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GRAHAMIMYCIN A_1

SYNTHESIS AND DETERMINATION OF CONFIGURATION AND CHIRALITY

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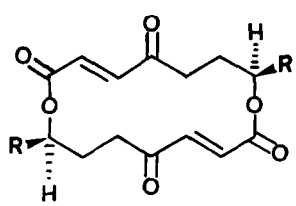
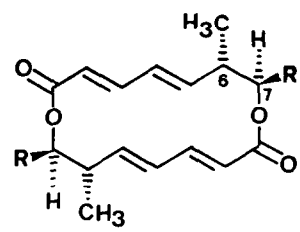
Summary: The two hydroxyacid derivatives 10 and 11, obtained from (S)-β-hydroxybutanoate and (S)-lactate, respectively, are joined to give the acetylenic ester 12. Cyclization and functional group manipulations lead to (S,S)-(+)-grahamimycin A_1, the enantiomer of the natural product.

The group of known antibiotic natural macrodiolides[1] can be subdivided into the C_2-symmetrical representatives 1, 2, and 3 with 16-membered rings and the asymmetric compounds 4

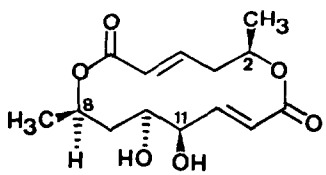


1: R=CH_3: (-)-Pyrenophorin [R,R]

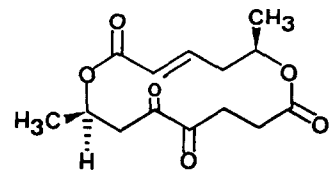
2: R=CH_2COCH_3: (-)-Vermiculin [S,S]



3: R=$C_{19}H_{35}O_7$: (-)-Elaiophylin [6S,7S]

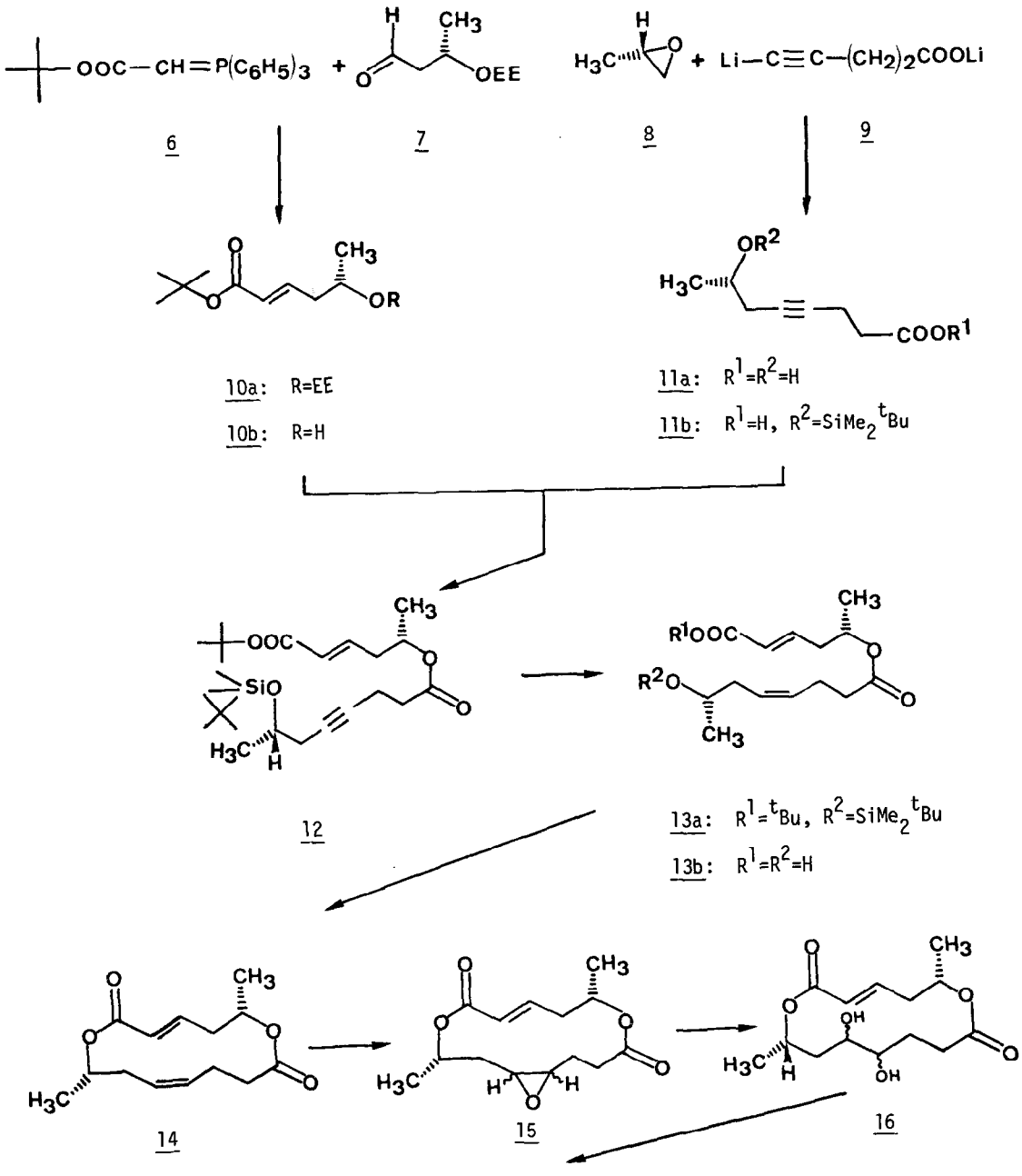


4: (+)-Colletodiol [2R,8R,10R,11R]



5: (-)-Grahamimycin A_1 [R,R]

and 5 with 14 ring members. It has been shown[2] by degradative or synthetic chemical correlation and/or by x-ray structure analysis, that the centres of chirality at the two ester moieties of the compounds 1 - 4 all belong to the same configurational family, as is evident from their *formulae*[3]. We have now proved by synthetic correlation with lactic acid and with β-hy-



(S.S)-(+)-grahamimycin A_1

droxy-butyric acid that the newest addition[4] to the series of diolides, i.e. *(-)-grahamimycin* A_1, only the constitution of which was known[4], has the cis-configuration and the (R,R) sense of chirality as depicted in *formula* 5.

Our synthesis of (+)-5, the first one of an unsymmetrical diolide, uses the protected

(S)-acetaldol 7 and the (S)-methyl-oxirane (8) as starting materials from the *pool of chiral building blocks*[5] and is outlined in the accompanying flow-sheet, with details about conditions, yields and some physical data given in the Table.

The most striking structural feature of the yellow grahamimycin A_1 is the 1.2-diketo group, the reactivity and generation of which dictated our synthetic strategy: direct RuO_4-oxidation of an acetylenic triple bond to the diketone could not successfully be performed in the presence of an α.β-unsaturated ester group in the same molecule; furthermore, hemiacetal formation or dehydration to enones prevented inter- or intramolecular esterifications when we generated intermediates containing the 4-hydroxy-1.2-diketone substructure. We therefore postponed the diketone formation to the very last step of the synthesis.

Table. *Reaction conditions, physical properties, and yields of (+)-5, 10 - 16.* (B.p. during Kugelrohr distillations. - Correct elemental analyses of 10a, 11b, 12, 14, 15).

10a: b.p. 100°C/0.005 mm, 13 g (85%) from 9.5 g of 7 (ref. 5) and 45 g of 6 (m.p. 151°C) in DMF, 20°C, 16 h.

10b: b.p. 95-110°C/0.002 mm, $[\alpha]_D$= +100° (c=1.2, $CHCl_3$), 8.4 g (89%) from 13 g of 10a in THF/5% H_2O, $HClO_4$, 20°C.

11b: b.p. 150°C/0.05 mm, 13 g (52%) from 9 g commercial 4-pentynoic acid, 2.1 equiv. BuLi (→ 9), and 5.8 g 8 in neat HMPT, 20°C, 48 h; with subsequent silylation (17 g TBDMSCl, 8 g imidazol, DMF) and hydrolysis of $COOSiR_3$ (THF/H_2O 3:1, HCl).

12: b.p. 230°C/0.005 mm, 2.0 g (94%) from 0.9 g 10b and 1.3 g 11b with 1 g DCC, 85 mg 4-dimethylamino-pyridine, in CH_2Cl_2, 20°C, 10 h.

13a: 8.6 g (100%) from 8.6 g 12 and H_2/*Lindlar* catalyst, in pentane.

13b: slowly cryst. oil, 4.8 g (90%) from 8.6 g 13a in 80 ml CF_3COOH, 0°C, 15 min.

14: m.p. 54-55°C, $[\alpha]_D$= -65°(c=1.5, $CHCl_3$); 1.0 g (50%) from 2.0 g 13b with 4 equiv. 2-chloro-1-methyl-pyridinium tosylate/Et_3N (ref. 6) in 1.5/0.2 l dry CH_3CN, reflux, 20 h addition time.

15: 2 diastereomers (fract. cryst. EtOEt/pentane), m.p. 117° (plates), 142° (needles), 0.8 g (95%) from 0.8 g 14 with MCPBA in $CHCl_3$, 40°C, 3 h.

16: mixt. of diastereomers, 0.55 g (66%) from 0.78 g 15 with 10 ml 20% $HClO_4$ in 15 ml THF, 40°C, 20 min.

(S,S)-(+)-grahamimycin A_1 [data of natural product from ref. 4 in brackets][7]: m.p. 90°C [91-92], $[\alpha]_D$= +12° (c=0.55, $CHCl_3$) [-15°], UV (EtOH): λ=428 nm, ε=16 [426/16], ^{13}C-NMR ($CDCl_3$): 19.7 [19.9], 20.5 [20.7], 28.3 [28.5], 31.1 [31.5], 38.0 [38.3], 39.3 [39.7], 68.6 [68.9], 70.4 [70.6], 123.8 [123.7], 144.8 [144.9], 164.2, 171.0, 196.3, 196.1 ppm.

The chiral electrophiles 7 (a^3-reagent) and 8 (a^2-reagent) were chain-elongated with the *Wittig*-d^2-reagent 6 and the acetylide-carboxylate 9 (d^5-reagent), respectively. Subsequent deprotection/protection led to the hydroxyester 10b and the TBDMS-O-substituted acid 11b, which were joined to give 12 by esterification with DCC. *cis*-Hydrogenation to 13a and deprotection of both functional groups (→ 13b) was followed by cyclizing esterification to the diolide 14 (50%), using the *Mukaiyama*-method[6]. The isolated double bond of 14 was then converted to the 1.2-diketone moiety *via* hydroxylation through the epoxides 15 and PCC-oxidation of 16 (see Table). Unfortunately, the yield of this last step could hitherto not be improved above 10%. The product was identical with an authentic[7] sample of natural grahamimycin A_1 in every respect except that the *sense of rotation* was opposite (see Table)[8,9]. This proves that the natural grahamimycin A_1 is the (R,R)-stereoisomer 5.

REFERENCES AND FOOTNOTES

1) In addition to the structures 1-5 shown, some congeners have been described, such as pyrenophorol, colletoketol, colletol, and colletallol, see the references given in[2].

2) Pyrenophorin and vermiculin: B. Seuring and D. Seebach, Liebigs Ann. Chem. 1978, 2044; R.S. Mali, M. Pohmakotr, B. Weidmann, and D. Seebach, ibid. 1981, in press, and references given therein. - Elaiophylin: H. Kaiser and W. Keller-Schierlein, Helv. Chim. Acta 64, 407(1981), and unpublished results, ETH Zürich. - Colletodiol: R. Amstutz, E. Hungerbühler, and D. Seebach, Helv. Chim. Acta 64 (1981), and references cited therein.

3) The CIP-symbols of the (R,S)-nomenclature given underneath the *formulae* do not disclose this relationship because of changes in the priority sequences, depending upon the nature of R in 2 and 3.

4) R.C. Ronald and S. Gurusiddaiah, Tetrahedron Lett. 1980, 681.

5) Review on syntheses of enantiomerically pure compounds (EPC-syntheses) with procedures: D. Seebach and E. Hungerbühler, in "Modern Synthetic Methods 1980", Ed. R. Scheffold; Salle (Frankfurt) and Sauerländer (Aarau) 1980, pg. 91-171. - 7: E. Hungerbühler, D. Seebach, and D. Wasmuth, Helv. Chim. Acta 64, 1467 (1981). - 8: B. Seuring and D. Seebach, Helv. Chim. Acta 60, 1175 (1977).

6) T. Mukaiyama, Angew. Chem. 91, 798 (1979), ibid. Int. Ed. Engl. 18, 707 (1979).

7) We thank Professor R.C. Ronald of the Washington State University, Pullman, USA, for supplying a sample of natural grahamimycin A_1[4].

8) An especially impressive proof of constitutional and configurational identity is the *superimposability* of the 300 MHz ^{1}H-NMR spectra.

9) Neither the unnatural grahamimycin A_1, nor the intermediates 13b, 14, 15 or 16 showed any antimicrobial activity against the previously tested 24 organisms[2]. This is in sharp contrast to the series of C_2-symmetrical macrodiolides 1, 2, or even the achiral didesmethyl pyrenophorine (1, H instead of CH_3), which are all active, irrespective of substitution, configuration or chirality[2]. (We thank *Dr. Pache* and *Dr. von Wartburg* of the Sandoz AG, Basel, for these tests.)

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