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

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A totally stereospecific synthesis of the insect pheromone, (−)-α-multistriatin, is reported starting from D-glucose.

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On rapporte la synthèse totalement stéréospécifique de la phéromone d'insecte, la (−)-α-multistriatine, à partir du D-glucose.

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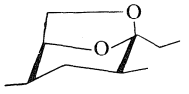
α-Multistriatin (**1**) is one of the essential components of the aggregation pheromone of the European elm bark beetle, *Scolytus multistriatus*, which is the principal vector of Dutch elm disease in North America (1). The severe devastation of elm populations in eastern North America has resulted in extensive studies on the isolation (2), structure elucidation (3), synthesis (4), and field utilization (5) of α-multistriatin. The three other diastereomers of **1** have been



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found to be biologically ineffective as attractants (5); however, all previous syntheses (4) of α-multistriatin have been nonstereoselective and have led to formation of the diastereomers of **1** in various amounts. We report a fully stereoselective synthesis of naturally occurring (−)-α-multistriatin with the relative and absolute configuration shown in **1**.

The epoxide **3** (6), prepared from D-glucose (**2**), gave a 75% yield of the 2-deoxy sugar **4** (7) on treatment with dimethyllithium cuprate. The alcohol **4** was converted into the corresponding xanthate **5** (7) in 94% yield and the resulting xanthate was deoxygenated with tri-*n*-butylstannane (8) to yield compound **6**, $[\alpha]_D^{28}$ +82.7° (142 mg/ml, ether), mp 70–72°C, in 90% yield from **5**. The benzylidene group in **6** was hydrolyzed (7) in 91% yield to give the diol **7** which was converted into the trityl ether **8**, $[\alpha]_D^{26}$ +26.0° (200 mg/ml, chloroform), mp 147–149°C, in 87% yield (9). Alcohol **8** was oxidized with chromium trioxide – pyridine (10) producing ketone **9**, $[\alpha]_D^{28}$ +98.8° (200 mg/ml, chloroform), ir 1730 cm^{-1}, as a white solid, mp 88–89°C, in 85% yield. A Wittig reaction (11) of **9** proceeded in 80% yield to give the alkene **10** which showed the appearance of two new vinyl hydrogens in the nmr spectrum at ca. δ 4.5. Compound **10** was also a crystalline solid, mp 153–154°C, $[\alpha]_D^{22}$ +45.4° (74 mg/ml, chloroform).

In the next very crucial step the 1,3-diaxial methyl system was generated in a stereoselective hydrogenation of **10** using Wilkinson's catalyst (12) to produce **11**, mp 140–142°C, $[\alpha]_D^{24}$ +27.0° (66 mg/ml, chloroform), in 81% yield. The nmr spectrum ($CDCl_3$) of **11** had the following features: δ 0.70 (d, J = 6 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 1–2 (m, 4H), 3.1 (m, 2H), 3.47 (s, 3H), 4.0 (br t, 1H), 4.23 (d, J = 5 Hz, 1H), and 7–7.6 (m, 15H). The new high-field, three-proton doublet clearly showed that reduction of the exocyclic double bond had occurred and the low-field doublet at δ 4.23 due to the hydrogen on the anomeric carbon indicated that **11** retained the chair conformation shown although the 5 Hz coupling with the hydrogen on C-2 did point to some flattening of the pyranose ring due to the 1,3-diaxial methyl interaction. It was clear from an examination of molecular models of the two possible chair conformations of **10** that the α-face of the olefin was the more accessible. This steric effect should be amplified with the bulky Wilkinson's catalyst. It has been established that axial methyl goups in cyclohexane rings normally have ^{13}C signals at δ 15–18 whereas the corresponding equatorial methyl groups are usually found at δ 18–25 (13). The ^{13}C nmr spectrum of **11** showed *only two* signals above δ 30, at 15.93 and 18.30 ppm from TMS. This would suggest that the methyl groups in **11** are both axial. Thus carbons 2,4 and 5 in **11** have the correct relative and absolute stereochemistry for conversion into natural (−)-α-multistriatin.

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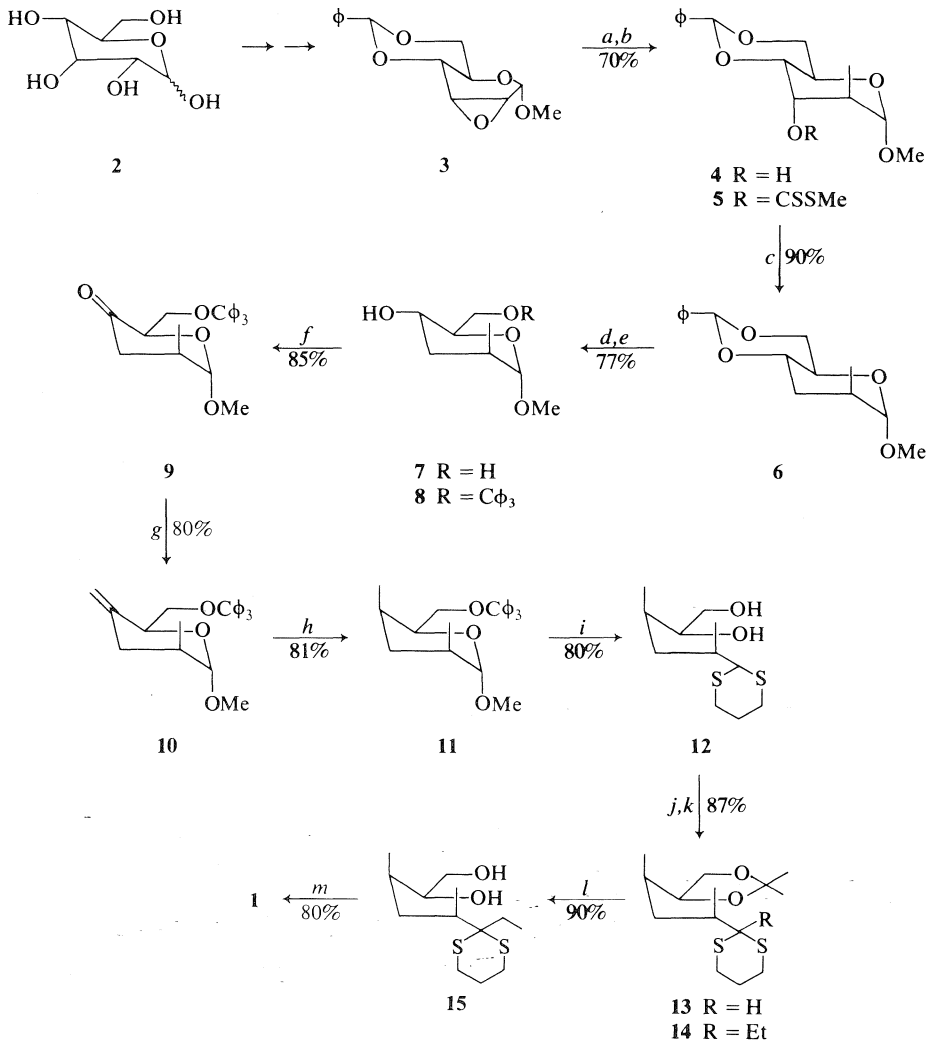

(*a*) Me_2CuLi, ether; (*b*) NaH, CS_2, MeI, ether; (*c*) $(nBu)_3SnH$, toluene; (*d*) TsOH, methanol; (*e*) trityl chloride, pyridine; (*f*) $CrO_3 \cdot 2Py$, dichloromethane; (*g*) $\phi_3\overset{+}{P}-\overset{-}{C}H_2$, ether; (*h*) H_2, $(\phi_3P)_3RhCl$, benzene; (*i*) $HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, dichloromethane; (*j*) TsOH, 2,2-dimethoxypropane; (*k*) *tert*-butyllithium, hexane followed by iodoethane, HMPA; (*l*) TsOH, methanol; (*m*) $HgCl_2$, HgO, acetonitrile.

The synthesis of **1** was completed using a sequence of reactions which should prove useful in the synthesis of more complex carbohydrates and in the utilization of carbohydrates as chiral precursors for the synthesis of natural products (14). Treatment of compound **11** with 1,3-propanedithiol and boron trifluoride etherate (15*a*) led to cleavage of the trityl group and formation of the dithioacetal **12** in 80% yield. The resulting diol was protected by formation (16) of the isopropylidene **13**, $[\alpha]_D^{25}$ −6.2° (150 mg/ml, ether), bp 120°C/0.1 Torr, in almost quantitative yield. We were unsuccessful in generating the anion of **13** using alkyllithium reagents in ether solvents (15). However, when the dithiane **13** was treated with *tert*-butyllithium in hexane at −20°C for 2 h and −10°C for 6 h a white precipitate formed. This mixture was alkylated with iodoethane in HMPA to produce **14**, $[\alpha]_D^{24}$ −28.0° (50 mg/ml, ether), bp 128°C/0.1 Torr, in 80% yield. The isopropylidene group in **14** was cleaved in 90% yield to give **15**, $[\alpha]_D^{24}$ −42.6° (50 mg/ml, chloroform), as a colourless oil.

Many of the previous syntheses of α-multistriatin involve an acid catalyzed cyclization of an epoxy ketone or a keto diol to generate the bicyclic ketal of **1**. These conditions lead to epimerization of the methyl group adjacent to the carbonyl. Hence we felt that it would be advantageous if we could

cyclize **15** without epimerization of carbon 4 in **15**. A solution of dithioketal **15** in *anhydrous* acetonitrile containing mercuric chloride and mercuric oxide (17) was refluxed for 4 h to yield **1** in 80% yield. 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, 4). The nmr spectrum (4*a*) is particularly diagnostic in distinguishing the isomers of multistriatin. Our synthetic material had an optical rotation $[\alpha]_D^{24}$ −46.0° (10 mg/ml, hexane) compared with a rotation $[\alpha]_D^{25}$ −47° (1.9 mg/ml, hexane) for the natural material (1, 4*b*). 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*b*, *d*, *e*).

Acknowledgements

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