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ANNULATED PYRANOSIDES—V

AN ENANTIOSPECIFIC ROUTE TO (+) AND (−) CHRYSANTHEMUM DICARBOXYLIC ACIDS†‡[1]

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Abstract—Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside undergoes the Wadsworth–Emmons cyclopropanation with phosphonopropionate to give a cyclopropyl carboxylate which is processed to give the *gem*-dimethylcyclopropano pyranoside. The glycosylic acetal of this substance is readily hydrolyzed by boiling water, and the resulting *cis*-cyclopropane carboxaldehyde may be epimerized quantitatively to the *trans*-analog by treatment with sodium methoxide. These aldehydes are now converted into the (+)- and (−)-chrysanthemum dicarboxylic acids, respectively, by the same sequence of reactions involving (a) olefination with methyl 2-(triphenylphosphoranylidene)propionate, (b) hydrolysis of the benzylidine ring and cleavage of the resulting triol with sodium metaperiodate, and (c) oxidation of the resulting aldehyde with silver I oxide. In the case of the (+)-enantiomer the last reaction is preceeded by epimerization. The overall yields from the D-allopyranoside are respectively 27%, in 10 steps for the (+)-enantiomer, and 24%, in 10 steps for the (−)-enantiomer, from the known epoxide 7.

INTRODUCTION

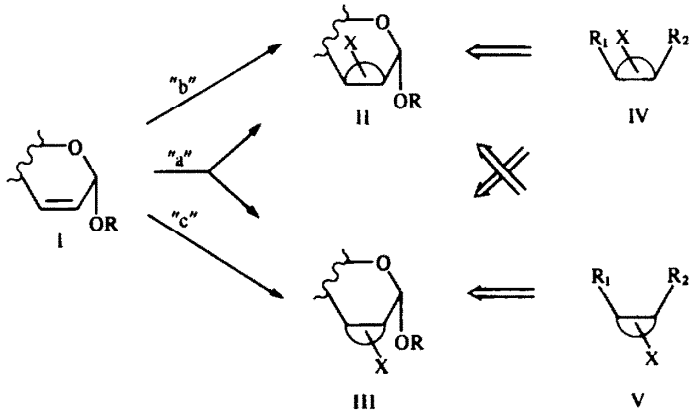
There is currently considerable interest in the use of carbohydrate derivatives as chiral synthons,[4-6] and judging from the burgeoning literature, the area of ionophore and macrolide syntheses has so far received favored attention.[7] This connection is highly plausible in view of the polyoxygenated nature of these targets.[8] The use of carbohydrates as chiral synthons for carbocycles has received comparatively, much less attention. Against this background, Stork's syntheses of prostaglandins are landmark achievements.[9] In this paper, we describe some of our work on the concept of "annulated pyranosides" as chiral synthons for carbocycles.

The development of synthetic routes to cycloalkano sugars has been of long-standing interest in our research group. Originally the program was connected with our studies on the exploratory chemistry of unsaturated sugars,[10] but it soon became apparent that these "annulated sugars" had enormous potential for stereocontrolled access to optically pure cycloalkyl compounds.[4] Thus as expressed schematically in Scheme 1, annulations of an unsaturated sugar I could occur from "above" and/or "below" to give II and III respectively. The orientation of the substituent(s), X, on the cycloalkyl ring could be adjusted and/or determined by taking advantage of the conformational properties of the pyranosidic moiety.[11] Structures II and III are, of course, diastereomers; but if X was of the proper configuration in each, the degradation products remaining after dismembering the sugar residue, IV and V respectively, would be enantiomers. The sugar moiety would thus have enabled us to carry out an asymmetric synthesis[12] of carbocycles.

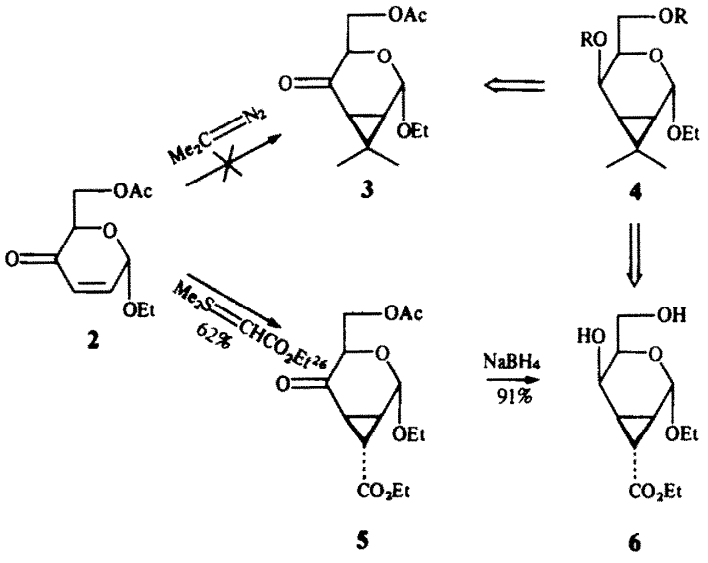
The foregoing format would apply if the annulation of sugar I occurred as in path "a", giving both

†Dedicated to Prof. Gilbert Stork on the occasion of his sixtieth birthday.

‡For Part IV see Ref. 14.



Scheme 1.



Scheme 2.

II and III as has been observed in some cases.[13] However for reactions where the annulation is completely stereoselective giving *either* II or III, as in paths "b" or "c",[14-18] preparation of both enantiomers IV and V could still be accomplished by epimerization(s) of the appropriate stereocenters in II and III at opportune stages during the synthetic manipulations. In this manuscript we exemplify the potential of this methodology with syntheses of the enantiomers of chrysanthemum dicarboxylic acids, (+)-**1** and (−)-**1**, from the same annulated pyranoside precursor.[19]

The gem-*dimethylcyclopropanopyranoside.* An appropriate sugar precursor for these targets would be a *gem*-dimethylcyclopropano pyranoside such as **4**. In keeping with one of our earlier approaches to cyclopropano sugars,[15] we examined the addition of dimethylcarbene, generated from 2-diazopropane, to enone **2**[20] (Scheme 2). This addition to **2** failed, as had the addition of methylene generated from diazomethane.[15]

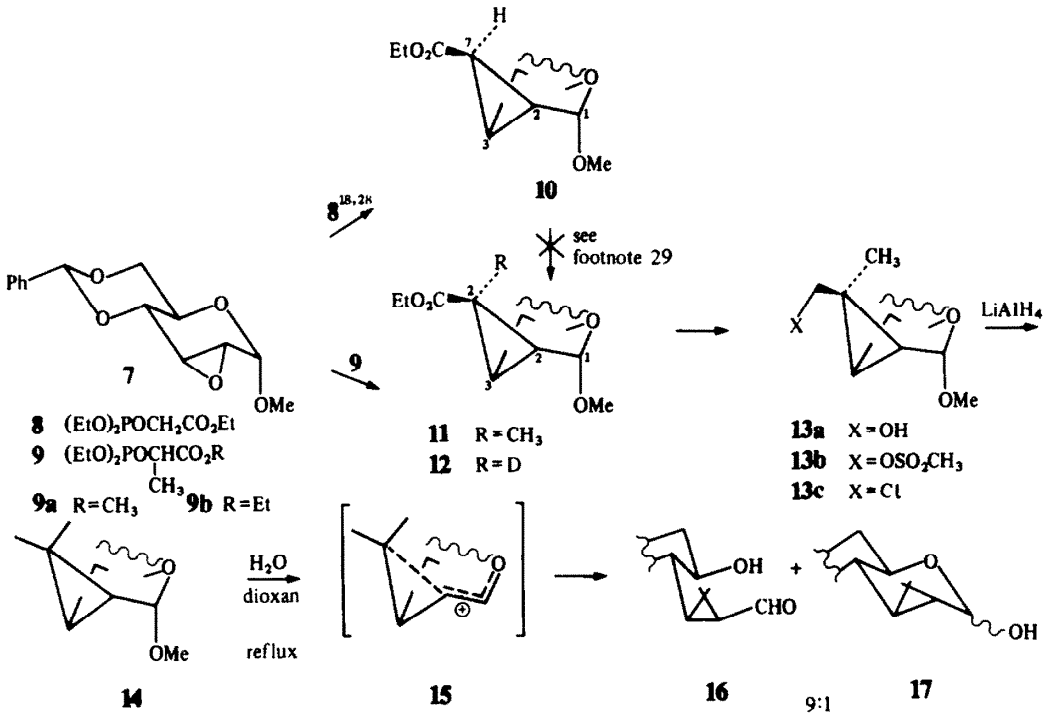
An indirect route of the *gem*-dimethyl grouping could involve α-alkylation of cyclopropyl esters such as **5** using methodology reported by Pehl and Brown[21] or Walborsky and Hornyak.[22] Our proposed route to **4** envisaged **5** and **6** as intermediates. Accordingly **5** was prepared in 64% yield from enone **2** by reaction the ylid obtained from ethyl (dimethylsulfuranylidene) acetate as described by Corey *et al.*[23] The isomer obtained gave evidence of cyclopropyl protons at δ 2.49 and 2.71 ppm in the ^{1}H NMR spectrum, and the fact that H-1 (located at δ 5.18 ppm) was a singlet, established the D-*lyxo* configuration on the pyranoside core. The configuration at C-7 was not established, although the representation in **5** would follow from the work of Payne, which shows that in these additions, the ester usually ends up being *trans* to the CO.[24]

Reduction of **5** with sodium borohydride occurred stereoselectively[15] giving **6** as a crystalline substance.

In spite of the successful preparation of **6**, the analog **10** (Scheme 3), was a more accessible and convenient substrate for studying the α-alkylation since it had been prepared previously.[15,25] However subjecting **10** to methyl iodide with a variety of bases, solvents and temperatures,[26] under conditions which had been found successful by Pehl[21] or Walborsky[22] in similar systems, failed to produce any detectable amounts of **11**. This failure could have been due to difficulty in deprotonating C-7 of **10** to give the corresponding enolate; on the other hand the enolate, if formed, would be very hindered to the approaching electrophile. In order to determine whether the anion was being generated, compound **10** was treated with lithium diisopropylamide (LDA) at −77°, then with D_2O. The isolated product gave no evidence for **12** since the signal for H-7 was still present in the ^{1}H NMR spectrum. The anion was therefore not being generated, and this approach was abandoned.

In view of the foregoing failure, we decided to examine the Wadsworth–Emmons cyclopropanation[27] of epoxides by which compound **10** had been successfully prepared.[15,25] In this interesting process, a pentacoordinate species is presumed to be a key intermediate[28] (e.g. **18**), which in the case of cyclohexene oxide (Scheme 4, equation (a)) is allowed by the conformational flexibility of the system.[29] In the case of the anhydro sugar **7**, the *trans*-fused benzylidene ring is a constraining factor. However, a timely publication by Hanessian and Dextraze[30] reported that upon treating compound **19** with sodium hydride, the lactone **20** was formed (Scheme 4, equation (b)). On this basis we reasoned that the oxaphosphocycle **21** was indeed a credible species.

Accordingly, anhydro sugar **7** was treated with ethyl 2-(diethylphosphono)propionate **9a**, under the conditions that had afforded ester **10** in the reaction of **7** with **8**.[15,25] However, analog **11** was isolated in only 1.8 percent yield. That the product was a single isomer was evident from GLC, and the gross structure was confirmed by 220 MHz ^{1}H NMR comparison of the spectra of **10** and **11**. The C-7 configuration was established by NOE measurements, which caused a 10% enhancement for H-1 (δ 4.61 ppm) when the cyclopropyl methyl (δ 1.38 ppm) was irradiated. This value corresponds

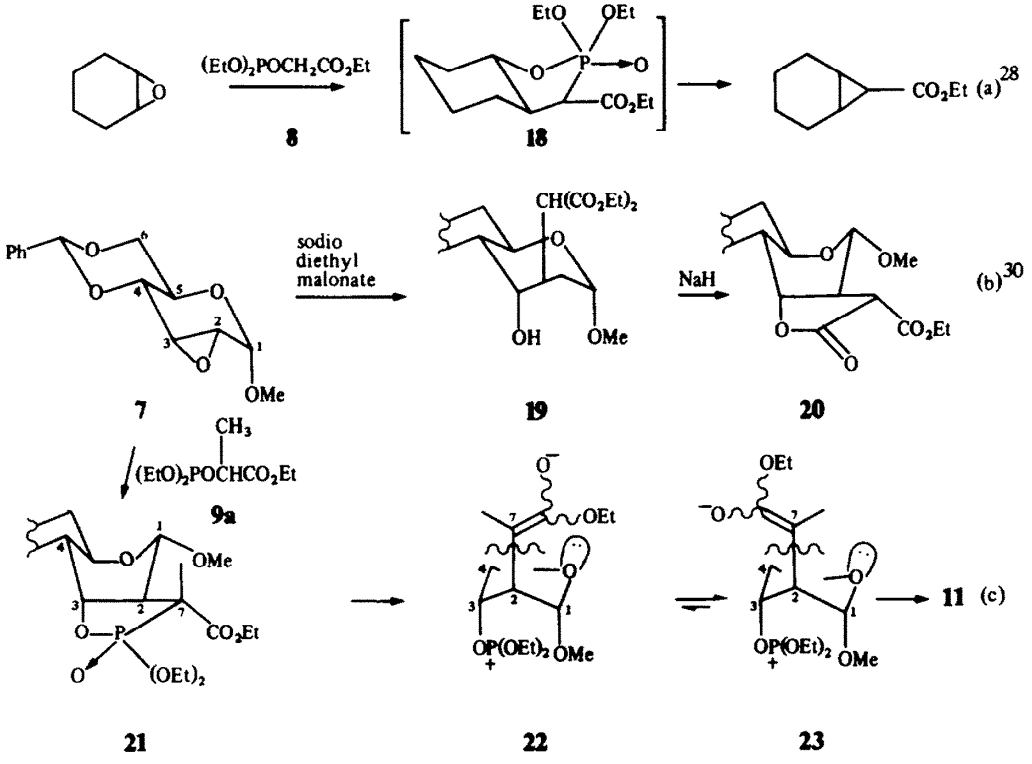


Scheme 3.

closely to that predicted on the basis of internuclear distances measured from Dreiding models.[31]

The exclusive formation of **11** can be rationalized with the help of the rotamers **22** and **23** (Scheme 4 equation (c)). In **22** the interaction between the electrons in the *p*-orbital of the ring oxygen and those in the π-cloud of the enolate ion is disfavored *vis a vis* **23**. Ring closure from the latter would then lead directly to **11**.

We were aware of a report by Denny on the failure



Scheme 4.

to obtain α-methylcyclopropyl esters with triphenylphosphorylidine propionates under conditions where the acetate homologs had been successful.[28] Nevertheless, we decided to make a major effort to improve the yield reported above, since compound **11** was clearly an attractive precursor for the *gem*-dimethylcyclopropyl residue.

As indicated in Table 1, entries 1–4, variation in the base did not improve the yields. Entries 3 and 5 indicate the advantage of longer reaction times, whereas entries 6, 7 and 8 indicate that higher temperatures caused lower yields. The variable results with dioxane showed that the properties of the solvent were crucial. In order to use this solvent but raise the temperature, the reaction was attempted in a Monel pressure vessel immersed in an oil bath at 160° (entry 9). After four days, compound **11** could be isolated in 28.0% yield, but use of a generous excess of reagent **9a** (entry 10) resulted in a 50% yield of **11**. There was no evidence for unconsumed epoxide **5** (TLC), and hence no further attempts to increase the yield were undertaken. (Nevertheless, our yields are far superior to those obtained by previous workers for other systems.)[27-29] It is noteworthy that attempts to use a stainless steel pressure vessel instead of the Monel reactor described above caused complete decomposition of the reactants, with no indication of **11** being formed.[32]

The procedure for obtaining the *gem*-dimethyl derivative **14** began with reduction of ester **11** with lithium aluminum hydride to the cyclopropyl carbinol **13a**. Treatment with methanesulfonyl chloride and pyridine at room temperature led to extensive decomposition; however, use of sulfene[33] at −77° afforded **13b** in 46% yield, and reduction with lithium aluminium hydride at room temperature gave compound **14** in 95% yield.

Owing to the poor yield of the sulfonate **13b**, alternative leaving groups were considered. Following a report by Evans on the chlorination of primary alcohols,[34] compound **13a** was treated with methanesulfonyl chloride in dimethylformamide at room temperature. Compound **13c** was thereby isolated in 92% yield. The material exhibited the characteristic $(M+2)^+$ ion in the mass spectrum (36% of M^+) expected for monochloroalkyl compounds. Reductive displacement of the chloride with LAH in refluxing THF gave **14** in 89% yield.

The key cyclopropylcarboxaldehydes. It was now necessary to hydrolyze the glycosylic methoxyl of **14**. Our studies of 2,3-cyclopropanated pyranosides had shown that such hydrolyses take place with great ease, a result which has been ascribed to the tandem activation of the anomeric center by the cyclopropyl ring and the lactol oxygen,[35] as expressed in **15**. Accordingly, compound **14** was hydrolyzed in refluxing aqueous dioxan in 1.5 h. The product was judged to be 9:1 equilibrium mixture of the hydroxyaldehyde **16** and the corresponding lactol **17**, based on the relative intensities of the C–CH_3 singlets (see Experimental). The *cis*-configuration about the cyclopropyl ring was confirmed by treating **16** with sodium methoxide, whereupon a new aldehyde **24** was obtained that exhibited a substantially different ^{1}H NMR spectrum, particularly with respect to the chemical shift of the doublets for the aldehydic protons (δ 9.45 in **16** versus δ 9.32 in **24** Scheme 5).

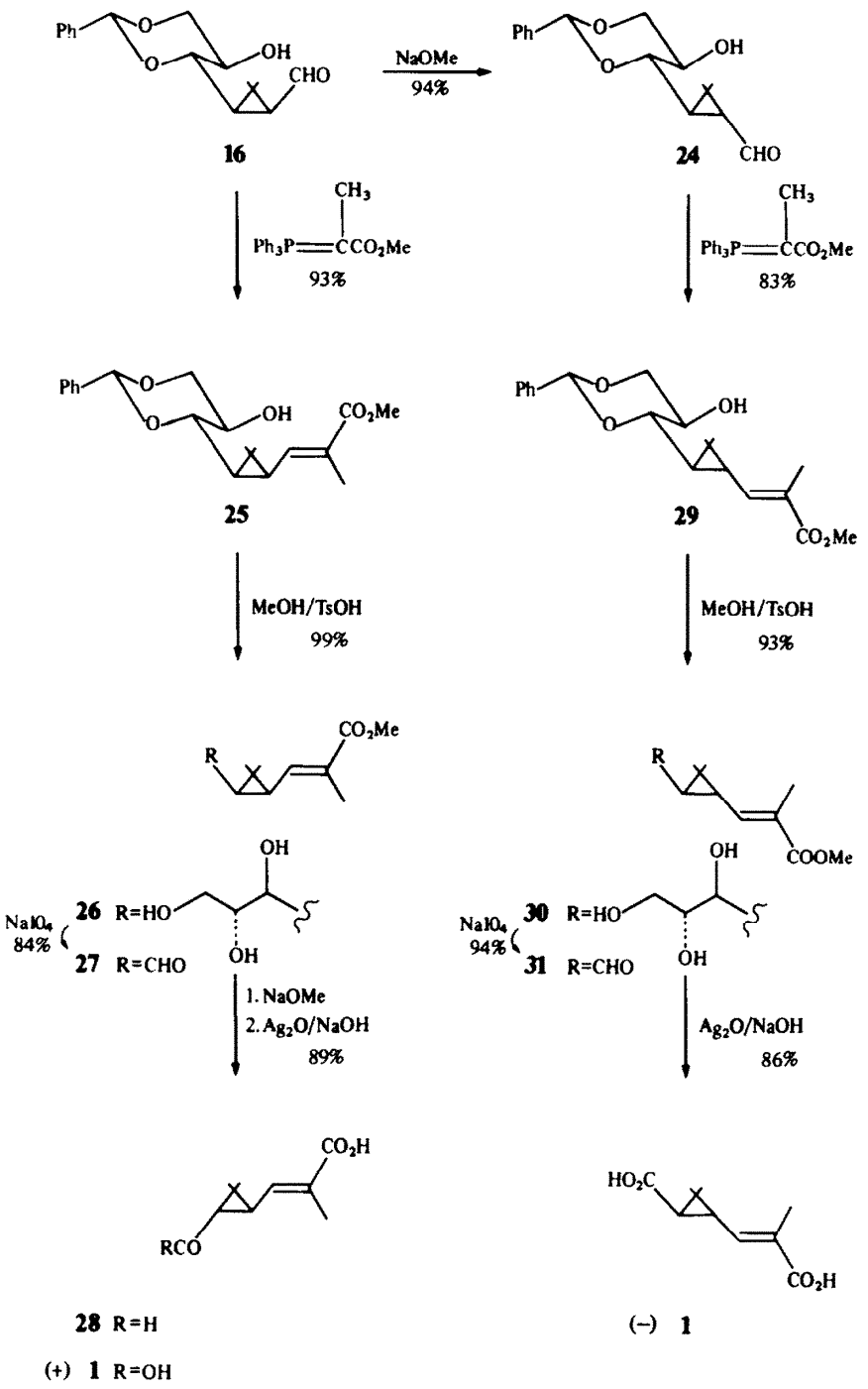
(+)-*Chrysanthemum dicarboxylic acid*, (+)-**1** (Scheme 5). Treatment of aldehyde **16** with methyl 2-(triphenylphosphoranylidene) propionate[36] gave the α,β-unsaturated ester **25** (93%) as the only geometric isomer. Cleavage of the benzylidine protecting group was effected with methanol and *p*-toluenesulfonic acid, and the resulting triol **26** was treated with sodium metaperiodate to give the *cis*-aldehyde **27** in 84% yield for the two steps. The *cis*-configuration of **27** was confirmed by treating the material with sodium methoxide, whereupon aldehyde (+)-**28** was formed quantitatively, the signals for the aldehydic protons being readily distinguishable at δ 9.60 ppm for **27** and δ 9.50 ppm for **28**.

Oxidation of the aldehyde (+)-**28** was effected with silver I oxide and sodium hydroxide which afforded the hemiester within 10 min (TLC), although the reaction was allowed to stand for an additional four hours at room temperature, in order to cause hydrolysis to the dicarboxylic acid, (+)-**1**, in 89% overall

Table 1. Reaction of Anhydro sugar **7** with $(EtO)_2POCH(CH_3)COOR$, **9**, to give **11**

	$CH_3SO_2CH_2Na$	DMSO	0.12	1	4	150	1.0
1	KH	dioxan	0.07	1	4	reflux	3.0
2.	NaH	dioxan	0.07	1	4	reflux	3.2
3.	NaH	dioxan/ HMPA	0.07	1	4	reflux	4.0
4							
5.	NaH	dioxan	0.14	1	16	reflux	17.1
6.	NaH	toluene	0.07	1	4	reflux	5.7
7.	NaH	xylene	0.07	1	4	reflux	1.0
8.	NaH	cumene	0.07	1	4	reflux	1.0
9.	NaH	dioxan	0.17	1	4	160	28.0
10.	NaH	dioxan	0.18	5	4	160	50.1

Number of equivalents of base is equal to the number of equivalents of phosphonopropionate, 9.



Scheme 5.

yield. The product, (+)-**1**, exhibited physical constants that were within the experimental error of those reported in the literature.[37,28] A mixed melting point with an authentic sample[39] confirmed (+)-**1** as the desired chrysanthemum dicarboxylic acid.

(−)-*Chrysanthemum dicarboxylic acid* (−)-**1** (Scheme 5). The synthesis of the levorotatory enantiomer (−)-**1** from **24** mirrored many of the steps used for the dextrorotatory enantiomer (+)-**1** (Scheme 5).

One notable difference was that, in this case, the ester **29** was contaminated with about 10% of the *Z*-isomer a result which finds precedent in some work of Crombie.[38]

The antipodes (+)-**1** and (−)-**1** could therefore be obtained enantiospecifically from the same *aldehydo* sugar **16**. The overall yields from the anhydro sugar, **7**, for (+)-**1** was 27% and for (−)-**1**, 24%, 10 steps being required for each enantiomer.

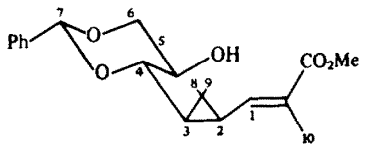
EXPERIMENTAL

General. M.ps were determined in capillary tubes and are uncorrected. Elemental analyses were performed by Microanalysis Laboratory, Toronto, Ontario, Canada. NMR

spectra were determined in $CDCl_3$ (TMS) with one of the following spectrometers: Varian T-60, Perkin–Elmer R-12B, Varian HR-220, Varian XL-100, or Bruker WP-80. Coupling constants were obtained by measuring the spacings of spectra judged to be first order. IR spectra were determined on a Beckmann model IR-10 or Perkin–Elmer model 298 spectrometer using either NaCl blanks for neat syrups or 0.1 mm NaCl cells and $CHCl_3$ as solvent. Low-resolution mass spectra were determined with one of the following spectrometers: Varian MAT-CM7 or Hitachi/Perkin–Elmer RMH-2. High-resolution mass spectra (HRMS) were determined either with a VG 7070F or a VG Micromass 7070H.

GLC was performed on a Hewlett Packard model 5730 with an Ultrabond packed coiled steel column (6 ft × 1/8 in.), or on a Varian model 3760 with a 3% OV-101 on Chromasorb-W (HP80/100) packed glass column (200 cm × 2 mm). The progress of all reactions was monitored by TLC which was performed on Al-sheets precoated with Silica Gel-60 (HF-254) to a thickness of 0.2 nm. (E. Merck, Cat. No. 5539). Unless otherwise stated, the following solvent systems were used to develop the plates: *A*, EtOAc–petroleum ether (30–60°), 1:4); *B*, EtOAc–petroleum ether (30–60°), (1:1); *C*, MeOH–CH_2Cl_2 (1:9); *D*, diethyl ether; *E*, EtOAc. The chromatograms were viewed under an UV light, sprayed with conc. H_2SO_4 and briefly heated to a temp. greater than 100° under a hot air gun. For column chromotography, E. Merck Silica Gel (0.063-60.20 mm, 70-230 mesh A.S.T.M.) was used. Preparative TLC was done on glass plates (20 × 20 cm) coated with Silica Gel-60 (F-254, E. Merck) to a depth of 2.0 mm.

For the purpose of NMR interpretation the numbering schemes shown below have been adopted.



Ethyl 2,3-*dideoxy*-2,3-C-[(*carboethoxy*)*methylene*]-6-O-*acetyl*-α-D-*lyxohexopyranosid*-4-*ulose* (**5**). To a stirred soln of **2**[20] (250 mg, 1.2 mmol) in dry benzene (25 mL), ethyl (dimethylsulphuranylidene)acetate[23] (0.35 mL, 2.4 mmol) was added. After 8 hr no further change was evident by TLC. The mixture was washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated. The residue was purified by PTLC to yield **5**(R_f 0.40, solvent *A*) (210 mg, 62%): ^{1}H NMR (60 MHz) δ 1.24 (t ,3, J = 7.3 Hz, $-OCH_2CH_3$), 1.27 (t, 3, J = 7 Hz, $CO_2CH_2-CH_3$), 2.00 (s, 3, CH_3CO_2-), 2.49 (cm, 2, H-2, -7), 2.71 (m, 1, H-3), 3.72 (cm, 2, $-OCH_2CH_3$), 1.19 (q, 2, $CO_2CH_2CH_3$), 4.11–4.49 (cm, 3, H-5, -6, -6′), 5.18 (s, 1, H-1).); IR (neat) 1685 and 1730 cm^{-1}.

Ethyl 2,3-*dideoxy*-2,3-C-[(*carboethoxy*)*methylene*]-α-D-*talopyranoside* (**6**). Compound **5** (200 mg, 0.70 mmol) was dissolved in absolute EtOH (20 mL) and $NaBH_4$ (100 mg, 2.63 mmol) was added with stirring. After 1 hr, TLC indicated that the reaction was complete and that a new compound (R_f 0.15, solvent *A*) had been formed. Water (50 mL) was then added cautiously, the resulting mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the combined extracts dried ($MgSO_4$) and evaporated to give **6** (156 mg, 91%) as a clear syrup that was crystallized from CH_2Cl_2-petroleum ether (30–60°) ^{1}H NMR (60 MHz) δ 1.20 (2t, 6, $-OCH_2CH_3$, CO_2CH-CH_3), 1.42–1.87 (cm, 3, H-2, -3, -7), 3.30–3.90 (cm, 6, H-4, -5, -6-OCH_2CH_3, 4.15 (q, 2, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.98 (s, 1, H-1); IR (neat) 1725 cm^{-1} (C=O). Found: C, 55.01; H, 7.73. Calc for $C_{12}H_{20}O_6$: C, 55.33; H, 7.70%).

Methyl 4,6-O-*benzylidene*-2,3-*dideoxy*-2,3-C-[R(*carboethoxy*) *ethylidene*)-α-D-*mannopyranoside* (**11**). The stated number of equivts (based on epoxide **7** used) of **9** (Table 1) were added dropwise to an equimolar amount of metal hydride suspended in the stated solvent. The epoxide **7** was then added and the mixture was stirred under the specified conditions. After the stated time the mixture was cooled to room temp., poured into NH_4Cl aq and extracted with ether. The ether layer was washed with water until the aqueous phase was no longer colored, dried over $MgSO_4$ and then evaporated to dryness. The residue, absorbed on to the minimum amount of silica gel, was then placed on top of a column of silica gel which had been prepared using petroleum ether (b.p. = 30–60°). Elution using solvent *A* yielded **11** (R_f 0.30, solvent *A*) in the stated yield as a clear syrup: ^{1}H NMR (220 MHz): δ 1.20 (t, 3, J = 6.8 Hz, $Co_2-CH_2CH_3$), 1.38 (s, 3, H-8′S), 1.78 (d, 1, $J_{2,3}$ = 9.0) Hz, H-2), 1.89 (dd, 1, $J_{3,4}$ = 2.5 Hz, H-3), 3.23–3.70 (cm, 3, H-4, -5, -6a), 3.39 (s, 3-OCH_3), 4.06 (q, 2, OCH_2CH_3), 4.26 (m, 1, H-6e), 4.61 (s, 1, H-1), 5.52 (s, 1, H-7), 7.27–7.55 (m, 5, phenyl), IR (neat) 1725 cm^{-1}; $[\alpha]_D^{22}$ + 50.8[6] (*c*, 4.0 in chloroform); *m/e*, 348 (M+), 317 (M+–OMe), 305(M + –H_2O–Me), 303 (M+–OEt), 275 (M+–CO_2Et), 242 (M+–CHO); HRMS. (Found: 348.15705. Per cent difference = 0.00007%. Calc. 348.15729%).

Methyl 4,6-O-*benzylidine*-2,3-*dideoxy*-2,3-C-[R(*hydroxymethyl*)*ethylidene*]-α-D-*mannopyranoside* (**13a**). The ester **11** (700 mg, 2.01 mmol) was dissolved in dry ether (100 mL) and excess $LiAlH_4$ (170 mg, 2.63 mmol) was added in small portions with stirring at room temp. After 2 h, TLC (solvent *A*) indicated that the reaction was complete and that a new compound (R_f 0.07, solvent *A*) has formed. Diethyl ether was added until effervescence no longer occurred and the resulting suspension was suction-filtered through a pad of Celite. The filtrate was evaporated to dryness to afford **13a** (596 mg, 97%): ^{1}H NMR (220 MHz): δ0.98 (d, 1, $J_{2,3}$ = 10.0 Hz, H-2); 1.16 (s, 3, H-8′s); 1.29 (dd, 1, $J_{3,4}$ = 2.9 Hz, H-3); 3.24 (bS; 2, H-9′s); 3.25–2.75 (cm, 3, H-4, -5, 6a); 3.34 (s, 3, $-OCH_3$); 4.28 (m, 1, H-6e); 4.58 (s, 1, H-1); 5.50 (s, 1, H-7); 7.27–7.55 (m, s, phenyl); IR (neat 3420 cm^{-1} (broad); $[\alpha]_D^{22}$ + 71.60° (*c*, 2.33 in chloroform. MS *m/e*, 305 (M+–H), 289 (M+–OH), 275 (M$^+$–CMe).

Methyl 4,6-O-*benzylidine*-2,3-*dideoxy*-2,3-C-[R(*methanesulfonyloxymethyl*)*ethylidene*)-α-D-*mannopyranoside* (**13b**). The alcohol **13a** (66 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (10 mL) at −78° and methanesulfonyl chloride (0.2 mL, 2.6 mmol) was added, followed by dropwise addition to dry Et_2N (0.36 mL, 2.6 mmol). After 1 hr at −78°, TLC indicated that the reaction was complete with the formation of a new compound (R_f 0.39, solvent *B*). CH_2Cl_2 (20 mL) was then added and the mixture poured into sat $NaHCO_3$ aq (20 mL). The organic phase was separated, washed with sat $NaHCO_3$ aq (2 × 20 mL), water (2 × 20 mL), dried over $NaSO_4$ and evaporated to dryness. The residue was purified by PTLC to yield **13b** (38 mg, 46%) as an unstable syrup that decomposed upon standing: ^{1}H NMR (60 MHz) δ 1.11 (d, 1, $J_{2,3}$ = 9 Hz, H-2); 1.28 (s, 3, H8′x), 1.44 (dd, 1, $J_{3,4}$ = 2 Hz, H-3); 2.96 (s, 3, O–SO_2CH_3); 3.38 (s, 3, OCH_3); 3.40–3.70 (m, 3, H-3); 2.96 (s, 3, OSO_2CH_3); 3.38 (s, 3, O–CH_3); 3.40–3.70 (m, 3, H-4, -5, -6a); 3.96 (m, 2, H9′s, 4.67 (s, 1, H-1); 5.58 (s, 1, H-7; 7.24–7.67 (m, 5, phenyl).

Methyl 4,6-O-*benzylidene*-2,3-*dideoxy*-2,3-C-[R(*chloromethyl*)*ethylidene*)-α-D-*mannopyranoside* (**13c**). The alcohol **13a** (3.50 g, 11.4 mmol) was dissolved in dry DMF (100 mL), methanesulphonyl chloride (4.4 mL, 57 mmol) was added, and the soln was stirred at room temp. After 4 hr TLC indicated the absence of starting material and the formation of new compound (R_f 0.44, solvent *A*). Sat. $NaHCO_3$ aq was added cautiously with stirring until the mixture was slightly basic, and this was poured into water (50 mL). This mixture was then extracted with ether (2 × total volume, 250 mL), and the combined ether extracts were washed with sat. $NaHCO_3$ aq (2 × 200 mL), and then water (4 × 200 mL) before drying over $MgSO_4$ and evaporation to dryness. This residue was chromatographed with solvent (*A*) to yield **13c** (3.41 g, 92%): ^{1}H NMR (220 MHz):

δ 1.06 (d, 1, $J_{2,3}$ = 10.0 Mz, H-2); 1.28 (s, 3, H-8); 1.36 (dd, 1, $J_{3,4}$ = 3.0 Hz, H-3); 3.25–3.75 (cm, 5, H-4, -5, 6a, H-9′s); 3.39 (s, 3, $-OCH_3$); 4.20 (m, 1, h-6e); 4.67 (s, 2, H-1); 5.58 (s, 1, H-7); 7.27–7.55 (m, 5, phenyl). $[\alpha]_D^{22}$ + 58.6° (*c*, 4.00 in $CHCl_3$)MS 326 [M(Cl^{37})$^+$], 324 [M(Cl^{35})$^+$], 295 [M(Cl^{37})$^+$], 324 [M(Cl^{35})$^+$], 295 [M(Cl^{37})$^+$OMe)], 293 [M(Cl^{35})]$^+$OMe. HRMS. (Found: 324.11245. Per cent difference = 0.00017%. Calc. 324.11284%).

Methyl 4,6-O-*benzylidene*-2,3-*dideoxy*-2,3-C-*isopropylidene*-α-D-*manopyranoside* (**14**). (a) Compound **13c** (1.90 g, 5.86 mmol) was dissolved in dry THF (300 mL), an excess of $LiAlH_4$ (250 mg, 6.58 mmol) was added, and the mixture was refluxed. After 12 hr, TLC indicated that the reaction was complete and the formation of a new compound (R_f 0.53, solvent *A*). The mixture was cooled to room temp., diethyl ether was added to destroy the excess $LiAlH_4$, and the resulting suspension was filtered through Celite and evaporated to dryness. The residue was chromatographed with solvent (*A*) to give **14** (1.51 g, 88.5%) as a clear syrup.

(b) Compound **13b** (35 mg, 0.09 mmol) was dissolved in dry ether (20 mL), excess $LiAlH_4$ (10 mg, 0.26 mmol) was added, and the mixture was stirred at room temp. After 14 hr, TLC indicated the absence of starting material and the formation of a new compound (R_f 0.53, solvent *A*). Diethyl ether was added until effervescence ceased and the resulting suspension was filtered through a pad of Celite. The filtrate was washed with sat. $NaHCO_3$ aq (2 × 10 mL), dried over $MgSO_4$ and evaporated to yield **14** (25 mg, 95%).

The materials from parts (a) and (b) were identical and exhibited the following spectral characteristics: ^{1}H NMR (220 MHz) δ 0.84 (d, 1, $J_{2,3}$ = 10.0, H-2); 1.07 (5, 3, H-9); 1.11 (s, 3, H-8); 1.19 (dd, 1, $J_{3,4}$ = 3.0, H-3); 3.33 (s, 3, $-OCH_3$); 3.36–3.73 (m, 3, H-4, -5, -6a); 4.20 (m, 1, H-6e); 4.58 (s, 1, H-1); 5.50 (s, 1, H-7); 7.27–7.55 (m, 5, phenyl); $[\alpha]_D^{22}$ + 75.0° (*c*, 4.78 in chloroform) MS *m/e*, 290 (M+), 259 (M+–OMe); HRMS. (Found: 290.15216. Per cent difference = 0.00007%. Calc. 290.15181%).

4,6-O-*Benzylidene*-2,3-*dideoxy*-2,3-C-*isopropylidene*-aldehydo-D-*mannose*, (**16**), *and* D-*mannopyranose* (**17**). Compound **14** (3.34 g, 11.5 mmol) was dissolved in refluxing dioxane (10 mL), then water was added until the mixyture remained turbid at reflux. After 1.5 hr when TLC indicated that hydrolysis was complete, the soln was cooled to room temp. and the solvent removed under reduced pressure. Traces of water were removed by evaporation of toluene (2 × 25 mL) from the residue **16** and **17** (3.11 g, 98%), 9:1 by NMR, as a clear oil: ^{1}H NMR(220 MHz). For **16**: δ 1.26 (s, 3, H-9′s); 1.43 (s, 3, H-8′s); 1.57 (dd, 1, $J_{3,4}$ = 10 Hz, H-3); 1.85 (dd, 1, $J_{2,3}$ = 8.7 Hz, H-2); 3.55 (t, 1, $J_{6,6}$ = $J_{5,6}$ = 10.5 Hz, H-6a); 3.64 (m, 1, H-5); 3.98 (t, 1, $J_{4,5}$ = $J_{3,4}$, H-4); 4.23 (dd, 1, $J_{5,6}$ = 4.5 Hz, H-6e); 5.41 (s, 1, H-7); 7.27–7.55 (m, 5, phenyl); 9.45 (d, 1, $J_{2,2}$ = 6.0 Hz, H-1). For **17**: δ 1.10 (s, H-9′s) and 1.13 (s, H-8′s) in a 1:1 ratio. IR: (neat) 1685 cm^{-1} (C=O); $[\alpha]_D^{22}$ – 58.0° (*c*, 3.46 in $CHCl_3$).

Methyl 6,8-O-*benzylidene*-2,3,4,5-*tetradeoxy*-4,5-C-*isopropylidene*-2-C-*methyl*-D-manno-*oct*-2-(E)-*enoate* (**25**). The mixture of **16** and **17** (500 mg, 181 mmol) was dissolved in CH_2Cl_2 (50 mL) and methyl 2-(triphenylphosphoranylidine) propionate (627 mg, 2.01 mmol) added. After 1.5 hr, TLC indicated that the reaction was complete with formation of a new compound (R_f 0.53, solvent *B*). The solvent was evaporated leaving a light yellow solid which upon silica gel chromatography using solvent(*A*) yielded **25** (6045 mg, 93%) as white crystals. The following data were obtained after recrystallization from CH_2Cl_2-petroleum ether (30–60): ^{1}H NMR (220 MHz): δ 1.20 (s, 3, H-8′s); 1.23 (s, 3, H-9′s); 1.30 (dd, 1, $J_{3,4}$ = 9.0, H-3); 1.68 (dd, 1, $J_{2,3}$ = 10.5 Hz, H-2); 1.92 (d, 3, $J_{1,10}$ = 1.0 Hz, H-10′s); 3.48 (t, (dd), 1, $J_{4,5}$ = 9.0 Hz, H-4); 3.54 (t, (dd), 1, $J_{6,6}$ = 10.0 Hz and $J_{5,6}$ = 10.0 Hz, H-6a); 3.68 (m, 1, H-5); 3.72, (s, 3, CO_2CH_3); 4.24 (dd, 1, $J_{5,6}$ = 5.0 Hz, H-6e); 5.41 (s, 1, H-7); 6.72 (dd, 1, $J_{1,2}$ = 9.5 Hz, H-1); 7.27–7.55 (m, 5, phenyl) IR 1705 cm^{-1} (C=O); $[\alpha]_D^{22}$ – 116.2° (*c*, 4.07 in chloroform); MS/ *m/e*, 315 (M+–OMe), 297 (M+–OMe–H_2O). m.p. 143.5–144°. (Found: C, 69.16; H, 7.63. Clac for $C_{20}H_{26}O_5$: C, 69.34; H, 7.5%).

Methyl (E)-2,3,4,5-*tetradeoxy*-4,5,-C-*isopropylidene*-2-C-*methyl*-D-manno-*oct*-2-(E)-*enoate* (**26**). Compound **25** (525 mg, 1.52 mmol) was dissolved in MeOH (50 mL), and a few crystals of *p*-toluenesulphonic acid were added with stirring. After 5 hr, TLC indicated the absence of starting material and the formation of a new compound (R_f 0.19, solvent *c*).

The volume was reduced to approx. 5 mL and sat. $NaHCO_3$ aq (25 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were dried (Na_2SO_4) and reduced to approx. 10 mL. Petroleum ether (30–60°, 75 mL) was added slowly, and the resulting crystals were collected and washed with a small amount of cold petroleum ether 30–60°, to give **26** (398 mg, 99%) as fine white crystals. The following data was obtained upon crystallization from CH_2Cl_2 petroleum ether (30–60°): m.p. 117–118°. ^{1}H NMR (60 MHz) δ 1.22 (bs, 6, H-8′s, -9′s); 1.35 (m, 2, -2, -3); 1.91 (bs, 3, H-1′s); 3.30–4.00 (m, 4, H-4, -5, -6, -6′); 3.72 (s, 3, CO_2CH_3); 6.82 (d, 1, $J_{1,2}$ = 10.0 Hz, H-1). $[\alpha]_D^{22}$: – 28.3° (*c*, 1.67 in MeOH). (Found: C, 60.34; H, 8.51. Calc for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58%).

(+) trans-*Chrysanthemum dicarboxylic acid* (+)-**1**. The triol **26** (500 mg, 1.79 mmol) was dissolved in dioxane–water (1:1) (50 mL), and sodium metaperiodate (1.20 g, 5.64 mmol) was added with stirring. After 10 min at room temp., TLC indicated the absence of starting material and the formation of a new compound (R_f 0.43, solvent *A*) and the mixture was extracted with ether (2 × 50 mL). The combined extracts were washed with water (5 × 20 mL), dried ($MgSO_4$) and evaporated to give **27** (327 mg, 84%) as a clear mobile oil: ^{1}H NMR (60 MHz): δ 1.30 (t, 3, J = 7.0 Hz, CO_2–$CHCH_3$); 1.43 (s, 3, H-8′s); 1.95 (d, 3, $J_{1,10}$ = 1 Hz, H-10′s); 2.18 [m(2dd), 2, H-2, H-3]; 4.22 (q, 2, CO_2CH_3); 7.08 (dm, 1, $J_{1,2}$ = 8.0 Hz, H-1); 9.60 (d, 1, $J_{3,4}$ = 5.3 Hz, H-4); IR 1685 cm^{-1}; $[\alpha]_D^{22}$ + 10.8° (*c*, 8.0 in $CHCl_3$). The *cis*-aldehyde **27** (100 mg, 0.49 mmol) was dissolved in methanol (20 mL) and a catalytic amount of sodium methoxide was added. After 12 hr at room temp. the volume of solvent was reduced to approx. 2 mL, water (10 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give **28**, in quantitative yield, as a clear mobile oil: ^{1}H NMR (220 MHz) δ 1.21 (s, 3, –C–CH_3); 1.28 (s, 3, –C–CH_3); 1.93 (d, 3, $J_{1,10}$ = 1.0 Hz, =CH_3); 1.98 (dd, 1, $J_{2,3}$ = 4.5 Hz, H-2); 2.45 (dd, 1, $J_{3,4}$ = 10.5 Hz, H-3); 3.72 (s, 3, CO_2CH_3); 6.44 (dm, 1, $J_{1,2}$ = 9.0 Hz, H-1); 9.50 (d, 1, H-4). IR 1695 cm^{-1}. $[\alpha]_D^{22}$ + 23.3° (*c*, 3.6 in $CHCl_3$). The *trans*-aldehyde **28** (450 mL, 37.5 mmol) and silver (I) oxide (2.1 g, 9.1 mmol) were added, and the mixture stirred at room temp. After 10 min, a silver mirror had formed and TLC indicated the absence of starting material and the appearance of a lower running compound. After 4 hr this compound had been replaced by another (R_f 0.31, solvent *C*). The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The aqueous phase was acidified with dil. HCl, and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with 20 mL portions of water until neutral, dried ($MgSO_4$), and evaporated to dryness to give (+)-**1** as yellow crystals (403 mg, 88.5%). Recrystallization from CH_2Cl_2-petroleum ether (30–60°) gave white crystals: ^{1}H NMR (60 MHz) δ 1.27 (s, 3, –C–CH_3); 1.37 (s, 3, –C–CH_3); 1.78 (d, 1, $J_{2,3}$ = 6.3 Hz, H-3); 1.96 (d, 3, $J_{1,10}$ = 1 Hz, H-10′s); 2.28 (dd, 1, $J_{1,2}$-10.0 Hz, H-2); 6.60 (dm, 1, H-1). $[\alpha]_D^{22}$: + 67.2° (*c*, 3.0 in MeOH). m.p. 163.5–165.0°; Lit[41] 164.0°, mixed m.p. 160.0°. Lit.[41] $[\alpha]_D^{22}$ + 71.1° (*c*, 1 in MeOH).

4,6-O-*Benzylidene*-2,3-*dideoxy*-2,3-C-*isopropylidene*-D-*glucose* (**24**). The *cis* aldehyde **16** (2.20 g, 7.97 mmol) was dissolved in MeOH (100 mL) and a catalytic amount of NaOMe was added with stirring. After 12 hr the soln was

reduced in volume to approximately 10 mL, water (50 mL) was added, and the resulting mixture extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and the solvent evaporated yielding **24** (2.07 g, 94%) as white crystals, which were recrystallized from CH_2Cl_2–petroleum ether (30–60°): m.p. 126–126°; R_f 0.38, solvent *B*); ^{1}H NMR (220 MHz): δ 1.30 (s, 3, H-8′s); 1.34 (s, 3, H-9′s); 1.94 (m, 2, H-2, -3); 3.34 (m, 1, H-6a); 3.55 (t(dd), 1, $J_{3,4} = J_{4,5} = 10.5$ Hz, H-4); 3.77 (m, 1, H-5); 4.24 (m, 1, H-6e); 5.40 (s, 1, H-7); 7.27–7.55 (cm, 5, phenyl); 9.32 (d, 1, $J_{1,2} = 5.2$ Hz, H-1); IR ($CHCl_3$)$_2$ 1695 cm^{-1}. $[\alpha]_D^{22} -$ 11.60° (*c*, 2.67 in chloroform). Found: C, 69.53; H, 7.26. Calc for $C_{16}H_{20}O_2$: C, 69.54; H, 7.29%).

Methyl 6,8-O-*benzylidene*-2,3,4,5-*tetradeoxy*-4,5-C-*isopropylidene*-2-C-*methyl*-D-gluco-*oct*-2-(E,Z)-*enoate* (**29**(E) *and* **29**(Z)). The *trans*-aldehyde **24** (2.5 g, 9.06 mmol) was dissolved in CH_2Cl_2 (250 mL) and methyl 2-(triphenylphosphoranylidine) propionate was added. After 1 hr, when TLC indicated the absence of starting material and the formation of major and minor products (R_f 0.53 and 0.49 respectively, solvent *B*), the solvent was evaporated leaving behind a light yellow solid. The residue was chromatographed to yield **29** (*E*) (2.6 g, 83%) and **29**(*Z*) (307 mg, 10%), after recrystallization from CH_2Cl_2–petroleum ether b.p. 30–60°. m.p. 132–133°. (Found: C, 69.41; H, 7.51. Calc for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57%). For compound **29**(*E*): ^{1}H NMR (220 MHz): δ 1.13 (dd, 1, $J_{3,4} =$ 9.0 Hz, H-3); 1.20 (s, 3, H-9′s); 1.31 (s, 3, H-8′s); 1.65 (dd, 1, $J_{2,3} = 5.0$ Hz, H-2); 1.91 (d, 3, $J_{1,10} = 1.5$ Hz, H.10′s); 3.32 (t(dd), $J_{5,6} = J_{5,6} = 9.0$ Hz, H-6a); 3.57 (t(dd), 1, $J_{3,4} = J_{4,5} = 10.0$ Hz, H-4); 3.70 (s, 3, $COCH_3$); 3.77 (m, 1, H-5); 4.25 (dd, 1, $J_{5,6} = 4.5$ Hz, H-6e); 5.43 (s, 1, H-7); 6.48 (dd, 1, $J_{1,2} = 10.5$ Hz, H-1); 7.27–7.55 (cm, 5, phenyl); IR ($CHCl_3$) 1700 cm^{-1} $[\alpha]_D^{22} + 92.4°$ (*c*, 3.85 in $CHCl_3$).

Methyl (E)-2,3,4,5-*tetradeoxy*-4,5-C-*isopropylidene*-2-C-*methyl*-D-gluco-*oct*-2-*enoate* (**30**). Compound **29**(*E*) (1.1 g, 3.2 mmol) was dissolved in MeOH (50 mL) and a catalytic amount of *p*-toluenesulphonic acid, monohydrate has added. After 1 hr TLC indicated that the reaction was complete and a new compound (R_f 0.19, solvent *C*) has been formed. The solvent was reduced to approx. 5 mL, sat. $NaHCO_3$ aq (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4), reduced in volume to approx. 5 mL, and then petroleum ether (30–60°) (50 mL) was added slowly. The resulting crystals (786 mg, 93%) were recrystallized from CH_2Cl_2–petroleum ether, b.p. (30–60°). For **30**: m.p. 110–120°; ^{1}H NMR (220 MHz): δ 1.11 (dd, 1, $J_{3,4} = 10.5$ Hz, H-3): 1.19 (s, 3, H-9′s); 1.27 (s, 3, H-8′s); 1.32 (dd, 1, $J_{2,3} = 5.0$ Hz, H-2); 1.89 (d, 3, $J_{1,10} =$ 1.3 Hz, H.10′s); 3.41–3.82 (m, 4, H-4, -5, -6, -6′); 3.71 (s, 3, CO_2CH_3); 6.41 (dd, 1, $J_{1,2} = 10.2$ Hz, H-1); $[\alpha]_D^{22} - 28.3°$ (*c*, 1.67 in $CHCl_3$). (Found: C, 60.38; H, 8.54. Calc for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58%).

(−)-trans-*Chrysanthemum dicarboxylic acid* (−)-**1**. The triol **30** (700 mg, 2.63 mmol) was dissolved in a 1:1 mixture of MeOH and water (80 mL), and sodium metaperiodate (1.6 g, 7.5 mmol) added with stirring. After 20 min, TLC indicated the reaction was complete and formation of a new compound (R_f 0.43, solvent *A*). The MeOH was removed on a rotary evaporator and the resulting mixture was extracted with CH_2Cl_2 (2 × 75 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give **31** (507 mg, 94%) as a clear mobile oil, which in addition to giving the following data, had identical NMR and IR spectra to the methyl ester of **28**: $[\alpha]_D^{22} - 21.4°$ (*c*, 2.0 in chloroform). Compound (−) **31** (150 mg, 0.74 mmol) was oxidized utilizing the same procedure as for **27** to give (−)-**1** (130 mg, 86.0%), which was identical to (+)-**1** in the ^{1}H NMR (both as the diacid and dimethyl ester) and IR. (−)-**1** gave the following additional data: $[\alpha]_D^{22} - 68.3°$ (*c*, 3.0 in $CHCl_3$). m.p.: 163–164°.

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FOOTNOTES AND REFERENCES

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