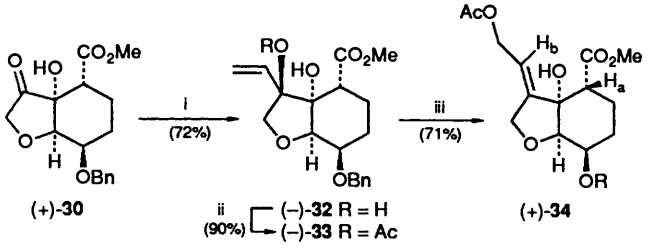
* Equilibration of the **22** α,β mixture with K_2CO_3 in MeOH for 2 d furnished the pure α epimer in 70% yield. Nonetheless, it proved more expedient to employ the 3:1 mixture in preparative experiments.

† For complete experimental details, see ref. 10.



Scheme 9

(Scheme 10). We first attempted an oxidative transposition,[24] using PCC, PDC or CrO_3 in conjunction with various solid supports and solvents. This approach provided none of the desired α,β-unsaturated aldehyde; most of the starting material generally was recovered unchanged. We then investigated the



Scheme 10 *Reagents and conditions:* i, $CH_2CHMgBr$, THF; ii, Ac_2O, Pry, 4-pyrrolidinopyridine, heat; iii, $(MeCN)_2PdCl_2$, benzoquinone

Pd(II)-catalysed [3,3]-sigmatropic rearrangement[25] of the corresponding tertiary allylic acetate (−)-**33**. The requisite acetate was prepared from alcohol **32** under forcing conditions (*i.e.*, acetic anhydride, pyridine, DMAP, 50 °C, 24 h; 90% yield). The desired allylic transposition occurred readily upon exposure of **33** to $Cl_2Pd(CH_3CN)_2$ and benzoquinone in CH_3CN, selectively furnishing allylic acetate (+)-**34** in 71% yield; the isomeric *Z*-isomer was not detected. Interestingly, the reaction failed in the absence of benzoquinone.[26,*] The *Z*-configuration derived from observation of a 12% NOE between Ha and Hb. Single-crystal X-ray analysis of **33** suggests that the stereoselectivity of the rearrangement may reflect the orientational preference of the vinyl group (Fig. 1).

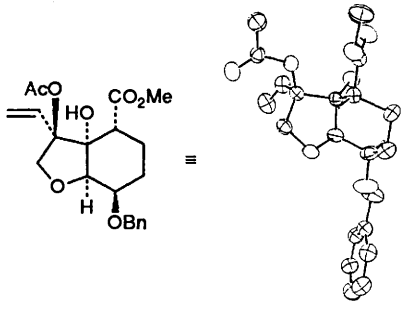
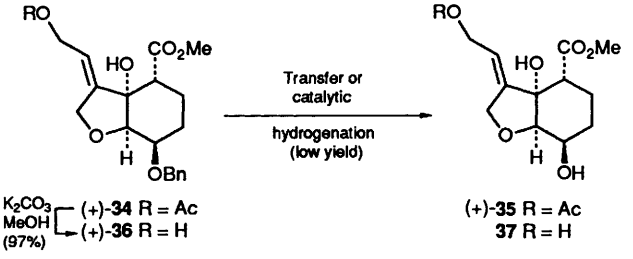


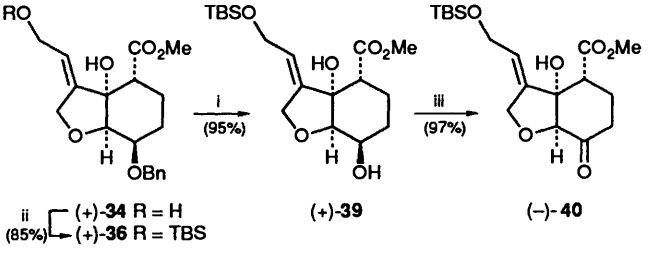
Fig. 1 X-ray crystal structure of allylic acetate (−)-**33**

Debenzylation of **34** would then provide **35**, the southern hemisphere required for 3,4-dihydro, 4-normethyl milbemycin and avermectin analogues. Not unexpectedly, this process was complicated by the lability of the allylic acetate moiety. In a related system, Jung cleaved a benzyl ether in the presence of a C(3,4) olefin *via* transfer hydrogenation.[7k] Exposure of **34** to the published conditions [18% HCO_2H, 10% Pd(C), MeOH] furnished (+)-**35** in low yield (Scheme 11), accompanied by products derived from reduction of the C(8,9) olefin and hydrogenolysis of the acetate. Other transfer hydrogenation protocols [*i.e.*, 18% HCO_2H, 10% Pd(C), EtOH; 1,4-cyclohexadiene, 10% Pd(C), EtOH; HCO_2NH_4, 10% Pd(C), MeOH] and catalytic hydrogenation [10% Pd(C), H_2, MeOH] were similarly unsuccessful. In an effort to circumvent hydrogenolysis, allylic acetate **34** was deesterified (K_2CO_3, MeOH), affording allylic alcohol (+)-**36**. As before, however, neither transfer nor catalytic hydrogenation of **36** provided synthetically useful quantities of debenzylated triol **37** (Scheme 11).



Scheme 11

Dissolving metal reductions are often useful for removal of benzyl ethers in the presence of isolated olefins. Because allylic acetates likewise undergo reductive cleavage, **34** was not a suitable substrate. We therefore converted the corresponding allylic alcohol **36** into the TBS derivative (+)-**38** (85% yield) (Scheme 12). Exposure to Na^0 in $NH_3(l)$[27] for 15 seconds then provided the desired alcohol (+)-**39** in 97% yield, whereas longer reaction times resulted in extensive decomposition. Finally, oxidation of **39** with tetrapropylammonium perruthenate[28] smoothly furnished ketone (−)-**40** (97%).



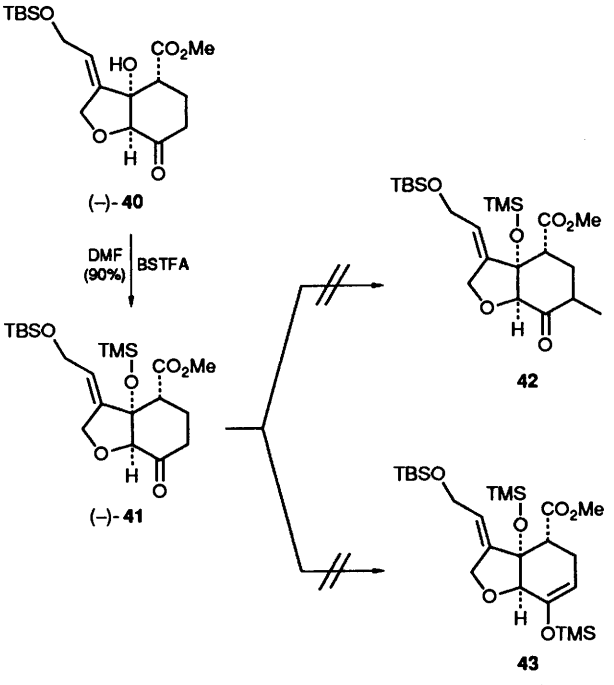
Scheme 12 *Reagents:* i, Na, NH_3; ii, TBSOTf, 2,6-lutidine; iii, TPAP, NMO

At this juncture, introduction of the C(4) methyl group and C(3,4) unsaturation followed by reduction of the C(5) ketone would complete the synthesis of oxahydrindene **5**, the southern hemisphere building block for milbemycin α_1. Before exploring the requisite enolate chemistry, we thought it prudent to protect the C(7) tertiary hydroxyl, thereby preventing both etherification and base-mediated retroaldol fragmentations. To this end, **40** was readily converted into the TMS (trimethylsilyl) derivative (−)-**41** by treatment with *N*,*N*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) (Scheme 13).[28]

Unfortunately, numerous attempts to prepare **42** *via* C(4) methylation of **41** were unsuccessful. Under a wide range of conditions, treatment of **41** with $KN(TMS)_2$, KH or $LiN(TMS)_2$ as base and methyl iodide as electrophile furnished only recovered starting material. Silyl enol ether **43** proved similarly elusive.

These results, juxtaposed with our success in executing a more economic synthetic strategy,[30] led us to abandon the approach described here. Nonetheless, it is important to recognize that these studies: (A) demonstrated the viability of the cyclobutene photoannulation-fragmentation tactic for construction of substituted cyclohexanones; (B) generated effective methodology for stereocontrolled introduction of the

* We thank Professor Carl R. Johnson, Wayne State University, for pointing out the utility of benzophenone as a palladium maintenance reagent.



Scheme 13

exocyclic trisubstituted olefin; and (C) furnished southern hemisphere analogue (+)-**39** which, upon incorporation into the milbemycin–avermectin framework, will permit us to elucidate structure–activity relationships involving the C(4) methyl and C(3,4) olefin functionalities.

Experimental

General.—Reactions were carried out in flame-dried glassware under an argon atmosphere, except where otherwise noted. All solvents were reagent grade. Ether and THF were distilled from sodium and benzophenone. Acetonitrile and methylene chloride were distilled from calcium hydride. 2,6-Lutidine, triethylamine and pyridine were distilled from KOH and stored over KOH. Acetone was dried over potassium carbonate prior to distillation. Analytical thin layer chromatography was performed with E. Merck 250-μm precoated silica gel plates with fluorescent indicator. Preparative thin layer chromatography was carried out with E. Merck 500-μm precoated silica gel plates with fluorescent indicator. Flash chromatography [29] was performed with distilled solvents and E. Merck 230–400-mesh silica gel. High pressure liquid chromatography (HPLC) was performed with a Waters analytical chromatograph equipped with a model 6000A solvent delivery system, U6K injector, and R400 refractive index detector, and a 46- × 25-cm column packed with 5-μm Ultrasphere-Si. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform with a Bruker AM250 (250 and 62.9 MHz) or AM500 (500 and 125 MHz) spectrometer; chemical shifts are reported in δ values relative to tetramethylsilane. J value are given in Hz. IR spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. M.p.s were obtained by using either a Thomas-Hoover apparatus or a Bristoline hot-stage microscope and are corrected. Microanalyses were performed by Robertson Labs, Madison, NJ. High resolution mass spectra were measured by the University of Pennsylvania Mass Spectrometry Service Center on a Hitachi-Perkin-Elmer RMH-2 or a VG 70-70 Micromass spectrometer inferfaced with a Kratos DS-50-s data system.

Methyl 2-tert-*Butyldimethylsilyloxycyclobut*-1-*ene*-1-*carboxylate* **12**.—At room temp. a solution of methyl 2,2-diethoxycyclobutane-1-carboxylate (10.0 g, 49.5 mmol) in methylene dichloride (490 cm^3) and tetrahydrofuran (THF) (15 cm^3) was treated dropwise with 10% perchloric acid (19 cm^3). The reaction was stirred for 3.5 h and then quenched with saturated aqueous $NaHCO_3$ (100 cm^3). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Without purification, the resultant cyclobutanone **16** was dissolved in dry methylene dichloride (50 cm^3). The solution was cooled to 0 °C and 2,6-lutidine (11.6 cm^3, 99.0 mmol) was added slowly, followed by dropwise introduction of *tert*-butyldimethylsilyl triflate (17.2 cm^3, 74.2 mmol). After 30 min the reaction mixture was poured into water and extracted with methylene dichloride, and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (ether–hexane, 1:50) afforded the title compound **12** (3.59 g, 30% yield) as a colourless oil: λ_{max}(pentane)/nm 220.8 (ε 2.97 × 10^4); ν($CHCl_3$)/cm^{-1} 2920s, 2830s, 1695s, 1673br, 1438s, 1385s, 1251br, 1115s, 1050s, 970w, 900w and 860br; δ_H(500 MHz; $CDCl_3$) 0.23 (s, 6 H), 0.96 (s, 9 H), 2.26 (dd, J 3.31, 3.36, 2 H), 2.52 (dd, J 3.31, 3.36, 2 H) and 3.68 (s, 3 H); δ_C(125.8 MHz; $CDCl_3$) 158.18, 107.78, 77.18, 52.45, 50.52, 25.29, 19.59, 18.08 and −4.29; high resolution mass spectrum (Cl, NH_3) m/z 243.1470 [(M + H)$^+$; calc. for $C_{12}H_{23}O_3Si$: M, 243.1430] Found: C, 59.58; H, 9.26. Calc. for $C_{12}H_{22}O_3Si$: C, 59.47; H, 9.15%).

Photoadducts (+)-**17**, **19** *and* **20**.—Cyclobutene **12** (2.5 g, 10.3 mmol) and dihydrofuran **11** (7.0 g, 49.3 mmol) were dissolved in Omni-Solv pentane (330 cm^3; 0.03 mol dm^{-3}). The solution was degassed with argon for 30 min, cooled to −78 °C, and then irradiated for 5 h with a 450 W Hanovia medium-pressure mercury lamp in a quartz immersion well with Vycor filter. The solution was then concentrated under reduced pressure at 25 °C. For product characterization, repeated flash chromatography (pentane–diethyl ether, 5:1; hexane–diethyl ether–acetone, 10:1:1) afforded methyl 5a-*tert*-butyldimethylsilyloxy-2,2-dimethyl 3a,3b,3c,4,5,5a,5b,6a-octahydrocyclobuta[1″,2″:3′,4′]cyclobuta[1′,2′:4,5]furo[2,3-*d*][1,3]-dioxole-3c-carboxylate **17** (2.13 g, 54% yield) as a colourless oil: R_f 0.41 (hexane–diethyl ether–acetone, 10:1:1); $[\alpha]_D^{20}$ + 10.7 (*c* 0.47, $CHCl_3$); ν($CHCl_3$)/cm^{-1} 2960s, 2940s, 2860s, 1725s, 1465w, 1445w, 1380w, 1370w, 1285s, 1250br, 1160s, 1070s, 980s, 910w, 870s and 840s; δ_H(250 MHz; $CDCl_3$) 0.08 (s, 6 H), 0.84 (s, 9 H), 1.33 (s, 3 H), 1.49 (s, 3 H), 1.70–1.80 (m, 1 H), 2.12–2.36 (m, 2 H), 2.66–2.78 (m, 1 H), 2.93 (d, J 4.57, 1 H), 3.67 (s, 3 H), 4.77 (d, J 4.58, 1 H), 5.06 (d, J 3.22, 1 H) and 6.02 (d, J 3.24, 1 H); δ_C(69.5 MHz; $CDCl_3$) 113.14, 108.58, 85.49, 83.05, 80.11, 77.20, 51.32, 49.58, 30.62, 28.12, 27.44, 27.06, 25.65, 24.47, 17.91, 15.33 and −3.41; high resolution mass spectrum (Cl, NH_3) m/z 385.2085 [(M + H)$^+$; calc. for $C_{19}H_{32}O_6Si$: M, 385.2046].

Following separation of compound **17** *via* initial chromatography with pentane–ether eluent, as described above, additional flash chromatography (pentane–diethyl ether, 5:1; hexane–acetone, 3:1; pentane–diethyl ether, 4:1) furnished an inseparable 1:2 mixture of methyl 3c-*tert*-butyldimethylsilyloxy-2,2-dimethyl-3a,3b,3c,4,5,5a,5b,6a-octahydrocyclobuta[1″,2″:3′,4′]-cyclobuta[1′,2′:4,5]furo[2,3-*d*][1,3]dioxole-5a-carboxylates **19** and **20** (0.53 g, 13.5% yield) as a colourless oil: R_f 0.17 (pentane–diethyl ether, 4:1); $[\alpha]_D^{20}$ +31.6 (*c* 0.52, $CHCl_3$); ν($CHCl_3$)/cm^{-1} 2980s, 2960s, 2860w, 1730s, 1460br, 1430w, 1385s, 1375s, 1250br, 1160s, 1080s, 1040w, 970s, 910s and 840s; δ_H(250 MHz; $CDCl_3$) 0.37 (s, 6 H), 0.51 (s, 6 H), 0.83 (s, 9 H), 0.84 (s, 9 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 150–1.76 (m, 2 H), 2.10–2.50 (m, 6 H), 3.24 (d, J 4.27, 1 H), 3.61 (d, J 0.74, 1 H),

3.63 (s, 3 H), 3.64 (s, 3 H), 4.64 (d, *J* 4.41, 1 H), 4.65 (d, *J* 4.42, 1 H), 4.80 (d, *J* 3.47, 1 H), 4.92 (d, *J* 3.82, 1 H), 6.01 (d, *J* 3.42, 1 H) and 6.18 (d, *J* 3.73, 1 H); δ_C(69.5 MHz; $CDCl_3$) 170.33, 112.90, 109.02, 108.49, 84.46, 84.37, 82.14, 81.85, 80.88, 77.52, 76.50, 61.03, 55.67, 51.27, 34.09, 28.45, 28.30, 27.91, 27.77, 27.26, 26.50, 25.85, 25.66, 22.65, 20.10, 18.04, −2.80, −3.20 and −3.54; high resolution mass spectrum (Cl, NH_3) *m/z* 385.2058 $[(M + H)^+$; calc. for $C_{19}H_{32}O_6Si$; *M*, 385.2046].

Methyl 2,2-Dimethyl-7-oxo-3a,3b,4,5,6,7,7a,8a-octahydrodioxolo[3,4-b][1]benzofuran-4-carboxylates (−)-**21α** *and* (−)-**21β**.—The crude mixture containing compounds **17**, **19** and **20** (2.66 g, 6.93 mmol) was dissolved in THF (250 cm^3; 0.04 mol dm^{-3}), the solution was cooled to −78 °C, and tetrabutylammonium fluoride (1.0 mol dm^{-3} in THF; 10.7 cm^3) was added dropwise. After 30 min, the reaction was treated with acetic acid (0.6 cm^3) in MeOH (2.5 cm^3), warmed to 0 °C, and neutralized with solid $NaHCO_3$. The mixture was filtered through a Celite plug, the filtrate concentrated under reduced pressure and the products purified by flash chromatography. Following initial elution of 2,2-dimethyl-3a,6a-dihydrofuro[2,3-*d*]dioxole **11** (pentane–ether, 4:1), use of a more polar eluent (hexane–acetone, 3:1) afforded a 3:1 mixture of the title compounds **21α** and **21β** (1.01 g, 54% yield overall from **12**). For characterization the epimers were separated by analytical HPLC (hexanes:ethyl acetate, 3:1). **21α**: less polar epimer; oil; $[\alpha]_D^{20}$ −10.2 (*c* 1.41, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3000s, 2975s, 1740br, 1445w, 1385s, 1260br, 1170br, 1080w, 1020s and 920s; δ_H(500 MHz; $CDCl_3$) 1.30 (s, 3 H), 1.49 (s, 3 H), 1.86 (dq, *J* 3.75, 12.66, 1 H), 2.23–2.46 (m, 3 H), 2.69 (dt, *J* 5.41, 14.12, 1 H), 2.88 (dd, *J* 4.08, 4.06, 1 H), 3.75 (s, 3 H), 4.26 (d, *J* 3.94, 1 H), 4.60 (d, *J* 3.42, 1 H) and 5.95 (d, *J* 3.44, 1 H); δ_C(125.8 MHz; $CDCl_3$) 204.96, 173.31, 112.21, 105.33, 83.85, 79.13, 52.41, 50.54, 40.12, 36.35, 28.52, 26.43 and 26.11; high resolution mass spectrum (Cl, NH_3) *m/z* 271.1183 $[(M + H)^+$; calc. for $C_{13}H_{19}O_6$: *M*, 271.1187].

21β: more polar epimer; oil; $[\alpha]_D^{20}$ −8.7 (*c* 0.30, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3000s, 2960s, 1740br, 1440w, 1380s, 1240br, 1170s, 1075br and 1030w; δ_H(500 MHz; $CDCl_3$) 1.33 (s, 3 H), 1.51 (s, 3 H), 2.07–2.12 (m, 2 H), 2.28–2.35 (m, 1 H), 2.67 (dt, *J* 4.92, 10.25, 1 H), 2.85 (q, *J* 6.76, 1 H), 3.15 (dt, *J* 1.61, 6.73, 1 H), 3.75 (s, 3 H), 4.54 (d, *J* 7.0, 1 H), 4.62 (q, *J* 2.27, 1 H) and 5.89 (d, *J* 3.95, 1 H); δ_C(125.8 MHz; $CDCl_3$) 206.88, 172.58, 112.93, 106.20, 82.95, 80.99, 52.23, 49.86, 39.85, 35.98, 27.41, 26.93 and 23.15; high resolution mass spectrum (Cl, NH_3) *m/z* 271.1184 $[(M + H)^+$; calc. for $C_{13}H_{19}O_6$: *M* 271.1187] (Found: C, 57.6; H, 7.04. Calc. for $C_{13}H_{18}O_6$: C, 57.75; H, 6.71%).

Methyl 7-Hydroxy-2,2-dimethyl-3a,3b,4,5,6,7,7a,8a-octahydrodioxolo[4,5-b][1]benzofuran-4-carboxylates **22α,β**.—A solution of ketones **21α,β** (1.02 g, 3.78 mmol) in methanol–THF (10:1, 40 cm^3) was cooled to −20 °C and sodium borohydride (135 mg, 4 equiv.) was added in one portion. After 30 min the reaction was quenched with water (0.25 cm^3). Concentration under reduced pressure and flash chromatography (gradient elution, hexane–acetone, 3:1 ⟶ 2:1) provided a mixture of the title compounds **22α** and **22β** (1.01 g, 99% yield) as a white solid: m.p. 115.5 °C; $[\alpha]_D^{20}$ −172.5 (*c* 0.52, MeOH); $\nu(CHCl_3)/cm^{-1}$ 3580s, 3000s, 2860s, 1740s, 1455s, 1440s, 1390s, 1380s, 1270br, 1175w, 1080s and 1020br; δ_H(500 MHz; $CDCl_3$) 1.30 (s, 3 H), 1.52 (s, 3 H), 1.86–2.09 (m, 5 H), 2.50 (dd, *J* 3.57, 11.49, 1 H), 3.72 (s, 3 H), 4.44 (t, *J* 3.47, 1 H), 4.50 (d, *J* 3.60, 1 H) and 5.85 (d, *J* 3.58, 1 H); δ_C(125.8 MHz; $CDCl_3$) 174.50, 111.53, 104.19, 83.90, 77.08, 69.05, 52.14, 46.44, 40.29, 28.19, 26.62, 26.35 and 26.03; high resolution mass spectrum (Cl, NH_3) *m/z* 290.1563 $[(M + NH_4)^+$; calc. for $C_{13}H_{24}NO_6$: *M*, 290.1604].

Methyl 7-Benzyloxy-2,2-dimethyl-3a,3b,4,5,6,7,7a,8a-octahydrodioxolo[4,5-b][1]benzofuran-4-carboxylate (+)-**23** *and* 2,2-*Dimethyl-3a,3b,4,5,6,7,7a,8a-octahydrodioxolo[4,5-b][1]benzocuran-4,7-carbolactone* (+)-**24**.—A suspension of potassium hydride (35% dispersion, 1.0 g, 8.86 mmol) in THF (45 cm^3) was cooled to 0 °C and a cold (0 °C) solution of alcohols **22α,β** (1.2 g, 4.43 mmol) and benzyl bromide (3 cm^3, 25.2 mmol) in THF (30 cm^3) was added dropwise *via* a cannula. After 1 h the reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted once with ethyl acetate and twice with CH_2Cl_2, and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 6:1) afforded the title compound **23** (1.22 g, 75% yield) as a yellow oil and the title compound **24** (279 mg, 25% yield) as a solid. Compound **23**: R_f 0.27 (hexane–acetone, 3:1); $[\alpha]_D^{20}$ +15.4 (*c* 0.41, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3010w, 3000s, 2960s, 2870w, 1730s, 1600w, 1450s, 1435w, 1380w, 1365s, 1260br, 1160br, 1090s, 1080s and 1010br; δ_H(500 MHz; $CDCl_3$) 1.30 (s, 3 H), 1.41 (qd, *J* 2.93, 13.22, 1 H), 1.52 (s, 3 H), 1.73 (dd, *J* 1.90, 3.26, 1 H), 1.86–1.90 (m, 1 H), 1.96–2.07 (m, 2 H), 2.42 (dd, *J* 3.51, 11.70, 1 H), 3.52 (dt, *J* 4.32, 7.96, 1 H), 3.70 (s, 3 H), 4.44 (d, *J* 3.64, 1 H), 4.50 (t, *J* 3.29, 1 H), 4.66 (d, *J* 12.32, 2 H), 5.89 (d, *J* 3.61, 1 H) and 7.27–7.38 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 174.58, 128.36, 128.30, 127.77, 127.60, 111.17, 104.67, 83.27, 74.81, 74.47, 70.15, 52.08, 46.70, 40.53, 26.72, 26.44, 26.04 and 24.83; high resolution mass spectrum (Cl, NH_3) *m/z* 380.2038 $[(M + NH_4)^+$; calc. for $C_{20}H_{30}NO_6$: *M*, 380.2073] (Found: C, 65.96; H, 7.02. Calc. for $C_{20}H_{26}O_6$: C, 66.26; H, 7.17%).

Compound **24**: m.p. 176.5–177.5 °C; R_f 0.36 (hexane–acetone, 3:1); $[\alpha]_D^{18}$ +2.6 (*c* 0.62, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 2990br, 1750s, 1370s, 1225br, 1160s, 1070s and 1020s; δ_H(500 MHz; $CDCl_3$) 1.34 (s, 3 H), 1.51 (s, 3 H), 1.59–1.67 (m, 1 H), 1.75–1.81 (m, 1 H), 1.87–1.93 (m, 1 H), 2.02–2.09 (m, 1 H), 2.75 (dd, *J* 2.30, 8.14, 1 H), 2.81 (q, *J* 2.71, 1 H), 4.56 (d, *J* 3.68, 1 H), 4.58 (dd, *J* 2.21, 3.68, 1 H), 4.71 (dd, *J* 0.98, 1.95, 1 H) and 5.82 (d, *J* 3.70, 1 H); δ_C(125.8 MHz; $CDCl_3$) 173.60, 128.38, 113.04, 106.07, 84.50, 78.62, 48.33, 38.76, 27.82, 27.02, 21.78 and 20.70; high resolution mass spectrum (Cl, NH_3) *m/z* 258.1375 $[(M + NH_4)^+$; calc. for $C_{12}H_{20}NO_5$: *M*, 258.1342] (Found: C, 59.77; H, 6.64. Calc. for $C_{12}H_{14}O_6$: C, 59.97; H, 6.66%).

Methyl 7-Hydroxy-2,2-dimethyl-3a,3b,4,5,6,7,7a,8a-octahydrodioxolo[4,5-b][1]benzofuran-4-carboxylate (−)-**22α**.—A suspension of lactone **24** (248 mg, 1.03 mmol) and K_2CO_3 (50 mg, 0.36 mmol) in dry MeOH (3.5 cm^3) was stirred at room temp. for 18 h. The mixture was then filtered through a Celite plug (methanol eluent) and the filtrate concentrated under reduced pressure. Flash chromatography (hexane–acetone, 3:1) provided the title compound **22α** (73 mg, 75% yield) as a white solid: m.p. 114–115 °C; $[\alpha]_D^{20}$ −176.2 (*c* 0.50, MeOH); $\nu(CHCl_3)/cm^{-1}$ 3580s, 3000s, 2860s, 1740s, 1455s, 1440s, 1390s, 1380s, 1270br, 1175w, 1080s and 1020br; δ_H(500 MHz; $CDCl_3$) 1.30 (s, 3 H), 1.52 (s, 3 H), 1.86–2.09 (m, 5 H), 2.50 (dd, *J* 3.57, 11.49, 1 H), 3.72 (s, 4 H), 4.42 (t, *J* 2.75, 1 H), 4.50 (d, *J* 3.60, 1 H) and 5.85 (d, *J* 3.58, 1 H); δ_C(125.8 MHz; $CDCl_3$) 174.50, 111.53, 104.19, 83.90, 77.08, 69.05, 52.14, 46.44, 40.29, 29.18, 26.62, 26.35 and 26.03; high resolution mass spectrum (Cl, NH_3) *m/z* 290.1563 $[(M + NH_4)^+$; calc. for $C_{13}H_{24}NO_6$: *M*, 290.1599].

4-Methoxycarbonyl-2,2-dimethyl-3a,3b,4,5,6,7,7a,8a-octahydrodioxolo[4,5,b][1]benzofuran-7-yl 4-Bromobenzoate (−)-**25**.—A solution of alcohol **22α** (14.4 mg, 0.05 mmol) and 4-bromobenzoyl chloride (15.1 mg, 0.06 mmol) in CH_2Cl_2 (0.05 cm^3) was cooled to 0 °C and triethylamine (8.9 mm^3, 0.06 mmol) was added dropwise. The reaction was then warmed to room temp. and stirred for 18 h. The resultant mixture was diluted with water and extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated under

reduced pressure. Flash chromatography (pentane–ether, 1:1) followed by recrystallization (hexane–ethyl acetate–ethanol) afforded the title compound **25** (9 mg, 39% yield) as a white crystalline solid: m.p. 103–105 °C; $[\alpha]_D^{25}$ −23.8 (*c* 0.32, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3015w, 2995w, 2960s, 1725s, 1595s, 1440w, 1435w, 1385w, 1375w, 1275s, 1175w, 1105s and 1020s; δ_H(500 MHz; $CDCl_3$) 1.27 (s, 3 H), 1.46 (s, 3 H), 1.53–1.63 (m, 1 H), 1.81–1.93 (m, 2 H), 2.02–2.10 (m, 2 H), 2.58 (dd, *J* 3.37, 11.47, 1 H), 3.71 (s, 3 H), 4.47 (d, *J* 3.63, 1 H), 4.50 (t, *J* 3.27, 1 H), 5.14 (dt. *J* 3.36, 6.79, 1 H), 5.89 (d, *J* 3.59, 1 H), 7.54 (d, *J* 8.44, 2 H) and 7.91 (d, *J* 8.51, 2 H); δ_C(125.8 MHz; $CDCl_3$) 174.17, 165.25, 131.64, 131.47, 128.94, 128.24, 114.47, 104.82, 83.25, 74.74, 71.68, 52.23, 46.95, 40.19, 26.58, 26.31, 25.99, 24.33; high resolution mass spectrum (Cl, NH_3) *m/z* 455.0727 $[(M + H)^+$; calc. for $C_{20}H_{24}BrO_7$: *M*, 455.0705].

X Ray Structure Determination of Compound (+)-**25**.—Compound (+)-**25**, $C_{20}H_{23}BrO_7$, crystallizes in the triclinic space group *P*1, with $a = 9.855(3)$, $b = 10.439(2)$, $c = 5.345(1)$ Å, $\alpha = 98.60(2)$, $\delta = 94.92(2)$, $\gamma = 109.93(3)°$, $V = 505.6(5)$ Å^3, $Z = 1$ and $d_{calc} = 1.495$ g/cm^3. The cell constants were determined from a least squares fit of the setting angles for 25 accurately centred reflections. X-ray intensity data were collected on an Enraf-Nonius CAD4 diffractometer employing graphite-monochromated Mo–K_α radiation ($\lambda = 0.710\,73$ Å) and using the ω–2θ scan technique. A total of 5110 reflections were measured over the ranges: $4 \leq 2\theta \leq 55°$, $-12 \leq h \leq 12$, $13 \leq k \leq 13$, $-6 \leq l \leq 6$. Three standard reflections measured every 3500 s of X-ray exposure showed no intensity decay over the course of data collection.

The intensity data were corrected for Lorentz and polarization effects but not for absorption. Of the reflections measured a total of 3149 unique reflections with $F^2 > 3\sigma(F^2)$ were used during subsequent structure refinement.

The structure was solved by standard heavy atom Patterson techniques followed by weighted Fourier syntheses. Refinement was by full-matrix least squares techniques based on *F* to minimize the quantity $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/\sigma^2(F)$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as constant contributions to the structure factors and were not refined. Refinement converged to $R_1 = 0.039$ and $R_2 = 0.049$.

Methyl 7-Benzyloxy-3-hydroxy-2-methoxy-2,3,3a,4,5,6,7,7a-octahydro-1-benzofuran-4-carboxylates (+)-**26**α *and* (−)-**26**β.—A solution of acetonide **23** (686 mg, 1.89 mmol) and toluene-*p*-sulfonic acid monohydrate (107 mg, 0.56 mmol) in anhydrous MeOH (38 cm^3) was heated at reflux for 1.5 h. The mixture was then cooled to room temp. and concentrated under reduced pressure. Flash chromatography (hexane–ethyl acetate, 2:1 → 1:1) afforded the title compounds **26**α (127 mg, 20% yield) and **26**β (483 mg, 76% yield) as oils. Compound **26**α: R_f 0.43 (hexane–acetone, 2:1); $[\alpha]_D^{26}$ +78.4 (*c* 0.62, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3590w, 3530br, 3000w, 2950s, 2940w, 1725s, 1445w, 1435w, 1360w, 1260w, 1190w, 1170w, 1090s and 1015s; δ_H(500 MHz; $CDCl_3$) 1.46–1.59 (m, 1, H), 1.72–1.76 (q, *J* 3.88, 2 H), 1.95–2.00 (dq, *J* 4.46, 13.77, 1 H), 2.34–2.39 (dt, *J* 4.12, 9.72, 1 H), 2.41–2.44 (m, 1 H), 2.92 (d, *J* 4.85, 1 H), 3.54 (s, 3 H), 3.55–3.59 (m, 1 H), 3.69 (s, 3 H), 4.17 (q, *J* 4.43, 1 H), 4.49 (t, *J* 3.82, 1 H), 4.63 (d, *J* 12.13, 2 H), 5.07 (d, *J* 4.46, 1 H) and 7.27–7.35 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 175.19, 137.52, 128.34, 127.52, 127.48, 102.57, 75.07, 74.97, 74.70, 70.75, 56.27, 51.99, 47.52, 40.68, 24.46 and 24.06; high resolution mass spectrum (Cl, NH_3) *m/z* 354.1941 $[(M + NH_4)^+$; calc. for $C_{18}H_{28}NO_6$: *M*, 354.1917] (Found: C, 64.33; H, 7.05. Calc. for $C_{18}H_{24}O_6$: C, 64.25; H, 7.13%).

Compound **26**β: R_f 0.39 (hexane–acetone, 2:1); $[\alpha]_D^{26}$ −32.4 (*c* 0.31, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3500w, 3460br, 2995s, 2950s, 1725s, 1600w, 1450s, 1430s, 1370br, 1250br, 1100s and 1020s; δ_H(500 MHz; $CDCl_3$) 1.26–1.35 (qd, *J* 3.14, 13.04, 1 H), 1.71–1.79 (qd, *J* 3.11, 12.68, 1 H), 1.82–1.86 (m, 1 H), 2.01–2.06 (m, 1 H), 2.13 (s, 1 H), 2.24 (dd, *J* 4.24, 11.26, 1 H), 2.76 (td, *J* 4.27, 11.80, 1 H), 3.44 (s, 3 H), 3.47 (q, *J* 3.68, 1 H), 3.67 (s, 3 H), 4.03 (s, 1 H), 4.60 (t, *J* 3.70, 1 H), 4.67 (s, 2 H), 4.88 (s, 1 H) and 7.26–7.38 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 175.59, 138.45, 128.26, 128.31, 127.83, 127.76, 127.63, 127.59, 111.06, 80.14, 76.89, 75.57, 70.17, 56.04, 51.92, 47.37, 39.25, 26.62 and 24.32; high resolution mass spectrum (Cl, NH_3) *m/z* 354.1900 $[(M + NH_4)^+$; calc. for $C_{18}H_{28}NO_6$: *M*, 354.1917] (Found: C, 65.97; H, 7.07. Calc. for $C_{18}H_{24}O_6$: C, 64.25; H, 7.13%).

Methyl 7-Benzyloxy-3-hydroxy-2,3,3a,4,5,6,7,7a-octahydro-1-benzofuran-4-carboxylate (+)-**27**.—A solution of acetals **26**α,β (827 mg, 2.45 mmol) and triethylsilane (5.8 cm^3, 36.8 mmol) in CH_2Cl_2 (50 cm^3) was cooled to 0 °C and boron trifluoride–diethyl ether (2.4 cm^3, 19.6 mmol) was added dropwise. The reaction was then warmed to room temp., stirred for 8 h, neutralized with solid $NaHCO_3$, diluted with water, and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 4:1) furnished the title compound **27** (668 mg, 89% yield) as a solid, m.p. 66.0 °C; $[\alpha]_D^{20}$ +4.3 (*c* 0.21, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3630s, 3010s, 2980br, 2960s, 2880s, 1730s, 1440s, 1430s, 1260w, 1160w, 1080br and 1030w; δ_H(500 MHz; $CDCl_3$) 1.38 (qd, *J* 3.16, 9.85, 1 H), 1.72 (qd, *J* 3.21, 12.87, 1 H), 1.84–1.88 (m, 1 H), 1.92 (s, 1 H), 1.97–2.08 (m, 1 H), 2.07 (dd, *J* 3.85, 12.20, 1 H), 2.29 (dd, *J* 3.75, 11.29, 1 H), 3.54 (dt, *J* 3.35, 4.43, 1 H), 3.69 (s, 3 H), 3.75 (dd, *J* 1.12, 10.23, 1 H), 4.26 (d, *J* 7.80, 1 H), 4.28 (t, *J* 5.14, 1 H), 4.39 (t, *J* 3.46, 1 H), 4.66 (d, *J* 12.37, 2 H) and 7.26–7.37 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 175.31, 138.43, 128.35, 127.73, 127.56, 75.74, 75.51, 75.34, 74.61, 70.18, 52.00, 50.16, 40.87, 26.63 and 24.76; high resolution mass spectrum (Cl, NH_3) *m/z* 324.1787 $[(M + NH_4)^+$; calc. for $C_{17}H_{26}NO_5$: *M*, 324.1811] (Found: C, 66.63; H, 7.18. Calc. for $C_{17}H_{22}O_5$: C, 66.58; H, 6.82%).

Methyl 7-Benzyloxy-3-oxo-2,3,3a,4,5,6,7,7a-octahydro-1-benzofuran-4-carboxylate (+)-**28**.—A solution of oxalyl chloride (0.159 cm^3, 1.83 mmol) in CH_2Cl_2 (27 cm^3) was cooled to −78 °C and a solution of DMSO (0.221 cm^3, 3.1 mmol) in CH_2Cl_2 (4 cm^3) was added dropwise. After 8 min a solution of alcohol **27** (435 mg, 1.41 mmol) in CH_2Cl_2 (7 cm^3) was introduced into the reaction mixture dropwise. The reaction mixture was stirred for 25 min, treated with triethylamine (0.884 cm^3, 6.34 mmol) in one portion and then warmed to room temp. The mixture was diluted with water and extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 4:1) gave the title compound **28** (411 mg, 96% yield) as an oil: $[\alpha]_D^{23}$ ±55.0 (*c* 0.48, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3020s, 2980s, 2940s, 1770br, 1730br, 1610w, 1460s, 1440w, 1365s, 1300w, 1240br, 1100w, 1050br and 930s; δ_H(500 MHz; $CDCl_3$) 1.42 (dt, *J* 2.38, 5.84, 1 H), 1.65–1.71 (m, 1 H), 1.81–1.96 (m, 2 H), 3.04 (dd, *J* 3.46, 8.10, 1 H), 3.17 (q, *J* 4.50, 1 H), 3.72 (s, 3 H), 3.87 (m, 1 H), 4.01 (d, *J* 16.30, 1 H), 4.21 (d, *J* 16.29, 1 H), 4.53 (d, *J* 17.08, 1 H), 4.58 (d, *J* 16.21, 1 H), 4.59 (m, 1 H) and 7.26–7.35 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 211.90, 174.76, 138.15, 128.41, 128.31, 127.53, 127.03, 76.94, 75.46, 70.87, 70.79, 52.24, 46.39, 37.80, 23.57 and 19.48; high resolution mass spectrum (Cl, NH_3) *m/z* 322.1684 $[(M + NH_4)^+$; calc. for $C_{17}H_{24}NO_5$: *M*, 322.1654].

Methyl 7-Benzyloxy-3-tert-butyldimethylsilyloxy-2,4,5,6,7,7a-hexhydro-1-benzofuran-4-carboxylate (−)-**29**.—A solution of ketone **28** (603 mg, 1.96 mmol) in CH_2Cl_2 (40 cm^3) was treated with 2,6-lutidine (2.3 cm^3, 19.6 mmol) followed by slow addition

of *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.0 cm^3, 8.82 mmol). Triethylamine (0.688 cm^3, 4.9 mmol) was then introduced in one portion and the reaction mixture was heated to 40 °C for 45 min. The mixture was cooled to room temp., diluted with water and extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 7:1) provided the title compound **29** (801 mg, 98% yield) as an oil: $[\alpha]_D^{20}$ −64.7 (*c* 0.44, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 2980s, 2960s, 2930s, 1725s, 1460s, 1375s, 1250s, 1230br, 1050br and 840s; δ_H(500 MHz; $CDCl_3$) 1.62 (td, *J* 4.75, 13.62, 1 H), 1.79–1.90 (m, 3 H), 3.64 (d, *J* 4.86, 1 H), 3.67 (s, 3 H), 3.81 (br s, 1 H), 4.43 (m, 2 H), 4.65 (1/2 ABq, *J* 12.34, 1 H), 4.73 (1/2 ABq, *J* 12.32, 1 H), 4.85 (dt, *J* 3.24, 5.94, 1 H) and 7.25–7.35 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 173.72, 143.86, 139.43, 128.12, 127.12, 127.09, 106.62, 84.89, 75.95, 72.83, 72.23, 51.78, 38.43, 25.45, 25.34, 22.03, 19.12, −4.35 and −4.43; high resolution mass spectrum (Cl, NH_3) *m/z* 419.2291 $[(M + H)^+$; calc. for $C_{23}H_{35}O_5Si$: *M*, 419.2253] (Found: C, 65.7; H, 7.97. Calc. for $C_{23}H_{34}O_5Si$: C, 65.99; H, 8.19%).

Methyl 7-Benzyloxy-3a-hydroxy-3-oxo-2,3,3a,4,5,6,7,7a-octahydro-1-benzofuran-4-carboxylate (+)-**30**.—A solution of silyl enol ether **29** (612 mg, 1.46 mmol) in CH_2Cl_2 (30 cm^3) containing solid $NaHCO_3$ (319 mg, 3.78 mmol) was cooled to −20 °C. A solution of *m*-CPBA (440 mg, 2.55 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise and the resultant suspension was stirred for 30 min. The mixture was then warmed to room temp., diluted with water and extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Following addition and evaporation of two portions of benzene, the residue was dissolved in CH_2Cl_2 (30 cm^3). The resultant solution was cooled to 0 °C and tetrabutylammonium fluoride (1 mol dm^{-3} in THF; 3.3 cm^3) was added dropwise. After 30 min the mixture was diluted with water and extracted with CH_2Cl_2, and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 4:1) gave the title compound **30** (349 mg, 75% yield) as a white powder: m.p. 67–69 °C; $[\alpha]_D^{20}$ +16.3 (*c* 0.35, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3450br, 3010s, 2960s, 2880s, 1775s, 1715s, 1440s, 1350br, 1280s, 1165w, 1090s and 1040s; δ_H(500 MHz; $CDCl_3$) 1.81–1.88 (m, 2 H), 1.93–2.26 (m, 2 H), 2.69 (d, *J* 3.38, 1 H), 3.70 (s, 3 H), 3.80 (m, 1 H), 4.07 (d, *J* 17.60, 1 H), 4.12 (d, *J* 11.06, 1 H), 4.40 (dd, *J* 17.74, 1 H), 4.58 (br s, 1 H), 4.65 (s, 2 H) and 7.28–7.36 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 218.47, 173.63, 137.90, 128.45, 127.81, 127.76, 78.89, 77.17, 73.70, 70.91, 70.11, 52.36, 41.29, 25.31 and 23.58; high resolution mass spectrum (Cl, NH_3) *m/z* 338.1613 $[(M + NH_4)^+$; calc. for $C_{17}H_{24}NO_6$: *M*, 338.1604] (Found: C, 63.54; H, 6.31. Calc. for $C_{17}H_{22}O_5$: C, 63.72; H, 6.29%).

Methyl 7-Benzyloxy-3a-hydroxy-3-methoxycarbonylmethylene-2,3,3a,4,5,6,7,7a-octahydro-1-benzofuran-4-carboxylate (+)-**31**.—A solution of ketone **30** (13.2 mg, 0.040 mmol) and methyl (triphenylphosphoranylidene)acetate (70 mg, 0.20 mmol) in THF (2.5 cm^3) was heated at reflux for 1.5 h, cooled to room temp. and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 5:1) furnished the title compound **31** (13.7 mg, 92% yield) as an oil: $[\alpha]_D^{23}$ +22.4 (*c* 0.46, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3480br, 3010w, 3000s, 2970s, 2890br, 1730s, 1680w, 1440s, 1360s, 1290w, 1230br, 1080br and 1030br; δ_H(500 MHz; $CDCl_3$) 1.72–1.97 (m, 4 H), 2.60 (dt. *J* 3.58, 8.84, 1 H), 3.70 (s, 1 H), 3.71 (s, 3 H), 3.76 (m, 3 H), 3.91 (d, *J* 3.27, 1 H), 4.64 (s, 2 H), 4.93 (dd, *J* 2.91, 5.82, 2 H), 5.18 (s, 1 H), 5.75 (t, *J* 2.54, 1 H) and 7.25–7.36 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 175.83, 166.37, 164.97, 138.21, 128.38, 127.76, 127.67, 110.64, 79.15, 78.58, 73.87, 70.73, 70.39, 52.27, 51.52, 44.66, 25.34 and 24.75; high resolution mass spectrum (Cl, NH_3) *m/z* 394.1895 $[(M + NH_4)^+$; calc. for $C_{20}H_{28}NO_7$: *M*, 394.1865].

Methyl 7-Benzyloxy-3,3a-dihydroxy-3-vinyl-2,3,3a,4,5,6,7,7a-octahydro-1-benzofuran-4-carboxylate (−)-**32**.—A solution of ketone **30** (258 mg, 0.80 mmol) in THF (16 cm^3) was cooled to −78 °C and added *via* a cannula to a solution of vinylmagnesium bromide in THF (1 mol dm^{-3}; 8.1 mmol) at −78 °C. The reaction mixture was stirred for 4 h and then quenched with saturated aqueous ammonium chloride. The mixture was warmed to room temp., diluted with water and extracted with diethyl ether, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexane–acetone, 4:1) afforded the title compound **32** (201 mg, 72% yield) as an oil and unreacted starting material (46 mg, 18%). Compound **32**: $[\alpha]_D^{20}$ −12.5 (*c* 0.52, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3420br, 3010w, 2960s, 2870w, 1700s, 1430s, 1350br, 1290w, 1175s, 1085s and 1040s; δ_H(500 MHz; $CDCl_3$) 1.78–1.83 (m, 2 H), 1.89–1.93 (m, 1 H), 3.21 (dd, *J* 2.89, 11.12, 1 H), 3.67 (s, 3 H), 3.74 (d, *J* 9.13, 1 H), 3.85 (q, *J* 4.11, 1 H), 3.93 (d, *J* 3.77, 1 H), 3.96 (s, 1 H), 4.07 (d, *J* 9.15, 1 H), 4.65 (d, *J* 11.87, 2 H), 4.71 (s, 1 H), 5.28 (dd, *J* 1.63, 10.98, 1 H), 5.44 (dd, *J* 1.63, 10.96, 1 H), 6.04 (qd, *J* 0.51, 10.99, 1 H) and 7.27–7.34 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 177.21, 137.49, 135.16, 128.48, 127.85, 127.76, 116.36, 85.54, 82.37, 81.91, 76.52, 74.54, 72.26, 51.92, 39.99, 23.96 and 21.46; high resolution mass spectrum (Cl, NH_3) *m/z* 366.1889 $[(M + NH_4)^+$; calc. for $C_{19}H_{28}NO_6$: 366.1916].

Methyl 3-Acetoxy-7-benzyloxy-3a-hydroxy-3-vinyl-2,3,3a,4,-5,6,7,7a-octahydro-1-benzofuran-4-carboxylate (−)-**33**.—A solution of alcohol **32** (168 mg, 0.48 mmol), acetic anhydride (0.205 cm^3, 2.17 mmol), pyridine (0.156 cm^3, 1.93 mmol) and 4-pyrrolidinopyridine (16 mg, 0.10 mmol) in CH_2Cl_2 (0.80 cm^3) was heated at 50 °C for 24 h. Concentration under reduced pressure followed by flash chromatography (hexane–ethyl acetate, 4:1) afforded the title compound **33** (169 mg, 90% yield) as a crystalline solid: m.p. 133–134 °C; $[\alpha]_D^{20}$ −10.6 (*c* 0.79, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3420br, 3120s, 2970s, 1760s, 1730s, 1650w, 1450s, 1370s, 1300w, 1260br, 1110w and 1025s; δ_H(500 MHz; $CDCl_3$) 1.73–1.93 (m, 2 H), 1.95 (s, 3 H), 2.68 (dd, *J* 3.23, 12.06, 1 H), 3.65 (m, 1 H), 3.77 (s, 3 H), 3.96 (d, *J* 3.03, 1 H), 4.05 (d, *J* 11.37, 1 H), 4.60 (s, 2 H), 4.63 (d, *J* 11.38, 1 H), 5.32 (s, 1 H), 5.42 (dd, *J* 11.07, 12.19, 2 H), 5.93 (dd, *J* 0.59, 10.47, 1 H) and 7.26–7.35 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 177.83, 168.81, 138.22, 134.83, 128.31, 127.74, 127.58, 116.78, 88.60, 81.84, 75.90, 74.65, 72.74, 70.79, 52.01, 42.41, 25.19, 24.80 and 20.75; high resolution mass spectrum (Cl, NH_3) *m/z* 408.2047 $[(M + NH_4)^+$; calc. for $C_{21}H_{30}NO_7$: *M*, 408.2022] (Found: C, 64.37; H, 6.74. Calc. for $C_{21}H_{26}O_7$: C, 64.58; H, 6.71%).

X Ray Structure Determination of Acetate (−)-**33**.—Acetate (−)-**33**, $C_{21}H_{26}O_7$, crystallizes in the monoclinic space group $P2_1$ (systematic absences 0*k*0: *k* = odd) with *a* = 9.130(1), *b* = 5.690(1), *c* = 19.788(3) Å, β = 97.10(1)°, *V* = 1020.1(5) $Å^3$, *Z* = 2 and d_{calc} = 1.271 g/cm^3. The cell constants were determined from a least squares fit of the setting angles for 25 accurately centred reflections. X-ray intensity data were collected on an Enraf-Nonius CAD4 diffractometer employing graphite-monochromated Cu-Kα radiation (λ = 1.541 84 Å) and using the ω-2θ scan technique. A total of 2132 reflections were measured over the ranges: $4 \leq 2\theta \leq 140$, $0 \leq h \leq 11$, $-6 \leq k \leq 6$, $-24 \leq l \leq 24$. Three standard reflections measured every 3500 sec of X-ray exposure showed no intensity decay over the course of data collection.

The intensity data were corrected for Lorentz and polarization effects but not for absorption. Of the reflections measured

a total of 1954 unique reflections with $F^2 > 3\sigma(F^2)$ were used during subsequent refinement.

The structure was solved by direct methods (MULTAN-11/82). Refinement was by full-matrix least squares techniques based on F to minimize the quantity $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/\sigma^2(F)$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as constant contributions to the structure factors and were not refined. Refinement converged to $R_1 = 0.068$ and $R_2 = 0.096$.

Methyl 3-(2-*Acetoxyethylidene*)-7-*benzyloxy*-3a-*hydroxy*-2,-3,3a,4,5,6,7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (+)-**34**.—A solution of acetate **33** (353 mg, 0.90 mmol), bis-acetonitrile)palladium(II) chloride (50 mg, 14% w/w), and benzoquinone (146 mg, 1.35 mmol) in dry CH_3CN (5 cm^3) was heated to reflux for 36 h. The resultant slurry was cooled to room temp. and filtered through a cotton plug (CH_3CN eluent). Concentration under reduced pressure and flash chromatography (hexane–acetone, 4:1) provided the title compound **34** (250 mg, 71% yield) as an oil and unreacted starting material (67 mg, 19% yield). Compound **34**: $[\alpha]_D^{20}$ +14.9 (*c* 0.26, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3450br, 3000s, 2940s, 2870w, 1740s, 1710w, 1440s, 1360s, 1230br, 1080s and 1035s; δ_H(500 MHz; $CDCl_3$) 1.75–1.95 (m, 4 H), 2.04 (s, 3 H), 2.56 (dd, *J* 3.57, 12.16, 1 H), 3.70 (s, 3 H), 3.73 (m, 1 H), 3.91 (d, *J* 3.37, 1 H), 4.47 (d, *J* 6.49, 2 H), 4.61 (s, 2 H), 4.63 (d, *J* 6.14, 2 H), 4.97 (s, 1 H), 5.43 (m, 1 H) and 7.26–7.36 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 176.02, 170.55, 147.47, 138.29, 128.36, 127.74, 127.61, 114.15, 79.04, 78.08, 74.10, 70.61, 67.67, 61.03, 52.03, 45.28, 25.45, 24.56 and 20.81; high resolution mass spectrum (Cl, NH_3) *m/z* 389.1595 $[(M - H)^+$; calc. for $C_{21}H_{25}O_7$: *M*, 389.1601] (Found: C, 64.3; H, 6.76. Calc. for $C_{21}H_{26}O_7$: C, 64.58; H, 6.71%).

Methyl 7-*Benzyloxy*-3a-*hydroxy*-3-(2-*hydroxyethylidene*)-2,-3,3a,4,5,6,7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (+)-**36**.—A suspension of acetate **34** (278 mg, 0.71 mmol) and K_2CO_3 (43 mg, 0.31 mmol) in dry MeOH (20 cm^3) was stirred at room temp. for 20 min. Concentration under reduced pressure and flash chromatography on activated neutral alumina (Brockmann I; ethyl acetate eluent) provided the title compound **36** (239 mg, 97% yield) as a semisolid: m.p. <30 °C; $[\alpha]_D^{20}$ +12.0 (*c* 0.41, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3610w, 3470br, 3000s, 2950s, 2870s, 1715s, 1600w, 1450w, 1430s, 1260br, 1170s, 1070br and 1025s; δ_H(500 MHz; $CDCl_3$) 1.72–1.95 (m, 4 H), 2.55 (dd, *J* 3.60, 7.29, 1 H), 2.62 (s, 1 H), 3.70 (s, 1 H), 3.69–3.77 (m, 1 H), 3.88 (d, *J* 3.40, 1 H), 4.09 (t, *J* 6.72, 2 H), 4.59 (s, 2 H), 4.63 (s, 2 H), 4.95 (s, 1 H), 5.47 (m, 1 H) and 7.27–7.36 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 176.02, 144.90, 138.32, 128.35, 127.74, 127.60, 118.93, 79.11, 77.99, 74.23, 70.63, 67.77, 59.97, 52.04, 45.39, 25.44 and 24.62; high resolution mass spectrum (Cl, NH_3) *m/z* 366.1901 $[(M + NH_4)^+$; calc. for $C_{19}H_{28}NO_6$: *M*, 366.1917].

Methyl 7-*Benzyloxy*-3-(2-tert-*butyldimethylsilyloxyethylidene*)-3a-*hydroxy*-2,3,3a,4,5,6,7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (+)-**38**.—A solution of allylic alcohol **36** (117 mg, 0.33 mmol) and 2,6-lutidine (0.117 cm^3, 1.01 mmol) in CH_2Cl_2 (5 cm^3) was cooled to 0 °C and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.116 cm^3, 0.50 mmol). The reaction mixture was stirred for 30 min, diluted with water and extracted with CH_2Cl_2, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on an oversized (12 × 1.5 in) silica column (hexane-acetone, 7:1) gave the title compound **38** (132 mg, 85% yield) as an oil: $[\alpha]_D^{21}$ +15.0 (*c* 0.67, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3460br, 3010w, 2960s, 2950s, 2870w, 1715s, 1610w, 1460br, 1440s, 1360br, 1260s, 1090s, 1030s and 840s; δ_H(500 MHz; $CDCl_3$) 0.03 (s, 6 H), 0.87 s, 9 H), 1.74–1.94 (m, 4 H), 2.56 (dd, *J* 3.46, 12.01, 1 H), 3.68 (s, 3 H), 3.69–3.75 (m, 1 H), 3.85 (d, *J* 3.40, 1 H), 4.11 (dt, *J* 1.25, 2.86, 2 H), 4.59 (d, *J* 0.76, 2 H), 4.63 (d, *J* 1.49, 2 H), 4.94 (s, 1 H), 5.37 (m, 1 H) and 7.26–7.35 (m, 5 H); δ_C(125.8 MHz; $CDCl_3$) 176.19, 142.93, 138.39, 128.32, 127.40, 127.55, 119.36, 78.96, 78.08, 74.29, 70.59, 68.22, 60.91, 51.94, 45.47, 25.86, 25.46, 24.70, 18.24, −5.33 and −5.38; high resolution mass spectrum (Cl, NH_3) *m/z* 480.2754 $[(M + NH_4)^+$; calc. for $C_{25}H_{42}NO_6Si$: *M*, 480.2786] (Found: C, 64.63; H, 7.99. Calc. for $C_{25}H_{38}O_6Si$: C, 64.90; H, 8.28%).

Methyl 3-(2-*Acetoxyethylidene*)-3a,7-*dihydroxy*-2,3,3a,4,5,6,-7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (+)-**35**.—A solution of benzyl ether **34** (27.3 mg, 0.06 mmol) in methanol (1 cm^3) was treated with 10% Pd(C) (30 mg). The flask was evacuated and flushed with argon several times, and 18% aqueous formic acid (1 cm^3) was then added. The resultant slurry was stirred in a bath preheated to 45 °C for 30 min. The mixture was cooled to room temp. and filtered through a Celite plug (MeOH eluent), and the filtrate was concentrated under reduced pressure. Flash chromatography (ethyl acetate–hexane, 2:1) afforded the title compound **35** (11 mg, 60% yield) as an oil contaminated with a trace of the triol deacetylated at C(3′): $[\alpha]_D^{20}$ +1.8 (*c* 0.55, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3590s, 3470br, 3010w, 3000s, 2960s, 2470w, 1735s, 1715s, 1440s, 1365s, 1240br, 1170s and 1040s; δ_H(500 MHz; $CDCl_3$) 1.54–1.70 (m, 2 H), 1.82–2.04 (m, 2 H), 2.05 (s, 3 H), 2.51 (m, 1 H), 3.71 (s, 3 H), 3.79 (d, *J* 3.64, 1 H), 3.95 (m, 1 H), 4.46 (d, *J* 6.38, 3 H), 4.60 (dd, *J* 1.37, 2.50, 2 H), 4.98 (br s, 1 H) and 5.45 (m, 1 H); δ_C(125.8 MHz; $CDCl_3$) 175.90, 170.52, 147.43, 114.42, 81.01, 77.87, 67.73, 67.55, 60.98, 52.03, 45.17, 28.82, 24.45 and 20.78.

Methyl 3-(2-tert-*Butyldimethylsilyloxyethylidene*)-3a,7-*dihydroxy*-2,3,3a,4,5,6,7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (+)-**39**.—Liquid ammonia (35 cm^3) was cooled to −78 °C and a solution of benzyl ether **38** (36.7 mg, 0.07 mmol) in THF (0.80 cm^3) was added in one portion, followed by sodium metal (*ca.* 10 mg, 0.43 mmol). The reaction was stirred for 15 s after the appearance of a persistent blue colour and then quenched with isoprene (0.35 cm^3). The mixture was warmed to room temp. and the residual ammonia evaporated with a stream of argon. Flash chromatography (ethyl acetate–hexane, 1:1→2:1) provided the title compound **39** (27.7 mg, 95% yield) as a white powder: m.p. 100.5–102 °C; $[\alpha]_D^{22}$ +2.6 (*c* 0.96, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 3590s, 3460br, 2970s, 2950s, 2870w, 1720s, 1560w, 1460br, 1440w, 1370s, 1255s, 1175s, 1080s and 1030br; δ_H(500 MHz; $CDCl_3$) 0.01 (s, 6 H), 0.86 (s, 9 H), 1.62 (m, 1 H), 1.78–1.90 (m, 3 H), 2.01 (s, 1 H), 2.48 (m, 1 H), 3.66 (s, 3 H), 3.73 (d, *J* 3.61, 1 H), 3.91 (dt, *J* 1.57, 5.08, 2 H), 3.92 (m, 1 H), 4.55 (d, *J* 1.86, 2 H), 4.94 (s, 1 H) and 5.36 (m, 1 H); δ_C(125.8 MHz; $CDCl_3$) 176.10, 142.99, 119.65, 80.91, 77.90, 68.12, 67.87, 60.92, 51.96, 45.38, 29.66, 28.89, 25.85, 24.61, 18.24, 14.16, −5.34 and −5.39; high resolution mass spectrum (Cl, NH^3) *m/z* 390.2336 $[(M + NH_4)^+$; calc. for $C_{18}H_{36}NO_6Si$: *M*, 390.2312] (Found: C, 58.28; H, 8.8. Calc. for $C_{18}H_{32}O_6Si$: C, 58.03: H, 8.66%).

Methyl 3-(2-tert-*Butyldimethylsilyloxyethylidene*)-3a-*hydroxy*-7-*oxo*-2,3,3a,4,5,6,7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (−)-**40**. Tetrapropylammonium perruthenate (1 mg, 5 mol %) was added to a mixture of 4-methylmorpholine-*N*-oxide (8.2 mg, 0.07 mmol), activated 4 Å molecular sieves (23 mg), alcohol **39** (17.4 mg, 0.04 mmol), and dry CH_2Cl_2 (0.80 cm^3). After 15 min, the suspension was filtered through a silica gel plug (ethyl acetate eluent) to provide the title compound **40** (16.5 mg, 97% yield) as an oil: $[\alpha]_D^{25}$ −3.1 (*c* 0.57, $CHCl_3$); $\nu(CHCl_3)$/cm 3530br, 2960s, 2940s, 2860w, 1740s, 1460w, 1440w, 1380s, 1250br, 1080w and 1040w; δ_H(500 MHz; $CDCl_3$) 0.02 (s, 6 H), 0.85 (s, 9 H), 1.83–1.97 (m, 1 H), 2.25–2.27 (m, 1 H), 2.41–2.49 (m, 1 H), 2.57–2.69 (m, 1 H), 3.17 (q, *J* 4.41, 1 H), 3.73 (s, 1 H), 3.76 (s, 3 H), 4.12 (m, 2 H), 4.37 (s, 1 H), 4.59 (dd, *J* 2.28,

14.21, 2 H) and 5.53 (m, 1 H); δ_C(125.8 MHz; $CDCl_3$) 205.44, 174.29, 139.13, 122.57, 86.67, 81.79, 77.20, 68.43, 60.97, 52.34, 45.81, 36.49, 25.84, 24.64, 18.24, 14.16, −5.29 and 5.40; high resolution mass spectrum (Cl, NH_3) *m/z* 388.2119 [$(M + NH_4)^+$; calc. for $C_{18}H_{34}NO_6Si$: *M*, 388.2156].

Methyl 3-(2-tert-*Butyldimethylsilyloxyethylidene*)-7-*oxo*-3a-*trimethylsilyloxy*-2,3,3a,4, 5,6,7,7a-*octahydro*-1-*benzofuran*-4-*carboxylate* (−)-**41**.—In a 5 cm^3 round-bottomed flask, a solution of alcohol **40** (2.0 mg, 54.4 μmol) and *N*,*N*-bis-(trimethylsilyl)trifluoroacetamide (17 mm^3, 31 μmol) in DMF (0.1 cm^3) was stirred for 25 h at room temp. Following dilution with water, the mixture was extracted with ethyl ether and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (hexane–ethyl acetate, 5:1) provided the title compound **41** (2.6 mg, 90% yield) as an oil: $[\alpha]_D^{25}$ −25.8 (*c* 0.40, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 2960s, 2940s, 2870w, 1730s, 1675w, 1460b, 1440w, 1375w, 1260s, 1180s, 1100w, 1085b and 840s; δ_H(500 MHz; $CDCl_3$) 0.03 (s, 6 H), 0.06 (s, 9 H), 0.86 (s, 9 H), 1.63–1.70 (td, *J* 4.64, 14.30, 1 H), 1.98–2.03 (m, 1 H), 2.24 (dt, *J* 3.66, 14.15, 1 H), 3.04 (td, *J* 6.23, 14.15, 1 H), 3.34 (dd, *J* 2.74, 4.38, 1 H), 3.74 (s, 3 H), 4.09 (t, *J* 1.80, 4 H), 4.41 (d, *J* 14.12, 1 H), 4.49 (d, *J* 14.79, 1 H), 4.74 (s, 1 H) and 5.54 (m, 1 H); δ_C(125.8 MHz; $CDCl_3$) 206.51, 173.19, 137.78, 123.79, 106.62, 88.79, 84.10, 67.83, 60.75, 51.80, 47.28, 36.27, 25.82, 23.39, 1.41, −0.02, −5.43 and −5.46.

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