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)-3hydroxybutyrate (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

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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 1981, 04, 401.
 (b) Neupert-Laves, K.; Dobler, M. Helv. Chim. Acta 1982, 65, 262. (c) Ley,
 (c) N.; Neuhaus, D.; Williams, D. J. Tetrahedron Lett. 1982, 23, 1207.
 (d) (a) Takahashi, S.; Ohki, E. Chem. Pharm. Bull. 1967, 15, 1726 and

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(5) ¹H 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, 14.2, 2H, 3.08 (s, 6 H), 3.13 (s, 6 H), 3.55-3.65 (m, 4H), 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), 5.15 (d of d, J = 9.5, 15.0 Hz, 2 H), 5.39 (d, J = 15.4 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), 5.15 (d of d, J = 9.5, 15.0 Hz, 2 H), 5.39 (d, J = 15.4 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), 5.15 (d of d, J = 9.5, 15.0 Hz, 2 H), 5.39 (d, J = 15.4 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), 5.15 (d of d, J = 9.5, 15.0 Hz, 2 H), 5.39 (d, J = 15.4 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), 5.15 (d of d, J = 15.4 Hz, 2 H), 5.15 (d of d, J = 15.4 Hz, 2 H), 5.15 (d of d, J = 15.4 Hz, 2 H), 5.15 (d of d, J = 15.4 Hz, 2 H), 5.15 (d of d, J = 15.4 Hz, 2 H), 5.15 (d of d) Hz, 2 Hz, 2 Hz, 2 H), 5.15 (d of d) Hz, 2 Hz, 22 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} [α]_D +68 ± 3° (c 0.54, CCl₄).
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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., (9) Nagaoka, H.; Kishi, Y. Tetrahedron 1981, 37, 3873.







Chart II







14 + R = H

15 : R = Me

CODE





10 : X = CH-CH-CH-CO.Me



11 :



Chart III



 $R = SiEt_3$ X = H.

= H, R^2 = Trit



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%. Swern¹¹ oxidation to the aldehyde

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

9 followed by Wittig reaction with the triphenylphosphorane¹² 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 procedure⁷ to give the diolide 19, which was then converted (MeOH/p-TsOH)to the diol 20 (mp 186-188 °C). Finally Swern¹¹ oxidation produced the dialdehyde 21¹⁶ (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 unstable¹⁷ (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) (TiCl₄/CH₂Cl₂, -78 °C, 5 min) gave a single unstable aldol¹⁶ 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 diisopropylethylamine²⁰ gave a single Z-boron enolate enolized toward C-2 (confirmed by reaction of the enolate with benz-

(12) Buchta, E.; Andrée, 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, CDCl₃) 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, 15.3 Hz, 1 H), 7.28 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.27 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.28 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.28 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.28 (d of d, J = 10.8, 15.3 Hz, 1 H), 7.28 (d of d, J = 10.8, 15.3 Hz, 10.8 (d of d), 15.3 Hz, 10.8 J = 10.8, 15.4 Hz, 1 H).

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(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, CDCl₃) 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 = 12.5, 12.0 + 70.127 (c J, J = 7.6 Hz, 1 H), 1.47 (d of q, J = 12.5, 10.1 Hz, 1 H), 1.34-1.41 (br, 1 H), 1.47 (d of q, J = 12.5, 10.1 Hz, 1 H), 1.34-1.41 (br, 1 H), 1.47 (d of q, J = 12.5, 10.1 Hz, 1 H), 1.34-1.41 (br, 1 H), 1.47 (d of q, J = 12.5, 11.0 Hz, 1 Hz, 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), 1.39–1.41 (d), 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.

aldehyde). Reaction of 4 equiv of this enolate with the dialdehyde 21 (Et₂O/CH₂Cl₂, -78 °C, 1 h; 0 °C, 30 min) gave, after oxidative workup (HMPT·py·MoO₅), 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

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

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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

(3) Sugawara, T.; Tukada, H.; Murata, S.; Iwamura, H., to be published elsewhere. The crystals of diphenyldiazomethanes carrying p-methoxy (4), elsewhere. The crystals of ulphenythazomethanes carrying p-intensory (τ_1 , 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 r_1 and r_2 where a companies of the strong triplet signals. 6-9. The irradiated 10 and 11 showed only isolated triplet signals. See also:
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(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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