Stereoselective synthesis of (−)-α-multistriatin from D-glucose

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D-Glucose was converted into (−)-α-multistriatin, the aggregation pheromone of the European elm bark beetle, via a highly stereoselective eighteen-step route.

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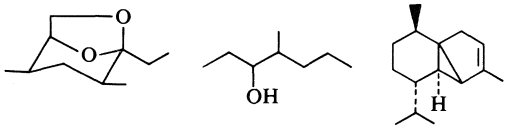
On a transformé le D-glucose en (−)-α-multistriatine, la phérémone d'agrégation du scolyte de l'orme européen, en utilisant une synthèse hautement stéréosélective en 18 étapes.

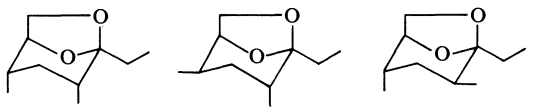
[Traduit par le journal]

The bicyclic ketal, α-multistriatin (**1**), is one of three components of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus*, which is the principal vector of Dutch elm disease in North America (1). The severe devastation of the elm populations in eastern North America and the steady march of the disease to the west coast have resulted in extensive studies on the use of pheromones to control this bark beetle and hence the Dutch elm disease. The volatile compounds from virgin female beetles were obtained and fractionated. The active attractant was found to be a combination of three components, α-multistriatin (**1**), 4-methyl-3-heptanol (**2**), and α-cubebene (**3**) (2). Compounds **1** and **2** were produced by the beetles, while compound **3** was produced by the host elm logs. In addition, the β-isomer **4** of multistriatin was also isolated from the beetles, but it was found to be inactive as an attractant (2). The structure of α-multistriatin was determined by extensive use of spectroscopic techniques and spectral analysis of the hydrogenolysis products from **1** (3). The natural α-multistriatin was optically active, $[\alpha]_D^{25}$ −47° (hexane) (3) and subsequently the absolute configuration of (−)-α-multistriatin was found to be 1*S*,2*R*,4*S*,5*R* by a chiral synthesis (4).



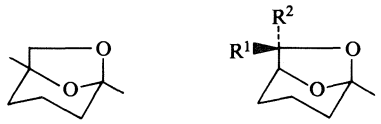
1 **2** **3**

A nonselective synthesis of multistriatin gave the four isomers α- (**1**), β- (**4**), γ- (**5**), and δ- (**6**) (5). However, only the α-isomer **1** was active as an attractant. Subsequently one of the intermediates in this route was partially resolved and converted into the enantiomers of α-multistriatin (4). This established the absolute configuration of (−)-α-multistriatin as shown in **1**. A second synthesis of (−)-**1** was reported by Mori starting from D-mannitol (6). Cernigliaro and Kocienski have synthesized (−)-**1** from (+)-citronellol (7). Unfortunately the low optical purity of this starting material gave a product with ca. 40% optical purity. Elliott and Fried have also reported a synthesis of (−)-**1** via a resolution of one of the intermediates in their synthesis (8). Bartlett and Myerson have stereoselectively converted the readily available *meso*-2,4-dimethylglutaric anhydride into racemic α-multistriatin (9). Recently Fraser-Reid and co-workers have reported a synthesis of (−)-**1** from D-glucose (10) which has many similarities to the synthesis reported here.[2]



4 **5** **6**

Earlier, we had developed facile synthetic routes to the 6,8-dioxabicyclo[3.2.1]octane pheromones frontalin (**7**), *exo*-brevicomin (**8**) and *endo*-brevicomin (**9**) (12). However, it was quickly apparent that this synthetic route which involved cyclization of an acyclic epoxy β-keto ester could



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8 R¹ = H, R² = Et
9 R¹ = Et, R² = H

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[2]For a preliminary communication of our work see ref. 11.

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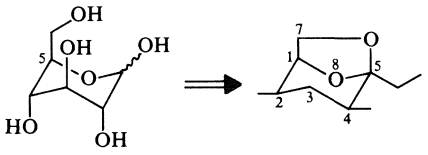
not be readily extended to a synthesis of **1**. In addition we recognized that the basic 6,8-dioxabicyclo[3.2.1]octane skeleton of all of these pheromones is present in certain anhydrohexoses (13) and we were intrigued with the potential synthesis of (−)-**1** from a readily available carbohydrate.[3] D-Glucose (**10**) shown in the unstable $^1C_4$ chair has the



10 **1**

same absolute stereochemistry at C-5 as C-1 in (−)-α-multistriatin. Our synthetic plan to convert D-glucose into **1** involved: (*a*) deoxygenation of C-3, (*b*) introduction of methyl groups at C-2 and C-4 with "inversion" of configuration, (*c*) introduction of an ethyl group at C-1, and (*d*) formation of the C-1,6 anhydro derivative of glucose.

Methyl α-D-glucopyranoside (**11**) was protected as its benzylidine derivative **12** in 70% yield (15). The benzylidine **12** was converted into the ditosylate which on treatment with base following the procedure of Richtymer (15) gave the epoxide **13** (15) in a yield of ca. 70% for the two steps. However, we have found that we could obtain slightly higher yields (ca. 75%) but after noticeably shorter reaction periods using the dimesylate as an intermediate to epoxide **13**. Reaction of epoxide **13** with lithium dimethylcuprate according to the method of Hicks and Fraser-Reid (16) afforded the 2-deoxy sugar **14** in 75% yield. Deoxygenation of the C-3 hydroxyl group in **14** was accomplished in ca. 85% yield using the method reported by Barton and McCombie (17). The alcohol **14** was first converted into the xanthate ester **15** by treatment with sodium hydride, carbon disulfide, and iodomethane. The xanthate **15** was then heated under reflux with an excess of tri-*n*-butylstannane in toluene to yield the deoxygenated product **16**.

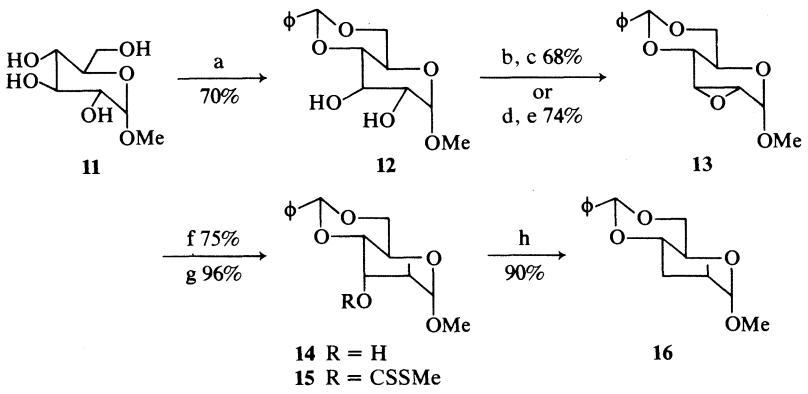
The next objective in our synthetic plan was the introduction of a β-methyl group at C-4 of the glucose derivative. A variety of catalysts was tried to effect the hydrogenolysis of the benzylidene in **16**. However, we were unsuccessful in carrying out a catalytic hydrogenolysis of **16**. We tentatively attribute the failure of this reaction in this case to the presence of trace amounts of tin–sulfur by-products derived from the previous stannane reduction. It was found that, after treatment of **16** with a catalytic amount of *p*-toluenesulfonic acid in methanol and careful work-up, the product **17** could be used directly in the preparation of the trityl ether **18** which was obtained in 77% overall yield for the two steps. The alcohol **18** gave the mesylate **19** in good yield. However, all attempts to displace this mesylate with a one carbon nucleophile failed. We had hoped to carry out a displacement with inversion at C-4 with lithium dimethylcuprate.[4] Presumably the axial methyl at C-2 provided sufficient steric interference to divert any nucleophile from approaching the backside of the mesylate at C-4.

This shielding of the top face of the molecule by the C-2 methyl group was turned to advantage in the following fashion. The alcohol at C-4 of **18** was oxidized (19) to the ketone **20** which on treatment with methylene triphenylphosphorane gave the exocyclic alkene **21** in good yield. In the crucial subsequent step the axial methyl group at C-4 was generated in a stereoselective hydrogenation of **21** using Wilkinson's catalyst (20). The stereoselectivity of this reduction was dependent on solvent and temperature. At 0°C in benzene alkene **21** was cleanly reduced to **22** and we could not detect any of the C-4 epimer by nmr or tlc. However, when ethanol was used as solvent or cosolvent (20) or if the hydrogenation was carried out at higher temperature the stereoselectivity fell. For example, hydrogenation of **21** at room temperature in anhydrous benzene gave **22** and its C-4 epimer in a ratio of 9:1. The effect of solvent (for example, ref. 21) and temperature (for example see ref. 22) on the stereoselectivity of homogeneous hydrogenations has been reported previously.

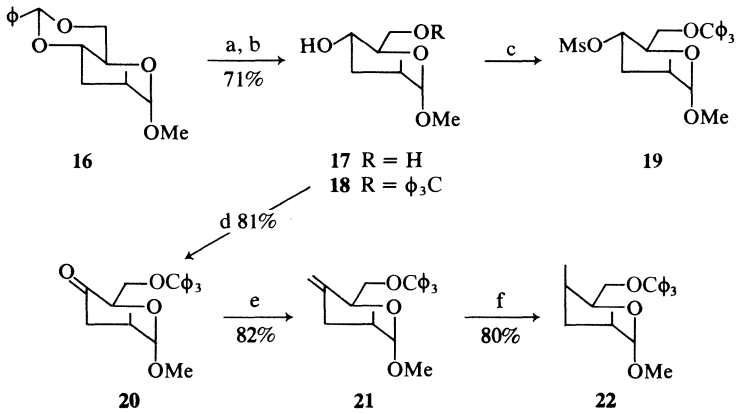
We had hoped to apply the alkylation of dithioacetal carbanions (23) to add the ethyl group at C-1 of **22** in the third phase of our synthetic plan. Compound **22** was smoothly converted into the diethyl dithioacetal **23** with concomitant cleavage of the trityl group by treatment with concentrated HCl and ethanethiol (24). The resulting diol **23** was then protected as its isopropylidene derivative **24**. Unfortunately all attempts to alkylate **24** were unsuccessful. The difficulty in this reaction was traced to our failure to generate the anion of **24**. We suspected that the methyl group at C-2 is responsible for the inertness of the dithioacetal **24**. Difficulties in alkylating α-substituted dialkyl dithioacetals have been reported (25). In contrast to our failure to alkylate **24**, the carbanion of a diethyl dithioacetal of a C-2 *unsubstituted* carbohydrate derivative has

[3]For two recent reviews on the use of carbohydrates in the synthesis of chiral natural products see ref. 14.

[4]For example (+)-2-butyl tosylate reacts with lithium diphenylcuprate to give (−)-2-phenylbutane with 100% inversion (18).

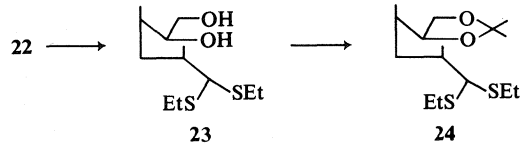


SCHEME 1. (a) ϕCHO, $ZnCl_2$; (b) TsCl, py, 7 days; (c) NaOMe, CH_2Cl_2, 6 days; (d) MsCl, py, 1 day; (e) NaOMe, CH_2Cl_2, $3\frac{1}{2}$ days; (f) Me_2CuLi, Et_2O; (g) NaH, CS_2, MeI, Et_2O; (h) Bu_3SnH, toluene, Δ.

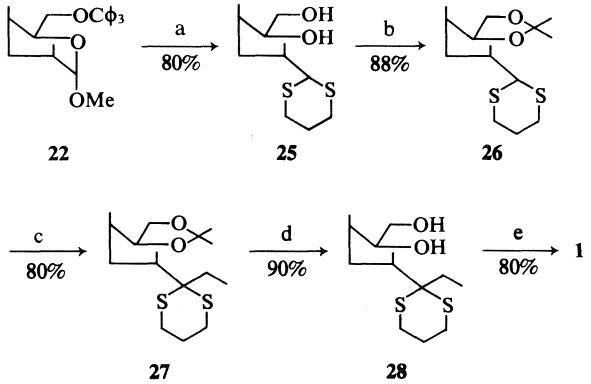


SCHEME 2. (a) TsOH, MeOH; (b) ϕ_3CCl, py; (c) MsCl, py; (d) $CrO_3 \cdot 2py$, CH_2Cl_2; (e) $\phi_3P^+-{}^-CH_2$, Et_2O; (f) H_2, $(\phi_3P)_3RhCl$, benzene.

been alkylated in good yield (26). Several reports have indicated that the dithiane derivatives of aldehydes are less susceptible to the steric effect of an α-substituent in carbanion alkylation than the corresponding diethyl dithioacetals. For this reason we prepared the protected dithiane as shown in Scheme 3. We found that *n*-butyllithium treatment of **26** followed by a D_2O quench led to partial (ca. 50%) anion formation whereas *tert*-butyllithium gave essentially quantitative formation of the desired carbanion. This carbanion was alkylated with iodoethane in HMPA–hexane to give **27** in 80% yield. A similar alkylation of another dithiane from D-glucose has recently been reported in the synthesis of the pheromone chalcogran (27).

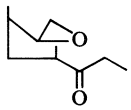


Hydrolysis of the isopropylidene **27** afforded the diol **28** in 90% yield. Several previous syntheses of α-multistriatin involved an acid-catalyzed cyclization of epoxy ketone **29** or diol **30**. These conditions



SCHEME 3. (a) $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2; (b) $Me_2C(OMe)_2$, TsOH; (c) *t*-BuLi, MeI, hexane–HMPA; (d) TsOH, MeOH; (e) $HgCl_2$, HgO, anhydrous MeCN.

usually resulted in the epimerization of the methyl group at C-4 (adjacent to the carbonyl) and the production of significant amounts of α-multistriatin (5).[5] With this in mind we attempted to cleave the thioketal of **28** with concomitant cyclization, and avoid going through the ketone **30**. Thus the



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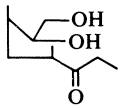

30

thioketal **28** in *anhydrous* acetonitrile containing mercuric chloride and mercuric oxide was cleanly converted into **1**. The structure of our synthetic material was fully confirmed by comparison of the spectral data of our synthetic material with that reported for α-multistriatin (3–8). The nmr spectrum (5) is particularly diagnostic in distinguishing the iomers of multistriatin. Our synthetic material had an optical rotation $[\alpha]_D^{25}$ −46.0° (*c* 1.00, hexane) compared with a rotation $[\alpha]_D^{25}$ −47 (*c* 0.19, hexane) for the natural material (1, 4). Finally, vpc analysis of our synthetic (−)-α-multistriatin with a 3% OV 101 column, under a variety of conditions which separated the multistriatin isomers, demonstrated that our product was 99.7% pure and no trace of the other multistriatin isomers could be detected. This confirms the absolute configuration of the natural (−)-α-multistriatin as that shown in **1** (4, 6, 7).

Experimental

General

Melting points (mp) were determined on a Kofler micro heating stage or a Thomas Hoover capillary melting point apparatus and are uncorrected. Gas–liquid chromatography was performed on a Hewlett Packard Model 5831A gas chromatograph, using a 6 ft × 1/8 in. column of 3% OV 101 Chromosorb W(HP) and nitrogen as carrier gas. The 60 MHz nuclear magnetic resonance spectra were recorded on a Varian Associates Model T-60, the 100 MHz spectra were recorded on Varian Associates Model HA-100 or Model XL-100, and the 270 MHz spectra were recorded on a homebuilt high resolution nmr spectrometer consisting of an Oxford Instruments' 63.4 KG magnet. Chemical shifts in ppm are reported using the δ scale with tetramethylsilane (TMS) as internal reference. Infrared spectra were recorded on a Perkin–Elmer model 710B spectrophotometer. Optical rotations $[\alpha]_D$ were measured with a Perkin–Elmer model 241 MC polarimeter. Low resolution mass spectra were determined on a Varian/Mat model CH4B mass spectrometer. High resolution mass measurements were obtained using a Kratos-AEI model MS902 or model MS50 instrument. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver. All solvents used for nmr, ir, and optical rotations were of Spectral grade.

Analytical thin layer chromatography plates and preparative tlc plates were prepared from silica gel GF-254 from E. Merck Co. Preparative tlc plates were about 1 mm thickness. Column chromatography was carried out with 100–200 mesh ASTM silica gel from Davison Chemical. The petroleum ether used was of boiling range ca. 30–60°C. Dry solvents or reagents, where indicated, were prepared as follows: ethyl ether by refluxing over lithium aluminum hydride followed by distillation; dichloromethane and acetonitrile by distillation from phosphorus pentoxide; hexamethylphosphoramide (HMPA) by distillation from calcium hydride followed by storage over molecular sieve (Type 4A); triethylamine by distillation from and storage over potassium hydroxide pellets; pyridine by distillation from barium oxide followed by storage over potassium hydroxide pellets; benzene, toluene, and *n*-hexane by distillation from calcium hydride; and methanol by refluxing over magnesium methoxide followed by distillation.

Methyllithium (in ethyl ether) and *n*-butyllithium (in hexane) were obtained from Aldrich Chemical Company, Inc. *tert*-Butyllithium (in pentane) was supplied by Alfa Division, Ventron Corporation. The alkyllithium solutions were standardized by titration against 1.0 *M* *tert*-butyl alcohol in benzene using 1,10-phenanthroline as indicator.

Methyl 4,6-O-benzylidene-α-D-gluco-pyranoside (12)

This compound, mp 161–163°C, was prepared from methyl α-*gluco*pyranoside (**11**) in 70% yield following the procedure of Richtymer (15).

Methyl 4,6-O-benzylidene-2,3-di-O-p-tolylsulfonyl-α-D-gluco-pyranoside

This compound, mp 148–149°C, was prepared from **12** in 80% yield following the procedure of Richtymer (15).

Methyl 4,6-O-benzylidene-2,3-di-O-methanesulfonyl-α-D-gluco-pyranoside

Benzylidene diol **12** (20.0 g, 70.9 mmol) was dissolved in ca. 125 mL of dry pyridine. The solution was cooled in ice and 19.95 g (175 mmol) of methanesulfonyl chloride was added. A white heavy precipitation was observed. The reaction was stirred at room temperature for 24 h. The mixture was then poured onto ice and extracted several times with dichloromethane. The combined extracts were washed several times with dilute hydrochloric acid until no trace of pyridine could be detected. The extracts were then washed once with water and once with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure to ca. 150 mL and ethyl ether was added to induce crystallization. The yield of the recrystallized methyl 4,6-*O*-benzylidene-2,3-di-*O*-methanesulfonyl-α-D-*gluco*-pyranoside was 25.0 g (81%); mp 186–18°C. This compound was characterized by ir ($CHCl_3$): 1100, 1130, 1180, and 1420 cm^{-1}; nmr ($CDCl_3$) δ: 2.87 (s, 3H), 3.17 (s, 3H), 3.48 (s, 3H), 3.6–4.8 (m, 5H), 4.8–5.2 (m, 2H), 5.51 (s, 1H), and 7.1–7.6 (m, 5H); mass spectrum: (*a*) high resolution calcd. for $C_{16}H_{22}O_{10}S_2$: 438.0655 amu; found: 438 0655; (*b*) low resolution *m/e* (relative intensity): 47(13), 49(100), 69(4), 79(4), 107(8), 116(6), 121(4), 149(3), 157(4), 185(4), 193(7), 229(3), 289(3), 299(8), 359(3), 437(11), and 438(7).

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allo-pyranoside (13)

(a) *From the ditosylate of* **12**

Compound **13**, mp 198–200°C, was prepared from the ditosylate of **12**, in 85% following the procedure of Richtymer (15).

[5]Recently Rao and co-workers (28) have suggested that ketal formation of five-membered rings may involve enol ether intermediates which would explain the epimerization of the C-4 methyl in **29** or **30**.

(b) *From the dimesylate of* ***12***

A solution of sodium methoxide was prepared using 12.7 g (552 mmol) of sodium and 188 mL of dry methanol. Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methanesulfonyl-α-D-*gluco*-pyranoside from above (48.18 g, 110 mmol) in 780 mL of dichloromethane was added to the sodium methoxide solution at 0°C. The reaction mixture was kept at 0°C for 3 days and stirred at room temperature for 10 h. The reaction mixture was diluted with water and the dichloromethane layer separated. The aqueous layer was extracted several times with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, and solvents were removed under reduced pressure. The product crystallized readily, and was filtered and washed with ether. The crude product was recrystallized from a mixture of dichloromethane and ethyl ether to give 26.40 g (91%) of pure epoxide **13**, mp 198–200°C. The spectral data were identical to the epoxide prepared from the ditosylate.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-*α*-D-*altro*-pyranoside (**14**)*

This compound, mp 112–113°C, was prepared in 75% from **13** using the procedure of Hicks and Fraser-Reid (16).

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-[(thiomethyl)-thiocarbonyl]-*α*-D-*altro*-pyranoside (**15**)*

Compound **15** was prepared in 96% crude yield from **14** using the procedure of Hicks and Fraser-Reid (16). The crude product was used directly in the next step. A small amount of compound **14** was purified by preparative tlc (CCl_4–Et_2O, 4:1 v/v) and characterized by the following spectral data. Infrared ($CHCl_3$): 950, 1005, 1040, 1060, 1100, 1140, and 2950 cm^{-1}; nmr ($CDCl_3$) δ: 1.18 (d, J = 7 Hz, 3H), 2.55 (s, 3H), 2.4–2.8 (m, 1H), 3.33 (s, 3H), 3.5–4.5 (m, 5H), 5.55 (br s, 1H), 5.75 (m, 1H), and 7.1–7.6 (m, 5H); mass spectrum *m/e* (relative intensity): 41(29), 43(30), 55(21), 57(29), 69(23), 85(44), 91(38), 105(56), 113(44), 121(32), 125(25), 131(29), 149(100), 150(14), 231(20), 262(47), 263(24), and 370(11).

*Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-methyl-*α*-D-*arabino*-hexopyranoside (**16**)*

A solution of 22.2 g (60.0 mmol) of the *S*-methyl dithiocarbonate compound **15** in 260 mL of dry toluene was added over 1.5 h to 34.92 g (120 mmol) of tri-*n*-butylstannane in 240 mL refluxing dry toluene under dry nitrogen. Refluxing was continued overnight, and the solvent was removed under reduced pressure. Purification was achieved by column chromatography using silica gel (100–200 mesh) and a mixture of petroleum ether and ethyl ether (9.5:1, v/v, then 1:1, v/v) to yield 14.30 g (90%) of pure compound **16** as a syrup, $[\alpha]_D^{28}$ +82.7° (*c* 14.2, ethyl ether); ir ($CHCl_3$): 930, 950, 1005, 1050, 1100, 1120, 1140, 1380, and 1460 cm^{-1}; nmr ($CDCl_3$) δ: 1.13 (d, J = 7 Hz, 3H), 1.4–2.3 (m, 3H), 3.33 (s, 3H), 3.5–4.3 (m, 4H), 4.33 (s, 1H), 5.50 (s, 1H), and 7.0–7.5 (m, 5H); mass spectrum: (*a*) high resolution calcd. for $C_{15}H_{20}O_4$: 264.1362 amu; found: 264.1374; (*b*) low resolution *m/e* (relative intensity): 55(15), 73(12), 83(19), 105(21), 115(100), 116(11), 149(11), 221(10), and 264(22).

*Methyl 2,3-dideoxy-2-*C*-methyl-*α*-D-*arabino*-hexopyranoside (**17**)*

To a solution of 12.41 g (47.0 mmol) of compound **16** in ca. 30 mL of methanol was added 0.40 g of *p*-toluenesulfonic acid monohydrate. The reaction mixture was stirred at room temperature and followed by tlc. After the reaction was complete (2.5 h), solid sodium carbonate was added to neutralize the acid. The reaction mixture was filtered, and the methanol was removed under reduced pressure. The residue was dissolved in water and ethyl ether, and extracted several times with water. The combined aqueous extracts were concentrated under reduced pressure and the residue dissolved in dichloromethane, dried over anhydrous magnesium sulfate, and filtered. The dichloromethane was removed under reduced pressure to give a thick oil, 6.81 g (82%) of which was pure enough for the next step. Compound **17** was characterized by the following spectral data. Infrared ($CHCl_3$): 960, 1050, 1100, 1150, 2975, 3500, and 3650 cm^{-1}; nmr ($CDCl_3$) δ: 1.03 (d, J = 7 Hz, 3H), 1.5–2.2 (m, 3H), 2.83 (br s, 2H), 3.33 (s, 3H), 3.6–4.2 (m, 4H), and 4.3 (br s, 1H); mass spectrum: (*a*) high resolution calcd. for $C_8H_{16}O_4$: 176.1049 amu, found: 176.1047; (*b*) low resolution *m/e* (relative intensity): 41(24), 43(27), 55(28), 56(29), 57(27), 72(100), 74(55), 83(23), 113(26), 115(27), 145(33), and 176(1).

*Methyl 2,3-dideoxy-2-*C*-methyl-6-*O*-triphenylmethyl-*α*-D-arabino-hexopyranoside (**18**)*

Compound **17** (3.17 g, 18 mmol) was treated with 7.5 g (27 mmol) of trityl chloride in 30 mL of anhydrous pyridine. The reaction mixture was stirred at room temperature for 3 days. It was then poured onto ice cold water, acidified, and extracted several times with dichloromethane. The combined extracts were washed with dilute sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and the solvents were removed under reduced pressure. Purification was achieved by column chromatography using silica gel (100–200 mesh) and a mixture of carbon tetrachloride and ethyl ether (4:1, v/v) as eluent to yield 6.465 g (86%) of **18**, mp 147–149°C, $[\alpha]_D^{26}$ +26° (*c* 20.0, chloroform); ir ($CHCl_3$): 1600 and 3570 cm^{-1}; nmr ($CDCl_3$) δ: 0.99 (d, J = 7 Hz, 3H), 1.4–2.1 (m, 3H), 2.39 (br s, 1H), 3.31 (s, 3H), 3.0–3.7 (m, 4H), 4.26 (s, 1H), and 6.7–7.4 (m, 15H); mass spectrum *m/e* (relative intensity): 43(4), 55(5), 72(4), 77(6), 83(6), 105(13), 113(13), 127(5), 165(27), 175(21), 183(15), 243(100), 244(27), 258(4), 259(7), 260(5), 309(5), 386(4), and 418(3). *Anal.* calcd. for $C_{17}H_{30}O_4$: C 77.48, H 7.22; found: C 77.61, H 7.21.

*Methyl 2,3-dideoxy-2-*C*-methyl-6-*O*-triphenylmethyl-*α*-D-threo-hexopyranosid-4-ulose (**20**)*

A sample of 6.0 g (60 mmol) of chromium trioxide was added to a magnetically stirred solution of 9.5 g (120 mmol) of anhydrous pyridine in ca. 150 mL anhydrous dichloromethane. The flask was stopped with a drying tube, and the deep burgundy solution stirred for 15 min at room temperature. At the end of this period, a solution of 4.18 g (10 mmol) of alcohol **18** in 5 mL of dry dichloromethane was added in one portion. A tarry, black deposit separated immediately. After stirring for 18 h at room temperature, the solution was decanted and the dichloromethane removed under reduced pressure. The residue was dissolved in ethyl ether and the reaction flask was rinsed several times with ethyl ether. The ether layers were combined and filtered through a bed of Celite. The slight yellow filtrate was washed with dilute hydrochloric acid and aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and the solvents were removed under reduced pressure to give 3.99 g (96%) of ketone **20** which was homogeneous from tlc. The crude product was purified by column chromatography using silica gel (100–200 mesh) and a mixture of carbon tetrachloride and ethyl ether (8:1, v/v) as eluent to give 3.35 g (81%) of pure **20**, mp 88–89°C; $[\alpha]_D^{28}$ +98.8° (*c* 20.0, chloroform), which was characterized by ir ($CHCl_3$): 1600, 1730, and 2960 cm^{-1}; nmr ($CDCl_3$) δ: 1.14 (d, J = 7 Hz, 3H), 1.9–2.6 (m, 3H), 3.2–3.6 (m, 2H), 3.5 (s, 3H), 3.83 (m, 1H), 4.6 (d, J = 4 Hz, 1H), and 7.0–7.7 (m, 15H); mass spectrum: (*a*) high resolution calcd. for $C_{27}H_{28}O_4$: 416.1988 amu; found: 416.1989; (*b*) low resolution *m/e* (relative intensity): 43(4), 45(6), 55(4), 59(7), 71(6), 72(8), 105(7), 157(6), 165(20), 173(5), 183(5), 243(100), 244(24), 259(6), 339(4), and 416(4).

*Methyl 2,3,4-trideoxy-2-C-methyl-4-methylene-6-O-triphenylmethyl-α-D-*threo*-hexopyranoside (**21**)*

A 250-mL 3-necked round bottom flask containing ca. 120 mL of anhydrous ethyl ether was fitted with a reflux condenser, an addition funnel, a septum stopper, and a nitrogen outlet. *n*-Butyllithium (8.86 mL of 1.58 *M*, 14 mmol) was added to the flask and 5.00 g (14 mmol) of triphenylmethylphosphonium bromide was added in portions to the *n*-butyllithium solution. The orange reaction mixture was refluxed for 4 h and 5.82 g (14 mmol) of ketone **20** in 30 mL of ethyl ether was added slowly. The orange color discharged and a white precipitate was observed. The reaction mixture was then refluxed for 24 h, cooled, and the precipitate was filtered off. The ether filtrate was washed with water and brine, dried over magnesium sulfate, filtered, and the solvents were evaporated under reduced pressure. Purification of the crude product by column chromatography using silica gel (100–200 mesh) and a mixture of carbon tetrachloride and ethyl ether (10:1, v/v) as eluent gave 4.53 g (78%) of compound **21**, mp 153–154°C, $[\alpha]_D^{22}$ +45.4° (*c* 7.4, chloroform), and 0.5 g of recovered **20**. Thus, the yield was 82% based on recovered starting material **20**. The olefin **21** was characterized by the following spectral data. Infrared ($CHCl_3$): 1600, 1660, 2960, 3040, and 3100 cm^{-1}; nmr ($CDCl_3$) δ: 0.93 (d, J = 7 Hz, 3H), 1.6–2.8 (m, 3H), 3.30 (d, J = 6 Hz, 2H), 3.43 (s, 3H), 4.2–4.4 (m, 2H), 4.62 (m, 2H), and 6.8–7.6 (m, 15H); mass spectrum: (*a*) high resolution calcd. for $C_{28}H_{30}O_3$: 414.2195 amu; found: 414.2214; (*b*) low resolution *m/e* (relative intensity); 41(2), 43(2), 77(2), 81(4), 105(5), 109(14), 139(2), 141(50), 142(5), 165(21), 166(4), 183(2), 215(2), 228(3), 241(3), 243(100), 244(21), and 414(1).

*Hydrogenation of compound **21***

A 100-mL round bottom flask containing 50 mL of anhydrous benzene, 0.7 g of tris(triphenylphosphine)rhodium chloride (20), and 3.31 g (8.0 mmol) of alkene **21** was fitted with a magnetic stirrer and connected to an atmospheric pressure hydrogenation apparatus equipped with a graduated burette to measure the uptake of hydrogen. The system was evacuated and filled with hydrogen. After 24 h, about 1 equiv. of hydrogen was absorbed. The solvent was removed under reduced pressure and the product was purified by column chromatography using silica gel (100–200 mesh) and a mixture of ethyl acetate and petroleum ether (10:1, v/v) as eluent. Two components were isolated from this chromatography, and these were, in order of elution: methyl 2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*arabino*-hexopyranoside (0.29 g, 9%), and methyl 2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*lyxo*-hexopyranoside (**22**) (2.74 g, 80%).

Methyl 2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*arabino*-hexopyranoside was characterized by ir ($CHCl_3$): 1600 cm^{-1}; nmr ($CDCl_3$) δ: 0.58 (d, J = 6 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.3–2.0 (m, 4H), 2.9–3.6 (m, 3H), 3.38 (s, 3H), 4.4 (br s, 1H), and 6.9–7.6 (m, 15H); mass spectrum: (*a*) high resolution calcd. for $C_{28}H_{32}O_3$: 416.2351 amu; found: 416.2328; (*b*) low resolution *m/e* (relative intensity): 83(10), 85(25), 105(15), 111(17), 141(9), 143(60), 165(40), 173(48), 243(100), 244(31), 258(8), and 416(5).

Methyl 2,3,4-trideoxy-2,4-di-*C*-methyl-α-D-*lyxo*-hexopyranoside (**22**) had mp 153–154°C and $[\alpha]_D^{24}$ +27.0° (*c* 6.6, chloroform) and was characterized by ir ($CHCl_3$): 1600 cm^{-1}; nmr ($CDCl_3$) δ: 0.70 (d, J = 7 Hz, 3H), 0.95 (d, J = 7 Hz, 3H), 1.3–2.0 (m, 4H), 3.0–3.3 (m, 2H), 3.45 (s, 3H), 3.8–4.1 (m, 1H), 4.2 (d, J = 5 Hz, 1H), and 6.9–7.6 (m, 15H); ^{13}C nmr ($CDCl_3$) δ: 15.93, 18.3, 30.61, 33.75, 34.73, 55.35, 63.10, 71.96, 104.34, 126.98, 127.77, 128.83, and 144.21; mass spectrum: low resolution *m/e* (relative intensity): 55(7), 72(7), 83(8), 85(20), 105(13), 111(16), 115(4), 141(8), 143(65), 144(7), 165(25), 166(6), 173(63), 174(9), 183(7), 229(5), 243(100), 244(36), 258(3), and 416(1). *Anal.* calcd. for $C_{28}H_{32}O_3$: C 80.73, H 7.74; found: C 80.51, H 7.55.

*(2S, 4S, 4'S)-1,1-Diethylthio-2-methyl-4-(2',2'-dimethyl-1',3'-dioxacyclopent-4'-yl)pentane (**24**)*

To a mixture of 0.83 g of **22** and 1.80 mL of concentrated hydrochloric acid at 0°C was added 1.80 mL of ethanethiol. The reaction mixture was stirred for 24 h at 0°C. Ice and water were added to the reaction mixture and the mixture extracted several times with ethyl acetate. The organic extract was washed with brine and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel 100–200 mesh) using a mixture of petroleum ether and ethyl ether (3:1, v/v); after the side-product had completely eluted, the solvent was changed to ethyl ether. The yield of compound **23** from this chromatography was 0.44 g (83%). The nmr ($CDCl_3$) of compound **23** had absorptions at δ: 0.92 (d, J = 7 Hz, 3H), 1.16 (d, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 6H), 1.4–2.3 (m, 4H), 2.2–3.0 (m, 4H), 3.26 (br s, 2H), 3.4–3.7 (m, 3H), and 3.75 (d, J = 3 Hz, 1H).

To a solution of diol **23** (0.43 g, 1.60 mmol) in 9 mL of 2,2-dimethoxypropane was added ca. 20 mg of *p*-toluenesulfonic acid. After stirring at room temperature for 2 h, the reaction mixture was diluted with chloroform, washed with 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and solvents were removed under reduced pressure. The crude product was distilled (Kugelrohr, bath temperature 100°C/0.2 Torr) to give 0.40 g (82%) of **24**. A small sample was purified by tlc using a mixture of petroleum ether and ethyl ether (4:1, v/v) to give pure **24** and was characterized by ir ($CHCl_3$): 860, 1060, 1160, 1260, 1280, 1380, and 1460 cm^{-1}; 270 MHz nmr ($CDCl_3$) δ: 0.98 (d, J = 6 Hz, 3H), 1.04 (d, J = 6 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.5–1.7 (m, 3H), 2.0–2.2 (m, 1H), 2.5–2.8 (m, 4H), and 3.6–4.2 (m, 4H); mass spectrum: (*a*) high resolution calcd. for $C_{15}H_{30}O_2S_2$: 306.1687 amu; found: 306.1690; (*b*) low resolution *m/e* (relative intensity): 43(38), 55(18), 75(27), 103(19), 107(55), 115(56), 125(29), 135(30), 169(19), 187(100), and 306(30).

*(2'S, 4'R, 5'S)-2-(2',4'-Dimethyl-5',6'-dihydroxyhex-2'-yl)-1,3-dithiane (**25**)*

To a solution of 2.08 g (5.0 mmol) of compound **22** in ca. 40 mL of dry dichloromethane was added 1.63 g (15 mmol) of 1,3-dithiolpropane and 1.4 mL of distilled boron trifluoride etherate at 0°C. The reaction was stirred at 0°C for 18 h. It was then diluted with ethyl acetate, washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and the solvents were removed under reduced pressure. Purification of the crude product was achieved by column chromatography using silica gel (100–200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent. After the side product had completely eluted, the eluting solvent was changed to ethyl acetate. The yield of compound **25** from this chromatography was 1.0 g (80%) and this product was characterized by ir ($CHCl_3$): 3500 and 3660 cm^{-1}; nmr ($CDCl_3$) δ: 0.98 (d, J = 6 Hz, 3H), 1.1 (d, J = 6 Hz, 3H), 1.5–2.5 (m, 8H), 2.7–3.1 (m, 4H) 3.4–3.7 (m, 3H), and 4.12 (d, J = 4 Hz, 1H); mass spectrum: (*a*) high resolution calcd. for $C_{11}H_{22}O_2S_2$: 250.1061 amu; found: 250.1085; (*b*) low resolution *m/e* (relative intensity): 41(10), 43(7), 55(6), 73(5), 119(100), 120(8), 121(10), 143(5), 219(5), and 250(16).

*(2'S, 4'R, 4''S)-2-[4'-(2'',2''-Dimethyl-1'', 3''-dioxacyclopent-4''-yl)pent-2'-yl]-1,3-dithiane (**26**)*

To a solution of 1.0 g (4.0 mmol) of diol dithiane **25** in 20 mL of 2,2-dimethoxypropane was added a catalytic amount of *p*-toluenesulfonic acid (0.10 g). The reaction was stirred at room temperature for 1.5 h. It was then diluted with chloroform, washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and the solvents were removed

under reduced pressure. The crude product was purified by column chromatography using silica gel (100–200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent. From this chromatography 1.02 g (88%) of compound **26** was isolated. Kugelrohr distillation (bath temperature 120°C/0.1 Torr) of **26** isolated from this column had $[\alpha]_D^{25}$ −6.2° (*c* 15.0, ethyl ether), and was characterized by ir ($CHCl_3$): 920, 1070, 1380, 1390, and 2975 cm^{-1}; 270 MHz nmr ($CDCl_3$) δ: 0.98 (d, J = 7 Hz, 3H), 1.07 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.5–1.9 (m, 4H), 1.95–2.2 (m, 2H), 2.75–3.0 (m, 4H), 3.65 (t, J = 7 Hz, 1H), 3.85 (q, J = 7 Hz, 1H), 4.01 (t, J = 7 Hz, 1H), and 4.16 (d, J = 4 Hz, 1H); mass spectrum *m/e* (relative intensity): 41(22), 43(38), 72(21), 119(100), 159(31), 161(18), 232(24), 275(44), and 290(58). *Anal.* calcd. for $C_{14}H_{26}O_2S_2$: C 57.89, H 9.02; found: C 57.70, H 9.00.

*(2′S, 4′R, 4″S)-2-Ethyl-2-[4′-(2″,2″-dimethyl-1″,3″-dioxacyclopent-4″-yl)pent-2′-yl]-1,3-dithiane (**27**)*

A solution of 0.58 g (2.0 mmol) of compound **26** in ca. 8 mL of dry *n*-hexane was placed in a 25-mL round bottom flask fitted with a magnetic stirrer and nitrogen outlet. The flask was cooled to ca. −20°C (Dry Ice and carbon tetrachloride) and 1.5 mL (2.0 *M* in pentane, 3 mmol) of *tert*-butyllithium was added dropwise. The reaction was stirred at ca. −20°C for 2 h, then kept in the freezer (ca. −10°C) for 16 h. The temperature of the reaction mixture was then raised to 0°C and 0.4 mL (0.78 g, 5 mmol) of iodoethane in 1.74 mL (5 equiv.) of hexamethylphosphoramide was added; a white precipitate formed immediately. The reaction was stirred for 5 h, diluted with ethyl ether, washed with ice cold dilute hydrochloric acid, sodium bicarbonate solution, and brine, dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. The crude product was purified by column chromatography using silica gel (100–200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent to yield 0.506 g (80%) of compound **27**. Kugelrohr distillation (bath temperature 128°C/0.1 Torr) of **27** isolated from this column had $[\alpha]_D^{25}$ −28.0° (*c* 5.0, ethyl ether), and was characterized by ir ($CHCl_3$): 860, 1060, 1160, 1380, 1480, and 2970 cm^{-1}; 270 MHz nmr ($CDCl_3$) δ: 0.98 (t, J = 7 Hz, 3H), 1.01 (d, J = 7 Hz, 3H), 1.1 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.41 (s, 3H), 1.5–2.2 (m, 8H), 2.6–3.0 (m, 2H), 3.7 (t, J = 7 Hz, 3H), and 3.9–4.1 (m, 2H); mass spectrum *m/e* (relative intensity): 41(12), 43(16), 134(15), 147(100), 148(13), 149(15), 303(18), and 320(16). *Anal.* calcd. for $C_{16}H_{30}O_2S_2$: C 60.30, H 9.49; found: C 60.20, H 9.53.

*(2′S, 4′R, 5′S)-2-Ethyl-2-(2′,4′-dimethyl-5′,6′-dihydroxyhex-2-yl)-1,3-dithiane (**28**)*

To a solution of 0.35 g (1.1 mmol) of compound **27** in ca. 15 mL of methanol was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (0.02 g). The reaction mixture was stirred at room temperature for 24 h. Solid sodium carbonate was added to neutralize the acid. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in ethyl acetate, dried over anhydrous magnesium sulfate, filtered, and the solvents were removed under reduced pressure. Purification was achieved by column chromatography using silica gel (100–200 mesh) and a mixture of petroleum ether and ethyl ether (9:1, v/v) as eluent to yield 0.20 g (90%) of compound **28**, $[\alpha]_D^{24}$ −42.6° (*c* 5.0, ethyl ether). This compound was characterized by the following spectral data. Infrared ($CHCl_3$): 900, 1005, 1050, 1280, 1380, 1460, 2970, 3500, and 3650 cm^{-1}; nmr ($CDCl_3$) δ: 0.87 (d, J = 7 Hz, 3H), 1.08 (d, J = 7 Hz, 3H), 1.02 (t, J = 7 Hz, 3H), 1.7–2.3 (m, 8H), 2.38 (br s, 2H), 2.6–3.0 (m, 4H), and 3.4–3.8 (m, 3H); mass spectrum: (*a*) high resolution calcd. for $C_{13}H_{26}O_2S_2$: 278.1374 amu; found: 278.1358; (*b*) low resolution *m/e* (relative intensity): 41(8), 47(11), 83(36), 85(23), 147(100), 148(12), 149(13), and 278(12).

*(−)-α-Multistriatin (**1**)*

To a stirred solution of 0.43 g (1.6 mmol) of mercuric chloride and 0.17 g (0.80 mmol) of mercuric oxide in ca. 5 mL of dry acetonitrile was added a solution of 0.197 g (0.71 mmol) of dithiane **28** in 5 mL of anhydrous acetonitrile under nitrogen. The reaction mixture was refluxed for 4 h with stirring. After cooling, the reaction mixture was filtered and the solid washed with pentane. An equal amount of saturated brine solution was added to the filtrate and this solution was extracted several times with pentane. The organic extracts were washed with aqueous ammonium acetate, dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. Kugelrohr distillation (bath temperature 110°C/20 Torr) of the crude produce gave 0.096 g (80%) of α-multistriatin (**1**), $[\alpha]_D^{24}$ −46.0° (*c* 1.0, hexane) (lit. (3) bp 90°C/20 Torr, bath temperature), and all the spectral data were identical to those reported (3–8). Gas–liquid chromatographic analysis showed a major component (> 98%). This was further identified by comparison with a sample of (±)-α-multistriatin kindly provided by Dr. J. W. Peacock; **1** was characterized by ir ($CHCl_3$): 895, 920, 1035, 1130, 1180, 1255, 1460, 2925, and 2980 cm^{-1}; nmr ($CDCl_3$) δ: 0.81 (d, J = 7 Hz, 3H), 0.81 (d, J = 7 Hz, 3H), 0.93 (t, J = 7 Hz, 3H), 1.4–2.2 (m, 6H), 3.68 (m, 1H), 3.89 (m, 1H), and 4.20 (m, 1H); mass spectrum: (*a*) high resolution calcd. for $C_{10}H_{18}O_2$: 170.1307 amu; found: 170.1298, (*b*) low resolution *m/e* (relative intensity): 41(8), 43(6), 54(9), 55(22), 57(100), 71(20), 81(16), 96(25), 99(11), 128(25), and 170(19).

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