Studies Related to Thromboxane A_2: A Formal Synthesis of Optically Active 9α,11α-Thiathromboxane A_2 Methyl Ester from Levoglucosan

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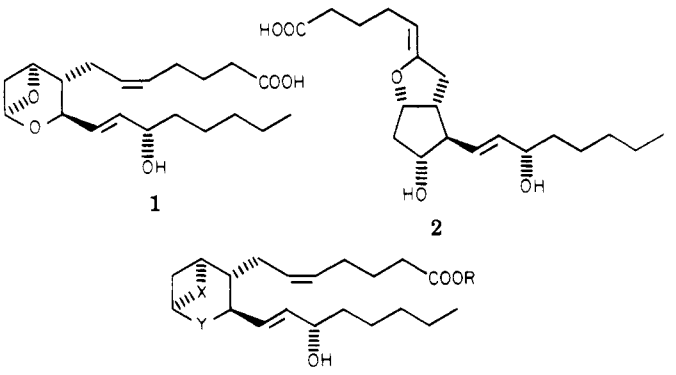
A synthesis of (±)-7-*exo*-(*n*-butyloxy)-2-oxa-6-thiabicyclo[3.1.1]heptane (**4**) from 2-(benzyloxy)-5,6-dihydropyran (**5**) (Scheme I) and the conversion of levoglucosan **20** into **36** (Scheme IV) are described. Compound **36** is an intermediate in a published synthesis (Scheme III) of the biologically active 9α,11α-thiathromboxane A_2 methyl ester (**19**).

Introduction

The metabolites of arachidonic acid constitute a large group of biologically important compounds, which are described in a very extensive literature.[1] This paper deals with the synthesis of analogues of one of these metabolites—thromboxane A_2. Both this substance (**1**) and another eicosanoid, prostaglandin I_2 (or prostacyclin) (**2**) are involved in mechanisms that control the behavior of blood platelets and blood vessels.[1b] Thromboxane A_2 causes platelets to aggregate and to adhere to blood vessel walls. It also causes vasoconstriction. Prostacyclin I_2, on the other hand, exerts opposing effects; both aggregation of platelets and adherence to blood vessel walls are prevented and the substance induces vasodilation.

Thromboxane A_2 is a very reactive substance under physiological conditions; it has a half-life of about 30 s at 37 °C in an aqueous medium of pH 7.[2a] More stable analogues could, in principle, be useful tools for biological studies; they would be easier to handle and they might differ from the natural material in ways that are quantitatively and/or qualitatively advantageous. The properties of analogues might also serve to corroborate the structure **1** that was assigned to thromboxane A_2 on the basis of the structures of *isolated* breakdown products and mass spectral data.[2]

A number of thromboxane A_2 analogues, e.g., **3**,[3] had been prepared when we began our synthesis and several were reported during the course of our work. We decided to make the thia compound **3** (X = S, Y = O, R = Me or Na) in the expectation that the bicyclo[3.1.1]heptane portion would have similar hydrophobicity and chemical properties to the corresponding unit of the natural product but would react more slowly[4] with water.



X	Y	R	ref
S	S	Na	3k
O	CH_2	H	3h
CH_2	O	H	3g

In order to gain experience in the preparation of the hitherto unknown 2-oxa-6-thiabicyclo[3.1.1]heptane system we decided, first of all, to attempt to synthesize **4** (Scheme I) in the hope that it would be a fairly readily accessible member of the compound class with a high enough boiling point to allow manipulation on a small scale. After making[5] compound **4**, we began the synthesis of **3** (X = S, Y = O, R = Me) from levoglucosan. During this work, the first synthesis of the same material was published,[6] and so we took our experiments only to the stage where they provided an intermediate that was common to both routes.

Synthesis of (±)-7-*exo*-(*n*-Butyloxy)-2-oxa-6-thiabicyclo[3.1.1]heptane (4). The approach to model compound **4** is summarized in Scheme I.

Epoxidation (*m*-chloroperbenzoic acid) of the substituted dihydropyran **5** afforded[7] epoxides **6** and **7** in a ratio of about 3:1. The expected[8] major product **6** (49%) had

(1) See, for example: (a) Nelson, N. A.; Kelly, R. C.; Johnson, R. A. *Chem. Eng. News* **1982**, August 16, 30. (b) "Prostaglandins and Thromboxanes", Newton, R. F., Roberts, S. M., Eds.; Butterworth Scientific: London, 1982. (c) Dusting, G. J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1977**, *13*, 3. (d) Moncada, S.; Vane, J. R. "Advances in Prostaglandin and Thromboxane Research"; Samuelsson, B., Ramwell, P. W., Paoletti, R., Eds.; Raven Press: New York, 1980; Vol 6, p 43. (e) Samuelsson, B.; Folco, G.; Granstrom, E.; Kindahl, H.; Malmsten, C. "Advances in Prostaglandin and Thromboxane Research"; Coceani, F., Olley, P. M., Eds.; Raven Press: New York, 1978; Vol 4, p 1. (f) Ackroyd, J.; Scheinmann, F. *Chem. Soc. Rev.* **1982**, *11*, 321.

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(3) For examples, see: (a) Nicolaou, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, D.; Smith, E. F.; Lefer, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2566. (b) Ansell, M. F.; Caton, M. P. L.; Palfreyman, M. N.; Stuttle, K. A. J. *Tetrahedron Lett.* **1979**, 4497. (c) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Ibid.* **1979**, 3661. (d) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404. (e) Barraclough, P. *Tetrahedron Lett.* **1980**, *21*, 1897. (f) Ansell, M. F.; Caton, M. P.; Stuttle, K. A. J. *Ibid.* **1982**, *23*, 1955. (g) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Ibid.* **1980**, *21*, 137. (h) Maxey, K. M.; Bundy, G. L. *Ibid.* **1980**, *21*, 445. (i) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Ibid.* **1981**, *22*, 1349. (j) Kosuge, S.; Hamanaka, N.; Hayashi, M. *Ibid.* **1981**, *22*, 1345. (k) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *J. Am. Chem. Soc.* **1981**, *103*, 4597. (l) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron Lett.* **1981**, *22*, 5301. (m) Kosuge, S.; Hamanaka, N.; Hayashi, M. *Ibid.* **1981**, *22*, 1345. (n) Kosuge, S.; Hayashi, M.; Hamanaka, N. *Ibid.* **1982**, *23*, 4027. (o) Schaaf, T. K.; Bussolotti, D. L.; Parry, M. J.; Corey, E. J. *J. Am. Chem. Soc.* **1981**, *103*, 6502.

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(5) Research Report to AFHMR: July, 1981.

(6) Ohuchida, S.; Hamanaka, N.; Hashimoto, S. *Tetrahedron Lett.* **1982**, *23*, 2883.

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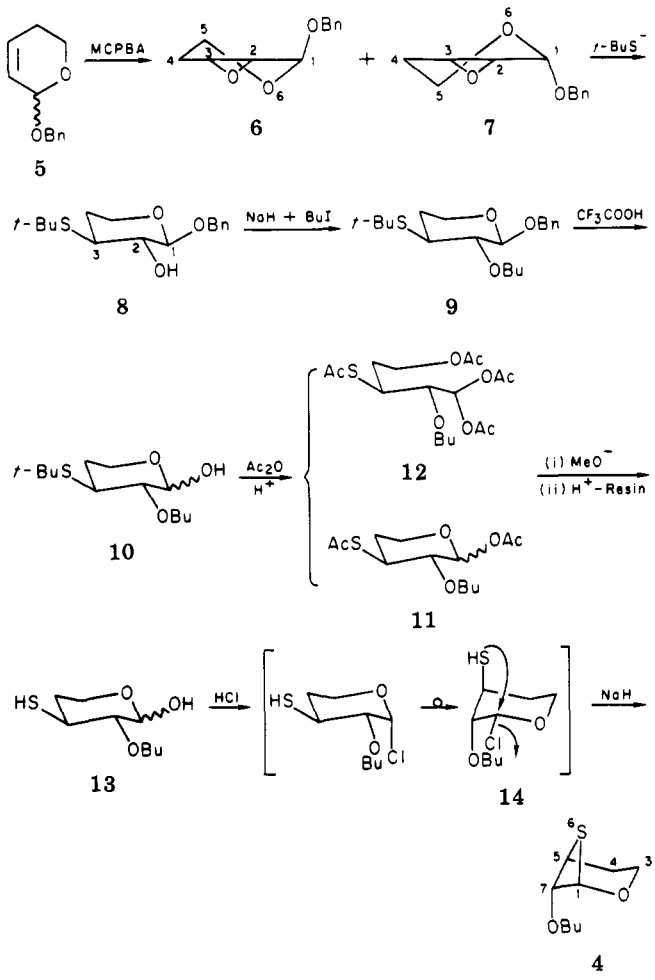
0022-3263/84/1949-1554$01.50/0

Scheme I[a]



[a] All compounds are racemic.

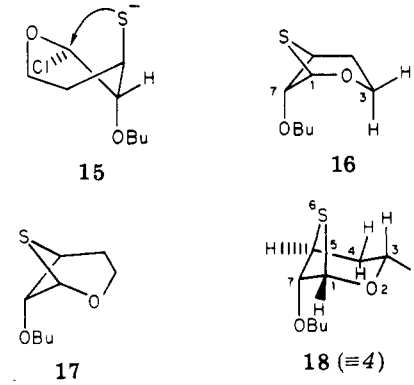
spectral characteristics consistent with the structure shown: $J_{1,2} \leq 1$ Hz for **6** and 3 Hz for the minor isomer.[8a,9] Epoxide **6** reacted cleanly (92% yield) with *tert*-butyl mercaptide to produce **8**, and alkylation with iodobutane–sodium hydride furnished **9** in 90% yield. In this sequence, the regiochemical course of the transformation **6** → **8** was expected on the basis of extensive precedent[8a,10] and was also proved by appropriate ^{1}H NMR decoupling experiments which showed that each of the substituents in **8** was in an equatorial conformation since the coupling constants, $J_{1,2}$ and $J_{2,3}$, were large (7 and 10.25 Hz, respectively).

Deprotection (61% yield) of the anomeric hydroxyl (**9** → **10**) was effected with 90% aqueous trifluoroacetic acid in dichloromethane and the *tert*-butyl group was removed[11] by treatment with acetic anhydride and concentrated sulfuric acid. This reaction afforded (57%) the diacetate **11**[12] (as a mixture of anomers) as well as the acyclic compound **12**.[13]

The acetyl groups were then removed (**11** → **13**, 84%) by methanolysis and the resulting mercapto aldose **13** was subjected to the action of dry hydrogen chloride in ether at 0 °C for 2 days—standard conditions[14] for replacement of an anomeric hydroxyl by chlorine. The unstable product, presumed on the basis of precedent[14,15] to be the desired pyranosyl chloride **14**, was employed directly for the final step of the synthesis. When the substance was refluxed with an excess of sodium hydride in a mixture of THF and benzene, it was converted into the desired 2-oxa-6-thiabicyclo[3.1.1]heptane derivative (**4**) which was isolated in 44% yield (from **13**) after flash chromatography. The material was contaminated by trace impurities as judged by TLC. The substance could be stored at 0 °C for several days and it could be distilled (Kugelrohr) under water pump vacuum with slight decomposition.

Presumably, the ring closure takes place through the skew conformation **15**. The structural assignment **4** rests in part on the mode of formation, on IR and MS measurements, and, in part, on the following spectroscopic study.

^{1}H and ^{13}C NMR Study of Compound 4. The small ring of compound **4** is a rigid unit and only the bridging fragment –O–C(3)–C(4)– is conformationally flexible. On this basis, three limiting conformations **16**, **17**, and **18** (≡**4**)



require consideration.[16] The first of these, **16**, is likely to be destabilized by severe nonbonded interactions between the pseudoaxial butyloxy group and the pseudoaxial hydrogen on C(3).

The ^{1}H NMR spectrum (at 400 MHz) of **18** (≡**4**) is described in Table I. The assignments indicated were made by consideration of chemical shift, intensity, and decoupling measurements. The ^{1}H NMR assignments to the butyloxy group were made by comparison with the spectrum of dibutyl ether (and confirmed by decoupling measurements). Of the remaining signals, those at highest field (2.61 and 2.14 δ) are due to protons [C(4)H_{ax} and

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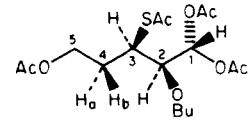
(12) Direct acetolysis of **9** gave a complex mixture. For a review on acetolysis, see: Guthrie, R. D.; McCarthy, J. F. *Adv. Carbohydr. Chem.* **1967**, *22*, 11.

(13) The coupling constants $J_{1,2}$ = 4, $J_{2,3}$ = 2.5, $J_{3,4a}$ = 5, and $J_{3,4b}$ = 10 Hz for compound **12** suggest that it exists predominantly (in $CDCl_3$) as the extended form (i).



i

Cf. Moore, R. E.; Bartolini, B.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776.

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(15) Ferrier, R. J.; Collins, P. M. "Monosaccharide Chemistry"; Penguin: London, 1972; p 96.

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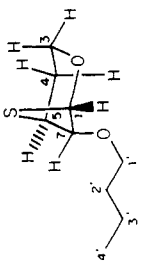
Table I[a]

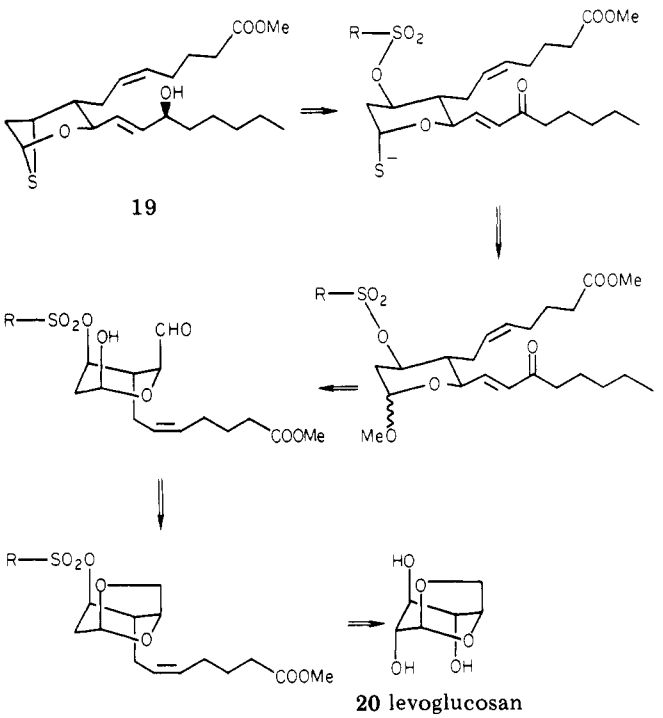


	C(1)H	C(3)H$_{ax}$	C(3)H$_{eq}$	C(4)H$_{ax}$	C(4)H$_{eq}$	C(5)H	C(7)H	C(1')H$_2$	C(2')H$_2$	C(3')H$_2$	C(4')H$_3$
^{1}H NMR, δ	5.54 q	4.51 octet	3.99 br q	2.61 m	2.14 m	3.72 m	4.31 q	3.45 m 3.52 m	1.60 m	1.41 m	0.93 t
$J_{H,H}$, Hz	$J_{1,5}$ = 5.25 $J_{1,7}$ = 3.25	$J_{3ax,3eq}$ = 11.0 $J_{3ax,4ax}$ = 9.5 $J_{3ax,4eq}$ = 6.7	$J_{3eq,3ax}$ = 11.0 $J_{3eq,4ax}$ = 8.0 $J_{3eq,4eq}$ = 1.0	$J_{4ax,4eq}$ = 13.0 $J_{4ax,3ax}$ = 9.5 $J_{4ax,3eq}$ = 8.0 $J_{4ax,5}$ = 1.5	$J_{4eq,4ax}$ = 13.0 $J_{4eq,3ax}$ = 6.7 $J_{4eq,3eq}$ = 1.0 $J_{4eq,5}$ = 5.0	$J_{5,1}$ [b] = 3.25 $J_{5,7}$ [b] = 5.00 $J_{5,4eq}$ [b] = 5.00 $J_{5,4ax}$ = 1.5	$J_{7,1}$ = 3.25 $J_{7,5}$ = 5.00				

	C(1)	C(3)	C(4)	C(5)	C(7)	C(1')	C(2')	C(3')	C(4')
^{13}C NMR, δ [c]	89.51 dt	60.23 tq	25.85 t	48.54 d	74.64 dm	67.22 t	31.76 t	19.28 t	13.79 q
$^1J_{C-H}$, Hz	177.0	147.5	129	158.0	157.3	140	126	126	123
$^3J_{C-H}$, Hz	7.0	5			3				

[a] ^{1}H NMR spectra were run at 400 MHz in $CDCl_3$ and ^{13}C NMR spectra at 50.32 MHz in the same solvent. J values are measured directly from the spectrum and, therefore, are based on the assumption that the spin systems are first order. Abbreviations used: s = singlet, d = doublet, m = multiplet, q = quartet, dt = doublet of triplets, tq = triplet of quartets, dm = doublet of multiplets, br = broad. [b] Values obtained from decoupled spectra. [c] Chemical shift assignments were confirmed by single frequency proton decoupling experiments.

Scheme II



C(4)H$_{eq}$] on carbon *not* attached to a heteroatom while the signal at lowest field (5.54 δ) is assigned to C(1)H. The above considerations, which are based on chemical shifts, led, tentatively, to the interpretation given and such an assignment was confirmed by the decoupling measurements.

The signal produced by C(4)H$_{eq}$ was identified by its large coupling to C(5)H. The flattened conformation **17** is excluded because $J_{5,4eq}$ and $J_{5,4ax}$ should be nearly equal for this conformation (as judged from examination of Dreiding models), whereas the values are quite different ($J_{4ax,5}$ = 1.5, $J_{4eq,5}$ = 5.0 Hz)—as expected for conformation **18**. The long range coupling, $J_{1,5}$, has ample precedent.[17]

The signal due to C(4)H$_{ax}$ is at lower field than that due to C(4)H$_{eq}$. This deshielding is due to the proximity of the C(7) oxygen atom. The axial proton attached to C(3) also resonates at lower field than the equatorial proton. Here, interaction with the sulfur atom is responsible.

In the ^{13}C NMR spectrum, the lowest field signal (89.51 δ) is assigned to the anomeric carbon, C(1).[18] This interpretation, and the others shown in Table I, were confirmed by single-frequency proton decoupling experiments. The $^1J_{C-H}$ values for C(5) and C(7) are larger than those reported for 3-hydroxythietane [$^1J_{C-H}$ = 147.4 Hz and $^1J_{C(3)-H}$ = 150.7 Hz].[19]

The anomeric carbon, C(1), showed two long-range couplings of about 5–7 Hz. These may be due to coupling with the proton attached to C(5) and with the equatorial proton attached to C(3), since C(1) has an approximately

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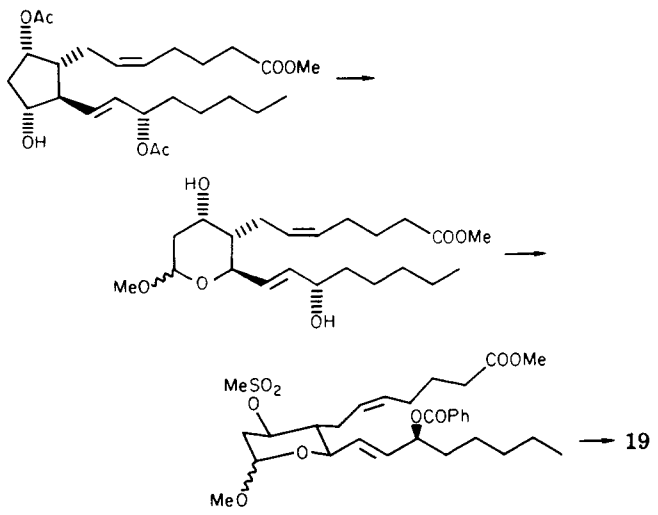
(18) Cf. Lundt, I.; Skelbaek-Pedersen, B. *Acta Chem. Scand. Ser. B* **1981**, *B35*, 637.

(19) Dittmer, D. C.; Patwardhan, B. H.; Bartholomew, J. T. *Org. Magn. Reson.* **1982**, *18*, 82.

Scheme III



21

antiperiplanar conformation with respect to each of these protons that are vicinal to it.[20]

Synthesis of 9α,11α-Thiathromboxane A_2 Methyl Ester (19) [≡3 (X = S, Y = O, R = Me)]. As the model compound **4**, having the representative 2-oxa-6-thiabicyclo[3.1.1]heptane skeleton appeared to be reasonably stable, we undertook the synthesis of 9α,11α-thiathromboxane A_2 methyl ester (**19**) [≡**3** (X = S, Y = O, R = Me)] in the natural, optically active, form. Our approach is summarized in Scheme II and is based upon levoglucosan[21] (**20**) as the chiral starting material. The initial experiments involved use of a tosylate (see Scheme II, R = *p*-toluenesulfonyl) but, part way through the project, a synthesis of **19**, by the route summarized in Scheme III was reported.[6,22] Therefore, we repeated our earlier experiments in the mesylate series so as to generate intermediate **21** (see Scheme III).

Levoglucosan (**20**), obtained by pyrolysis of starch,[21] was converted by literature procedures into **22**,[23] **23**,[23] and **24**.[24] Reduction of **24** with Superhydride[24] produced the alcohol **25** which was converted directly into its benzoate **26** (71% from **24**). Generation of the formyl group (**26** → **27**) did not proceed cleanly with sodium metaperiodate and a catalytic amount of osmium tetroxide, but ozonolysis and reductive workup (dimethyl sulfide) was effective and gave the aldehyde in 88% yield.

At this stage the α-chain was introduced by reaction of aldehyde **27** with the Wittig reagent generated (in THF) from (4-carboxybutyl)triphenylphosphonium bromide and potassium *tert*-butoxide. The product was debenzoylated with sodium methoxide and then esterified with diazomethane. Ester **28**, produced in this way (64% from **27**), was contaminated by a small amount (ca. 10%) of the corresponding *E* olefin as judged by the presence of several extra peaks in the olefinic region of the ^{13}C NMR spectrum. These impurities were removed at a later stage.

Treatment of **28** with methanesulfonyl chloride and triethylamine in dichloromethane at room temperature[25] afforded **29** in 85% yield. Methanolysis in the presence of an acidic resin and at room temperature slowly generated the methyl glycosides **30** as an 85:15 mixture of α and β anomers (90% yield). Collins oxidation[26] then afforded (74%) the corresponding aldehydes **31**. Wadsworth–Emmons olefination[27] served to produce (87%) the two α,β-unsaturated ketones **32** (66%) and **33** (4.7%), which were separated[28] by flash chromatography and identified by their NMR characteristics. The anomeric proton of the α-isomer produced a signal at 4.87 δ ($CDCl_3$) with $J_{10ax,11}$ = 3 Hz, while the corresponding values for the β-anomer were 4.41 δ and 9.25 Hz. Both **32** and **33** showed, in their NMR spectra, large *E* olefinic couplings: $J_{13,14}$ = 16 Hz for **32** and $J_{13,14}$ = 15.5 Hz for **33**.

In principle, both anomers could be used for the remaining steps but the compounds were separated at this stage in order to avoid the formation of complicated diastereoisomeric mixtures and, in the event, only the α-isomer **32** was processed further. Reduction with sodium borohydride in methanol at −40 °C produced two isomeric alcohols, **34** and **35**, in approximately equal amounts (76% yield). The compounds, which were separated chromatographically, were free (^{13}C NMR) of the impurity detected in **29**. The more polar material (**34**) is tentatively considered[29] to be the (natural) 15-(*S*)-isomer by analogy with the chromatographic behavior of related compounds.[29] Finally, benzoylation of **34** produced **36** which, together with the corresponding β-anomer, has been converted[6] into 9α,11α-thiathromboxane A_2 methyl ester (**19**). The alcohol **35** was also benzoylated in order to obtain a reference compound for spectral comparison.

The 15(*S*)-allylic benzoate **36** shows in its CD spectrum (methanol) at ca. 230 nm a positive Cotton effect, while the 15(*R*)-isomer (**37**) is characterized by a negative effect.[30]

Spectroscopic Study of 34, 35, 36, and 37. The ^1H NMR spectra of the alcohols **34** and **35** are very similar. In both, the magnitude of $J_{12,13}$ is 7.6 Hz and this value suggests, but by itself does not prove, that they exist extensively in a conformation in which C(12)H and C(13)H are near antiperiplanarity.[31] Such a conformation has been found in the crystalline state for TXB_2.[32] The effect of temperature on $J_{12,13}$ and $J_{14,15}$ in both alcohols **34** and **35** was studied in order to evaluate[31,33] the conformational preferences about C(12)–C(13) and C(14)–C(15). As the temperature is lowered the value of $J_{12,13}$ should increase[31,34] because the population of the favored confor-

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(22) Reference 6 does not indicate explicitly whether the compound is optically active.

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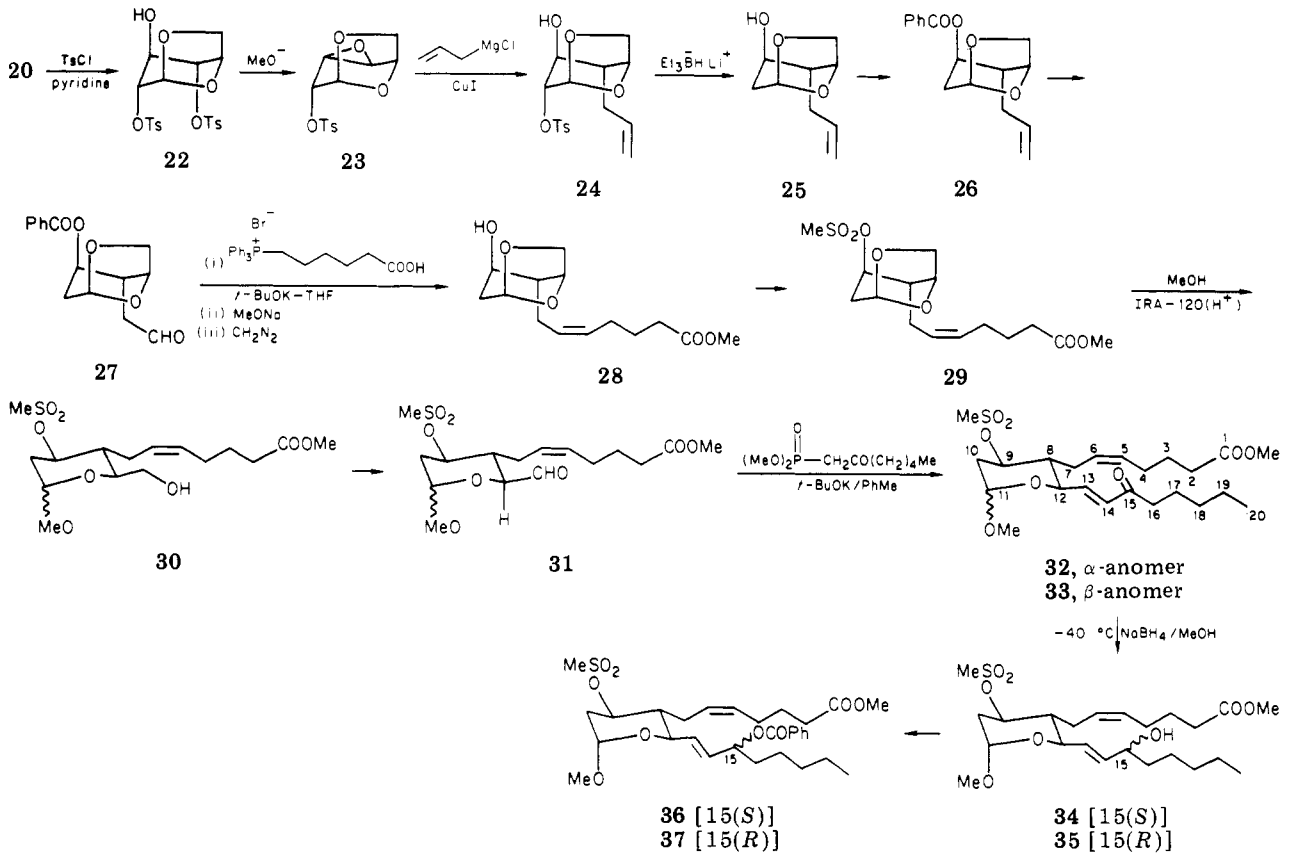
Scheme IV



mation (probably that with C(12)H and C(13)H antiperiplanar) increases. Measurement of the ^1H NMR spectrum of **34** in CD_2Cl_2 at 298 and 203 °K showed the expected trend: $J_{12,13}$ rose from 7.6 to 8.6 ± 0.02 Hz. Similar results were obtained with the alcohol **35**.

The magnitude of $J_{14,15}$ for **34** is 6.0 Hz and for **35** it is 7.0 Hz. Both values increase only slightly on lowering the temperature and so no conclusions could be drawn regarding the preferred conformation about C(14)–C(15). Partly for this reason, the spectra of the benzoates **36** and **37** were examined. Although the spectra of the alcohols are similar, those of the derived benzoates are readily distinguished. In the spectrum of **36** the signals due to C(13)H and C(14)H are well separated while those produced by C(5)H and C(6)H are superimposed. For **36** the coupling constant $J_{12,13}$ is 7.4 Hz. In the case of **37** the signals produced by C(13)H and C(14)H are superimposed while now those of C(5)H and C(6)H are separated. The value of $J_{12,13}$ is a little smaller (6.25 Hz).

The signals due to $C(2)H_2$, $C(3)H_2$, and $C(4)H_2$ of **37** are more shielded than the corresponding signals of **36**. In the latter, the $C(2)H_2$ signals appear as a triplet but in **37** they appear as two closely spaced triplets. These effects are understandable in terms of anisotropic shielding produced by the benzoate group. The ^1H NMR spectrum of **37** was measured at 298, 263, and 233 °K. As the temperature was lowered the C(2)–C(4) protons became progressively more shielded and the separation of the $C(2)H_2$ multiplets increased.

Experimental Section

Except where stated to the contrary, the following particulars apply. For reactions carried out under nitrogen, oven-dried glassware (130 °C, 12 h) was used. The apparatus was allowed to cool in a desiccator or assembled hot, capped with rubber septa, and swept with nitrogen. Reactions were performed under a slight static pressure of nitrogen which was purified by passage through a column (3.5 × 40 cm) of R-311 catalyst[35] and then through a similar column of Drierite. All solvents were distilled before use for chromatography. Solvents were dried, where specified, by distillation under a static nitrogen atmosphere from suitable desiccants, and transferred via oven-dried syringes. Dry ether and THF were distilled from sodium (benzophenone, indicator); dichloromethane, benzene, toluene, pyridine, triethylamine, and dimethylformamide were distilled from calcium hydride [the last solvent under reduced pressure]. Methanol was distilled from magnesium methoxide.

During product isolation, solutions were dried over magnesium sulfate and evaporated under water pump vacuum at room temperature. Where compounds were isolated simply by evaporation of their solutions, the residues were kept under oil pump vacuum and checked for constancy of weight. Isolated products were submitted directly for combusion analysis without need for additional purification, unless otherwise stated.

Commercial thin-layer chromatography (TLC) plates were used: silica gel was Camag type DF-B or Merck 60F-254; alumina was Camag type DSF-B or Merck 60F-254. UV active spots were detected at 254 nm; spots detected by spraying with sulfuric acid (50% in methanol) were charred on a hot plate. Silica gel for column chromatography was Merck type 60, 70–230 mesh ASTM; silica gel for flash chromatography[36] was Merck type 60, 230–400 mesh ASTM.

Infrared spectra were recorded on a Perkin-Elmer 297 infrared spectrometer or on a Nicolet 7199 FT-IR spectrometer. Liquids and oils were usually run as thin films on sodium chloride plates; solids were run as solutions in the specified solvent, using 0.5 mm sodium chloride cells, or as nujol mulls. Proton NMR spectra were recorded on Varian HA-100 (at 100 MHz), Bruker WH-200 (at 200 MHz), or Brucker WH-400 (at 400 MHz) spectrometers, in the specified deuterated solvent with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a Brucker HFX-90 (at 22.6 MHz), Brucker WH-200 (at 50.3 MHz), or Brucker WH-400 (at 100.4 MHz) spectrometers with tetra-

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methylsilane or deuterated chloroform as an internal standard. Electron-impact mass spectra were determined on an Associated Electrical Industries (AEI) MS-9 double-focusing high-resolution mass spectrometer and chemical-ionization mass spectra were recorded on an AEI MS-12 using ammonia as reagent gas. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 589 nm in a 1-dm cell. Melting points were determined on a Kofler block melting point apparatus. Cuprous chloride was freshly prepared by the literature method.[37]

Benzyl 2,3-Anhydro-4-deoxy-β-DL-*erythro*-pentopyranoside (6) and Benzyl 2,3-Anhydro-4-deoxy-α-DL-*erythro*-pentopyranoside (7). A solution of *m*-chloroperbenzoic acid (16 g, 85%, 78 mmol) in dichloromethane (100 mL) was added dropwise to a solution (130 mL) of 2-benzyloxy-5,6-dihydro-α-pyran (**5**)[7] (27.51 g, 144 mmol) in the same solvent. A further portion of *m*-chloroperbenzoic acid (10.4 g, 85%, 51 mmol) in dichloromethane (100 mL) was added after 6 h. The mixture was stirred for an additional 4 h and filtered. The solids were washed with hexane (500 mL) and the combined organic phase was washed with 10% w/v aqueous sodium thiosulfate (200 mL), saturated aqueous sodium bicarbonate (2 × 200 mL), water (2 × 150 mL), and brine (150 mL). The organic extract was dried and evaporated. Flash chromatography of the residue over silica gel (5 × 20 cm) with 1:9 ethyl acetate–hexane gave the epoxide **6**[7] (14.8 g, 49%) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate–hexane) oil: FT-IR (mull) 1447, 1010, 695 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.81 (m, J = 2.5, 4.5, 5, 15 Hz, 1 H, H-4_{eq}), 2.08 (m, 1 H, H-4_{ax}), 3.05 (br d, J = 4 Hz, 1 H, H-2), 3.34 (m, J = 1, 4, 5 Hz, 1 H, H-3), 3.42 (m, J = 1, 2.5, 7, 12 Hz, 1 H, H-5_{eq}), 3.77 (m, J = 0.75, 5, 11, 12 Hz, 1 H, H-5_{ax}), 4.56 and 4.81 (AB q, J = 11.5 Hz, 2 H, $-CH_2Ph$), 5.03 (br s, $W_{1/2}$ = 2 Hz, 1 H, H-1), 7.3 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$, 22.6 MHz) ppm 23.41 (C-4), 49.86, 54.47, 69.93 ($-CH_2Ph$), 94.56 (C-1), 127.86, 128.05, 128.49 and 137.41 (aromatic carbons); exact mass, 206.0938; calcd for $C_{12}H_{14}O_3$, 206.0943. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.63; H, 6.91.

On further elution, epoxide **7** (4.63 g, 15%) was obtained: FT-IR (film) 1045, 1020 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.95 (m, 2 H, HH-4), 3.25 (q, J = 3, 4 Hz, 1 H, H-2), 3.33 (br t, 1 H, H-3), 3.43 (m, 1 H, H-5_{eq}), 3.85 (m, 1 H, H-5_{ax}), 4.60 and 4.80 (AB q, J = 12 Hz, 2 H, $-CH_2Ph$), 5.00 (d, J = 3 Hz, 1 H, H-1), 7.3 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$, 22.6 MHz) ppm 24.76 (C-4), 49.78 and 51.29, 55.43, 68.95 ($-CH_2Ph$), 92.69 (C-1), 127.71, 128.15, 128.42 and 137.72 (aromatic carbons); exact mass, 206.0942; calcd for $C_{12}H_{14}O_3$, 206.0943. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.73; H, 6.90.

Benzyl 3-(*tert*-Butylthio)-3,4-dideoxy-α-DL-*threo*-pentopyranoside (8). *tert*-Butyl mercaptan (1.46 g, 1.83 mL, 16 mmol) was added to a solution of sodium methoxide (0.88 g, 16 mmol) in absolute methanol (10 mL). The solution was stirred for 15 min and then epoxide **6** (3.05 g, 14 mmol) in methanol (10 mL) was added. The mixture was refluxed for 2 h, cooled, and diluted with water (10 mL). Most of the methanol was evaporated and the residue was extracted with ether (2 × 75 mL). The organic phase was washed with water (50 mL) and brine (50 mL), dried, and evaporated to give compound **8** (4.07 g, 92%) which was used for the next stage without further purification. An analytical sample was prepared by crystallization from hexane. The purified material: FT-IR (nujol) 3420, 1455, 1077 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.34 (s, 9 H, $-C(CH_3)_3$), 1.70–2.09 (m, 2 H, HH-4), 2.66 (m, J = 5, 10.25, 12 Hz, 1 H, H-3), 2.76 (d, J = 1.75 Hz, 1 H, –OH), 3.22 (m, J = 1.75, 7, 10.25 Hz, 1 H, H-2), 3.49 (m, J = 3, 11.25, 11.75 Hz, 1 H, H-5_{ax}), 3.97 (m, J = 2, 4.5, 11.75 Hz, 1 H, H-5_{eq}), 4.37 (d, J = 7 Hz, 1 H, H-1), 4.66 and 4.91 (AB q, J = 11.5 Hz, 2 H, $-CH_2Ph$), 7.3 (m, 5 H, aromatic protons); ^{13}C NMr ($CDCl_3$, 22.6 MHz) ppm[38] 31.64 ($-C(CH_3)_3$), 35.66 (C-4), 43.79 ($-C(CH_3)_3$), 45.36 (C-3), 64.20 (C-5), 70.44 and 72.72 (C-2 and $-CH_2Ph$), 103.39 (C-1), 127.76, 128.03, 128.42 and 137.52 (aromatic carbons); exact mass, 296.1451; calcd for $C_{16}H_{24}O_3S$, 296.1446. Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16; S, 10.82. Found: C, 65.04; H, 8.23; S, 10.84.

Benzyl 2-*O*-*n*-Butyl-3-(*tert*-butylthio)-3,4-dideoxy-α-DL-*threo*-pentopyranoside (9). Sodium hydride (50% w/w as an oil dispersion, 2.0 g, 40 mmol) was added to a solution (50 mL) of compound **8** (8.28 g, 27.8 mmol) in dry DMF. The mixture was stirred for 30 min and then 1-iodobutane (7.71 g, 4.7 mL, 40 mmol) was added over 0.5 h. After 5 h more sodium hydride dispersion (1.5 g, 30 mmol) and a further portion of 1-iodobutane (4.85 g, 3 mL, 26 mmol) were added. Stirring at room temperature was continued overnight. The mixture was diluted with water (100 mL) and extracted with ether (3 × 100 mL). The combined organic extract was washed with water (2 × 50 mL) and with brine (1 × 50 mL). The extract was dried and evaporated. Flash chromatography of the residue over silica gel (5 × 18 cm) with 1:19 ethyl acetate–hexane gave pure **9** (9.0 g, 90%) as a colorless oil: FT-IR (film) 1115, 1085 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.34 (s, 9 H, $-C(CH_3)_3$), 1.35 (m, 2 H, $-CH_2CH_3$), 1.54 (m, 2 H, $-CH_2CH_2CH_3$), 1.74 (m, 1 H, H-4_{ax}), 2.07 (m, 1 H, H-4_{eq}), 2.68 (m, J = 4.5, 8, 13.5 Hz, 1 H, H-3), 2.97 (q, J = 5.25, 8 Hz, 1H, H-2), 3.43 (m, 1 H, H-5_{ax}), 3.65 (dt, 1 H) and 3.75 (dt, 1 H, C(2)–O–CH_2–), 3.94 (dt, 1 H, H-5_{eq}), 4.43 (d, J = 5.25 Hz, 1 H, H-1), 4.60 and 4.87 (AB q, J = 12 Hz, 2 H, $-CH_2Ph$), 7.3 (m, 5 H, aromatic protons); ^{13}C NMR ($CDCl_3$, 100.6 MHz) ppm 13.92 (q, $-CH_2CH_3$), 19.31 (t, $-CH_2CH_3$), 31.53 (q, $-C(CH_3)_3$), 32.32 (t, C(2)–O–CH_2CH_2–), 34.87 (q, C-4), 42.47 (d, C-3), 43.50 (s, $-C(CH_3)_3$), 62.23 (q, C-5), 70.33 (t) and 72.78 (t) ($-CH_2Ph$ and C(2)–O–CH_2–), 80.72 (d, C-2), 103.22 (d, C-1), 127.52, 127.79, 128.30 and 138.04 (aromatic carbons); exact mass, 352.2072; calcd for $C_{20}H_{32}O_3S$, 352.2072. Anal. Calcd for $C_{20}H_{32}O_3S$: C, 68.14; H, 9.15; S, 9.10. Found: C, 67.97; H, 9.12; S, 9.35.

2-*O*-*n*-Butyl-3-(*tert*-butylthio)-3,4-dideoxy-α,β-DL-*threo*-pentopyranose (10). Trifluoroacetic acid (80% in water, 20 mL) was added to a solution of compound **9** (9.50 g, 26 mmol) in dichloromethane (25 mL). The mixture was stirred at room temperature for 40 h, cooled in an ice bath, and diluted slowly with triethylamine (32 mL). The mixture was stirred at room temperature for 3 h and washed with water. The organic layer was dried and evaporated. Flash chromatography of the residue over silica gel (5 × 20 cm) with 0.75:9.25 ethyl acetate–hexane gave compound **10** (4.32 g, 61%) as a pure, pale yellow oil: FT-IR (film) 3400, 1115 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.93 (two sets of t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.3–1.4 (m, 11 H, $-C(CH_3)_3$ and $-CH_2CH_3$), 1.59 (m) and 1.72 (m) (3 H, $-CH_2CH_2CH_3$ and H-4_{ax}), 2.15 (m, 1 H, H-4_{eq}), 2.70 (m, 0.5 H, H-3, of the β-isomer), 2.93 (q, J = 5.5, 8 Hz, 0.5 H, H-2 of the β-isomer), 3.30 (br q, 0.5 H, H-3 of the α-isomer, 3.25 (q, J = 2.25, 6 Hz, 0.5 H, H-2 of the α-isomer), 3.45–3.86 (three sets of m, 4 H, HH-5 and C(2)–O–CH_2–), 3.53 (d, J = 8 Hz, 0.5 H, α-OH), 3.84 (d, J = 6 Hz, 0.5 H, β-OH), 4.70 (t, J = 5.50, 6 Hz, 0.5 H, H-1 of the β-isomer (it collapsed to a doublet with J = 5.5 Hz on D_2O exchange)), 4.98 (q, J = 2.25, 8 Hz, 0.5 H, H-1 of the α-isomer (it collapsed to a doublet with J = 2.25 Hz on D_2O exchange)); ^{13}C NMR ($CDCl_3$, 22.6 MHz) ppm[38] 13.70 and 13.76 ($-CH_2CH_3$), 19.12 ($-CH_2CH_3$), 31.15 and 31.28 ($-C(CH_3)_3$), 31.87, 32.03 and 34.11 (C-4 and C-(2)–O–CH_2–CH_2–), 38.33 and 41.65 (C-3), 43.56 and 43.69, ($C(CH_3)_3$), 60.72 and 61.69 (C-5), 70.67 and 72.49 (C(2)–O–CH_2–), 79.60 and 80.91 (C-2), 91.44 (C-1 of the α-isomer), 97.74 (C-1 of the β-isomer); exact mass, 262.1600; calcd for $C_{13}H_{26}O_3S$, 262.1603. Anal. Calcd for $C_{13}H_{26}O_3S$: C, 59.50; H, 9.99; S, 12.22. Found: C, 59.53; H, 10.00; S, 12.09.

1-*O*-Acetyl-3-*S*-acetyl-2-*O*-*n*-butyl-3,4-dideoxy-α,β-DL-*threo*-pentopyranose (11) and (±)-*threo*-1,1,5-Triacetoxy-3-(acetylthio)-2-(butyloxy)pentane (12). Concentrated sulfuric acid (0.75 mL) was added over 10 min to a stirred, ice cold solution of **10** (4.1 g, 15.6 mmol) in acetic anhydride (35 mL). Stirring at 0 °C was continued for a further 30 min and then anhydrous sodium acetate (2.00 g) was added. The mixture was allowed to attain room temperature and was then evaporated. Ethanol (50 mL) was added and the solution was again evaporated. This evaporation procedure was repeated with ethanol (2 × 50 mL) and then with toluene (1 × 50 mL). The residue was partitioned between ether and saturated aqueous sodium bicarbonate. The organic extract was washed with brine, dried, and evaporated. Flash chromatography of the residue over silica (5 × 16 cm) with 1:9 ethyl acetate–hexane gave **11** (2.60 g, 57%) as a homogeneous

(37) Vogel, A. I. "Practical Organic Chemistry", 3rd ed.; Longmans, Green & Co.: London, 1956; p 190.

(38) These assignments are tentative; they were not confirmed by measuring a ^{13}C Spin Echo Spectrum with gated proton decoupling: Brown, D. W.; Nakashima, T. T.; Rabenstein, D. L. *J. Magn. Reson.* **1981**, *45*, 302.

(TLC, silica gel, 1:9 ethyl acetate–hexane), pale yellow oil: FT-IR (film) 1742, 1692, 1229, 1118 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87 (two sets of t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.35 (m, 2 H, $-CH_2CH_3$), 1.51 (m, 2 H, $-CH_2CH_2CH_3$), 1.61–2.28 (series of m, 2 H, HH-4), 2.11 (s) and 2.14 (s) (3 H, $-OCOCH_3$), 2.34 (s) and 2.35 (s) (3 H, $-SCOCH_3$), 3.16 (q, J = 5, 7 Hz, 0.31 H, H-2 of the β-isomer), 3.36 (q, J = 3, 11 Hz, 0.66 H, H-2 of the α-isomer), 3.39–3.98 (series of m, 5 H, H-3, HH-5, and C(2)–O–CH_2–), 5.69 (d, J = 5 Hz, 0.31 H, H-1 of the β-isomer), 6.30 (d, J = 3 Hz, 0.66 H, H-1 of the α-isomer); ^{13}C NMR ($CDCl_3$, 22.6 MHz) ppm[38] 13.78 ($-CH_2CH_3$), 19.08, 19.17 and 21.03 ($-CH_2CH_3$ and $-OCOCH_3$), 29.73, 30.64, 30.84, 31.81, 32.07 and 32.31 ($-SCOCH_3$, $-CH_2CH_2CH_3$, and C-4) 41.34 and 41.49 (C-3), 60.90 and 62.01 (C-5), 70.81 and 71.85 (C(2)–O–CH_2–), 76.4 and 76.72 (C-2), 89.98 (C-1 of the α-isomer), 94.43 (C-1 of the β-isomer), 169.01 and 169.63 ($-OCOCH_3$), 194.76 ($-SCOCH_3$); exact mass, 290.1177; calcd for $C_{13}H_{22}O_5S$, 290.1178. Anal. Calcd for $C_{13}H_{22}O_5S$: C, 53.77; H, 7.64; S, 11.04. Found: C, 53.82; H, 7.76; S, 11.16.

On further elution, compound **12** (0.72 g, 11.74%) was obtained as a colorless thick oil, which solidified on standing. An analytical sample was obtained by keeping the material for one day under oil pump vacuum. The material was homogeneous by TLC (silica gel, 1:9 ethyl acetate–hexane). Compound **12**: FT-IR (nujol) 1689, 1735, 1749, 1767 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.34 (m, 2 H, $-CH_2CH_3$), 1.52 (m, 2 H, $-CH_2CH_2CH_3$), 1.92 (m, 1 H, H-4), 2.07 (s, 3 H, $-OCOCH_3$), 2.08 (s, 3 H, $-OCOCH_3$), 2.09 (s, 3 H, $-OCOCH_3$), 2.14 (m, 1 H, H-4), 2.31 (s, 3 H, $-SCOCH_3$), 3.57 (dt) and 3.67 (dt) (C(2)–O–CH_2–), 3.63 (q, J = 2.5, 7 Hz, 1 H, H-2), 3.91 (m, J = 2.5, 5, 10 Hz, 1 H, H-3), 4.14 (m, 2 H, HH-5), 6.91 (d, J = 7 Hz, 1 H, H-1); ^{13}C NMR ($CDCl_3$, 22.6 MHz) ppm 13.57 (q, $-CH_2CH_3$), 18.90 (t, $-CH_2CH_3$), 20.43 and 20.58 ($-OCOCH_3$), 30.21, 31.48 and 31.89 ($-SCOCH_3$, $-CH_2CH_2CH_3$, and C-4), 41.17 (d, C-3), 61.24 (t, C-5), 72.94 (t, C(2)–O–CH_2–), 80.94 (d, C-2), 87.99 (d, C-1); mass (chemical ionization, NH_3), 410 (M + 18). Anal. Calcd for $C_{17}H_{28}O_8S$: C, 52.03; H, 7.19; S, 8.17. Found: C, 52.05; H, 7.30; S, 8.34.

2-*O*-*n*-Butyl-3,4-dideoxy-3-mercapto-α,β-DL-*threo*-pentopyranose (13). A solution (6.5%, w/v, 1 mL) of sodium methoxide in methanol was added to a solution of the diacetate **11** (2.00 g, 6.88 mmol) in dry methanol (25 mL). The mixture was stirred for 3.5 h, neutralized with IRA-120 (H^+) resin, filtered, and concentrated at room temperature. Flash chromatography of the residue over silica gel (4.5 × 16 cm) with 2:8 ethyl acetate–hexane gave the mercapto alcohol **13** (1.20 g, 84%) as a homogeneous (TLC, silica gel, 2:8 ethyl acetate–hexane) oil which solidified on standing for several days. Compound **13**: FT-IR (nujol) 3400, 1460 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.93 (br t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.3–2.08 (series of m, 6 H), 1.97 (d, J = 4.5 Hz, –SH), 2.85–4.1 (series of m, 7 H), 4.52 (q, J = 5.5, 6.5 Hz, 0.31 H, H-1 of the β-isomer (it collapsed to a doublet, J = 6.5 Hz on D_2O exchange)), 5.27 (t, J = 3 Hz, 0.63 H, H-1 of the α-isomer (it collapsed to a doublet, J = 3 Hz on D_2O exchange)); ^{13}C NMR ($CDCl_3$, 22.6 MHz) ppm 13.70 (q, $-CH_2CH_3$), 19.14 (t, $-CH_2CH_3$), 31.89, 32.16, 33.39 and 34.05 ($-CH_2CH_2CH_3$ and C-4), 35.59 and 39.83 (d, C-3), 58.74 and 63.74 (t, C-5), 70.57 and 72.90 (t, C-(2)–O–CH_2–), 82.39 and 85.06 (d, C-2), 90.45 (d, C-1 of the α-isomer), 98.64 (d, C-1 of the β-isomer); exact mass, 188.0870; calcd for $C_9H_{16}O_2S$ (M – H_2O), 188.0871; 173.1176; calcd for $C_9H_{17}O_3$ (M – SH), 173.1178. Anal. Calcd for $C_9H_{18}O_3S$: C, 52.40; H, 8.79; S, 15.54. Found: C, 52.53; H, 8.85; S, 15.53.

(±)-7-*exo*-(*n*-Butyloxy)-2-oxa-6-thiabicyclo[3.1.1]heptane (4). The mercapto alcohol **13** (0.182 g, 0.88 mmol) was dissolved in dry ether (20 mL) and the solution was cooled in an ice bath. A slow stream of nitrogen was passed over the solution and dry hydrochloric acid was passed through it with magnetic stirring. After an arbitrary period of 30 min, the reaction flask was tightly stoppered and the mixture was kept at 0 °C (refrigerator) for 2 days. The mixture was then allowed to attain room temperature, the stopper was replaced by a septum, and excess of hydrochloric acid was removed with a stream of nitrogen. Dry benzene (10 mL) was injected and bubbling of nitrogen was continued for 30 min. Powdered 3-Å molecular sieves (0.8 g) were added and passage of nitrogen was continued for 1 h with magnetic stirring. By using a syringe and a sintered funnel the mixture was filtered under nitrogen into a flask containing sodium hydride (0.81 g, 50% w/v in mineral oil, 17 mmol, washed with dry hexane (3 × 5 mL)) in THF (15 mL). Quantitative transfer was achieved by using dry benzene (2 × 3 mL) as a rinse. The THF solution was refluxed for 1.5 h, cooled, filtered and evaporated. Flash chromatography over silica gel (1 × 10 cm) using 2:98 ether–hexane gave a colorless liquid which was diluted with benzene (10 mL) and evaporated. The residue weighed 0.073 g, (44%) after being kept under oil pump vacuum for 20 min. Trace impurities were detected by TLC (silica gel, 1:9 ethyl acetate–hexane) but a satisfactory analysis was obtained on this material. Compound **4**: FT-IR (film) 1462, 1120 cm^{-1}; mass (chemical ionization, NH_3) 206 (M + 18); exact mass, 126.1045; calcd for $C_8H_{14}O$ (M – CH_2OS), 126.1044. Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.57; S, 17.03. Found: C, 57.63; H, 8.75; S, 16.92.

1,6-Anhydro-4-deoxy-4-*C*-allyl-2-*O*-((4-methylphenyl)-sulfonyl)-β-D-glucopyranose (24). Allylmagnesium chloride (~2.5 M THF solution, 175 mL, ~6 equiv) was added slowly to a stirred, cooled (0 °C) mixture of 1,6:3,4-dianhydro-2-*O*-((4-methylphenyl)sulfonyl)-β-D-galactopyranose (**23**)[23] (17.20 g, 57 mmol) and cuprous chloride (0.57 g, 5.7 mmol) in THF (75 mL). Stirring at 0 °C was continued for 10 h by which stage the reaction was over (TLC control, silica gel, 1:1 ethyl acetate–hexane). The mixture was cooled to −20 °C and acetic acid (22 mL) was injected slowly, followed by water (10 mL). The mixture was partitioned between dichloromethane (1 L) and water. The organic layer was washed with brine, dried, and evaporated. Flash chromatography of the residue over silica gel (6 × 18 cm) with 3.5:6.5 ethyl acetate–hexane gave pure **24** as a white crystalline solid (14.55–15.90 g, 75–82%) homogeneous by TLC (silica gel, 1:1 ethyl acetate–hexane): mp 70–71 °C (lit.[24] 65–67 °C); $[\alpha]^{23}_D$ −58.4 (*c* 0.9, chloroform) (lit.[24] −58 (*c* 0.9, chloroform)); IR ($CHCl_3$) 3595, 1600, 1360, 1197, 1182 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.68 (m, J = 1, 2.5, 7.5 Hz, 1 H, H-4), 2.36 (m, 3 H, $-CH_2CH=CH_2$ and –OH), 2.40 (s, 3 H, $-CH_3$), 3.70 (m, 2 H, H-3 and H-6_{exo}), 4.02 (br d, J = 6.75 Hz, 1 H, H-6_{endo}), 4.18 (br t, J = 1.25 Hz, 1 H, H-2), 4.41 (br d, J = 5 Hz, 1 H, H-5), 5.12 (m, 2 H, $-CH=CH_2$), 5.28 (br s, 1 H, H-1), 5.75 (m, 1 H, $-CH=CH_2$), 7.36 (d) and 7.82 (d) (4 H, aromatic protons); ^{13}C NMR[39] ($CDCl_3$, 50.3 MHz) ppm 21.62 (q, $-CH_3$), 35.35 (t, $-CH_2-CH=CH_2$), 43.08 (d, C-4), 68.22 (t, C-6), 69.81 (d, C-3), 74.27 (d, C-5), 78.80 (d, C-2), 99.63 (d, C-1), 117.91 (t, $-CH=CH_2$), 127.89, 130.08, 133.27 and 145.36 (aromatic carbons), 135.51 (d, $-CH=CH_2$); exact mass, 185.0812; calcd for $C_9H_{13}O_4$ (M – $C_6H_7SO_2$), 185.0814; 167.0706; calcd for $C_9H_{11}O_3$ (M – ($C_6H_7SO_2$ + H_2O)), 167.0708.

1,6-Anhydro-4-*C*-allyl-3-*O*-benzoyl-2,4-dideoxy-β-D-*arabino*-hexopyranose (26). Lithium triethylborohydride (150 mL, THF solution, ca. 4 equiv) was added dropwise at room temperature to a solution (50 mL) of the hydroxy tosylate **24** (13.52 g, 37 mmol) in dry THF. The mixture was stirred overnight and the excess of reagent was destroyed by addition of water. A cold (0 °C) mixture of 30% hydrogen peroxide (80 mL) and sodium hydroxide (3 N, 100 mL) was added slowly with ice bath cooling. The mixture was allowed to attain room temperature and was stirred for 3 h. It was then extracted with dichloromethane (5 × 100 mL). The extract was dried and concentrated. The residue was diluted with toluene (50 mL) and concentrated again in vacuo. The resulting oil was kept for 3 h under oil pump vacuum to afford crude 1,6-anhydro-4-*C*-allyl-2,4-dideoxy-β-D-*arabino*-hexopyranose (**25**) (5.77 g) which was used directly for the next step.

Attempted distillation of a portion of the crude product resulted in decomposition (TLC control, silica gel, 1:1 ethyl acetate–hexane). For characterization, a sample was purified by flash chromatography over silica gel (1.5 × 15 cm), with 1:1 ethyl acetate–hexane). Compound **25**: IR (film) 3440, 3080, 1640, 1130, 1050, 870 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.85 (br d, J = 15 Hz, 1 H, H-2), 1.90 (br t, J = 8 Hz, 1 H, H-4), 2.06 (m, J = 1.5, 5, 15 Hz, 1 H, H-2), 2.20 and 2.32 (two sets of m, 2 H, $-CH_2CH=CH_2$), 2.85 (d, J = 7.5 Hz, 1 H, –OH), 3.73 (m, 1 H, H-3 (it collapsed into a broad doublet with J = 5 Hz on D_2O exchange)), 3.77 (q, J = 5, 7 Hz, 1 H, H-6_{exo}), 4.32 (br d, J = 7 Hz, 1 H, H-6_{endo}), 4.41 (br d, J = 5 Hz, 1 H, H-5), 5.09 and 5.13 (two sets of m, 2 H, $-CH=CH_2$), 5.60 (br s, 1 H, H-1), 5.82 (m, 1 H, $-CH=CH_2$); ^{13}C NMR[38] ($CDCl_3$, 50.3 MHz) ppm 35.50 (t) and 36.18 (t) (C-2 and $-CH_2CH=CH_2$), 44.94 (d, C-4), 67.81 (d, C-3), 67.92 (t, C-6),

(39) Tentative assignment.

74.79 (d, C-5), 101.15 (d, C-1), 117.12 (t, —CH=CH_2), 136.16 (d, —CH=CH_2); mass (chemical ionization, NH_3) 188 (M + 18), 153 (MH - H_2O).

Benzoyl chloride (9.08 g, 7.5 mL, 64 mmol) was added dropwise to a solution of crude **31** (5.52 g) in dry pyridine (15 mL). The mixture was stirred overnight and the excess reagent was destroyed by addition of water. The mixture was stirred at room temperature for 2 h and was extracted with dichloromethane (4 × 75 mL). The organic extract was washed with dilute hydrochloric acid (1 × 50 mL), saturated aqueous bicarbonate (1 × 20 mL), water (1 × 50 mL), and brine (1 × 50 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (5 × 18 cm) with 1:9 ethyl acetate–hexane gave **26** (7.33 g, 71% overall yield) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate–hexane oil: $[\alpha]^{23}_D$ -121.6 (*c* 1, $CHCl_3$); FT-IR (film) 1717, 1450, 1280, 1115, 1028, 715 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.91 (br t, 8 Hz, 1 H, H-4), 1.96 (br d, J = 15.5 Hz, 1 H, H-2), 2.11 (m, J = 1.5, 5.25, 15.5 Hz, 1 H, H-2), 2.42 (m, 2 H, —CH_2CH=CH_2), 3.87 (q, J = 5.5, 7 Hz, 1 H, H-6_{exo}), 4.33 (d, J = 7 Hz, 1 H, H-6_{endo}), 4.45 (br d, J = 5.5 Hz, 1 H, H-5), 5.08 (br d, J = 5.25 Hz, 1 H, H-3), 5.17 (m, 2 H, —CH=CH_2), 5.60 (br s, 1 H, H-1), 5.89 (m, 1 H, —CH=CH_2), 7.44–8.1 (three sets of m, 5 H, aromatic protons); ^{13}C NMR[38] ($CDCl_3$, 22.6 MHz) ppm 33.51 (C-2), 35.26 (—CH_2CH=CH_2), 42.67 (C-4), 67.79 (C-6), 69.77 (C-3), 73.99 (C-5), 100.15 (C-1), 117.71 (—CH=CH_2), 128.47, 129.60 and 133.04 (aromatic carbons), 135.52 (—CH=CH_2), 165.87 (-OOCPh); exact mass, 274.1203; calcd for $C_{16}H_{18}O_4$, 274.1205. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.86; H, 6.57.

1,6-Anhydro-4-*C*-(*aldehydo*-methyl)-3-*O*-benzoyl-2,4-dideoxy-β-D-*arabino*-hexopyranose (27). A stream of ozone was passed into a cold (-78 °C) solution of **26** (0.34 g, 1.2 mmol) in methanol (10 mL) until a blue coloration developed. Nitrogen was then passed through the solution for 10 min and then an excess of dimethyl sulfide (0.5 mL) was added. The mixture was allowed to stand at room temperature overnight and it was then concentrated. Flash chromatography of the residue over silica gel (1.5 × 15 cm) using 2:8 ethyl acetate–hexane gave **27** (0.3 g, 88%) as white, homogeneous (TLC, silica gel, 3:7 ethyl acetate–hexane) solid: mp 88–91 °C; $[\alpha]_{23D}$ -118.2 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1717, 1710, 1600, 1115, 1017, 867 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 2.00 (br d, J = 15.5 Hz, 1 H, H-2), 2.10 (m, J = 2, 5.25, 15.5 Hz, 1 H, H-2), 2.54 (br q, J = 5, 9 Hz, 1 H, H-4), 2.73 (m, J = 1, 5, 18 Hz, 1 H) and 3.11 (m, J = 1, 9, 18 Hz, 1 H) (-CH_2CHO), 3.89 (q, J = 6, 7 Hz, 1 H, H-6_{exo}), 4.40 (q, J = 1, 7 Hz, 1 H, H-6_{endo}), 4.45 (br d, J = 6 Hz, 1 H, H-2), 4.97 (m, 1 H, H-3), 5.61 (br s, 1 H, H-1), 7.48 (m, 2 H), 7.59 (m, 1 H) and 8.07 (m, 2 H) (aromatic protons), 9.89 (d, J = 1 Hz, 1 H, -CHO); ^{13}C NMR ($CDCl_3$, 100.6 MHz) ppm 33.69 (t, C-2), 37.52 (d, C-4), 44.70 (t, -CH_2CHO), 67.63 (t, C-6), 69.78 (d, C-3), 73.94 (d, C-5), 99.97 (d, C-1), 128.40, 129.49, 130.10 and 133.05 (aromatic carbons), 165.67 (s, -OOCPh), 199.63 (d, -CHO); exact mass, 154.0629; calcd for $C_8H_{10}O_3$ (M - $C_7H_6O_2$), 154.0630; mass (chemical ionization, NH_3) 294 (M + 18). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.92; H, 5.95.

1,6-Anhydro-2,4-dideoxy-4-*C*-(1-methoxy-1-oxo-5(*Z*)-hepten-7-yl)-β-D-*arabino*-hexopyranose (28). (4-Carboxybutyl)-triphenylphosphonium bromide (3.49 g, 7.8 mmol) was added in one lot to an ice cold solution of potassium *tert*-butoxide (1.76 g, 15.6 mmol) in dry THF (10 mL). The resulting dark red solution was stirred for 40 min at room temperature and then a solution (3 mL plus 0.5 mL as rinse) of the aldehyde **27** (0.540 g, 1.9 mmol) in dry THF was injected over 5 min. Stirring was continued for 45 min, the mixture was brought to pH 2 by addition of saturated aqueous dihydrogen sodium phosphate, and then the solution was extracted with ether (4 × 75 mL). The ether layer was dried, concentrated, redissolved in ether (100 mL), filtered, and concentrated. The resulting oil was evaporated from toluene (50 mL) and stirred for 48 h with sodium methoxide (0.75 g, 13.8 mmol) in dry methanol (10 mL). The solution was acidified with saturated aqueous dihydrogen sodium phosphate and extracted with ether (4 × 60 mL). The extract was dried, concentrated, dissolved in dichloromethane (10 mL) and was treated with an excess of diazomethane. Excess of reagent was destroyed by addition of small portions of silica gel and the solution was filtered. The filterate was evaporated and flash chromatography of the residue over silica gel (3 × 14 cm) with 4:6 ethyl acetate–hexane gave **28** (0.348 g, 64% overall yield) as a homogeneous (TLC, silica, 1:1 ethyl acetate–hexane) oil: $[\alpha]^{23}_D$ -61.2 (*c* 1, $CHCl_3$); IR (film) 3480, 1732, 1437, 1127, 1046, 865 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, 2 H, -CH_2CH_2COOCH_3), 1.83 (br t, J = 7.5 Hz, 1 H, H-4), 1.85 (br d, J = 14 Hz, 1 H, H-2), 2.04 (m, J = 1.5, 5, 15.5 Hz, 1 H, H-2), 2.12 (m, 3 H, —CHCH=CHCH_2CH$_2$—), 2.30 (m, 1 H, —CHCH=CHCH$_2$CH_2—), 2.33 (t, J = 7 Hz, 2 H, -CH_2COOCH_3), 2.86 (br d, J = 8 Hz, 1 H, -OH), 3.67 (s, 3 H, -COOCH_3), 3.70 (m, 1 H, H-3), 3.79 (q, J = 5, 7 Hz, 1 H, H-6_{exo}), 4.31 (d, J = 7 Hz, 1 H, H-6), 4.37 (br d, J = 5 Hz, 1 H, C(5)-H), 5.47 (m, 2 H, —CH=CH—), 5.60 (br s, 1 H, H-1); ^{13}C NMR[40] ($CDCl_3$, 100.6 MHz) ppm 24.72 (t, -CH_2CH_2COOCH_3), 26.58 (t, -$CH_2CH_2CH_2$COOCH_3), 28.81 (t, C(4)—CH_2CH=CH—), 33.39 (t, -CH_2COOCH_3), 36.19 (t, C-2), 45.63 (d, C-4), 51.36 (q, -COOCH_3), 67.94 (t, C-6), 68.10 (d, C-3), 74.78 (d, C-5), 101.20 (d, C-1), 128.04 (d, C(4)—CH_2CH=CH—), 131.10 (d, C(4)—CH_2CH=CH—), 173.87 (s, -$COOCH_3$); mass (chemical ionization, NH_3) 288 (M + 18), 271 (MH), 253 (MH - H_2O); exact mass, 252.1358; calcd for $C_{14}H_{20}O_4$ (M - H_2O), 252.1362; 239.1282; calcd for $C_{13}H_{19}O_4$ (M - OCH_3), 239.1283. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.44; H, 8.24.

1,6-Anhydro-2,4-dideoxy-3-*O*-(methylsulfonyl)-4-*C*-(1-methoxy-1-oxo-5(*Z*)-hepten-7-yl)-β-D-*arabino*-hexopyranose (29). Methanesulfonyl chloride (0.178 g, 0.12 mL, 1.5 mmol) was added dropwise to a mixture of alcohol **28** (0.337 g, 1.2 mmol) and triethylamine (0.189 g, 0.26 mL, 1.86 mmol) in dry dichloromethane (5 mL). The mixture was stirred at room temperature for 15 min and was then diluted with dichloromethane (75 mL). The organic phase was washed with dilute hydrochloric acid (20 mL), saturated aqueous bicarbonate (20 mL), water (1 × 20 mL), and brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 12 cm) using 1:1 ether–hexane gave **29** (0.369 g, 85%) as a homogeneous (TLC, silica gel, 1:1 ethyl acetate–hexane) oil: $[\alpha]^{23}_D$ -51.5 (*c* 1, $CHCl_3$); IR (film) 1730, 1436, 1340, 1170, 870 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.71 (quintet, J = 7 Hz, 2 H, -CH_2CH_2COOCH_3), 2.01–2.14 (m, 5 H, HH-2, H-4, —CH_2CH_2CH=CH—), 2.22–2.40 (m, 2 H, C(4)—CH_2CH=CH), 2.33 (t, J = 7 Hz, 2 H, -CH_2COOCH_3), 3.03 (s, 3 H, -O_3SCH_3), 3.64 (s, 3 H, -COOCH_3), 3.78 (q, J = 5.5, 7 Hz, 1 H, H-6_{exo}), 4.22 (d, J = 1, 7 Hz, 1 H, H-6_{endo}), 4.34 (br d, J = 5.5 Hz, 1 H, H-5), 4.72 (m, 1 H, H-3), 5.42–5.6 (two sets of m, 2 H, —CH=CH—), 5.54 (br s, 1 H, H-1); ^{13}C NMR[40] ($CDCl_3$, 50.3 MHz) ppm 24.44 (t, -CH_2CH_2COOCH_3), 26.38 (t, —CH_2CH_2CH=CH—), 28.07 (t, C(4)—CH_2CH=CH—), 33.12 (t, -CH_2COOCH_3), 33.78 (t, C-2), 38.57 (q, -O_3SCH_3), 43.55 (d, C-4), 51.17 (q, -COOCH_3), 67.31 (t, C-6), 73.57 (d, C-5), 76.61 (d, C-3), 99.15 (d, C-1), 126.61 (d, C(4)—CH_2CH=CH—), 131.87 (d, C(4)—CH_2CH=CH—), 173.52 (-$COOCH_3$); mass (chemical ionization, NH_3) 366 (M + 18), 270 [(M + 18) - CH_3SO_3H]. Anal. Calcd for $C_{15}H_{24}O_7S$: C, 51.71; H, 6.94; S, 9.20. Found: C, 51.46; H, 7.00; S, 8.93.

Synthesis of 30. A solution of mesylate **29** (0.572 g, 1.64 mmol) in absolute methanol (15 mL) was treated with dry Amberlite IRA-120 (H^+) resin (1.25 g). The mixture was stirred at room temperature for 60 h. The resin was removed by filtration and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.5 × 12 cm) using 4:6 ethyl acetate–hexane gave starting material **29** (0.032 g), followed by **30** (0.536 g, 90% yield, 95% conversion) as a mixture of α- and β-isomers (α/β ratio ca. 80:20, NMR). The α- and β-isomers were not separable at this stage by column chromatography. The mixture was used for the next step without further purification. The spectral data for the α-isomer were obtained using this material: IR (film) 3520, 1730, 1170 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.69 (m, J = 7.5 Hz, 2 H, HH-3), 1.91 (m, 2 H, H-8 and H-10_{ax}), 1.99 (t, 1 H, J = 6 Hz, -OH), 2.09 (br q, 2 H, HH-4), 2.16–2.30 (m, 2 H, HH-7), 2.32 (t, J = 7.25 Hz, 2 H, HH-2), 2.41 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 3.05 (s, 3 H, -O_3SCH_3), 3.33 (s, 3 H, -OCH_3), 3.68 (s, 3 H, -COOCH_3), 3.62–3.84 (m, 3 H, H-12 and HH-13), 4.86 (q, J = 1.5, 3.5 Hz, 1 H, H-11), 4.98 (m, J = 5, 11 Hz, 1 H, H-9), 5.49 (m, 2 H, —CH=CH—); ^{13}C NMR[41] ($CDCl_3$, 50.3 MHz) ppm 24.48 (t) and 24.56 (t) (C-3 and C-7), 26.79 (t, C-4), 33.42 (t, C-2), 37.28 (t, C-10), 38.82 (q, -O_3SCH_3), 41.49 (d, C-8), 51.45 (q, -COOCH_3), 54.74 (q,

(40) Assignment based on comparison with data given in the following: (a) Ritchie, R. G. S.; Cyr, N.; Perlin, A. S. *Can. J. Chem.* **1976**, *54*, 2301. (b) Paulsen, H.; Sinnwell, V.; Greve, W. *Carbohydr. Res.* **1976**, *49*, 27. (c) Cooper, G. E.; Freid, J. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1579.

$-OCH_3$), 62.98 (t, C-13), 71.57 (d, C-12), 77.35 (d, C-9), 98.19 (d, C-11), 126.00 (d, C-6), 131.09 (d, C-5), 173.87 ($-COOCH_3$); mass (chemical ionization, NH_3) 398 (M + 18), 366 [(M + 18) - CH_3OH].

Synthesis of 31. A solution containing **30** (0.51 g, 1.34 mmol) in dry dichloromethane (10 mL) was added rapidly to a solution of the Collins reagent prepared from chromium trioxide (1.46 g, 14.6 mmol) and dry pyridine (2.30 g, 2.36 mL, 29.3 mmol) in dichloromethane (90 mL). After stirring vigorously for 1.5 h the mixture was poured into ice water (50 mL) and dichloromethane (10 mL). The organic layer was washed with water (3 × 50 mL) and brine (50 mL), dried, and evaporated. The residue was dissolved in toluene (50 mL) and again evaporated. Flash chromatography over silica gel (1.5 × 15 cm) using 4:6 ethyl acetate–hexane gave the aldehyde **31** (0.38 g, 74%) as a homogeneous (TLC, silica gel, 1:1 ethyl acetate–hexane) oil. The spectral data for the α-isomer were obtained using this material: IR (film) 1735, 1440, 1355, 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, J = 7.25 Hz, 2 H, HH-3), 1.98 (m, 2 H), 2.07 (m, 2 H, HH-4), 2.32 (t, J = 7.25 Hz, 2 H, HH-2), 2.32–2.4 (m, 3 H, HH-7 and H-10), 3.05 (s, 3 H, $-O_3SCH_3$), 3.4 (s, 3 H, $-OCH_3$), 3.68 (s, 3 H, $-COOCH_3$), 4.02 (q, J = 1.5, 9.5 Hz, 1 H, H-12), 4.95 (t, 1 H, H-11), 5.03 (m, J = 5, 10 Hz, H-9), 5.40–5.55 (m, 2 H, H-5 and H-6), 9.48 (d, J = 1.5 Hz, 1 H, –CHO); ^{13}C NMR[41] ($CDCl_3$, 50.3 MHz), ppm 24.21 (t) and 24.38 (t) (C-3 and C-7), 26.57 (t, C-4), 33.23 (t, C-2), 36.03 (t, C-10), 38.69 (q, $-O_3SCH_3$), 40.66 (d, C-8), 51.27 (q, $-COOCH_3$), 55.19 (q, $-OCH_3$), 75.19 (d, C-12), 76.54 (d, C-9), 97.94 (d, C-11), 125.07 (d, C-6), 132.16 (d, C-5), 173.36 ($-COOCH_3$), 198.12 (d, –CHO); mass (chemical ionization, NH_3) 396 (M + 18).

Synthesis of 32 and 33. Dimethyl (2-oxoheptyl)phosphonate (0.205 g, 0.19 mL, 0.92 mmol) was added dropwise and with stirring to a cold (0 °C) suspension of potassium *tert*-butoxide (0.103 g, 0.92 mmol) in toluene (10 mL). The mixture was stirred at room temperature for 1 h and then a solution (3 mL plus 1 mL rinse) of aldehyde **31** (0.28 g, 0.73 mmol) was added slowly. The solution was stirred for an additional 15 min and then it was diluted with ether (100 mL). The organic layer was washed with 10% aqueous sodium dihydrogen phosphate (20 mL), water (20 mL), and brine (30 mL), dried, and concentrated. Flash chromatography over silica gel (1.5 × 16 cm) using 2:8 ethyl acetate–hexane gave **32** (0.229 g, 66%), mixed fractions (0.0567 g, 16.7%), and **33** (0.0164 g, 4.7%) (total yield, 87%) in that order.

Compound **32**: $[\alpha]^{23}_D$ +71 (c 1, $CHCl_3$); FT-IR (film) 2953, 2934, 1735, 1697, 1676, 1355, 1174, 1046, 939, 894 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 6.8 Hz, 3 H, $-CH_2CH_3$), 1.31 (m, 4 H, HH-18 and HH-19), 1.58–1.82 (m, 5 H, HH-3, HH-17, and H-8), 1.95 (m, J = 3.5, 11, 12.5 Hz, 1 H, H-10_{ax}), 2.06 (br q, J = 7.25 Hz, 2 H, HH-4), 2.26 (m, 2 H, HH-7), 2.31 (t, J = 7.25 Hz, 2 H, HH-2), 2.44 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 2.55 (t, J = 7.25 Hz, 2 H, HH-16), 3.03 (s, 3 H, $-O_3SCH_3$), 3.31 (s, 3 H, $-OCH_3$), 3.67 (s, 3 H, $-COOCH_3$), 4.20 (br q, J = 6, 10 Hz, 1 H, H-12), 4.87 (br d, J = 2.5, 3 Hz, 1 H, H-11), 4.99 (m, J = 5, 11 Hz, 1 H, H-9), 5.45 (m, 2 H, H-5 and H-6), 6.34 (q, J = 1, 16 Hz, 1 H, H-14), 6.75 (q, J = 6, 16 Hz, 1 H, H-13); ^{13}C NMR[41] ($CDCl_3$, 100.6 MHz) ppm 13.89 (q, C-20), 22.46 (t, C-19), 23.69 (t), 24.58 (t) and 24.70 (t) (C-3, C-7 and C-17), 26.92 (t, C-4), 31.47 (t, C-18), 33.43 (t, C-2), 37.27 (t, C-10), 38.90 (q, $-O_3SCH_3$), 40.67 (t, C-16), 46.08 (d, C-8), 51.41 (q, $-COOCH_3$), 54.96 (q, $-OCH_3$), 70.53 (d, C-12), 77.12 (d, C-9), 98.36 (d, C-11), 125.87 (d, C-6), 130.93 (d, C-14), 131.32 (d, C-5), 141.68 (d, C-13), 173.80 (s, C-1), 200.12 (s, C-15); mass (chemical ionization, NH_3) 492 (M + 18), 396 [(M + 18) - CH_3SO_3H], 364 [(M + 18) - (CH_3SO_3H + CH_3OH)]. Anal. Calcd for $C_{23}H_{38}O_8S$: C, 58.21; H, 8.07; S, 6.76. Found: C, 58.50; H, 8.19; S, 6.56.

Compound **33**: $[\alpha]^{23}_D$ –10 (c 1, $CHCl_3$); FT-IR (film) 2930, 1735, 1700, 1675, 1357, 1336, 1174, 1057, 932 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.32 (m, 4 H, HH-18 and HH-19), 1.63 (m, 2 H) and 1.71 (m, 3 H, HH-17, HH-3, and H-8), 1.81 (m, 1 H, H-10_{ax}), 2.07 (br q, J = 7 Hz, 2 H, HH-4), 2.29 (m, 4 H, HH-7 and HH-2), 2.54 (m, 1 H, H-10_{eq}), 2.55 (t, J = 7.25 Hz, 2 H, HH-16), 3.06 (s, 3 H, $-O_3SCH_3$), 3.52 (s, 3 H, $-OCH_3$), 3.68 (s, 3 H, $-COOCH_3$), 3.88 (m, J = 1.25, 5.75, 10 Hz, 1 H, H-12), 4.41 (q, J = 2, 9.25 Hz, 1 H, H-11), 4.74 (m, J = 5, 10.25 Hz, 1 H, H-9), 5.41 (m, 1 H) and 5.5 (m, 1 H) (H-5 and H-6), 6.37 (q, J = 1.25, 15.5 Hz, 1 H, H-14), 6.78 (q, J = 5.75, 15.5 Hz, 1 H, H-13); ^{13}C NMR[39,41] ($CDCl_3$, 100.6 MHz) ppm 13.86 (C-20), 22.42 (C-19), 23.66, 24.20 and 24.53 (C-3, C-7 and C-17), 26.87 (C-4), 31.43 (C-18), 33.38 (C-2), 38.50 (C-10), 39.28 ($-O_3SCH_3$), 40.76 (C-16), 45.59 (C-8), 51.41 ($-COOCH_3$), 56.65 ($-OCH_3$), 74.39 (C-12), 78.06 (C-9), 100.01 (C-11), 125.21 (C-6), 130.84 (C-13), 131.70 (C-5), 140.75 (C-13), 173.72 ($-COOCH_3$), 199.99 (C-15); mass (chemical ionization, NH_3) 492 (M + 18), 396 [(M + 18) - CH_3SO_3H], 364 [(M + 18) - (CH_3SO_3H + CH_3OH)]; exact mass, 442.2023; calcd for $C_{22}H_{34}O_7S$ (M - CH_3OH), 442.2026; 346.2146; calcd for $C_{21}H_{30}O_4$ [M - (CH_3SO_3H + CH_3OH)], 346.2144; 317.2106; calcd for $C_{20}H_{29}O_3$, 317.2117; 315.1960; calcd for $C_{20}H_{27}O_3$ [M - (CH_3SO_3H + CH_3OH + CH_3O)], 315.1960.

Reduction of 32 and Isolation of the "C(15)" Diastereomeric Alcohols 34 and 35. A solution of the enone **32** (57 mg, 0.12 mmol) in absolute methanol (1 mL plus 0.5 mL) rinse was added dropwise to a cold (–40 °C) solution (3 mL) of sodium borohydride (17.3 mg, 0.45 mmol). The mixture was stirred for 1.5 h and excess of reagent was destroyed by addition of 10% aqueous sodium dihydrogen phosphate (3 mL). Most of the methanol was evaporated and the residue was extracted with ether (3 × 30 mL). The ether layer was washed with water (2 × 20 mL) and brine (20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 19 cm) using 3:7 ethyl acetate–benzene gave **35** (23 mg, 40%) as a homogeneous (R_f 0.38, TLC, silica gel, 1:1 ethyl acetate–hexane) oil and its "C(15)" epimer **34** (21 mg, 36%) as a homogeneous (R_f 0.31, TLC, silica gel, 1:1 ethyl acetate–hexane) oil.

Compound **35**: $[\alpha]^{23}_D$ +37.8 (c 1, $CHCl_3$); FT-IR (film) 3480, 2951, 2931, 1735, 1353, 1337, 1174, 1126, 1048, 972, 944, 894 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 6.75 Hz, 3 H, $-CH_2CH_3$), 1.25–1.37 (m, 6 H), 1.47–1.59 (m, 2 H, HH-16), 1.62–1.76 (m, 3 H, 1.93 (m, J = 3.5, 11, 12.5 Hz, 1 H, H-10_{ax}), 2.05 (br q, 3 H, including –OH and HH-4), 2.25 (br t, 2 H, HH-7), 2.32 (t, J = 7 Hz, 2 H, H-2), 2.42 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 3.01 (s, 3 H, $-O_3SCH_3$), 3.29 (s, 3 H, $-OCH_3$), 3.67 (s, 3 H, $-COOCH_3$), 4.01 (q, J = 7.6, 10.5 Hz, 1 H, H-12), 4.17 (m, 1 H, H-15), 4.83 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.99 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.42 (m, 2 H, H-5 and H-6), 5.65 (m, J = 1, 7.6, 15.25 Hz, 1 H, H-13), 5.79 (q, J = 6, 15.25 Hz, 1 H, H-14); ^{13}C NMR[41] ($CDCl_3$, 100.6 MHz) ppm 13.86 (C-20), 22.56 (C-19), 24.57, 24.94 and 25.11 (C-3, C-7 and C-17), 26.88 (C-4), 31.72 (C-18), 33.40 (C-2), 37.13 and 37.36 (C-10 and C-16), 38.88 ($-O_3SCH_3$), 45.88 (C-8), 51.51 ($-COOCH_3$), 54.78 ($-OCH_3$), 71.80 (C-12), 72.01 (C-15), 77.80 (C-9), 98.22 (C-11), 126.26 (C-6), 127.94 (C-13), 130.64 (C-5), 138.25 (C-14), 170.06 ($-COOCH_3$); mass (chemical ionization, NH_3) 494 (M + 18), 363 [MH - (CH_3SO_3H + $2H_2O$)], 331 [MH - (CH_3SO_3H + $2H_2O$ + CH_3OH)]; exact mass, 362.2460; calcd for $C_{22}H_{34}O_4$ [M - (CH_3SO_3H + H_2O)], 362.2457; 330.2191; calcd for $C_{21}H_{30}O_3$ [M - (CH_3SO_3H + H_2O + CH_3OH)], 330.2195.

Compound **34**: $[\alpha]^{23}_D$ +47 (c 1, $CHCl_3$); FT-IR (film) 3480, 2951, 2931, 1735, 1353, 1337, 1174, 1123, 1047, 940, 893 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.20–1.40 (m, 6 H, HH-17, HH-18, HH-19), 1.46–1.58 (m, 2 H, HH-16), 1.60–1.77 (m, 3 H, HH-3, H-8), 1.79 (d, J = 5 Hz, 1 H, –OH), 1.93 (m, J = 3.5, 11, 12.5 Hz, 1 H, H-10_{ax}), 2.05 (br q, 2 H, HH-4), 2.24 (br t, 2 H, HH-7), 2.31 (t, J = 7 Hz, 3 H, HH-2), 2.42 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 3.01 (s, 3 H, $-O_3SCH_3$), 3.32 (s, 3 H, $-OCH_3$), 3.67 (s, 3 H, $-COOCH_3$), 4.04 (q, J = 7.5, 10.5 Hz, 1 H, H-12), 4.13 (m, 1 H, H-15), 4.83 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.98 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.44 (m, 2 H, H-5 and H-6), 5.66 (br q, J = 7.5, 15.5 Hz, 1 H, H-13), 5.84 (q, J = 5, 15.5 Hz, 1 H, H-14); ^{13}C NMR[41] ($CDCl_3$, 100.6 MHz) ppm 13.94 (C-20), 22.55 (C-19), 24.58, 24.86 and 25.06 (C-3, C-7 and C-17), 26.86 (C-4), 31.71 (C-18), 33.42 (C-2), 37.08 and 37.33 (C-10 and C-16), 38.87 ($-O_3SCH_3$), 45.78 (C-8), 51.44 ($-COOCH_3$), 54.78 ($-OCH_3$), 71.67 (C-12), 71.87 (C-15), 77.74 (C-9), 98.20 (C-11), 126.04 (C-6), 127.79 (C-13), 130.66 (C-5), 138.01 (C-14), 174.18 ($-COOCH_3$); mass (chemical ionization, NH_3) 494 (M + 18), 363 [MH - (CH_3SO_3H + $2H_2O$)], 331 [MH - (CH_3SO_3H + $2H_2O$ + CH_3OH)]; exact mass, 444.2156; calcd for $C_{22}H_{36}O_7S$ (M - CH_3OH), 444.2182; 426.2067; calcd for $C_{22}H_{34}O_6S$ [M - (CH_3OH + H_2O)], 426.2076; 362.2453; calcd for $C_{22}H_{34}O_4$ [M - (CH_3SO_3H + H_2O)], 362.2457; 349.2370; calcd for $C_{21}H_{33}O_4$ [M - (CH_3SO_3H + CH_3O)], 349.2379; 348.2298; calcd for $C_{21}H_{32}O_4$ [M - (CH_3SO_3H + CH_3OH)], 348.2300;

(41) Tentative: cf. ref 40c.

330.2191; calcd for $C_{21}H_{30}O_3$ [M – (CH_3SO_3H + H_2O + CH_3OH)], 330.2194; 299.2007; calcd for $C_{20}H_{27}O_2$ [M – (CH_3SO_3H + H_2O + CH_3OH + CH_3O)], 299.2011; 291.1591; calcd for $C_{17}H_{23}O_4$ [M – (CH_3SO_3H + H_2O + C_5H_{11})], 291.1596; 221.1536; calcd for $C_{14}H_{21}O_2$, 221.1542.

Synthesis of "15-*S*" Benzoate 36. Benzoyl chloride (0.05 mL, 0.4 mmol) was added to a solution of the alcohol **34** (12 mg, 0.025 mmol) and dry pyridine (0.075 mL, 0.9 mmol) in dry dichloromethane (1.5 mL). The solution was stirred at room temperature for 5 h. Most of the dichloromethane was evaporated and the residue was diluted with pyridine (0.5 mL) and water (0.5 mL). The mixture was allowed to stand for 2 h. The mixture was then extracted with ether (3 × 15 mL); the ether layer was washed with saturated aqueous sodium bicarbonate (2 × 10 mL), water (10 mL), and brine (10 mL), dried, and concentrated. The residue was diluted with toluene (10 mL) and was again evaporated. TLC of the residue over silica gel using 4:6 ethyl acetate–hexane gave **36** (13.5 mg, 92%) as a homogeneous (TLC, silica gel, 3:7 ethyl acetate–hexane) oil: $[\alpha]^{23}_D$ +40 (*c* 1, $CHCl_3$); FT-IR (film) 2930, 1735, 1718, 1450, 1355, 1272, 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.27–1.35 (m, 6 H, HH-19, HH-18, HH-17), 1.57–1.84 (m, 5 H, HH-3, H-8, HH-16), 1.92 (m, J = 3.5, 11, 12.5 Hz, 1 H, H-10_{ax}), 2.02 (m, 2 H, HH-4), 2.13–2.25 (m, 2 H, HH-7), 2.28 (t, J = 7 Hz, 2 H, HH-2), 2.41 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 2.99 (s, 3 H, $-O_3SCH_3$), 3.31 (s, 3 H, $-OCH_3$), 3.66 (s, 3 H, $-COOCH_3$), 4.03 (q, J = 7.4, 10.5 Hz, 1 H, H-12), 4.82 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.97 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.4 (m, 2 H, H-5 and H-6), 5.55 (br, q, 1 H, H-15), 5.72 (m, J = 1, 7.4, 15.25 Hz, 1 H, H-13), 5.85 (q, J = 5.2, 15.25 Hz, 1 H, H-14), 7.42 (t, 2 H), 7.54 (t, 1 H) and 8.04 (q, 2 H) (aromatic protons); ^{13}C NMR[38] ($CDCl_3$, 100.6 MHz) ppm 13.91 (C-20), 22.43 (C-19), 24.58, 24.66 and 24.82 (C-3, C-7 and C-17), 26.78 (C-4), 31.52 (C-18), 33.39 (C-2), 34.33 (C-16), 37.26 (C-10), 38.82 ($-O_3SCH_3$), 45.75 (C-8), 51.37 ($-COOCH_3$), 54.82 ($-OCH_3$), 71.44 (C-12), 73.72 (C-15), 77.51 (C-9), 98.12 (C-11), 125.77 (C-6), 128.29, 129.38, 129.54, 130.83, 132.66, 132.83, 173.74 ($-COOCH_3$); mass (chemical ionization, NH_3) 598 (M + 18); exact mass, 549.2518; calcd for $C_{29}H_{41}O_8S$ (M – CH_3O), 549.2522; 453.2621; calcd for $C_{28}H_{37}O_5$ [M – (CH_3SO_3H + CH_3O)], 453.2641; 331.2246; calcd for $C_{21}H_{31}O_3$ [M – (CH_3O + CH_3SO_3H + PhCOOH)], 331.2273; 330.2193; calcd for $C_{21}H_{30}O_3$ [M – (CH_3OH + CH_3SO_3H + PhCOOH)], 330.2195.

Synthesis of "15-*R*" Benzoate 37. Benzoyl chloride (0.05 mL, 0.4 mmol) was added to a solution of the alcohol **35** (13 mg, 0.027 mmol) and dry pyridine (0.075 mL, 0.9 mmol) in dry dichloromethane (1.5 mL). The solution was stirred at room temperature for 8 h. Most of the dichloromethane was evaporated and the residue was diluted with pyridine (0.5 mL) and water (0.5 mL). The mixture was allowed to stand at room temperature for 2 h. The mixture was then extracted with ether (3 × 15 mL); the ether layer was washed with saturated aqueous sodium bicarbonate (2 × 10 mL), water (10 mL), and brine (10 mL), dried, and evaporated. The residue was diluted with toluene (15 mL) and was again evaporated. TLC of the residue over silica gel using 4.5:6.5 ethyl acetate–hexane gave **37** (12.5 mg, 80%) as a homogeneous (TLC, silica gel, 3:7 ethyl acetate–hexane) oil: $[\alpha]^{23}_D$ +31.5 (*c* 1, $CHCl_3$); FT-IR (film) 2930, 1735, 1718, 1450, 1355, 1272, 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.25–1.45 (m, 6 H, HH-17, HH-18, and HH-19), 1.5 (m, J = 7 Hz, 2 H, HH-3), 1.67–1.85 (m, 3 H, i.a. H-8), 1.92 (m, 3 H, including H-10_{ax}), 2.15 (m, J = 7 Hz, 2 H, HH-3), 2.22 (m, 2 H, HH-7), 2.42 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 2.99 (s, 3 H, $-O_3SCH_3$), 3.31 (s, 3 H, $-OCH_3$), 3.64 (m, 3 H, $-COOCH_3$), 4.02 (q, J = 6.25, 11 Hz, 1 H, H-12), 4.82 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.92 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.32 (m, 1 H) and 5.42 (m, 1 H) (H-5 and H-6), 5.53 (br q, 1 H, H-15), 5.8 (m, 2 H, H-13 and H-14), 7.42 (t, 2 H), 7.54 (t, 1 H) and 8.04 (q, 2 H) (aromatic protons); ^{13}C NMR[38] ($CDCl_3$, 50.3 MHz) δ 13.86 (C-20), 22.40 (C-19), 24.40, 24.62 and 24.77 (C-3, C-7 and C-17), 26.68 (C-4), 31.47 (C-18), 33.26 (C-2), 34.34 (C-16), 37.26 (C-10), 38.78 ($-O_3SCH_3$), 45.74 (C-8), 51.32 ($-COOCH_3$), 54.78 ($-OCH_3$), 71.52 (C-12), 74.32 (C-15), 77.47 (C-9), 98.15 (C-11), 125.86 (C-6), 128.17, 128.29, 129.50, 130.50, 130.71, 132.59, 132.83, 165.67 ($-OOCPh$), 173.80 ($-COOCH_3$); mass (chemical ionization, NH_3) 598 (M + 18); exact mass, 549.2514; calcd for $C_{29}H_{41}O_8S$ (M – CH_3O), 549.2524; 362.2461; calcd for $C_{22}H_{34}O_4$ [M – (CH_3SO_3H + PhCOOH)], 362.2457; 330.2193; calcd for $C_{21}H_{30}O_3$ [M – (CH_3OH + CH_3SO_3H + PhCOOH)], 330.2195.

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