Total Synthesis of (+)-11,11′-Di-*O*-methylelaiophylidene: An Aglycone of Elaiophylin

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Several 16-membered ring macrodiolides with C_2 symmetry have been isolated: pyrenophorin,[1a] vermiculin,[1b] conglobatin,[1c] and elaiophylin (**1a**).[2] Of these the latter presents the greatest challenge as a synthetic target. Elaiophylin (**1a**) was isolated, originally, from cultures of *Streptomyces melanosporus*[2a] and exhibits activity against *gram*-positive bacteria. Compounds that ultimately proved to be identical with Elaiophylin were subsequently isolated from other strains of *Streptomyces*.[2b-d] The constitution of Elaiophylin was first elucidated in 1981[3a] and subsequently the relative and absolute configuration were determined by X-ray analysis[3b,c] and NMR studies[3c] (Chart I). The aglycone **1b** from elaiophylin has never been reported,[4] but we have found that treatment of elaiophylin with MeOH/*p*-TsOH gave (+)-Di-*O*-methylelaiophylidene (**1c**),[5] which is also biologically active. This dimethylaglycone **1c** thus became our target.

Our strategy was based on the use of the chiral building blocks, "Roche" ester **2**[6a] or diethyl (*S*)-malate (**3**)[6b] and ethyl (*R*)-3-hydroxybutyrate (**4**).[6c] We planned to prepare the hydroxy acid **18**, dimerize it,[7] and subsequently convert the dimer to the C_2-symmetrical dialdehyde **21**, before coupling **21** with the ketone **25**. This last, crucial step would, we realized, be hard to control,[8] but an alternative strategy involving postponement of the macrodiolide ring formation to the final step would have required an unmanageable array of protecting groups in such a sensitive molecule.[4]

Our starting material for the preparation of **21** was the aldehyde **5**[9] (Chart II), which was converted to the aldol product **6** by using the propionyloxazolidinone derived from (*D*)-valine according to Evans' method.[10] Subsequent methanolysis of **6**,[10b] followed by reduction (LAH), gave a crystalline monoprotected triol **7** (mp 52–53.5 °C), which was converted to the alcohol **8** (mp 66–67 °C) by a known procedure.[9] The overall yield of the alcohol **8** from the aldehyde **5** was 57%. Swern[11] oxidation to the aldehyde

Chart I

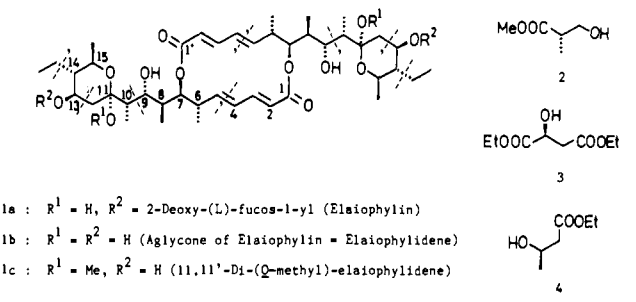


Chart II

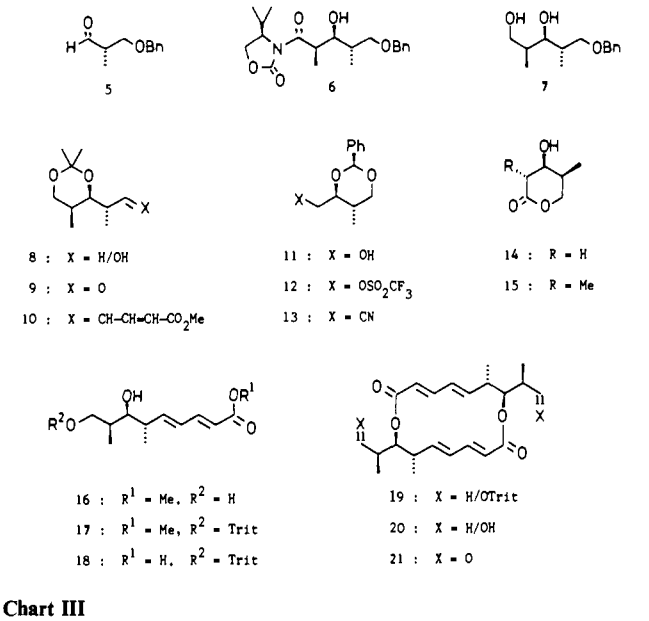
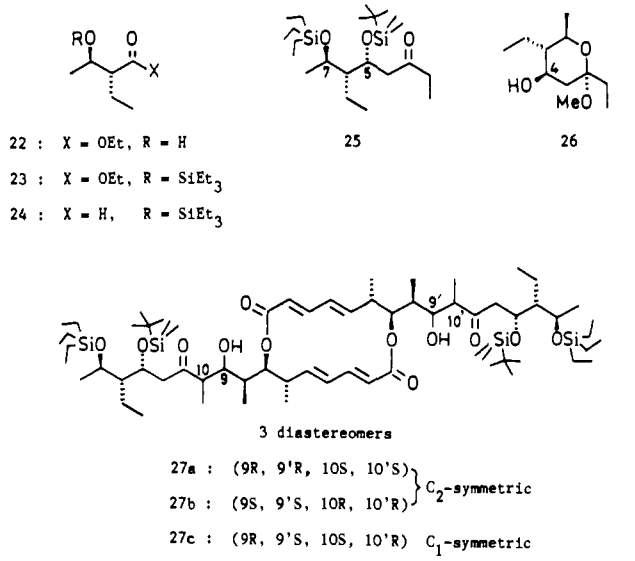


Chart III



(1) Most recent publications: (a) Wakamatsu, T.; Yamada, S.; Ozaki, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, *26*, 1989; (b) *Synform* **1983**, *1*, 138. (c) Schregenberger, C.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 5881. And references cited in these papers.

(2) (a) Arcamone, F. M.; Bertazzoli, C.; Ghione, M.; Scotti, T. *G. Microbiol.* **1959**, *7*, 207. (b) Azalomycin B: Arai, M. *J. Antibiot., Ser. A* **1960**, *13*, 46, 51. (c) Antibiotic 255 E: Khlebarova, E. I.; Georgieva-Borisova, I. Kh.; Sheikova, G. N.; Blinov, N. O. *Farmatsiya (Sofia)* **1972**, *22*, 3. (d) Salbomycin: Hoechst Patent DE 3248-280-A, 1982.

(3) (a) Kaiser, H.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 407. (b) Neupert-Laves. K.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 262. (c) Ley, S. V.; Neuhaus, D.; Williams, D. J. *Tetrahedron Lett.* **1982**, *23*, 1207.

(4) (a) Takahashi, S.; Ohki, E. *Chem. Pharm. Bull.* **1967**, *15*, 1726 and references cited therein. (b) Kaiser, H. P. Ph.D. Thesis, No. 6774, ETH-Zürich, 1981.

(5) ^{1}H NMR (300 MHz, C_6D_6) 0.61 (d, J = 6.7 Hz, 6 H), 0.84 (d, J = 6.5 Hz, 6 H), 0.95 (t, J = 7.6 Hz, 6 H), 1.24 (d, J = 6.2 Hz, 6 H), 1.32 (d, J = 7.0 Hz, 6 H), 1.10–2.00 (m, 12 H), 2.18–2.32 (m, 4 H), 2.84 (d of d, J = 4.6, 13.2 Hz, 2 H), 3.08 (s, 6 H), 3.13 (s, 6 H), 3.55–3.65 (m, 4 H), 3.90 (d of d, J = 3.8, 9.4 Hz, 2 H), 4.03 (d, J = 3.7 Hz, 2 H), 5.05 (d of d, J = 1.7, 9.9 Hz, 2 H), 5.15 (d of d, J = 9.5, 15.0 Hz, 2 H), 5.39 (d, J = 15.4 Hz, 2 H), 5.73 (d of d, J = 11.2, 15.1 Hz, 2 H), 7.02 (d of d, J = 11.2, 15.3 Hz, 2 H). The signal at 3.13 corresponds to two molecules of methanol strongly associated with **1c**,[3b,c] $[\alpha]_D$ +68 ± 3° (*c* 0.54, CCl_4).

(6) (a) Fischli, A. In "Modern Synthetic Methods 1980"; Scheffold, R., Ed.; Salle and Sauerländer: Aarau, 1980; p 269. (b) Aebi, J. D.; Sutter, M. A.; Wasmuth, D.; Seebach, D. *Liebigs Ann. Chem.* **1983**, *2114*; **1984**, 407. Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1984**, *63*, 109. (c) Seebach, D.; Züger, M. F. *Tetrahedron Lett.* **1984**, *25*, 2747. And references cited in these papers.

(7) We have shown that it is possible to construct a model for such a 16-membered diolide ring by Yamaguchi's mixed anhydride procedure: Sutter, M. A.; Seebach, D. *Liebigs Ann. Chem.* **1983**, 939. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(8) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(9) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(10) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Paterson, I.; Patel, S. K.; Porter, J. R. *Tetrahedron Lett.* **1983**, *24*, 3395.

(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480.

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9 followed by Wittig reaction with the triphenylphosphorane[12] derived from methyl 4-bromocrotonate gave the diene **10**, and removal of the isopropylidene group (MeOH/*p*-TsOH) then produced the crystalline (*E,E*)-dihydroxyester **16** (mp 84–86 °C) in 53% yield from **8**.[13]

An alternative procedure leading to the carbon skeleton of **8** with the correct configuration was also developed from diethyl (*S*)-malate via the benzylidene acetal **11**.[6b] Chain extension using the triflate **12** gave the cyanide **13**, which could be converted to the lactone **14**. This lactone can be methylated with high diastereoselectivity to give **15** in 30% overall yield from **11**.[14] A method for the conversion of **15** to **8** is currently being sought.

The preparation of the dialdehyde **21** was achieved as follows. Selective protection of the primary hydroxyl group of **16** (tritylpyridinium tetrafluoroborate/MeCN, 20 °C, 1 h)[15] gave **17** (mp 120.5–121 °C), and subsequent hydrolysis of the methyl ester (KOH/MeOH/THF, 16 h, 20 °C) then gave the seco-acid **18**. Dimerization of **18** was accomplished by Yamaguchi's procedure[7] to give the diolide **19**, which was then converted (MeOH/*p*-TsOH) to the diol **20** (mp 186–188 °C). Finally Swern[11] oxidation produced the dialdehyde **21**[16] (29% yield from the dihydroxyester **16**, and 8.7% overall from the aldehyde **5** over 13 steps).

Earlier studies on the ketone **25**, unprotected at C-5, indicated that it was very unstable[17] (Chart III). We therefore reasoned that two different protecting groups would be required at C-5 and C-7 to ensure that in the final step the free β-hydroxy ketone function would not be exposed. Selective removal of the C-7 hydroxyl protective group should permit the cyclization to a δ-lactol which would then not be so prone to elimination. The aldol derivative **25** was prepared as follows. Treatment[6b] of ethyl (*R*)-3-hydroxybutyrate **4**[6c] with 2 equiv of LDA and 3 equiv of EtI (−40 °C, 16 h) gave the ester **22** as the only product. The hydroxyl group of **22** was protected to give the triethylsilyl ether **23**, which was converted over two steps (DIBAH, −60 °C and Swern oxidation) to the aldehyde **24** (67% overall yield from **4**). Mukaiyama reaction between the aldehyde **24** and 2-[(trimethylsilyl)oxy]-1-butene (2 equiv) ($TiCl_4/CH_2Cl_2$, −78 °C, 5 min) gave a *single* unstable aldol[18] which could be protected (*tert*-butyldimethylsilyl chloride/imidazole) to give **25** (16% from **24**). Methanolysis of **25** led to the 2-methoxy-4-hydroxypyran **26**,[19] a reaction that served as a model for the final step in the total synthesis of **1c**.

Treatment of the ketone **25** with dibutylboron triflate and diisopropylethylamine[20] gave a single *Z*-boron enolate enolized toward C-2 (confirmed by reaction of the enolate with benzaldehyde). Reaction of 4 equiv of this enolate with the dialdehyde **21** (Et_2O/CH_2Cl_2, −78 °C, 1 h; 0 °C, 30 min) gave, after oxidative workup (HMPT·py·MoO_5), **27a**, **27b**, and **27c** (3:5:6, 42% combined yield) as the *only* isolable aldol adducts, which were easily separable by flash chromatography. Treatment of **27a** with MeOH/*p*-TsOH gave the aglycone **1c** of elaiophylin (17%) identical by 300-MHz ^1H NMR, IR, $[\alpha]_D$, and TLC with our sample prepared from elaiophylin.[5,21]

Experiments to improve the yields of the last two steps are underway. Once we have converted the lactone **15** to the alcohol **8**, a unique feature in our macrolide synthesis will be that all but two (C-9 and C-10) of the asymmetric carbon atoms will have been derived solely from "chiral pool" starting materials with only one asymmetric carbon atom (formally by 1,2-asymmetric inductions).[22]

(12) Buchta, E.; Andrēe, F. *Chem. Ber.* **1959**, *92*, 3111.

(13) The diene **10** was formed in 89% yield, from the alcohol **8**, as a mixture of isomers containing 80% of the *E,E* isomer. The *E,E*-dihydroxy ester **16** was obtained free from other isomers by a single recrytallization. ^1H NMR (300 MHz, $CDCl_3$) 0.97 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.82–1.94 (m, 3 H), 2.42 (m, 1 H), 3.61 (d of d, J = 2.7, 8.5 Hz, 1 H), 3.68–3.80 (m, 2 H), 3.74 (s, 3 H), 5.84 (d, J = 15.4 Hz, 1 H), 6.08 (d of d, J = 8.6, 15.3 Hz, 1 H), 6.28 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.4 Hz, 1 H).

(14) Part of the projected Ph.D. Thesis of J. Zimmermann, ETH-Zürich.

(15) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, 3555.

(16) ^1H NMR (300 MHz, $CDCl_3$) 1.10 (d, J = 6.7 Hz, 6 H), 1.19 (d, J = 7.0 Hz, 6 H), 2.52 (d of d of q, J = 9.5, 10.3, 6.7 Hz, 2 H), 2.71 (d of q, J = 2.5, 7.0 Hz, 2 H), 5.39 (d of d, J = 2.5, 10.3 Hz, 2 H), 5.57 (d, J = 15.4 Hz, 2 H), 5.65 (d of d, J = 9.5, 15.0 Hz, 2 H), 6.05 (d of d, J = 11.2, 15.0 Hz, 2 H), 6.96 (d of d, J = 11.2, 15.4 Hz, 2 H), 9.67 (s, 2 H).

(17) Sutter, M. A. Ph.D. Thesis, No. 7659, ETH-Zürich, 1984.

(18) In a related example the "Cram product" was also observed in a system in which chelation control would have been possible: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120.

(19) ^1H NMR (300 MHz, $CDCl_3$) 0.87 (t, J = 7.6 Hz, 3 H), 0.92 (t, J = 7.6 Hz, 3 H), 1.11 (t of t, J = 10.2, 3.9 Hz, 1 H), 1.21 (d, J = 6.3 Hz, 3 H), 1.31 (d of d, J = 12.5, 11.0 Hz, 1 H), 1.34–1.41 (br, 1 H), 1.47 (d of q, J = 14.4, 7.5 Hz, 1 H), 1.50–1.70 (m, 2 H), 1.77 (d of q, J = 14.3, 7.6 Hz, 1 H), 2.14 (d of d, J = 12.4, 4.9 Hz, 1 H), 3.11 (s, 3 H), 3.52 (d of q, J = 6.3, 10.2 Hz, 1 H), 3.90 (d of t, J = 4.8, 10.5 Hz, 1 H). The signal at 3.90 is due to H-4, which must be axial for two large coupling constants to be observed.

(20) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J Am. Chem. Soc.* **1981**, *103*, 3099.

(21) Satisfactory ^1H NMR, IR, MS, and microanalyses were obtained for all stable, crystalline, or distillable compounds.

(22) We gratefully acknowledge the Royal Society (England) Postdoctoral Fellowships to R.J. and K.L. and generous financial support by the Sandoz AG (Basel) and by the Schweizerischer Nationalfonds zur Förderung der Wissensch. Forschung (Project 2.253-0.84).

Design of Molecular Assembly of Diphenylcarbenes Having Ferromagnetic Intermolecular Interactions

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Molecular design of organic ferromagnets is the current topic of interest in organic material science.[1] Some high-spin hydrocarbons were found to behave as superparamagnets and can be regarded as "micro" domains in ferromagnets.[2] Therefore introduction of ferromagnetic intermolecular (interdomain) interaction is expected to lead to macroscopic ferromagnetism.[3] We wish to propose here one of the strategies for designing an assembly of carbene molecules which may display macroscopic magnetic properties. We have taken advantage of the dispersion force of alkyl chains,[4] and have introduced octyloxy groups at the para positions of diphenyldiazomethane to realize a favorable orientation and overlap in the resulting carbene species in crystals.[5] The ESR spectrum of the photolyzate of polycrystalline bis[*p*-(octyloxy)-phenyl]diazomethane (**1**) at 10 K showed a complex multiplet

(1) (a) Iwamura, H.; Sugawara, T.; Itoh, K.; Takui, T. *Mol. Cryst. Liquid Cryst.* **1985**, *125*, 251. (b) Breslow, R. *Ibid.* **1985**, *125*, 261. (c) Izuoka, A.; Murata, S.; Sugawara, T.; Iwamura, H. *J. Am. Chem. Soc.* **1985**, *107*, 1786.

(2) Sugawara, T.; Bandow, S.; Kimura, K.; Iwamura, H.; Itoh, K. *J. Am. Chem. Soc.* **1984**, *106*, 6449.

(3) Sugawara, T.; Tukada, H.; Murata, S.; Iwamura, H., to be published elsewhere. The crystals of diphenyldiazomethanes carrying *p*-methoxy (**4**), *p,p'*-dimethoxy (**5**), *p*-bromo (**6**), *p*-cyano (**7**), *m*-chloro (**8**), *m,m'*-dibromo (**9**), *p,p'*-dichloro (**10**), and *p,p'*-bis[(3-hydroxypropyl)oxy] (**11**) substituents have been scrutinized. Only **4** and **5** gave strong quintet and higher multiplet signals. Weak quintet signals were accompanied by strong triplet signals in **6**–**9**. The irradiated **10** and **11** showed only isolated triplet signals. See also: (a) Murai, H.; Torres, M.; Strausz, O. P. *J. Am. Chem. Soc.* **1980**, *102*, 5104. (b) Murai, H.; Torres, M.; Strausz, O. P. *Ibid.* **1980**, *102*, 7391.

(4) Long-chain alkyl groups are known to have a tendency to line up side by side in crystals and liquid crystals. A typical example is found in fatty acids, e.g., 2-methyloctadecanoic acid: (a) Abrahamsson, S. *Acta Crystallogr.* **1959**, *12*, 301; (b) *Ibid.* **1959**, *12*, 304.

(5) Long alkyl chains have been introduced into organic donors in order to enhance their physicochemical properties in liquid crystal phases. (a) Mueller-Westerhoff, U. T.; Nazzal, A.; Cox, R. J.; Giround, A. M. *J. Chem. Soc., Chem. Commun.* **1980**, 497. (b) Babeau, A.; Tinh, N. H.; Gasparoux, H.; Polycarpe, C.; Torreilles, E.; Giral, L. *Mol. Cryst. Liquid Cryst.* **1982**, *72*, 171. (c) Piechocki, C.; Simon, J.; Skoulios, A.; Guillon, D.; Weber, P. *J. Am. Chem. Soc.* **1982**, *104*, 5245. (d) Inokuchi, H.; Saito, G., private communication.

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