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Total Synthesis of Natural (+)-Ambruticin

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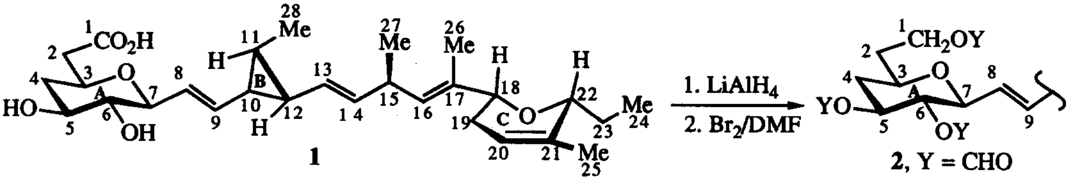
Abstract: The structurally unique antifungal antibiotic ambruticin (**1**) has been prepared for the first time in a convergent synthesis. The strategy for its synthesis involved the independent preparation of the enantiomerically pure fragments **19**, **31**, and **49**. The required C(7)-C(8) β-C-glycoside bond was formed by coupling the glycosyl fluoride **19** with the *in situ* formed vinyl alane derivative **32**. Formation of the C(13)-C(14) trans double bond was accomplished by condensation of the sulfone fragment **49** with the aldehyde intermediate **35** leading to the complete skeletal framework of ambruticin. Saponification of **51** and then cleavage of the benzyl protecting groups gave natural ambruticin.

INTRODUCTION

In 1977-1978, Warner-Lambert scientists isolated, from fermentation extracts of the Myxobacteria species *Polyangium cellulosum var. fulvum*, a new antibiotic, W-7783,[1] which exhibited unprecedented oral *in vivo* activity against the systemic fungal infections histoplasmosis and coccidiomycosis.[2] In view of the unique biological potency of this compound, officially renamed ambruticin, its structure elucidation was swiftly carried out by the D. T. Connor group at Warner-Lambert.[3] Ambruticin was found to be a $C_{28}H_{42}O_6$ carboxylic acid having 3 rings and 4 carbon-carbon double bonds. Elegant spectroscopic analyses, degradative studies and chemical transformations indicated that the antibiotic contained a novel 1,2-divinylcyclopropane structure, and the full molecular structure was established by single-crystal X-ray analysis of the triol triformate **2**, leading to the structure and relative configuration **1** for ambruticin (Scheme 1).

Scheme 1



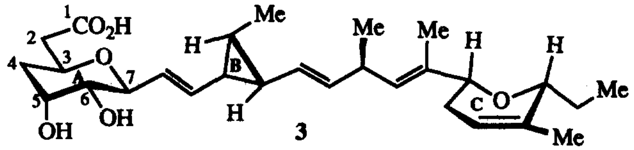
1

2, Y = CHO

Subsequent papers by the Warner-Lambert group reported the presence of the minor antifungal congener 5-epiambruticin (**3**) (Figure 1) in the *Polyangium* fermentation extracts, and described extensive chemical transformations of **1** and **3** which were entirely consistent with the structures depicted.[4]

Dedicated in honor and admiration of Professor D. H. R. Barton on the occasion of his 75th birthday.

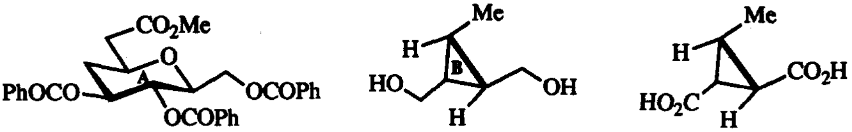
Figure 1



3

In 1980, Just and Potvin established the absolute stereochemistry of ambruticin (1) by ozonolysis of the antibiotic and subsequent isolation of the derived fragments **4** and **5a** (Scheme 2), corresponding to rings A and B, respectively.[5] Fragment **4** was independently synthesized from L-arabinose, whereas **5a** was prepared from the known (R,R)-Feist's acid. These studies established the absolute configuration of ambruticin as depicted in **1**. In 1981, a group led by Davidson and Procter described an independent synthesis of the degradation diacid **5b**,[6] confirming the stereochemical assignment for ring B by Just and Potvin.

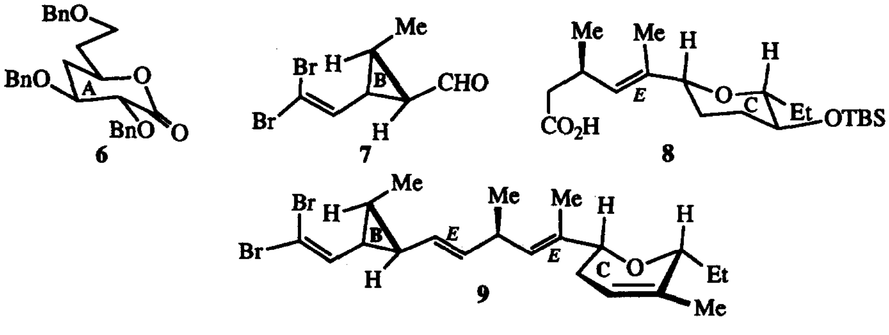
Scheme 2



4 5a 5b

Ambruticin has elicited considerable synthetic interest, notably by the Sinaÿ team in France[7] who carried out elaborate reaction sequences, starting from chiral pool carbohydrates, to achieve the syntheses of the ambruticin segments **6**, **7**, and **8**. A dianion coupling of acid **8** with aldehyde **7** led ultimately to the intermediate **9**, segment B-C of ambruticin (Scheme 3). However, further efforts to complete the synthesis appear to have been abandoned.

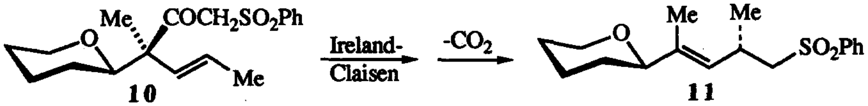
Scheme 3



6 7 8 9

More recently, the Davidson-Procter team in the U.K. described the model enolate-Claisen rearrangement of the tetrahydropyran ester **10** to the sulfone **11** (Scheme 4).[8]

Scheme 4



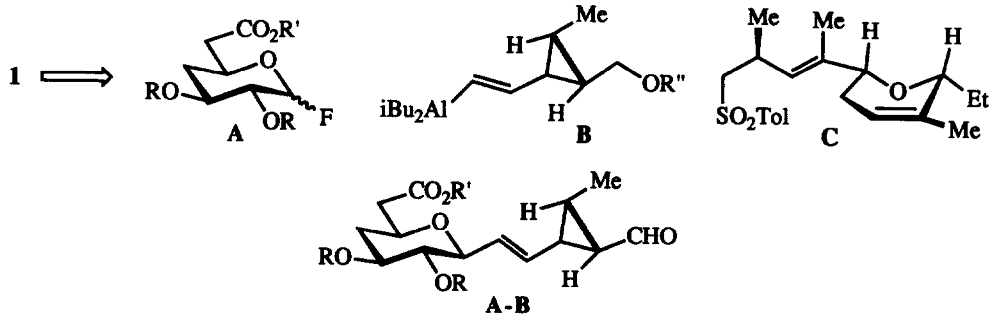
10 11

In the following sections, we report details of the first total synthesis of natural (+)-ambruticin.

RESULTS AND DISCUSSION

We anticipated that the synthesis of (+)-ambruticin could be accomplished by the independent preparation of the enantiomerically pure fragments A, B, and C of the target molecule (Scheme 5). Formation of the key C(7)-C(8) β-C-glycoside bond could be achieved by coupling the fluoride fragment A with the vinyl metal derivative segment B following the methodology developed by Posner et al.[9] It was envisioned that the C(13)-C(14) double bond could be formed by condensation of sulfone C with the aldehyde intermediate A-B using the well known Julia olefination sequence;[10] this would then produce the complete carbon framework of ambruticin.

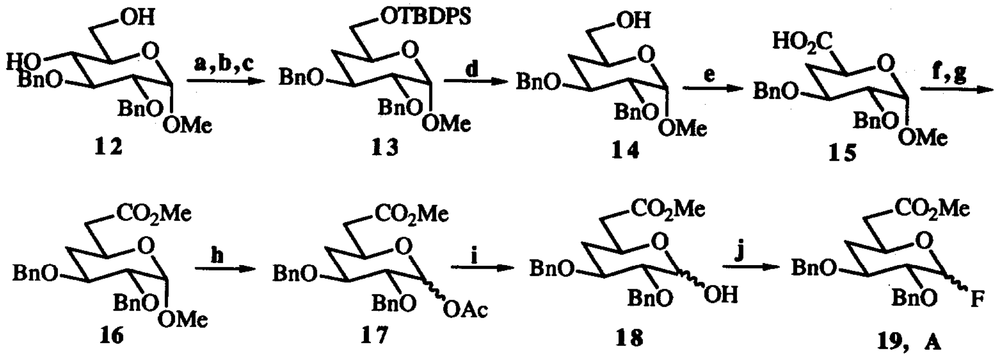
Scheme 5



Synthesis of Ring A and Model Studies on the Construction of the A-B Coupled Unit

The synthesis of the required segment A was achieved starting with the known methyl 2,3-di-*O*-benzylglucopyranoside **12** (Scheme 6).[11] The C-4 deoxygenated glucose derivative **13** was prepared in 73% overall yield by selective protection of the primary hydroxyl group in **12**, followed by a Barton radical deoxygenation reaction.[12] Oxidation of the carbinol **14** with PDC[13] gave the corresponding acid **15** in 83% yield, which was then submitted to a photochemical Arndt-Eistert sequence[14] to provide the one-carbon homologated ester **16** in good yield.

Scheme 6

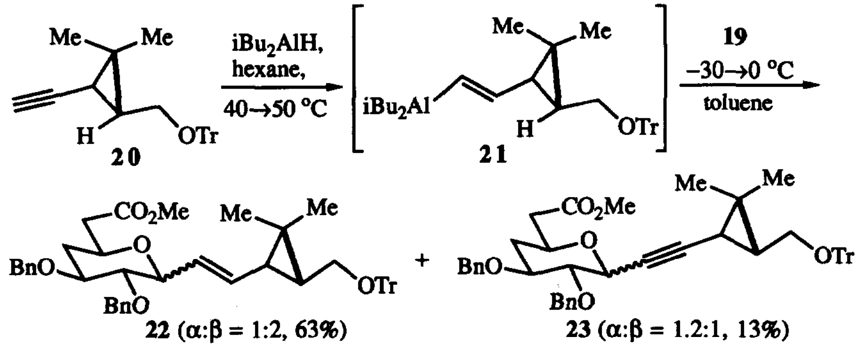


a) TBDPSCl, imidazole, DMF, 99%. b) Im_2CS, toluene, reflux, 93%. c) nBu_3SnH, toluene, reflux, 83%. d) nBu_4NF, THF, 95%. e) PDC, DMF, 83%. f) 1. $(COCl)_2$, cat. DMF, CH_2Cl_2; 2. CH_2N_2, Et_2O 78%. g) *hv*, MeOH, 68%. h) Ac_2O, cat. H_2SO_4, -20 °C, 88%. i) MeONa, MeOH, 97%. j) Et_2NSF_3, CH_2Cl_2, 92%.

The final task in completing the synthesis of the required segment was the conversion to glycosyl fluorides. In our hands, attempted cleavage of the methyl glycoside **16** to the corresponding lactols using trimethylsilyl iodide (TMSI) failed, and only an unidentified mixture of products was obtained. However, lactols **18** were obtained by a two step sequence. Acetolysis[15] of compound **16** gave a mixture of α– and β–acetyl glycosides **17** in 88% yield. The acetyl group was then cleaved by sodium methoxide in MeOH to afford lactols **18**, which upon reaction with diethylaminosulfur trifluoride (DAST)[16] gave a mixture (α:β = 27:73) of the requisite glycosyl fluorides **19**, ring A of ambruticin. Segment A was thus prepared in 25% overall yield in 11 steps from known methyl 2,3-di-*O*-benzylglucopyranoside **12**.

With fragment A in hand, the formation of the required C(7)-C(8) β-C-glycoside bond was investigated. The readily available racemic cyclopropane **20** was used as a model compound for these exploratory studies.[17] Acetylene **20** was hydroaluminated[18] to the (*E*)-alkenylalane derivative **21**. This on treatment with the glycosyl fluorides **19** (Scheme 7) afforded a 2:1 mixture of C-glycosides **22** in 63% combined yield, in which the desired β-C-glycoside **22β** predominated over the corresponding α-isomer **22α** (only one diastereomer is shown for each product).

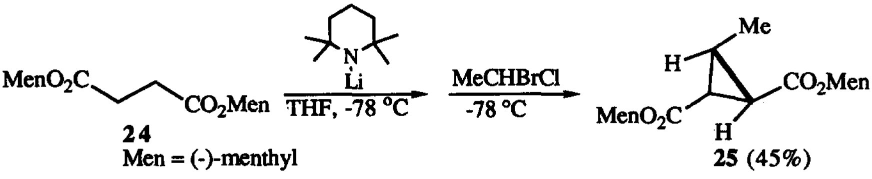
Scheme 7



Synthesis of Ring B and Construction of the A-B Coupled Unit

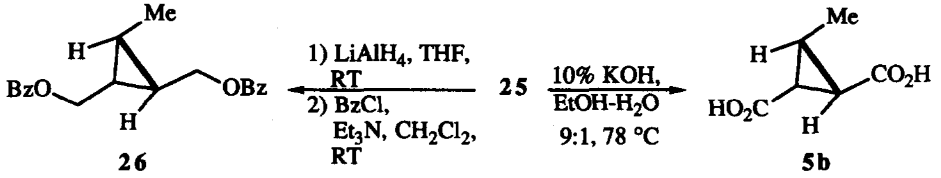
The required enantiomerically pure cyclopropane ring of ambruticin was prepared in multigram quantities using the strategy developed by Yamamoto.[19] Accordingly, reaction of the commercially available diester **24** with lithium 2,2,6,6-tetramethylpiperidide in THF at -78 °C (Scheme 8) and then treatment of the *in situ* generated dianion with 1,1-bromochloroethane afforded, after purification by chromatography, 45% yield of the desired cyclopropane **25** ($[\alpha]_D^{21}$ = -34° (c 0.5, $CHCl_3$)). This cyclopropane dimenthyl ester was shown to be >97% homogeneous by ^1H NMR and ^{13}C NMR. The following characteristic signals were observed in its ^1H NMR spectrum: δ 4.74-4.62 (2H, CHOCO, m), δ 2.24 (1H, dd, J=9.7, 4.6 Hz) due to the proton on the cyclopropane ring cis to the methyl group, and at δ 1.22 (3H, d, J=6.3 Hz) assigned to the methyl group on the cyclopropane ring. Its ^{13}C NMR spectrum showed characteristic signals at δ 171.60 and 169.46 (2 CO_2-) and also at δ 74.76 and 74.63 (2 CHOCO).

Scheme 8



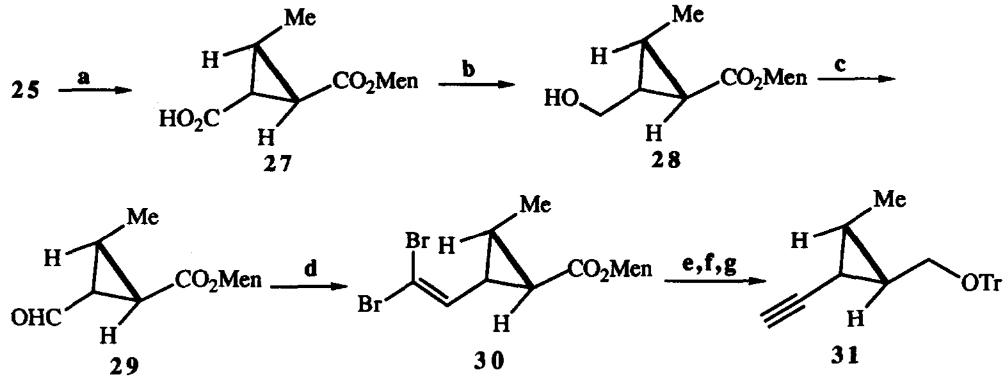
The absolute configuration of **25** was established after hydrolysis with 10% KOH in EtOH/H_2O (9:1) at 78 °C and acidic work-up, affording the known crystalline diacid **5b** ($[\alpha]_D^{21}$ = +101° (c 0.8, EtOH); lit.[6] $[\alpha]_D^{21}$ = +100° (c 0.001, EtOH)). Moreover, reaction of the dimenthyl cyclopropane **25** with $LiAlH_4$ in THF at rt gave the corresponding diol, which upon treatment with benzoyl chloride, Et_3N in CH_2Cl_2 gave the known dibenzoate **26** ($[\alpha]_D^{21}$ = -16.2° (c 0.7, $CHCl_3$); lit.[5] $[\alpha]_D^{21}$ = -12.9° (c 1.5, $CHCl_3$)). The ^1H NMR spectra of **5b** and **26** were in accord with those reported in the literature for these cyclopropane derivatives.[5]

Scheme 9



After the successful preparation of diester **25**, the selective differentiation of one of the two menthyl ester groups was addressed. Based on steric factors, we anticipated that the least hindered ester group (the one located trans to the methyl substituent) would be more reactive under hydrolysis conditions, thus affording the requisite cyclopropane monoacid **27**. In fact, reaction of **25** with 10% KOH (1.2 equivalents) in EtOH/H_2O (9:1) for 3.5 days at rt gave, after acidic work-up, the required monoacid **27** in 83% yield (Scheme 10). No mixture of acids was observed in its ^1H NMR and ^{13}C NMR spectra. The structural assignment to **27** was based on careful ^1H NMR analyses. A small but noticeable change in the chemical shifts between the cyclopropane methyl groups of **5b** and **27** was an indication that the required monoacid **27** was indeed obtained under these reaction conditions. The ^1H NMR spectra of the starting material **25** and the product **27** showed signals due to the cyclopropane methyl substituents at δ 1.22 as a doublet with J=6.3 Hz and at δ 1.25 as a doublet with J=6.3 Hz, respectively. However, the signal corresponding to the cyclopropane methyl group of diacid **5b** was observed at δ 1.32 as a doublet with J=6.2 Hz.

Scheme 10

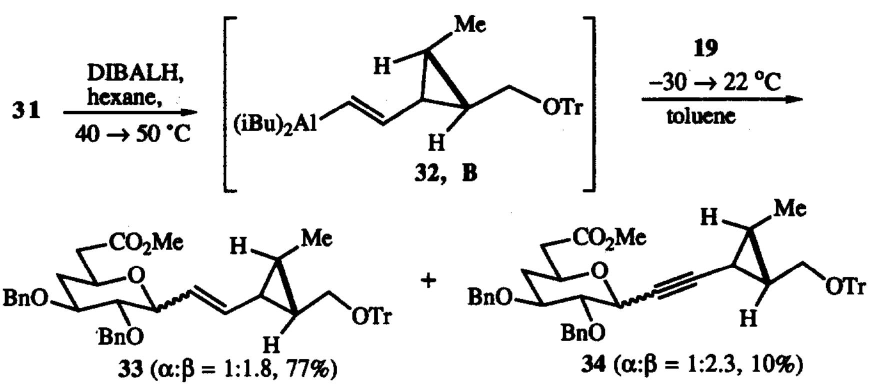


a) 10% KOH (EtOH-H_2O, 9:1), rt, 83%. b) B_2H_6-THF, 0 °C → rt, 8 h, 100%. c) Dess-Martin periodinane, rt, 96%. d) Ph_3P, CBr_4, CH_2Cl_2, 0 °C, 30 min, 98%. e) DIBALH, toluene, 0 °C, 30 min, 90%. f) TrCl, DMAP, Et_3N, CH_2Cl_2, rt, 72 h, 90%. g) nBuLi, THF, -78 °C, 10 min, 92%.

Treatment of monoacid **27** with B_2H_6-THF[20] (Scheme 10) gave the corresponding alcohol **28** in 100% yield; this was submitted to Swern oxidation[21] or Dess-Martin periodinane oxidation[22] to provide aldehyde **29** in 96% yield after chromatography. The one-carbon homologation was achieved by reaction of aldehyde **29** with Ph_3P and CBr_4 in CH_2Cl_2 at 0 °C[23] to give the required dibromomethylene compound **30** in 98% yield. The menthyl ester in **30** was reduced to the corresponding primary alcohol in 71% yield using $LiBH_4$/MeOH[24] in Et_2O at 42 °C, or in 90% yield using diisobutylaluminum hydride (DIBALH) in toluene at 0 °C.[25] Finally, the required acetylenic intermediate **31**, a suitable precursor to segment **B** of ambruticin, was obtained in high overall yield by protection of the primary alcohol and then treatment of the dibromomethylene derivative with nBuLi (two equivalents) in THF at 78 °C.

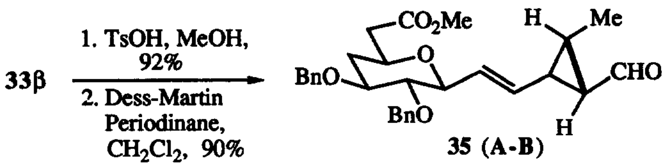
As in the model system, the acetylene compound **31** was hydroaluminated to the (*E*)-alkenylalane **32** intermediate (*cf.* segment **B**). This upon treatment with glycosyl fluorides **19** gave, after silica gel chromatography, the requisite β-C-glycoside **33β** in 49% yield and 28% yield of the α-isomer **33α**. The other isolated minor products were identified as **34α** and **34β** (Scheme 11). Careful examination of the coupling constants between the C-1 and C-2 protons in their ^1H NMR spectra allowed us to assign the structures to these compounds.

Scheme 11



To complete the synthesis of the "left hand" segment **A-B** of ambruticin, a two-step derivatization of (*E*)-alkenyl β-C-glycoside **33β** was performed as shown in Scheme 12. Cleavage of the triphenylmethyl ether with *p*-toluenesulfonic acid in MeOH and oxidation of the corresponding alcohol using the Dess-Martin periodinane afforded the enantiomerically pure aldehyde **35**, segment **A-B**, in 83% yield for the two steps.

Scheme 12

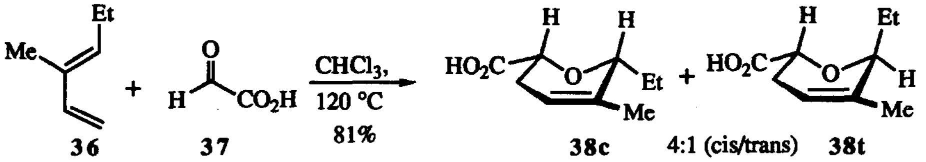


Synthesis of Ring C and the Total Synthesis of (+)-Ambruticin

The C_{14} right half of ambruticin, segment **C**, was prepared starting with the thermal Diels-Alder addition of (*E*)-3-methyl-1,3-hexadiene with glyoxylic acid in $CHCl_3$, producing a 4:1 ratio of **38c/38t** in 81% yield (Scheme 13).[26] The structures of these isomers were established by ^{13}C NMR analyses of the corresponding methyl ester derivatives; the trans isomer exhibited signals for C-2 and C-6 at δ 76.5 and 67.9

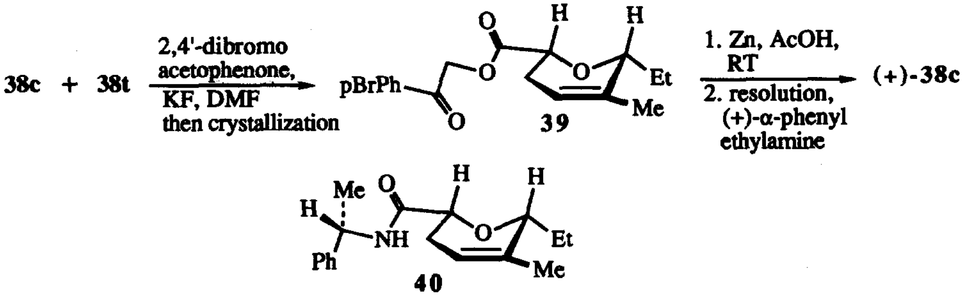
and the desired major cis isomer methyl ester at δ 78.4 and 72.4, respectively. These values were in full accord with the diagnostic chemical shifts for cis/trans pairs of 6-substituted-3,6-dihydro-2*H*-pyran-2-carboxylic esters.[27]

Scheme 13



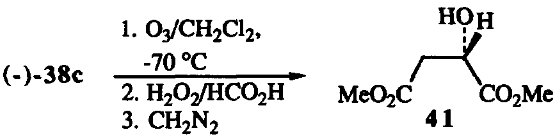
The major cis adduct **38c** was easily separated from the trans isomer **38t** by way of its crystalline *p*-bromophenacyl derivative **39**, which after deprotection with zinc in AcOH[28] and resolution[29] of the pure racemic acid **38c** employing (+)-α-phenylethylamine in a mixture of MeOH/Et_2O gave in 32% yield (+)-**38c**, $[\alpha]^{21}_{D}$ = +169.4° (c 0.85, EtOH). This was shown to be >98% homogeneous by ^1H NMR, ^{13}C NMR, and GC by conversion to its amide **40** (Scheme 14).

Scheme 14



The absolute configuration of (+)-**38c** was established after treatment of the antipode (-)-**38c** ($[\alpha]^{21}_{D}$ = -142° (c 0.84, EtOH) with ozone[30] in CH_2Cl_2 at -70 °C, followed by H_2O_2/HCO_2H work-up, and finally reaction with diazomethane, producing (L)-dimethyl malate **41**, $[\alpha]^{21}_{D}$ = -7.31° (c 1.92, EtOAc); lit.[31] $[\alpha]^{21}_{D}$ = -7.95° (c 6.42, EtOAc).

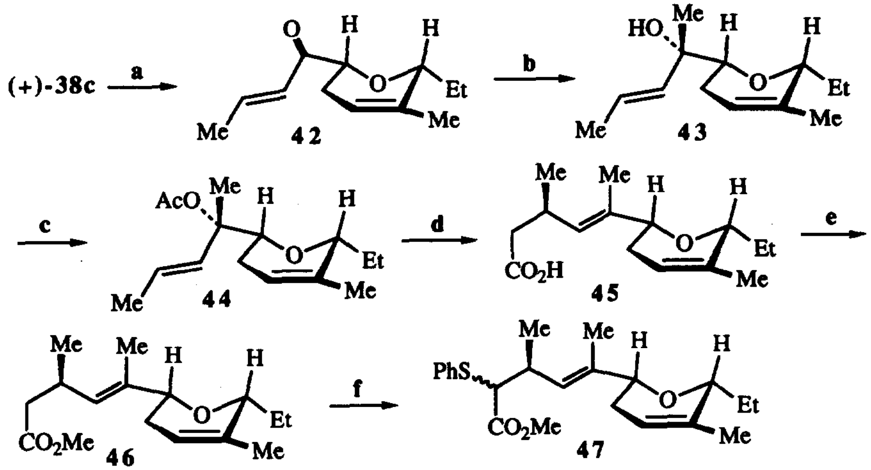
Scheme 15



The introduction of the side chain to form the required α,β-unsaturated ketone was achieved using the method reported by Milstein and Stille.[32] Accordingly, treatment of the acid chloride derivative of (+)-**38c** with trans-propenyltrimethyltin[33] in the presence of a catalytic amount of benzylchlorobis(triphenylphosphine)palladium(II) in HMPA at 70 °C gave the unsaturated ketone **42** in 90% yield. This then underwent chelated-Cram addition[34] of MeMgBr to yield the single carbinol **43** in 92% yield (Scheme 16). These results were in accord with the earlier studies of the Sinaÿ group.[7] The preparation of acetate **44** was accomplished by reaction of alcohol **43** with freshly distilled Ac_2O, DMAP, and Et_3N in CH_2Cl_2 at rt for 72 h.

The next goal in these synthetic studies was the crucial Ireland-enolate Claisen rearrangement[35] of acetate **44**. Treatment of acetate **44** with LDA in THF, followed by TBSCl gave, after hydrolysis, a 12:1 (*E*:*Z*) mixture of acids **45** in 61% yield. These results were in agreement with those obtained by Sinaÿ using the ortho Claisen rearrangement in a similar system.[7] Treatment of the isomeric mixture of acids with diazomethane provided, after purification, the single (*E*)-isomer methyl ester **46**. The complete formation of the sulfonyl fragment C was attempted by treatment of the methyl ester **46** with LDA at -78 °C, followed by diphenyl disulfide,[36] producing a diastereomeric mixture of sulfides **47** in 71% yield. Unfortunately, all attempts to oxidize **47** to the corresponding sulfones using *m*-CPBA or potassium hydrogen persulfate ($KHSO_5$, oxone)[37] failed to provide the desired product.

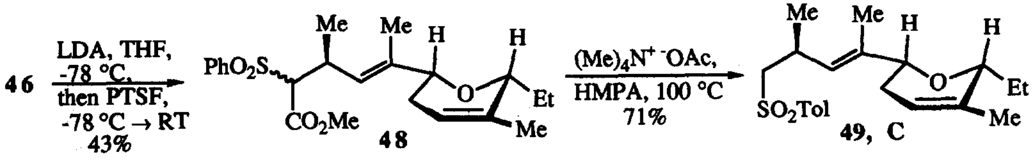
Scheme 16



a) 1. $(COCl)_2$, cat. DMF, CH_2Cl_2; 2. trans-propenyltrimethyltin, cat. $PhCH_2ClPd(PPh_3)_2$, HMPA, 70 °C, 3 h, 90%. b) MeMgBr, THF, 0 °C, 92%. c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 72 h, 72%. d) 1. LDA, THF, -78 °C; 2. TBSCl, -78 °C to 60 °C; 3. H_3O^+, 61%. e) CH_2N_2, Et_2O, rt 92%. f) 1. LDA, THF, -78 °C; 2. PhSSPh, 71%.

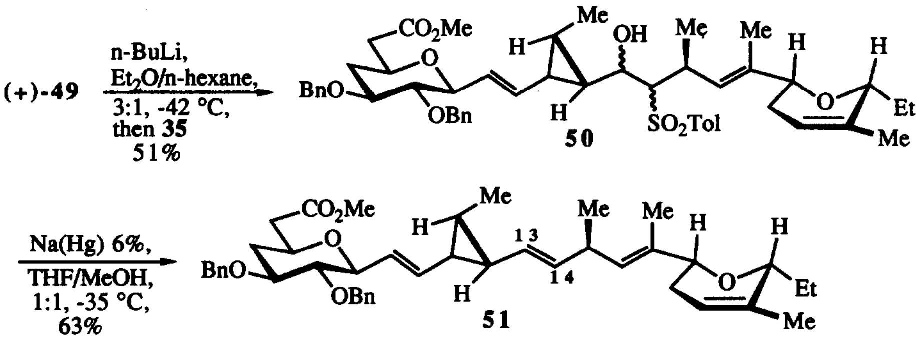
However, it was found that the required sulfones could be obtained by a simple sulfonylation reaction of (+)-methyl ester **46**.[38] Upon treatment of **46** with LDA in THF at -78 °C, followed by *p*-toluenesulfonyl fluoride (PTSF), the epimeric sulfones **48** were obtained in 43% yield (isolated yield) and 38% of starting material was recovered (Scheme 17). Nucleophilic decarbomethoxylation[39] gave (+)-sulfone **49**, segment C of ambruticin, in 71% yield ($[\alpha]_D^{21}$ = +32.3° (c 1.3, $CHCl_3$)). Thus, the requisite fragment was synthesized in 10% overall yield from (+)-**38c**.

Scheme 17



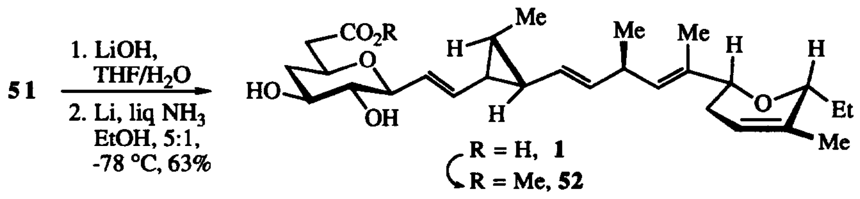
With the sulfone fragment C in hand, we were in the position to form the complete carbon framework of ambruticin.[10] This was accomplished by reaction of the enantiopure sulfone (+)-**49** with nBuLi in a mixture of Et_2O/hexane,[40] followed by treatment of the corresponding lithium salt with aldehyde **35** at -42 °C, affording the adduct **50** as a 1:1 diastereomeric mixture in 51% yield. This mixture was then treated with 6% Na(Hg) to give 13(*E*)-tetraene **51** as the main product, accompanied by ca. 8% of the corresponding 13(*Z*)-isomer in 63% overall yield (Scheme 18). The 13(*Z*)-impurity in **51** was established by its ^1H NMR spectrum: the H(13) signal at δ 4.98 was shown as a triplet (J=8.9 Hz) compared to the same signal at δ 5.10, as a doublet of doublets (J=14.5, 8.8 Hz) for the 13(*E*)-isomer. Silica gel chromatography of this *E*/*Z* mixture gave pure 13(*E*)-tetraene compound **51**.

Scheme 18



To complete the total synthesis of ambruticin, it was necessary to hydrolyze the methyl ester and deprotect the two secondary hydroxyl groups. Cleavage of the benzyl groups in **51** using TMSI[41] or BBr_3[42] in CH_2Cl_2 did not give good results. Reaction with BF_3 in the presence of dimethyl sulfide also failed to cleave the benzyl ethers.[43] Reductive cleavage by hydrogen transfer from cyclohexene catalyzed by palladium hydroxide failed again to provide the required material. Fortunately, deprotection of the two hydroxyl groups was finally accomplished by Birch reduction[44] of the corresponding acid. The methyl ester **51** was saponified using LiOH in THF/H_2O to give the corresponding carboxylic acid. This was then dissolved in liq. NH_3/EtOH (5:1) and treated with lithium (10 equivalents) at -78 °C to give, after purification by chromatography, an amorphous powder ($[\alpha]_D^{22}$ = +37° (c 0.10, $CHCl_3$)) in 63% yield. This material was shown by 300 MHz ^1H NMR, IR, TLC in several systems, and FD-MS to be identical with natural ambruticin, $[\alpha]_D^{22}$ = +42° (c 0.22, $CHCl_3$). Moreover, compound **1** was converted into its methyl ester **52** by treatment with diazomethane (Scheme 19). Synthetic **52**, $[\alpha]_D^{22}$ = +55° (c 0.11, $CHCl_3$), was identical in all respects with **52**, $[\alpha]_D^{22}$ = +55° (c 0.18, $CHCl_3$), derived from natural ambruticin (**1**). Thus, natural (+)-ambruticin has been prepared for the first time in a convergent synthesis from methyl 2,3-di-*O*-benzyl-glucopyranose in 18 steps or from glyoxylic acid in a 16-step sequence.

Scheme 19



EXPERIMENTAL SECTION

General Method. All commercially available reagents were used without further purification unless otherwise noted. All reactions were conducted under an inert atmosphere unless otherwise indicated. Et_2O and THF were distilled from sodium benzophenone ketyl. CH_2Cl_2, hexane, benzene, toluene, and N,N-diisopropylamine were distilled from calcium hydride. Melting points were determined on a Mel-Temp apparatus and are reported uncorrected. Infrared spectra were recorded on a Perkin Elmer 1310 spectrophotometer and were standardized with the 1601 cm^{-1} stretch of polystyrene. Nuclear magnetic resonance (NMR) spectra were recorded on Nicolet QE-300 (300 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Low resolution mass spectra were obtained on a VG7035 mass spectrometer (EI) or Nermag R10-10 (CI) quadrupole mass spectrometer. High resolution mass spectra were obtained on a VG7035 mass spectrometer.

Methyl 2,3-Di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-4-deoxy-α-D-glucopyranoside (13). To a stirred solution of the methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **12** (1.01 g, 2.70 mmol) in DMF (10 mL) was added imidazole (0.37 g, 5.40 mmol) followed by a solution of t-butyldiphenylsilyl chloride (0.89 g, 3.24 mmol) in DMF (3.5 mL) at 0 °C. The resulting solution was stirred at rt for 2 h, cooled to 0 °C, H_2O (1 mL) was added, and the mixture was stirred for 10 min. The resulting solution was poured into H_2O (100 mL) and extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 7:3) to afford 1.64 g (99%) of methyl 2,3-Di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-α-D-glucopyranoside as a colorless viscous oil. $[\alpha]_D^{22}$ +13.4° (c 2.55, $CHCl_3$). IR ($CHCl_3$): 3580, 3500, 3000, 2930, 1455, 1428, 1365, 1110, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73-7.67 (4H, m), 7.45-7.29 (16H, m), 5.00 (1H, d, J=11.3 Hz), 4.80 (1H, d, J=12.0 Hz), 4.78 (1H, d, J=11.3 Hz), 4.69 (1H, d, J=12.0 Hz), 4.65 (1H, d, J=3.5 Hz), 3.92-3.79 (3H, m), 3.70-3.59 (2H, m), 3.52 (1H, dd, J=9.5, 3.5 Hz), 3.38 (3H, s), 2.38 (1H, d, J=2.0 Hz), 1.06 (9H, s). Anal. Calcd for $C_{37}H_{44}O_6Si$: C, 72.51; H,7.24. Found: C, 72.33; H, 7.40.

To a stirred solution of methyl 2,3-Di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-α-D-glucopyranoside (0.617 g, 1.01 mmol) in toluene (5 mL) was added 1,1'-thiocarbonyldiimidazole (0.359 g, 2.01 mmol) at rt. The solution was heated at reflux until TLC (hexane-EtOAc, 7:3) showed no starting material. The reaction mixture was poured into 0.5 N HCl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with sat. sodium bicarbonate solution followed by brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a crude yellow oil, which was purified by column chromatography over silica gel (hexane-EtOAc, 7:3) to afford 0.676 g (93%) of methyl 2,3-Di-*O*-benzyl-6-*O*-*t*-butyldiphenylsilyl-4-*O*-imidazolyl-thiocarbonyl-α-D-glucopyranoside as a colorless viscous oil. $[\alpha]_D^{22}$ -0.7° (c 3.0, $CHCl_3$). IR ($CHCl_3$): 3060, 2935, 2860, 1460, 1390, 1330, 1285, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.61-7.56 (4H, m), 7.42-7.24 (15H, m), 7.13 (4H, s), 5.77 (1H, t, J=9.6 Hz), 4.86 (1H, d, J=12.0 Hz), 4.86 (1H, d, J=11.6 Hz), 4.70 (1H, d, J=12.0 Hz), 4.64 (1H, d, J=3.5 Hz), 4.58 (1H, d, J=11.6 Hz), 4.07 (1H, t, J=9.3 Hz), 3.90-3.82 (1H, m), 3.70-3.62 (3H, m), 3.42 (3H, s), 0.99 (9H, s). Anal. Calcd for $C_{41}H_{46}N_2O_6SSi$: C, 68.11; H, 6.41; N, 3.88. Found: C, 68.26; H, 6.50; N, 3.75.

To a stirred solution of nBu_3SnH (0.24 g, 0.83 mmol) in toluene (4.2 mL) was added a solution of thiocarbonylimidazolide prepared above (0.30 g, 0.42 mmol) in toluene (2 mL) over 2 min at 100 °C. The resulting solution was heated at reflux for 12 h. The solvent was removed *in vacuo* and the resulting crude oil was purified by column chromatography over silica gel (hexane-Et_2O, 9:1) to afford 0.20 g (83%) of the corresponding 4-deoxy-α-D-glucopyranoside **13** as a colorless viscous oil. $[\alpha]_D^{22}$ +18.5° (c 1.57, $CHCl_3$). IR ($CHCl_3$): 2995, 2920, 2855, 1110, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70-7.65 (4H, m), 7.45-7.27 (21H, m), 4.86 (1H, d, J=12.2 Hz), 4.77 (1H, d, J=11.8 Hz), 4.72 (1H, d, J=12.2 Hz), 4.68 (1H, d, J=11.8 Hz), 4.68 (1H, d, J=3.5 Hz), 3.95 (1H, ddd, J=12.1, 9.4, 5.1 Hz), 3.82 (1H, m), 3.70 (1H, dd, J=10.5, 5.7 Hz), 3.59

(1H, dd, J=10.5, 4.9 Hz), 3.46 (1H, dd, J=9.4, 3.5 Hz), 3.37 (3H, s), 2.08 (1H, ddd, J=12.1, 5.1, 2.1 Hz),1.39 (1H, q, J=12.1 Hz), 1.06 (9H, s). Anal. Calcd for $C_{37}H_{44}O_5Si$: C, 74.46; H, 7.43. Found: C, 74.80; H, 7.61.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-α-D-glucopyranoside (14). To a stirred solution of the 4-deoxy sugar **13** (25.9 g, 43.4 mmol) in THF (400 mL) was added dropwise a 1 M solution of nBu_4NF (65.1 mL, 65.1 mmol) in THF over 30 min at rt. The resulting solution was stirred at rt for 18 h and then poured into H_2O (500 mL). The mixture was extracted with Et_2O (3 x 500 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless oil, which was purified by column chromatography over silica gel (hexane-EtOAc, 1:1) to afford 14.81 g (95%) of **14** as a colorless viscous oil. $[\alpha]_D^{22}$ +48.8° (c 1.5, $CHCl_3$). IR ($CHCl_3$): 3595, 3600-3200, 3000, 2930, 1720, 1452, 1365, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.26 (10H, m), 4.87 (1H, d, J=12.2 Hz), 4.78 (1H, d, J=11.8 Hz), 4.75 (1H, d, J=12.2 Hz), 4.68 (1H, d, J=11.8 Hz), 4.67 (1H, d, J=3.6 Hz), 3.97 (1H, ddd, J=12.0, 9.6, 5.1 Hz), 3.85 (1H, m), 3.63 (1H, ddd, J=10.7, 7.4, 3.2 Hz), 3.52 (1H, ddd, J=10.7, 5.6, 5.6 Hz), 3.47 (1H, dd, J=9.6, 3.6 Hz), 3.39 (3H, s), 2.01 (1H, ddd, J=12.0, 5.1, 2.1 Hz), 1.95 (1H, dd, J=7.4, 5.6 Hz), 1.49 (1H, q, J=12.0 Hz). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.36; H, 7.31. Found: C, 70.08; H, 7.29.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-α-D-glucopyranosiduronic acid (15). To a stirred solution of alcohol **14** (6.12 g, 17.1 mmol) in DMF (69 mL) was added 21.81 g (58 mmol) of PDC at rt. The resulting red-brown viscous solution was stirred at rt for 20 h. The reaction mixture was diluted with Et_2O (100 mL) and stirred for 10 min. The clear yellow liquid was collected by decantation. The gummy brown residue was extracted with Et_2O (3 x 100 mL). The extracts were combined, and concentrated *in vacuo* to give a yellow viscous oil, which was purified by column chromatography over silica gel (CH_2Cl_2-MeOH, 10:1) to give 5.60 g (88%) of **15** as an amorphous powder. $[\alpha]_D^{22}$ +61.4° (c 0.97, $CHCl_3$). IR ($CHCl_3$): 3600-3000, 3000, 2925, 1600, 1440, 1100, 1040 cm^{-1}. ^1H NMR (300 MHz, MeOH-d_4): δ 7.40-7.10 (10H, m), 4.80-4.55 (5H, m), 4.21 (1H, dd, J=11.7, 2.0 Hz), 3.32 (3H, s), 3.89 (1H, m), 3.53 (1H, dd, J=7.0, 2.0 Hz), 2.55 (1H, m), 1.61 (1H, q, J=11.7 Hz).

Methyl (Methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-glucoheptopyranosiduronate) (16). To a stirred solution of the glucuronic acid **15** (1.73 g, 4.65 mmol) in CH_2Cl_2 (30 mL) was added oxalyl chloride (0.943 g, 0.65 mL, 7.43 mmol) followed by DMF (0.23 mmol) at rt. The resulting clear solution was stirred at rt for 2 h, and then concentrated *in vacuo* .

To a solution of the crude acyl chloride derivative in Et_2O (50 mL) was added a solution of diazomethane in Et_2O (30 mL) at 0 °C over 20 min. The resulting clear yellow solution was stirred at rt for 30 min and then evaporated *in vacuo* at under 20 °C to give a crude yellow oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 1:1) to afford 1.44 g (78%) of the corresponding diazoketone as a yellow viscous oil. $[\alpha]_D^{22}$ -23.6° (c 2.59, $CHCl_3$). IR ($CHCl_3$): 3130, 3000, 2930, 2110, 1630, 1350, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.30 (10H, m), 5.73 (1H, s), 4.89 (1H, d, J=12.2 Hz), 4.72 (2H, s), 4.72 (1H, d, J=12.2 Hz), 4.71 (1H, d, J=3.6 Hz), 4.22 (1H, dd, J=12.2, 2.0 Hz), 3.98 (1H, ddd, J=12.2, 9.5, 4.9 Hz), 3.46 (1H, dd, J=9.5, 3.6 Hz), 3.39 (3H, s), 2.56 (1H, q, J=12.2 Hz). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.86; H, 6.14; N, 6.86.

A solution of the diazoketone prepared as described above (1.39 g, 3.52 mmol) in MeOH (60 mL) was placed in a 100 mL pyrex test tube, and irradiated by a Hanovia 30620 type medium pressure UV arc under constant cooling by running H_2O for 48 h. The reaction mixture was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 3:2) to afford 0.96 g (68%) of **16** as a colorless viscous oil. $[\alpha]_D^{22}$ +38.7° (c 1.50, $CHCl_3$). IR ($CHCl_3$): 3000, 2950, 1738, 1440, 1360, 1170, 1100, 1040, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.26 (10H, m), 4.85 (1H, d, J=12.3 Hz), 4.78 (1H, d, J=11.7 Hz), 4.71 (1H, d, J=12.3 Hz), 4.68 (1H, d, J=11.7 Hz), 4.62 (1H, d, J=3.5 Hz), 4.22 (1H, m), 3.96 (1H, ddd, J=12.0, 9.4, 5.0 Hz), 3.70 (3H, s), 3.45 (1H, dd, J=9.4, 3.5 Hz), 3.39 (3H, s), 2.51 (1H, dd, J=15.4, 8.7 Hz), 2.44 (1H, dd, J=15.4, 4.7 Hz), 2.12 (1H, ddd, J=12.0, 5.0, 2.0 Hz), 1.46 (1H, q, J=12.0 Hz). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.27; H, 7.10.

Methyl (Acetyl 2,3-Di-*O*-benzyl-4-deoxy-α/β-D-glucoheptopyranosiduronate) (17α, 17β). To a stirred solution of the methyl glucoside **16** (0.705 g, 1.76 mmol) in acetic anhydride (7 mL) was added 1 mL of a 10% solution of H_2SO_4 in acetic anhydride at -30 °C. The resulting solution was stirred at -20 °C for 10 min. The reaction mixture was poured into a sat. sodium bicarbonate solution (100 mL) and stirred well for 30 min at rt to destroy the excess of acetic anhydride. The resulting mixture was extracted with Et_2O (3 x 100 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 3:2) to afford 0.664 g (88%) of 82:18 mixture of **17α** and **17 β** acetyl glycosides.

17α:

IR ($CHCl_3$): 3000, 2955, 1755, 1735, 1440, 1376, 1230, 1100, 1010 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.27 (10H, m), 6.29 (1H, d, J=3.6 Hz), 4.77 (1H, d, J=11.5 Hz), 4.72 (2H, s), 4.70 (1H, d, J=11.5 Hz), 4.32 (1H, m), 3.94 (1H, ddd, J=12.0, 9.4, 4.9 Hz), 3.69 (3H, s), 3.58 (1H, dd, J=9.4, 3.6 Hz), 2.60 (1H, dd, J=15.7, 7.3 Hz), 2.44 (1H, dd, J=15.7, 6.0 Hz), 2.25 (1H, ddd, J=12.0, 4.9, 2.0 Hz), 2.17 (3H, s), 1.48 (1H, q, J=12.0 Hz). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 66.92; H, 6.59.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-α/β-D-glucoheptopyranuronate (18α, 18β). To a freshly prepared solution of sodium methoxide (1.931 mmol) in MeOH (15 mL) was added a solution of acetyl glycosides **17** (413 mg, 0.966 mmol) in MeOH (5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 10 min and then poured into H_2O (50 mL). The mixture was extracted with Et_2O (3 x 50 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a residue, which was purified by column chromatography over silica gel (hexane-EtOAc, 3:2) to afford 360 mg (97%) of the mixture of **18** α and **18** β lactols. IR ($CDCl_3$): 3600, 3600-3200, 3000, 2955, 1735, 1440, 1170, 1080 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.37; H, 6.78. Found: C, 68.20; H, 6.85.

Methyl 2,3-Di-*O*-benzyl-1,4-dideoxy-1α/1β-fluoro-D-glucoheptopyranuronate (19α, 19β). To a stirred solution of lactols **18** (472 mg, 1.22 mmol) in CH_2Cl_2 (12 mL) was added diethylaminosulfur trifluoride (DAST) (590 mg, 3.66 mmol) at -30 °C. The resulting colorless solution was stirred at 0 °C for 20 min and then cooled again to -30 °C. MeOH (1 mL) was added to the reaction mixture to destroy the excess of DAST. After stirring at 0 °C for 10 min, the solution was poured into a sat. sodium bicarbonate solution (50 mL) and extracted with Et_2O (3 x 50 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless oil, which was purified by column chromatography over silica gel (hexane-Et_2O, 3:2) to afford 454 mg (96%) of 27:73 mixture of **19α** and **19β**.

19β:

IR ($CHCl_3$): 3000, 2955, 2900, 1740, 1440, 1170, 1120 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (10H, m), 5.22 (1H, dd, J=52.5, 6.4 Hz), 4.85 (1H, d, J=11.2 Hz), 4.80 (1H, d, J=11.2 Hz), 4.69 (2H, s), 4.03 (1H, m), 3.72 (3H, s), 3.66 (1H, m), 3.46 (1H, ddd, J=8.3, 6.4, 6.4 Hz), 2.76 (1H, dd, J=16.0, 7.2 Hz), 2.55 (1H, dd, J=16.0, 5.7 Hz), 2.19 (1H, dt, J=12.6, 2.5 Hz), 1.55 (1H, q, J=12.6 Hz). Anal. Calcd for $C_{22}H_{25}O_5F$: C, 68.02; H, 6.49. Found: C, 68.12; H, 6.45.

Dimenthyl (1S,2S)-3-methylcyclopropane-1,2-dicarboxylate (25). A dry, 1.0 L three-necked, round-bottomed flask containing a magnetic stirring bar, and a thermometer was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (29.7 mL, 176 mmol) and dry THF (240 mL). The solution was cooled to 0 °C and nBuLi (2.5 M in hexane, 70.4 mL, 176 mmol) was added dropwise over 45 min. Following the addition, the mixture was stirred for 20 min at 0 °C, then cooled to -78 °C. A solution of (-)-dimenthyl succinate **24** (31.56 g, 80 mmol) in THF (80 mL) was added dropwise over 1 h. The resulting yellow solution of succinate dianion was stirred for 1 h. To the reaction mixture was added a solution of 1,1-bromochloroethane (10.1 g, 70.4 mmol) in THF (15 mL) over a 5 h-period. After the reaction mixture was stirred for 2.5 h, it was poured into ice-cooled 0.5 N HCl (320 mL) and the product extracted with Et_2O (3 x 300 mL). The combined organic phases were washed with brine (1 x 400 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed over silica gel (hexane-Et_2O, 20:1) to give 13.23 g (45 %) of **25** as colorless crystals. mp: 98-99 °C. $[\alpha]_D^{23}$ -34° (c 0.5, $CHCl_3$). IR ($CHCl_3$): 2960, 2880, 1710, 1450, 1370, 1310, 1180 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.74-4.62 (2H, m), 2.24 (1H, dd, J=9.7, 4.6 Hz), 2.08 (1H, t, J=5.0 Hz), 1.99 (2H, m), 1.90-1.78 (3H, m), 1.71-1.61 (4H, m), 1.53-1.32 (4H, m), 1.22 (3H, d, J=6.3 Hz), 1.08-0.8 (6H, m), 0.90 (12H, d, J=7.4 Hz), 0.77 (3H, d, J=6.7 Hz), 0.75 (3H, d, J=6.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.60, 169.46, 74.76, 74.63, 46.99, 46.95, 41.00, 40.84, 34.19, 31.42, 31.34, 28.14, 26.27, 23.48, 21.98, 20.73, 20.65, 16.40, 16.26, 11.40. MS: m/e (relative intensity) 281 (M^+ $-C_{10}H_{19}$, 8.4), 266 (19), 265 (84), 139 (68), 138 (100), 127 (38), 96 (38), 95 (87), 83 (54), 82 (26). Anal. Calcd for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54. Found: C, 74.49; H, 10.70.

(1S,2S)-3-Methylcyclopropane-1,2-dicarboxylic acid (5b). The cyclopropane dimenthyl ester **25** (0.17 g, 0.40 mmol) was treated with an excess of a 10% KOH solution in 9:1 MeOH/H_2O (1.75 mL). The reaction mixture was stirred at rt for 72 h, then at 78-80 °C for 6 h. Progress of the reaction was monitored by GC and ^1H-NMR. The resulting mixture was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified by addition of a 10% HCl solution and extracted with Et_2O several times. The combined organic layers were dried over sodium sulfate and concentrated. Recrystallization of this material from Et_2O-petroleum ether gave 0.03 g (52%) of **5b** as a white solid. mp: 167-168.5 °C. Lit.[5] 163-164 °C. $[\alpha]_D^{23}$ +101° (c 0.8, EtOH). Lit.[5] $[\alpha]_D^{23}$ +92°(c 0.8, EtOH). IR ($CHCl_3$-DMSO, 9:1): 3400, 3200-2800, 1710, 1440, 1410, 1210 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.00 (2H, br s), 2.32 (1H, dd, J=10.0, 4.7 Hz), 2.16 (1H, t, J=4.8 Hz), 2.00-1.86 (1H, m), 1.32 (3H, d, J=6.2 Hz). MS: m/e (relative intensity) 127 (3), 126 (M^+-H_2O, 6), 100 (9), 99 (100), 81 (22), 69 (9).

(1S,2S)-1,2-Bis(benzyloxymethyl)-3-methylcyclopropane (26). Lithium aluminum hydride (76 mg, 2 mmol) in THF (8 mL) was cooled to 0 °C, and a solution of the dimenthyl ester **25** (210 mg, 0.5 mmol) in THF (2.5 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 1.5 h. The reaction was then cooled to -70 °C, and H_2O (53 μL) was slowly added, followed by a 15% NaOH solution (53 μL) and H_2O (0.16 mL). The mixture was allowed to warm to rt and stirred for 1 h. The slurry was filtered through Celite, and the cake was washed with EtOAc. Evaporation of the solvent *in vacuo* followed by chromatography over silica gel (EtOAc-MeOH, 90:10) gave 46 mg (79%) of the corresponding diol derivative.

To a solution of the diol above (44 mg, 0.38 mmol) in CH_2Cl_2 (4 mL) cooled to -70 °C was added benzoyl chloride (213 mg, 1.516 mmol), and the solution was stirred at -70 °C for 30 min. Et_3N (0.42 mL, 3.03 mmol) was added, and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction was quenched with H_2O (2 mL) and stirred for 1 h. The aqueous layer was extracted with CH_2Cl_2 several times, and the combined organic layers were washed with H_2O, brine, and then dried over sodium sulfate. Evaporation of the solvent *in vacuo* followed by chromatography over silica gel (petroleum ether-EtOAc, 97:3) afforded 80 mg (65%) of **26** as an oil. $[\alpha]_D^{23}$ -16.17° (c 0.68, $CHCl_3$). Lit.[5] $[\alpha]_D^{23}$ -12.9° (c 1.53, $CHCl_3$). IR ($CHCl_3$): 3020, 2950, 1720, 1610, 1585, 1450, 1320, 1275 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (4H, d, J=7.9 Hz), 7.54 (2H, t, J=7.2 Hz), 7.39 (4H, m), 4.48-4.31 (3H, m), 4.07 (1H, dd, J=11.5, 7.5 Hz), 1.44-1.34 (1H, m), 1.22 (3H, d, J=5.4 Hz), 1.17-1.10 (2H, m). ^{13}C NMR ($CDCl_3$): δ 166.59, 132.81, 130.31, 129.55, 128.30, 68.03, 64.51, 24.09, 20.62, 16.20, 12.73. MS: m/e (relative intensity) 324 (M^+, 1), 204 (5), 203 (37), 189 (2), 105 (100), 81 (18), 77 (52), 51 (18).

Menthyl (1S,2S,3S)-2-carboxy-3-methylcyclopropane-1-carboxylate (27). To a solution of the cyclopropane dimenthyl ester **25** (2.5 g, 5.94 mmol) in THF (10 mL) was added a 10% KOH solution in 9:1 EtOH/H_2O (3.94 mL, 7.02 mmol) at rt. The reaction mixture was stirred at rt for 3.5 days, then the solvent was evaporated, diluted with H_2O, and extracted with Et_2O. The aqueous layer was acidified with a 10% HCl solution to pH ~ 3 and extracted several times with Et_2O. The combined organic layers were washed successively with H_2O, brine, and dried over sodium sulfate. Evaporation of the solvent *in vacuo* afforded 1.4 g (83%) of the monoacid **27** as a clear oil. $[\alpha]_D^{23}$ +8.76° (c 0.685, $CHCl_3$). IR ($CDCl_3$): 3200-2700, 1730-1710, 1460, 1390, 1370, 1310, 1190, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.73 (1H, dt, J=10.9, 4.3 Hz), 2.33 (1H, dd, J=9.8, 4.5 Hz), 2.10 (1H, t, J=5.0 Hz), 2.03-1.96 (1H, m), 1.90-1.80 (2H, m), 1.71-1.65 (2H, m), 1.56-1.35 (2H, m), 1.25 (3H, d, J=6.3 Hz), 1.09-1.00 (2H, m), 0.91 (3H, d, J=6.4 Hz), 0.90 (3H, d, J=7.0 Hz), 0.92-0.8 (1H, m), 0.75 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 178.60, 169.01, 75.02, 46.98, 40.95, 34.17, 31.39, 28.99, 27.69, 26.31, 24.34, 23.41, 21.96, 20.62, 16.26, 11.20. MS: m/e (relative intensity) 155 (M^+ - $C_6H_7O_3$, 5), 139 (11), 138 (63), 127 (100), 109 (5), 99 (20), 95 (82), 83 (30), 81 (56).

Menthyl (1S,2S,3S)-2-hydroxymethyl-3-methylcyclopropane-1-carboxylate (28). To a solution of the cyclopropane monoacid **27** (1.32 g, 4.68 mmol) in dry THF (40 mL) cooled to 0 °C was added dropwise a 1.0 M solution of B_2H_6-THF complex (5.62 mL, 5.62 mmol) over a 20 min-period. The reaction mixture was allowed to warm to rt and stirred for 8 h, followed by the addition of a second equivalent of B_2H_6-THF complex (5.617 mL, 5.617 mmol). The reaction was carefully monitored by TLC (hexane-EtOAc, 70:30). When all the starting material had disappeared, the reaction mixture was carefully quenched at rt by a dropwise addition of 1:1, H_2O/AcOH (1 mL) with stirring until no more gas evolution occurred. The reaction mixture was concentrated at rt, and the slurry was diluted with EtOAc (80 mL) and washed with H_2O (30 mL). The aqueous phase was extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with a sat. sodium bicarbonate solution, brine, and then dried over sodium sulfate. Solvent removal and purification of the residue by chromatography (hexane-EtOAc, 8:2) gave 1.25 g (100%) of **28** as a white solid. mp: 85-86 °C. $[\alpha]_D^{23}$ -48° (c 0.5, $CHCl_3$). IR ($CDCl_3$): 3600, 2960, 2880, 1710, 1410, 1390, 1370, 1290, 1185, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.69 (1H, dt, J=11.0, 4.3 Hz), 3.60-3.45 (2H, m), 2.10-1.80 (3H, m), 1.70-1.56 (4H, m), 1.55-1.19 (3H, m), 1.19 (3H, d, J=5.8 Hz), 1.10-0.81 (3H, m), 0.89 (3H, d, J=6.5 Hz), 0.88 (3H, d, J=7.0 Hz), 0.73 (3H, d, J=7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 171.46, 74.18, 64.59, 47.10, 41.11, 34.24, 31.39, 29.63, 26.28, 24.05, 23.44, 22.01, 20.67, 16.29, 11.80. MS: m/e 237 (M^+ -CH_3O), 155, 138, 113, 99, 95, 81, 69, 55. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.51. Found: C, 71.58; H, 10.48.

Menthyl (1S,2S,3S)-2-formyl-3-methylcyclopropane-1-carboxylate (29). A solution of the cyclopropane alcohol **28** (0.536 g, 2 mmol) in CH_2Cl_2 (10 mL) was added to a suspension of periodinane (1.017 g, 2.4 mmol) in CH_2Cl_2 (10 mL) with stirring. The reaction mixture was stirred at rt for 1.5 h, followed by the addition of a second equivalent of the periodinane reagent. The reaction was carefully monitored by TLC (hexane-EtOAc, 8:2). When all the starting material had disappeared, the reaction mixture was filtered through Celite, and the filter cake was washed with CH_2Cl_2. The solvent was evaporated *in vacuo*, and the residue was chromatographed over silica gel (hexane-EtOAc, 95:5) to give 0.51 g (96%) of **29** as a white crystalline solid. mp: 66-67 °C. $[\alpha]_D^{23}$ +23.5 (c 3.2, $CHCl_3$). IR ($CHCl_3$): 2950, 2920, 2865, 1720, 1710, 1455, 1390, 1370, 1290, 1180, 950 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.38 (1H, d, J=3.4 Hz), 4.74 (1H, dt, J=10.9, 6.6 Hz), 2.42-2.36 (2H, m), 2.04-1.95 (1H, m), 1.95-1.80 (2H, m), 1.75-1.65 (2H, m), 1.60-1.35 (2H, m), 1.29 (3H, d, J=6.3 Hz), 1.15-1.00 (2H, m), 0.92 (3H, d, J=6.3 Hz), 0.91 (3H, d, J=7.0 Hz), 0.95-0.80 (1H, m), 0.76 (3H, d, J=7.0 Hz). MS: m/e (relative intensity) 155 (M^+ -$C_6H_7O_2$, 2), 138 (87), 123 (29), 111 (64), 95 (95), 83 (90), 81 (83), 55 (100). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.38; H, 9.92.

Menthyl (1S,2S,3S)-2-(2,2-dibromovinyl)-3-methylcyclopropane-1-carboxylate (30). A solution of triphenylphosphine (1.42 g, 5.41 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and treated with CBr_4 (0.896 g, 2.70 mmol). A solution of aldehyde **29** (0.360 g, 1.35 mmol) in CH_2Cl_2 (10 mL) was then added dropwise. The yellow solution was stirred at 0 °C for 30 min. The solvent was evaporated *in vacuo*, and the residue was chromatographed over silica gel (hexane-EtOAc, 96:4) to give 0.56 g (98%) of **30** as a white solid. mp: 75-76 °C. $[\alpha]_D^{23}$ -20.9° (c 2.06, $CHCl_3$). IR ($CHCl_3$): 2955, 2925, 2870, 1715, 1455, 1370, 1180 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (1H, d, J=8.8 Hz), 4.74 (1H, dt, J=10.9, 4.3 Hz), 2.14 (1H, ddd, J=8.8, 6.0, 4.7 Hz), 2.06-1.96 (1H, m), 1.94-1.85 (1H, m), 1.83 (1H, dd, J=9.4, 4.7 Hz), 1.75-1.65 (2H, m), 1.55-1.30 (3H, m), 1.25 (3H, d, J=6.2 Hz), 1.15-1.00 (2H, m), 0.92 (3H, d, J=6.9 Hz), 0.90 (3H, d, J=6.5 Hz), 0.94-0.82 (1H, m), 0.76 (3H, d, J=7.0 Hz). MS: m/e (relative intensity) 284 (M^+ -138, 25), 205 (24), 203 (24), 160 (7), 138 (11), 83 (100), 55 (48). Anal. Calcd for $C_{17}H_{26}Br_2O_2$: C, 48.36; H, 6.21. Found: C, 48.61; H, 6.29.

(1S,2S,3S)-3-Ethynyl-2-methylcyclopropylmethyl Triphenylmethyl Ether (31). To a stirred solution of the menthyl ester **30** (3.96 g, 9.37 mmol) in toluene (50 mL) was added a 1 M solution of DIBALH (28.1 mL, 28.1 mmol) in hexane at -78 °C. The resulting solution was stirred at -78 °C for 10 min and then at

0 °C for 30 min. The reaction mixture was poured into 0.2 N HCl (200 mL) and extracted with Et$_2$O (3 x 200 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless crude oil, which was purified by column chromatography over silica gel (hexane-Et$_2$O, 1:1) to afford 2.29 g (90%) of the corresponding cyclopropylcarbinol as a colorless oil. [α]$_D^{23}$ -19.7° (c 2.54, CHCl$_3$). IR (CHCl$_3$): 3610, 3600-3300, 2960, 2925, 2880, 1388, 1263, 1077, 1020 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.90 (1H, d, J=8.6 Hz), 3.80 (1H, dt, J.11.7, 5.9 Hz), 3.63 (1H, ddd, J=11.7, 7.9, 5.4 Hz), 1.38 (1H, dd, J=5.9, 5.4 Hz), 1.38-1.15 (3H, m), 1.20 (3H, s). ^{13}C NMR (CDCl$_3$): δ 140.71, 85.84, 61.28, 28.51, 27.54, 19.49, 12.35. MS: m/e (relative intensity) 270 (M$^+$, 11), 239 (21), 226 (37), 199 (10), 160 (62), 158 (60), 91 (35), 79 (100). Anal. Calcd for $C_7H_{10}Br_2O$: C, 31.14; H, 3.73. Found: C, 31.53; H, 3.81.

To a stirred solution of the cyclopropylcarbinol obtained from **30** by the procedure described above (2.33 g, 8.64 mmol) in DMF (35 mL) was added triphenylmethyl chloride (9.64 g, 34.6 mmol) followed by Et$_3$N (9.63 mL, 69.1 mmol) and DMAP (0.21 g, 1.73 mmol) at rt. The resulting mixture was stirred at rt for 72 h, poured into an aqueous ammonium chloride solution (100 mL), and then extracted with Et$_2$O (3 x 200 mL). The organic layer was combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless oil, which was purified by column chromatography over silica gel (hexane-CH$_2$Cl$_2$, 8:1) to afford 3.98 g (90%) of the triphenylmethyl ether as a colorless viscous oil. [α]$_D^{23}$ +28.4° (c 1.20, CHCl$_3$). IR (CHCl$_3$): 3050, 3000, 2920, 2860, 1490, 1448, 1060 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.52-7.47 (6H, m), 7.36-7.23 (9H, m), 5.89 (1H, d, J=8.7 Hz), 3.38 (1H, dd, J=9.9, 6.0 Hz), 2.92 (1H, dd, J=9.9, 8.3 Hz), 1.41-1.28 (1H, m), 1.23-1.10 (2H, m), 1.02 (3H, d, J=5.8 Hz). Anal. Calcd for $C_{26}H_{24}Br_2O$: C, 60.95; H, 4.72. Found: C, 61.38; H, 4.83.

To a stirred solution of the triphenylmethyl ether prepared as described above (128.6 mg, 0.251 mmol) in THF (5 mL) was added dropwise a 1.42 M solution of nBuLi (0.35 mL, 0.50 mmol) in hexane at -78 °C. After stirring at -78 °C for 10 min, the solution was poured into H$_2$O (30 mL) and extracted with Et$_2$O (3 x 30 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless residue, which was purified by column chromatography over silica gel (hexane-Et$_2$O, 20:1) to afford 81.4 mg (92%) of **31** as a colorless viscous oil. [α]$_D^{23}$ +85.9° (c 0.84, CHCl$_3$). IR (CHCl$_3$): 3310, 3050, 3000, 2960, 2920, 2110, 1600, 1490, 1450, 1060 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.52-7.45 (6H, m), 7.35-7.20 (9H, m), 3.36 (1H, dd, J=10.0, 6.0 Hz), 2.79 (1H, dd, J=10.0, 8.9 Hz), 1.86 (1H, d, J=1.9 Hz), 1.55 (1H, m), 1.32 (1H, m), 0.98 (3H, d, J=6.4 Hz), 0.72 (1H, dt, J=4.9, 1.9 Hz). MS: m/e (relative intensity) 275 (M$^+$-77, 14), 243 (100), 183 (14), 165 (62), 105 (39), 77 (42). Anal. Calcd for $C_{26}H_{24}O$: C, 88.60; H, 6.86. Found: C, 88.45; H, 6.62.

Methyl (8E,10S,11S,12S)-2,3-Di-*O*-benzyl-1,4-dideoxy-1β-[11-methyl-12-triphenylmethoxymethylcyclopropylethenyl]-D-glucoheptopyranuronate (33β) and Methyl (8E,10S,11S,12S)-2,3-Di-*O*-benzyl-1,4-dideoxy-1α-[11-methyl-12-triphenylmethoxymethylcyclopropylethenyl]-D-glucoheptopyranuronate (33α). To a stirred solution of the cyclopropylacetylene compound **31** (333 mg, 0.945 mmol) in hexane (3 mL) was added a 1.0 M solution of DIBALH (0.95 mL, 0.95 mmol) in hexane at 40 °C. The resulting solution was stirred at 50 °C for 2 h. After cooling to rt, the reaction mixture was diluted with toluene (4 mL). To this *in situ*-generated vinylalane solution was added a solution of glycosyl fluoride **19** (anomeric mixture, α:β=27:73, 282 mg, 0.727 mmol) in toluene (1 mL) at -20 °C. The resulting colorless solution was stirred at -20 °C for 10 min then at rt for 30 min. The reaction mixture was poured into 0.2 N HCl (20 mL) and extracted with Et$_2$O (3 x 30 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless crude residue, which was purified by column chromatography over silica gel (hexane-CH$_2$Cl$_2$-EtOAc, 20:20:1) to afford 0.256 g (49%) of **33β** and 0.150 g (28%) of **33α**, as colorless oils.

33β:

[α]$_D^{22}$ +22.6 ° (c 0.53, CHCl$_3$). IR (CHCl$_3$): 3050, 3000, 2940, 2860, 1733, 1490, 1450, 1070, 910 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.55-7.50 (25H, m), 5.46-5.38 (2H, m), 4.82 (1H, d, J=10.5 Hz), 4.70 (2H, s), 4.63 (1H, d, J=10.5 Hz), 3.83 (1H, m), 3.69 (3H, s), 3.69-3.60 (2H, m), 3.41 (1H, dd, J=9.8, 5.4 Hz), 3.16 (1H, t, J=9.0 Hz), 2.76 (1H, t, J=9.8 Hz), 2.68 (1H, dd, J=15.5, 6.5 Hz), 2.45 (1H, dd, J=15.5, 6.5 Hz), 2.23 (1H, ddd, J=12.0, 3.8, 0.8 Hz), 1.43 (1H, q, J=12.0 Hz), 1.27 (1H, m), 1.02 (1H, m), 1.01 (3H, s), 0.88 (1H, m). Anal. Calcd for $C_{48}H_{50}O_6$: C, 79.75; H, 6.97. Found: C, 79.88; H, 7.04.

33α:

IR ($CHCl_3$): 3000, 2960, 2930, 1740, 1453, 1080 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.45 (5H,m), 7.40-7.20 (20H, m), 5.68 (1H, dd, J=15.7, 5.6 Hz), 5.41 (1H, dd, J=15.7, 8.3 Hz), 4.76-4.60 (4H, m), 4.52 (1H, t, 5.6 Hz), 4.25-4.16 (1H, m), 3.78-3.68 (1H, m), 3.69 (3H, s), 3.58 (1H, dd, J=8.8, 5.6 Hz), 3.42 (1H, dd, J=9.4, 5.6 Hz), 2.79 (1H, t, J=9.4 Hz), 2.58 (1H, dd. J=15.2, 7.9 Hz), 2.46 (1H, dd, J=15.2, 5.4 Hz), 2.19-2.10 (1H, m), 1.44 (1H, q, J=9.8 Hz), 1.15-0.85 (3H, m), 1.00 (3H, d, J=5.5 Hz).

Methyl (8E,10S,11S,12S)-2,3-Di-*O*-benzyl-1,4-dideoxy-1β-[11-methyl-12-formylcyclopropylethenyl]-D-glucoheptopyranuronate (35). To a stirred solution of 33β (173 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added a solution of *p*-toluenesulfonic acid (9 mg, 0.048 mmol) in MeOH (2 mL) at rt. The resulting solution was stirred at rt for 2 h and then poured into a sat. sodium bicarbonate solution (20 mL). This mixture was extracted with Et_2O (3 x 30 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless residue, which was purified by preparative thin layer chromatography (hexane-EtOAc, 1:1) to afford 106 mg (92%) of the corresponding deprotected primary alcohol as a colorless oil. $[\alpha]_D^{22}$ -10.8° (c 1.25, $CHCl_3$). IR ($CHCl_3$): 3600, 3600-3400, 3000, 2950, 2870, 1735, 1440, 1360, 1230, 1080 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.27 (10H, m), 5.50 (1H, dd, J=15.3, 6.8 Hz), 5.39 (1H, dd, J=15.3, 8.1 Hz), 4.84 (1H, d, J=10.7 Hz), 4.71 (1H, d, J=11.7 Hz), 4.68 (1H, d, J=11.7 Hz), 4.65 (1H, d, J=10.7 Hz), 3.90-3.85 (2H, m), 3.69 (3H, s), 3.70-3.62 (2H, m), 3.60-3.50 (1H, m), 3.18 (1H, t, J=9.0 Hz), 2.67 (1H, dd, J=15.6, 6.6 Hz), 2.45 (1H, dd, J=15.6, 6.4 Hz), 2.23 (1H, ddd, J=12.2, 4.9, 1.1 Hz), 1.44 (1H, q, J=12.2 Hz), 1.28 (1H, br s), 1.25-1.15 (1H, m), 1.18 (3H, d, J=5.8 Hz), 1.10-1.00, (2H, m). Anal. Calcd for $C_{29}H_{36}O_6$: C, 72.47; H, 7.55. Found: C, 72.27; H, 7.72.

To a stirred solution of alcohol prepared above (96.2 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin's periodinane (127 mg, 0.30 mmol) at rt. The resulting reaction mixture was stirred at rt for 30 min and then diluted with Et_2O (20 mL). This mixture was poured into a sat. sodium bicarbonate solution (10 mL) containing sodium thiosulfate (0.5 g). The organic layer was separated and the aqueous layer was washed with Et_2O (2 x 20 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a crude residue, which was purified by preparative thin layer chromatography (hexane-EtOAc, 3:1) to afford 86.5 mg (90%) of 35 as a colorless oil. $[\alpha]_D^{22}$ +29.4° (c 1.30, $CHCl_3$). IR ($CHCl_3$): 3000, 1735, 1700, 1075 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.50 (1H, d, J=4.7 Hz), 7.40-7.28 (10H, m), 5.62 (1H, dd, J=15.5, 6.4 Hz), 5.36 (1H, dd, J=15.5, 8.6 Hz), 4.88 (1H, d, J=11.0 Hz), 4.71 (1H, d, J=11.6 Hz), 4.67 (1H, d, J=11.6 Hz), 4.63 (1H, d, J=11.0 Hz), 3.90-3.80 (1H, m), 3.70 (3H, s), 3.70-3.60 (2H, m), 3.16 (1H, t, J=9.1 Hz), 2.66 (1H, dd, J=15.6, 6.9 Hz), 2.45 (1H, dd, J=15.6, 6.2 Hz), 2.22 (1H, ddd, J=12.3, 5.0, 1.6 Hz), 2.20-2.10 (1H, m), 1.95 (1H, dt, J=9.0, 4.7 Hz), 1.60-1.52 (1H, m), 1.43 (1H, q, J=12.3 Hz), 1.31 (3H, d, J=6.4 Hz). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.67; H, 7.35.

3-Methyl-1,3-hexadiene (36). Sodium hydride (16 g, 0.4 mol, as a 60% dispersion in mineral oil) in a 1.0 L three-necked flask was washed with hexane (3 x 50 mL) to remove the mineral oil. The flask was then equipped with rubber stoppers, a reflux condenser, and a mechanical stirrer. The system was alternatively evacuated and filled with nitrogen; DMSO (140 mL) was introduced rapidly, and the mixture was heated at 75-80 °C for ca. 60 min, or until the evolution of hydrogen ceased. The resulting black-greenish solution of methylsulfinyl carbanion was cooled in an ice-H_2O bath, and methyltriphenylphosphonium bromide (142.8 g, 0.4 mol) in warm DMSO (320 mL) was added, keeping the internal temperature between 15-20 °C. The resulting solution of the ylide was allowed to warm to rt and stirred for 10 min, then at 30-32 °C for 10 min (or until a red-brownish color developed). The reaction mixture was cooled to 15 °C and the aldehyde (43.34 g, 0.44 mol) was added dropwise (through a cannula), keeping the temperature between 15-20 °C. The reaction mixture was stirred at rt for 25 min, then at 30-32 °C for 20 min. The reaction was immediately distilled in the presence of a cat. amount of hydroquinone under reduced pressure to give 32 g (75%) of **36** (collected in a solid carbon dioxide trap). bp: 35-37 °C/59 mm Hg. Lit.[45] 101-103 °C/760 mm Hg. IR ($CHCl_3$): 3100, 2980, 1650, 1610, 990, 900, 870 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (1H, dd, J=17.4, 10.7 Hz), 5.60 (1H, t, J=7.2 Hz), 5.19 (1H, d, J=17.4 Hz), 5.04 (1H, d, J=10.6 Hz), 2.26 (2H), 1.85 (3H, s), 1.12 (3H, t, J=7.6 Hz). MS: m/e (relative intensity) 96 (M^+, 4), 57 (3), 44 (4), 41 (5), 32 (19), 28 (100).

(+)-6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-carboxylic acid (38c). Freshly distilled 3-methyl-1,3-hexadiene (**36**) (15.6 g, 0.162 mol) was placed into a Carius tube containing a cat. amount of hydroquinone, glyoxylic acid monohydrate (22.45 g, 0.244 mol), and $CHCl_3$ (80 mL). The tube was sealed and heated at 115-120 °C for 12 h. The reaction mixture was cooled to 0 °C and diluted with H_2O (30 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were washed with H_2O (1 x 100 mL), brine (1 x 100 mL), and dried over sodium sulfate. Complete removal of solvent afforded 22.5 g (81%) of a 4:1 mixture of acids (**38c**/**38t**; cis:trans) as a reddish viscous oil, which was used directly in the next step without further purification

A mixture of potassium fluoride (33.83 g, 0.582 mol), 2,4'-dibromoacetophenone (80.93 g, 0.291 mol), and DMF (350 mL) was stirred at rt for 5 min. A solution of acids **38c**/**38t** (45 g, 0.265 mol) in DMF (50 mL) was then added to the reaction mixture and the whole stirred at rt for 3 h, then at 100 °C for 30 min. The reaction mixture was cooled to rt and diluted with H_2O (200 mL). The aqueous solution was extracted with Et_2O (4 x 400 mL). The combined ethereal extracts were washed with H_2O (3 x 400 mL) and dried over sodium sulfate. After the solvent was partially removed in vacuo, a precipitate was formed. The slurry was the filtered to give 51 g (53%) of **39** as a white solid material. mp: 137-138 °C. IR ($CHCl_3$): 3005, 2940, 1765, 1710, 1580, 1170 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (2H, d, J=8.5 Hz), 7.64 (2H, d, J=8.5 Hz), 5.62 (1H, d, J=4.6 Hz), 5.42 (1H, d, J=16.3 Hz), 5.31 (1H, d, J=16.3 Hz), 4.33 (1H, dd, J=10.6, 3.8 Hz), 4.18 (1H, br s), 2.37-2.18 (2H, m), 1.90-1.82 (1H, m), 1.62 (3H, s), 1.67-1.55 (1H, m), 0.94 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 190.87, 170.84, 135.37, 132.90, 132.16, 129.23, 129.04, 119.63, 78.51, 72.37, 65.86, 28.50, 25.34, 18.32, 8.26. MS: m/e 339, 337, 185, 183, 157, 155, 125, 95, 81, 76, 67. Anal. Calcd for $C_{17}H_{19}BrO_4$: C, 55.59; H, 5.22. Found: C, 55.84; H, 5.27.

To a solution of the phenacyl ester **39** prepared as described above (46.0 g, 0.125 mol) in glacial AcOH (650 mL) was slowly added zinc (dust, 49.31 g, 0.754 mol) in a 60 min-period at rt. The reaction mixture was stirred at rt for 8 h, then filtered on Celite, and the zinc residue washed with AcOH (200 mL), then THF (200 mL). Most of the solvent was evaporated and the crude reaction mixture diluted with Et_2O and washed with H_2O (2 x 150 mL). The organic layer was treated with a diluted NaOH solution to pH ~ 10. The aqueous phase was washed with Et_2O several times, then acidified with a 1.0 N HCl solution to pH ~ 4, and extracted with Et_2O. The combined organic extracts were successively washed with H_2O, brine, and dried over sodium sulfate. After evaporation of the solvent, 19.23 g (90%) of pure acid **38c** was obtained as a yellowish solid. mp: 61-63 °C. This acid was used in the next step without further purification.

To a solution of acid **38c** (21 g, 0.123 mol) in MeOH (125 mL) was added (+)-α-methylbenzylamine (14.97 g, 0.123 mol) with stirring. The solvent was partially evaporated *in vacuo* and Et_2O (100 mL) was added. The solvents were partially evaporated and more Et_2O was added. The process was repeated until crystallization occurred. The reaction mixture was cooled to 0 °C and filtered to give 19 g of the salt. The recrystallization process was repeated four more times or until the optical rotation of the corresponding acid was constant. After five recrystallizations, 6 g of the corresponding salt were obtained. This salt was then acidified with a 1.0 N HCl solution to pH ~ 4 and extracted with Et_2O several times. The organic phase was successively treated with H_2O, brine, and then dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave 3.4 g (32%, from the racemic acid **38c**) of the optically pure acid (+)-**38c** as a clear viscous oil. $[\alpha]_D^{23}$ +169.4° (c 0.85, EtOH). IR ($CDCl_3$): 3400, 2980, 1770, 1720, 1330, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (1H, br), 5.60 (1H, d, J=4.4 Hz), 4.21 (1H, br s), 4.16 (1H, dd, J=10.6, 4.2 Hz), 2.40-2.26 (2H, m), 1.86-1.80 (1H, m), 1.61 (3H, s), 1.66-1.57 (1H, m), 0.91 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 174.98, 135.13, 119.61, 78.67, 71.73, 27.94, 25.19, 18.67, 8.07. MS: m/e (relative intensity) 170 (M^+, 18), 113 (54), 95 (100), 57 (46), 41 (64). HRMS: Calcd for $C_9H_{14}O_3$ (M^+): 170.0943. Found: 170.0980.

***N*-(6-Ethyl-5-methyl-3,6-dihydro-2*H*-pyran-2-oyl)-*N*-α-methylbenzylamide (40).** To a stirred solution of the acid (+)-**38c** (36 mg, 0.21 mmol), N-methylmorpholine (0.03 mL, 0.28 mmol), in THF (1 mL) cooled to -18 °C was added isobutyl chloroformate (0.04 mL, 0.28 mmol). The reaction mixture was stirred at -18 °C for 1 min, and then (-)-α-methylbenzylamine was added. The solution was stirred at -18 °C for 45 min. The reaction was quenched by addition of H_2O and then extracted with Et_2O several times. The organic phase was washed with H_2O, brine, dried over sodium sulfate, and the solvent evaporated *in vacuo*. GC and ^1H NMR analyses of the crude residue showed it to be > 98% homogeneous.

IR ($CHCl_3$): 3420, 3005, 2980, 1670, 1525, 1460, 1115, 1060 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.24 (5H, m), 6.91 (1H, br d, J=7.8 Hz), 5.60 (1H, d, J=5.7 Hz), 5.17 (1H, m), 4.15 (1H, br s), 4.02 (1H, dd, J=11.1, 3.5 Hz), 2.42-2.38 (1H, m), 2.17-2.02 (1H, m), 1.86-1.78 (1H, m), 1.61 (3H, s), 1.53 (3H, d, J=6.9 Hz), 1.57-1.51 (1H, m), 0.93 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 170.96, 143.38, 134.92, 128.63, 127.16, 125.83, 120.28, 78.48, 73.16, 47.78, 28.52, 25.55, 22.21, 18.76, 8,62. MS: m/e (relative intensity) 273 (M^+, 8), 169 (5), 125 (33), 120 (25), 105 (100), 97 (25), 95 (23), 79 (25), 77 (29), 57 (27). HRMS: Calcd for $C_{17}H_{23}NO_2$ (M^+): 273.1729. Found: 273.1692.

(L)-Dimethyl malate (41). Ozonolysis of the acid (-)-**38c** (200 mg) in CH_2Cl_2 (15 mL) was performed at -70 °C. The solvent was then evaporated under reduced pressure. To the gelatinous ozonide a 90% HCO_2H solution (1 mL) and a 30% H_2O_2 solution (1 mL) were added; the mixture was carefully heated at 100 °C for 30 min, whereupon the H_2O_2 and HCO_2H were removed *in vacuo*.

Crude malic acid (100 mg) from the degradation was dissolved in MeOH (5 mL), and an ethereal solution of diazomethane was added until the reaction was complete. After removal of the solvents under reduced pressure, the residual yellow oil was purified by chromatography (hexane-EtOAc, 8:2) to yield 70 mg of product as a colorless oil, identical by IR, ^1H NMR and ^{13}C NMR to commercial (L)-dimethyl malate. $[\alpha]_D^{23}$ -7.31° (c 1.915, EtOAc). Lit.[31] $[\alpha]_D^{23}$ -7.95° (c 6.42, EtOAc).

(*E*)-Propenyltrimethylstannane. A dry 250 mL, three-necked, round-bottomed flask equipped with a Teflon-covered magnetic stirring bar, thermometer, and an efficient reflux condenser was capped with serum stoppers and flushed with argon. Lithium dispersion (1% sodium, 30% oil suspension, 18.7 g, 0.8 g-atoms of lithium) was rapidly weighed in air and transferred to the flask. The lithium was washed three times by transferring approximately 30 mL portions of anhydrous Et_2O into the flask through a no-air stopper by forced siphon through a stainless steel cannula, stirring the resulting suspension of lithium briefly, allowing the suspension to separate and finally withdrawing the major part of the Et_2O by forced siphon through a cannula (a syringe can be used instead). After separating the last washings, Et_2O (125 mL) was added. The reaction mixture was cooled to approximately 0 °C. The surface of the lithium was cleaned by injecting 1,2-dibromoethane (150 μL). A solution of freshly distilled *E*-1-chloropropene (17.5 g, 0.229 mol) in Et_2O (60 mL) was slowly added through a cannula over a 1.5 h-period, while the internal temperature of the reaction was maintained at 10-15 °C. A brown precipitate began to form. The reaction mixture was allowed to stir at rt for 30 min, and stirring stopped. The precipitate was allowed to settle, and the solution transferred by a large-gauge cannula through a syringe (with a glass wool pad) into a 500 mL three-necked flask. The precipitate was washed with Et_2O (1 x 10 mL), and the solution transferred to the flask through the filter. A solution of trimethyltin chloride (25 g, 0.122 mol) in dry Et_2O (20 mL) was then added to the lithium solution over a 45 min-period, keeping the internal temperature at 28-31 °C. The reaction mixture was stirred at rt for 2.5 h, then cooled to 0 °C, and quenched with a sat. ammonium chloride solution (50 mL), then H_2O (50 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with a sat. sodium chloride solution, dried over sodium sulfate, and evaporated *in vacuo*. Distillation of the crude reaction gave 10 g (34%) of (*E*)-propenyltrimethylstanne as a clear colorless liquid. bp: 124-126 °C/760 mm Hg. IR ($CHCl_3$): 2980, 2910, 1600, 1440, 980 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.18-5.83 (2H, m), 1.86 (3H, d, J=4.2 Hz), 0.12 (9H, s).

Preparation of (+)-Enone 42. To a stirred solution of the acid (+)-**38c** (3 g, 17.65 mmol) in CH_2Cl_2 (60 mL), and DMF (0.12 mL) at 0 °C was added oxalyl chloride (1.82 mL, 21.18 mmol) over a 30 min-period. The reaction mixture was stirred at 0 °C for 1 h, then at rt for 2 h. The solvent was evaporated *in vacuo*, and the residue was used directly in the next reaction without further purification.

In a 50 mL, two-necked, round-bottomed flask equipped with a Teflon-covered magnetic stirring bar, a drierite filled trap, and a thermometer was placed the crude acid chloride in HMPA (16 mL). Freshly prepared trans-propenyltrimethyltin (4.34 g, 21.18 mmol) was then added followed by the addition of benzylchlorobis(triphenylphosphine) palladium (II) (13.6 mg, 0.02 mmol). The yellow solution was heated at 65-70 °C with stirring under an air atmosphere for 3 h. The reaction mixture was cooled to rt and H_2O (15 mL) was added. The mixture was extracted with Et_2O (3 x 60 mL). The ethereal solutions were combined and washed with H_2O, brine, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue was purified by chromotography over silica gel (hexane-EtOAc, 98:2) to give 3.1 g (90%) of **42** as a colorless volatile oil. $[\alpha]_D^{23}$ +230.9° (c 1.13, $CHCl_3$). IR ($CHCl_3$): 3010, 2980, 1690, 1620, 1440, 1310, 1290, 1110 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06-6.96 (1H, m), 6.62 (1H, dd, J=14.2, 1.4 Hz), 5.56 (1H, br s), 4.10 (1H, br s), 4.04 (1H, t, J=7.9 Hz), 2.18-2.09 (2H, m), 1.90 (3H, dd, J=7.0, 1.3 Hz), 1.86-1.73 (1H, m), 1.59 (3H, s), 1.59-1.48 (1H, m), 0.93 (3H, t, J=7.4 Hz). ^{13}C NMR ($CDCl_3$): δ 198.52, 144.06, 135.32, 126.46, 119.79, 78.30, 77.79, 27.57, 25.49, 18.82, 18.41, 8.53. MS: m/e (relative intensity) 194 (M$^+$, 10), 165 (14), 125 (100), 107 (22), 97 (20), 81 (23), 69 (68).

Preparation of (+)-Alcohol 43. A solution of the α,β-unsaturated ketone **42** (3.02 g, 15.44 mmol) in THF (80 mL) was cooled to 0 °C and MeMgBr (3.1 M solution in Et_2O, 6.5 mL, 20.1 mmol) was added dropwise over a 30 min-period. After the addition, the reaction mixture was stirred at 0 °C for 2 h under argon. The reaction mixture was quenched at 0 °C by addition of a sat. ammonium chloride solution (14 mL), then H_2O (14 mL). The mixture was extracted with Et_2O (3 x 70 mL). The ethereal solutions were combined and washed with brine (1 x 50 mL), dried over sodium sulfate and the solvent removed by evaporation. The residue was purified by chromatography over silica gel (hexane-EtOAc, 98:2) to give 3.0 g (92 %) of the alcohol **43** as a clear volatile liquid. $[\alpha]_D^{23}$ +88.57° (c 0.7, $CHCl_3$). IR ($CDCl_3$): 3560, 2980, 1450, 1210, 1110, 1050 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75-5.63 (1H, m), 5.53 (1H, dd, J=14.1, 1.0 Hz), 5.50 (1H, br s), 4.02 (1H, br s), 3.30 (1H, dd, J=10.9, 3.2 Hz), 2.73 (1H, s), 2.12-2.00 (1H, m), 1.83-1.76 (2H, m), 1.69 (3H, dd, J=5.9, 1.0 Hz), 1.57 (3H, s), 1.53-1.44 (1H, m), 1.26 (3H, s), 0.89 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 134.88, 133.48, 124.43, 120.58, 79.08, 78.40, 73.56, 25.61, 24.10, 18.73, 17.92, 8.63. MS: m/e (relative intensity) 210 (M$^+$, 2), 192 (4), 126 (11), 125 (100), 107 (18), 69 (55). HRMS: Calcd for $C_{13}H_{22}O_2$ (M$^+$): 210.1620. Found: 210.1648. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.11; H, 10.50.

Preparation of (+)-Acetate 44. Acetic anhydride (3.02 mL, 31.96 mmol) was added to a stirred solution of alcohol **43** (3.36 g, 15.98 mmol), Et_3N (4.46 mL), and DMAP (0.39 g, 3.2 mmol) in CH_2Cl_2 (15 mL) at rt. The solution was stirred at rt for three days in a sealed tube. Excess of anhydride was quenched by the addition of MeOH. Evaporation of the solvents gave a reddish-oily residue, which was suspended in Et_2O and successively treated with 1.0 N HCl, aqueous sodium hydrogen carbonate, and sodium chloride sat. solution. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. Purification of the residue by chromatography over silica gel (hexane-EtOAc, 98:2) gave 2.9 g (72%) of the acetate **44** as a colorless oil. $[\alpha]_D^{23}$ +47.06° (c 0.765, $CHCl_3$). IR ($CDCl_3$): 3020, 2980, 1730, 1450, 1370, 1260, 1220, 1120, 1060 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75-5.59 (2H, m), 5.51 (1H, br d, J=4.8 Hz), 3.96 (1H, br s), 3.80 (1H, dd, J=10.8, 3.1 Hz), 2.18-2.02 (1H, m), 1.99 (3H, s), 1.84-1.68 (2H, m), 1.70 (3H, d, J=5.6 Hz), 1.56 (3H, s), 1.53 (3H, s), 1.50-1.40 (1H, m), 0.88 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 169.96, 135.44, 132.33, 125.56, 120.27, 83.64, 78.51, 77.01, 25.55, 25.29, 22.28, 19.40, 18.73, 18.00, 8.69. MS: m/e (relative intensity) 252 (M$^+$, 1), 192 (9), 163 (28), 125 (77), 107 (31), 96 (100), 85 (76), 69 (31). HRMS: Calcd for $C_{13}H_{20}O$ (M$^+$-AcOH): 192.1514. Found: 192.1500.

Preparation of (+)-Methyl ester 46. To a stirred solution of dry N,N-diisopropylamine (1.1 mL, 7.85 mmol) in THF (10 mL) cooled to 0 °C was added nBuLi (2.5 M in hexanes, 3.14 mL, 7.85 mmol) over several min. After the solution was stirred for 10 min following the addition, the reaction mixture was cooled to -78 °C, and an additional 1 mL of THF was added. The ester **44** (1.65 g, 6.54 mmol) in THF (7 mL) was slowly added over a 40 min-period, keeping the internal temperature between -78 °C and -70 °C. After the reaction was stirred for 5 min, TBSCl (1.18 g) in THF-HMPA (1:1, 6 mL) was added in one portion. The cooling bath was then removed, and the reaction mixture was allowed to warm to 0 °C and stirred for 1 h, then at rt for an additional 1 h, and finally 1.5 h at 65 °C. The yellow solution was cooled to rt and diluted with THF (60 mL), then treated with a 10% HCl aqueous solution (16 mL). The reaction mixture was stirred at rt for 3 h The solvent was evaporated and the residue diluted with Et_2O and treated with a 1.0 N KOH aqueous solution; the organic phase was discarded, and the aqueous solution was washed with Et_2O. The basic solution was acidified with 10% HCl and the product isolated by ether extraction. This afforded 1.0 g (61%) of a 12:1 mixture of acids **45** as a colorless oil. This mixture was carried through the next reaction without further purification. $[\alpha]_D^{23}$ +27.27° (c 0.55, $CHCl_3$). IR ($CDCl_3$): 2980, 1710, 1450, 1300, 1120, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): (major component) δ 9.90-9.40 (1H, br), 5.56 (1H, d, J=4.9 Hz), 5.25 (1H, d, J=9.3 Hz), 4.11 (1H br s), 3.83 (1H, dd, J=10.4, 2.5 Hz), 2.98-2.92 (1H, m), 2.30 (2H, d, J=7.2 Hz), 2.18-2.03 (1H, m), 1.91-1.70 (2H, m), 1.69 (3H, s), 1.59 (3H, s), 1.61-1.50 (1H, m), 1.05 (3H, d, J=6.7 Hz), 0.89 (3H, t, J=7.4 Hz). ^{13}C NMR ($CDCl_3$): (major component) δ 178.49, 136.17, 135.03, 128.93, 120.82, 77.86, 77.76, 41.68, 30.12, 29.09, 25.60, 20.53, 18.92, 12.26, 8.20. MS: m/e (relative intensity) 252 (M^+, 0.3), 223 (1), 177 (2), 139 (4), 109 (4), 96 (79), 81 (100), 77 (5), 67 (9). HRMS: Calcd for $C_{13}H_{19}O_3$ (M^+-C_2H_5): 223.1334. Found: 223.1364. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.02; H, 9.55.

A solution of acids **45** (1 g, 3.96 mmol) in Et_2O (20 mL) was treated with an excess of diazomethane. The solvent was then evaporated, and the two isomers were cleanly separated by chromatography over silica gel (hexane-EtOAc, 98:2) to give 0.97 g (92%) of the methyl ester **46** as a clear liquid. $[\alpha]_D^{23}$ +30° (c 0.90, $CHCl_3$). IR ($CDCl_3$): 2980, 1730, 1440, 1290, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.54 (1H, d, J=5.8 Hz), 5.21 (1H, d, J=9.4 Hz), 4.07 (1H, br s), 3.80 (1H, dd, J=10.6, 2.8 Hz), 3.62 (3H, s), 3.00-2.82 (1H, m), 2.25 (2H, d, J=7.3 Hz), 2.17-2.03 (1H, m), 1.88-1.70 (2H, m), 1.66 (3H, s), 1.57 (3H, s), 1.58-1.45 (1H, m), 1.00 (3H, d, J=6.7 Hz), 0.88 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 172.98, 135.91, 135.04, 129.14, 120.79, 77.81, 77.77, 51.28, 41.80, 30.13, 29.28, 25.59, 20.56, 18.89, 12.15, 8.18. MS: m/e (relative intensity) 266 (M^+, 2), 237 (8), 171 (19), 139 (25), 123 (9), 107 (18), 96 (100), 82 (36). HRMS: Calcd for $C_{15}H_{23}O_2$ (M^+-OCH_3): 235.1698. Found: 235.1719.

Preparation of (+)-Sulfone 49. A solution of N,N-diisopropylamine (0.24 mL, 1.7 mmol) in THF (3 mL) was treated with nBuLi (2.5 M in hexane, 0.68 mL, 1.7 mmol) at 0 °C, under a nitrogen atmosphere. After 20 min at 0 °C, the solution was cooled to -78 °C, and a solution of the methyl ester **46** (266 mg, 1 mmol) in THF (3 mL) was slowly added. After 1 h at -78 °C, *p*-toluenesulfonyl fluoride (348 mg, 2.0 mmol) in THF (2 mL) was added all at once. The reaction mixture was allowed to warm to rt and stirred for 24 h, then cooled to 0 °C, quenched by careful addition of a sat. ammonium chloride solution, and extracted with EtOAc several times. The combined organic extracts were washed with H_2O and brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel (hexane-EtOAc, 9:1) to give 180 mg (43% isolated yield) of **48** as a mixture of diastereomers plus 38% of recovered starting material. This diastereomeric mixture was used directly in the next step without further purification. mp: 129-131 °C. IR ($CHCl_3$): 3020, 2920, 1740, 1600, 1330, 1140, 1000 cm^{-1}. MS: m/e (relative intensity) 420 (M^+, 1), 391 (8), 325 (19), 157 (12), 139 (25), 109 (15), 96 (100), 81 (92), 69 (15). HRMS: Calcd for $C_{21}H_{27}SO_5$ (M^+-C_2H_5): 391.1579. Found: 391.1542.

To a stirred solution of sulfone methyl esters **48** (130 mg, 0.31 mmol) in HMPA (2 mL) was added $(Me)_4N^+\ ^-OAc$ (370 mg, 2.78 mmol) and the mixture was heated at 96-100 °C for 17 h. The reaction mixture was cooled and diluted with EtOAc, washed with H_2O several times, brine, dried over magnesium sulfate, and the solvent removed *in vacuo*. The residue was purified by chromatography over silica gel (hexane-EtOAc, 9:1) to give 0.080 g (71%) of **49** as a clear liquid. $[\alpha]_D^{23}$ +32.3° (c 1.3, $CHCl_3$). IR ($CHCl_3$): 2980, 2940, 1600, 1450, 1300, 1145 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (2H, d, J=8.1 Hz), 7.33 (2H, d, J=8.1 Hz), 5.53 (1H, d, J=4.5 Hz), 5.15 (1H, d, J=8.6 Hz), 4.02 (1H, br s), 3.71 (1H, dd, J=10.3, 2.9 Hz), 3.11-2.95 (3H, m), 2.45 (3H, s), 2.01-1.90 (1H, m), 1.89-1.66 (2H, m), 1.58 (3H, s), 1.56 (3H, s), 1.59-1.43 (1H, m), 1.14 (3H, d, J=6.2 Hz), 0.88 (3H, t, J=7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 144.33, 137.14, 136.62, 135.14, 129.73, 127.95, 127.31, 120.64, 77.92, 77.17, 62.59, 29.95, 27.82, 25.62, 21.60, 20.83, 18.89, 12.50, 8.35. MS: m/e (relative intensity) 362 (M^+, 0.3), 333 (3), 267 (3), 157 (8), 139 (10), 96 (100), 81 (91), 65 (9). HRMS: Calcd for $C_{19}H_{25}SO_3$ (M^+-C_2H_5): 333.1524. Found: 333.1527.

Methyl 5β,6α-dibenzyloxypolyangioate (51). To a stirred solution of sulfone **49** (54.4 mg, 0.15 mmol) in dry Et_2O (1 mL) cooled to 0 °C was added dropwise a solution of nBuLi (1.5 M in hexane, 0.18 mmol). The yellow solution was stirred at 0 °C for 10 min, then at -42 °C for 15 min. Dry hexane (0.5 ml) was added, and a solution of the aldehyde **35** (60 mg, 0.125 mmol) in Et_2O (0.5 ml) was added dropwise. The reaction mixture was stirred at -42 °C for 2 h, then quenched with ammonium chloride, and extracted with EtOAc several times. The combined organic extracts were washed with brine, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue was chromatographed over silica gel (hexane-EtOAc, 8:2) to give 53.7 mg (51%) of hydroxy sulfones **50** as a mixture of diastereomers. The mixture was used in the next reaction without further purification.

To a stirred solution of the hydroxy sulfones **50** (10 mg, 0.012 mmol) in a mixture of MeOH-THF (1:1, 0.8 mL) cooled to -35°C was added an excess of Na(Hg) 6% (300 mg) in one portion. The reaction mixture was stirred at -35 °C for 3.5 h, then diluted with Et_2O and filtered through Celite; the cake was washed several times with Et_2O. To the ether solution was added a sat. solution of ammonium chloride and then 1.0 N HCl solution until pH ~ 4. The aqueous phase was extracted several times with EtOAc, and the combined organic phase was washed with H_2O, brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel (hexane-EtOAc, 9:1) to give 13(*E*)-tetraene **51** as the main product, accompanied by ca. 8% of the corresponding 13(*Z*)-isomer, in 63% overall yield, as a clear colorless liquid. Careful chromatography of this *E*/*Z* mixture eluted with CH_2Cl_2/hexane/Et_2O (10:10:1) produced pure 13(*E*) product, homogeneous by TLC and ^{1}H NMR. IR ($CHCl_3$): 3000, 2960, 1735, 1460, 1440, 1365, 1090 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.34 (10H, m), 5.57 (1H, d, J=4.6 Hz), 5.50-5.40 (3H, m), 5.26 (1H, d, J=8.5 Hz), 5.10 (1H, dd, J=14.5, 8.8 Hz), 4.83 (1H, d, J=10.6 Hz), 4.70 (2H, s), 4.64 (1H, d, J=10.6 Hz), 4.11 (1H, br s), 3.90-3.80 (2H, m), 3.69 (3H, s), 3.70-3.50 (2H, m), 3.18 (1H, t, J=9.0 Hz), 3.15-3.04 (1H, m), 2.68 (1H, dd, J=15.7, 6.4 Hz), 2.44 (1H, dd, J=15.6, 6.5 Hz), 2.24-2.10 (2H, m), 1.93-1.72 (2H, m), 1.66 (3H, s), 1.60 (3H, s), 1.63-1.40 (3H, m), 1.20-1.05 (2H, m), 1.09 (3H, s), 1.06 (3H, d, J=6.6 Hz), 0.90 (3H, t, J=7.2 Hz). FDMS: Calc for $C_{43}H_{56}O_6$: 668. Found: 668 (M^+).

(+)-Ambruticin (1). To a stirred solution of methyl 5β,6α-dibenzyloxypolyangioate (**51**) (7 mg, 0.0105 mmol) in THF (1.5 mL) was added a solution of LiOH (1.3 mg, 0.0525 mmol) in H_2O (0.5 mL) at rt. The resulting solution was stirred at rt for 18 h and then poured into 0.2 N HCl (10 mL). This mixture was extracted with Et_2O (3 x 20 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give 7 mg of crude 5β,6α-dibenzyloxypolyangioic acid as a colorless oil. This crude acid was used in next debenzylation step without further purification.

To a stirred solution of the crude 5β,6α-dibenzyloxypolyangioic acid (7 mg, 0.0105 mmol) in liquid ammonia (10 mL, distilled from sodium) and EtOH (2 mL) at -78 °C was added 0.7 mg (0.105 mmol) of lithium wire. The resulting mixture was stirred at -78 °C for 30 min. Ammonium chloride (20 mg) was added to this mixture to quench the excess lithium and stirred for 30 min at -78 °C. To the resulting mixture was added CH_2Cl_2 (10 mL), stirred for 1 h at rt, then poured into 0.2 N HCl (10 mL), and extracted with $CHCl_3$ (3 x 20 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a colorless oil, which was purified by preparative thin layer chromatography (EtOAc-*i*-PrOH-H_2O, 85:10:5) to afford 3.2 mg (63% from **51**) of ambruticin (**1**) as an amorphous powder. $[\alpha]_D^{22}$ +37° (c 0.10, $CHCl_3$). Ambruticin from natural source; $[\alpha]_D^{22}$ +42° (c 0.22,

$CHCl_3$). IR ($CHCl_3$): 2960, 2920, 1715, 1065, 970 cm^{-1} (identical with ambruticin from natural source). ^{1}H NMR (300 MHz, MeOH-d_4): δ 5.59 (1H, d, J=5 Hz, C-20), 5.55-5.30 (3H, m, C-8, C-9, C-14), 5.23 (1H, d, J=9 Hz, C-16), 5.17 (1H, dd, J=15, 8 Hz, C-13), 4.10 (1H, br s, C-22), 3.95-3.80 (2H, m, C-3, C-18), 3.60-3.45 (2H, m, C-5, C-7), 3.15-3.05 (1H, m, C-15), 2.98 (1H, t, J=9 Hz, C-6), 2.55-2.35 (2H, m, C-2), 2.15-2.00 (2H, m, C-4, C-19), 1.95-1.80 (1H, m, C-19), 1.80-1.65 (1H, m, C-23), 1.65 (3H, s, C-26), 1.60 (3H, s, C-25), 1.65-1.40 (3H, m, C-4, C-12, C-23), 1.20-1.05 (2H, m, C-10, C-11), 1.05 (3H, s, C-28), 1.04 (3H, d, J=7 Hz C-27), 0.88 (3H, t, J=7 Hz, C-24) (identical with ambruticin from natural source). FABMS (1% CF_3CO_2H): 475 (M^++1, 38), 473 (30), 457 (23), 439 (15), 379 (34), 316 (34), 288 (95), 277 (100), 241 (34), 207 (43), 193 (72), 191 (72), 185 (100). Ambruticin from natural source; EIMS: 475 (M^++1, 61), 473 (34), 457 (36), 439 (30), 379 (13), 369 (23), 277 (95), 241 (26), 207 (34), 193 (46), 191 (32), 185 (100).

(+)-Ambruticin methyl ester (52). To a stirred solution of ambruticin (**1**) (4 mg, 0.0084 mmol) in Et_2O (5 mL) and MeOH (1 mL) was added a solution of diazomethane in Et_2O at 0 °C. The resulting yellow solution was stirred at rt for 10 min and evaporated *in vacuo* at under 20 °C to give a crude oil, which was purified by preparative thin layer chromatography (hexane-EtOAc, 1:2) to afford 3.5 mg (85%) of ambruticin methyl ester (**52**) as a colorless oil. $[\alpha]_D^{22}$ +55° (c 0.11, $CHCl_3$). Ambruticin methyl ester derived from natural source ambruticin; $[\alpha]_D^{22}$ +55° (c 0.18, $CHCl_3$). IR ($CHCl_3$): 2955, 2920, 1730, 1435, 1160 cm^{-1} (identical with **52** derived from natural ambruticin). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.58 (1H, d, J=4.9 Hz, C-20), 5.47 (1H, dd, J=15.4, 6.5 Hz, C-14), 5.46-5.40 (2H, m, C-8, C-9), 5.27 (1H, d, J=8.9 Hz, C-16), 5.08 (1H, dd, J=15.4, 8.7 Hz, C-13), 4.11 (1H, br s, C-22), 3.98-3.90 (1H, m, C-3), 3.86 (1H, dd, J=10.8, 3.0 Hz, C-18), 3.70 (3H, s, CO_2CH_3), 3.74-3.66 (1H, m, C-5), 3.57-3.52 (1H, m, C-7), 3.14 (1H, t, J=9.0 Hz, C-6), 3.15-3.05 (1H, m, C-15), 2.66 (1H dd, J=15.7, 6.9 Hz, C-2), 2.46 (1H, dd, J=15.7, 6.1 Hz, C-2), 2.20-2.05 (2H, m, C-4, C-19), 1.95-1.80 (1H, m, C-19), 1.80-1.70 (1H, m, C-23), 1.65 (3H, s, C-26), 1.60 (3H, s, C-25), 1.68-1.45 (3H, m, C-4, C-12, C-23), 1.20-1.05 (2H, m, C-10, C-11), 1.07 (3H, s, C-28), 1.06 (3H, d, J=7.0 Hz, C-27), 0.90 (3H, t, J=7.3 Hz, C-24) (identical with **52** derived from natural ambruticin). FDMS: Calcd. for $C_{29}H_{44}O_6$: 488. Found: 488 (M^+).

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