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A SYNTHESIS OF (S,S)-(+)-GRAHAMIMYCIN A_1

Dario Ghiringhelli

Dipartimento di Chimica del Politecnico di Milano, Centro del C.N.R. di Studio delle Sostanze Organiche Naturali. Piazza Leonardo da Vinci 32, I-20133 Milano, Italy.

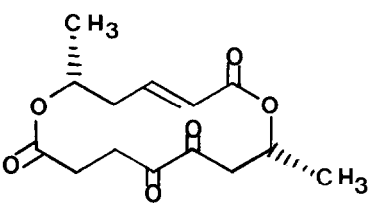
Summary: The preparation of (S)-1-(1,3-dithian-2-yl)-2-hydroxypropane 3 and its transformation into (S,S)-(+)-grahamimycin A_1, through intramolecular pinacolic coupling of dialdehyde 9, are described.

Among the few known members of natural asymmetric macrodiolides[1], grahamimycin A_1[2] 1 is unique for its antibiotic activity and the presence of the 1,2-diketo group.

The synthesis of grahamimycin A_1 was planned, when the sole constitution was known, with three purposes in mind: to search for a new, easy to make, chiral building block especially fitting the synthetic scheme; to prove the stereochemistry of natural grahamimycin A_1; to form the macrocycle by making the bond between the two carbon atoms which should bear the 1,2-diketo group in grahamimycin A_1.

The scheme illustrating the synthesis of (S,S)-(+)-grahamimycin A_1 and the table with yields, conditions and properties show that all purposes were reached.

Fermenting baker's yeast efficiently reduces 1,3-dithian-2-yl-acetone[3] 2 to (S)-1-(1,3-dithian-2-yl)-2-hydroxypropane 3 of more than 99% enantiomeric purity, as proved by two independent methods[4].



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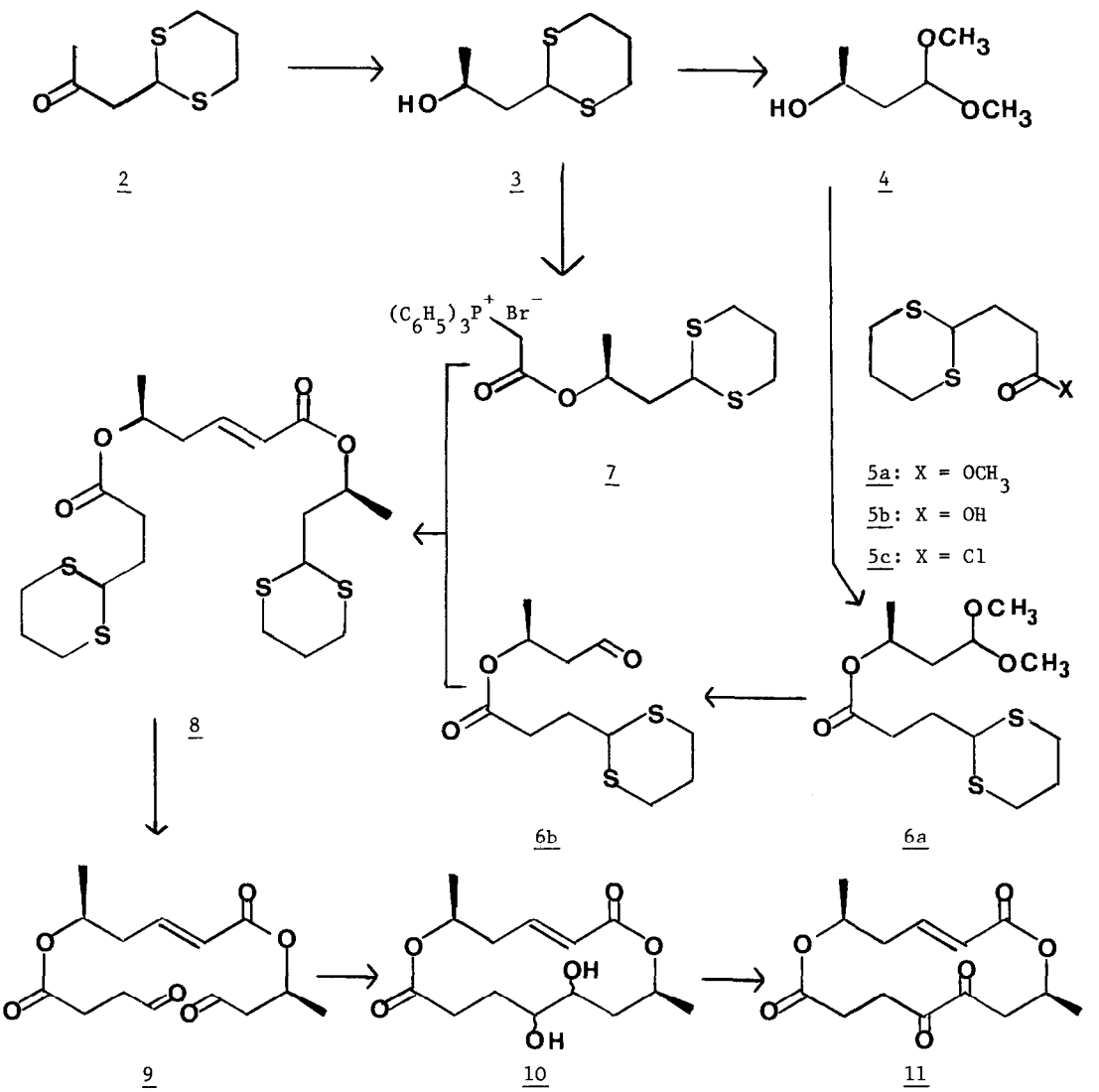
The synthetic correlation of 3 with (S,S)-(+)-grahamimycin A_1 demonstrates that natural (-)-grahamimycin A_1 has a cis relationship between the methyl groups and the (R,R) sense of chirality. The same result was recently reported[1] while this work was in progress.

The idea of making the macrocycle by a C-C bond forming, seemed particularly advantageous for two reasons: first of all the two ester groups present in grahamimycin A_1 could be formed separately, avoiding the need for selective protection and deprotection of carboxyls and hydroxyls;



secondly the formation of the C-C bond could give directly the 1,2- diketone or something easy to be transformed into the 1,2-diketone group.

Three kinds of reactions were examined as possible ways of intramolecular cyclization: the coupling of acyl chlorides into 1,2-diketones promoted by SmJ_2[5], the acyloin coupling of aldehydes catalized by thiazolium salts[6] and the pinacolic coupling of aldehydes promoted by low valent titanium species[7].

The first two possibilities were discarded because SmJ_2 was ineffective in cyclizing dodecan-

dioic acid dichloride and similarly dodecandial was not cyclized by N-lauryl-thiazolium bromide[6a] nor by 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride[6b].

Better results were obtained by the reductive pinacolic coupling. In fact dodecandial was cy-

Table of physical properties, yields and reaction conditions. All products show IR, NMR and MS spectra consistent with reported structures. Compounds 5b, 8, 10 have correct elemental analyses.

3: b.p. 105°/0.1mm, $|\alpha|_D^{20}$ = 24.7°(C = 2.0, $CHCl_3$); 18.2g (90%) from 20g of 2 by 500g of fermenting baker's yeast, 100g sucrose and 25g $Na_4P_2O_7$ in 1500ml of water, 28°C, 4h; 99% pure by GLC on column A[10].

4: b.p. 87°C/25mm, $|\alpha|_D^{20}$ = -13.1°(C = 1.1, $CHCl_3$); 4.7g (70%) from 9.0g of 3 in 25ml CH_3OH with PbO_2 and BF_3[9], 20°C, 2h; more than 99% pure by GLC on column B[10].

5a: dense oil; 17.0g (95%) from 9.2g of methyl 4-oxobutanoate and 1,3-propandithiol with BF_3.

5b: m.p. 87-88°C; 14.2g (90%) from 16.7g of 5a by treatment with 1.1 equivalent of a 2N solution of NaOH in EtOH/H_2O (3/1), 20°C, 18h.

6a: dense oil; 5.4g (87%) from 2.8g of 4 and 5c (obtained from 4.1g of 5b with oxalyl chloride) in benzene and pyridine, 0°C, 18h.

6b: oil; 3.9g (85%) from 5.4g of 6a in CH_3COOH/H_2O (4/1), N_2atmosphere, 80°C, 0.5h.

7: m.p. 143-144°C, $|\alpha|_D^{20}$ = -5.3°(C = 2.0, $CHCl_3$); 33.0g (88%) from 12.9g of 3, 1.1 eq. of pyridine and $BrCH_2COBr$ in benzene, 0°C, 16h, and subsequent reaction with Ph_3P in benzene.

8: dense oil, $|\alpha|_D^{20}$ = 0.0°(C = 1.3, $CHCl_3$); 1.8g (80%) from 1.3g of 6b and the ylide from 3.1g of 7, in benzene, 20°C 16h.

9: dense oil, $|\alpha|_D^{20}$ = -18.7°(C = 1.0, $CHCl_3$); 0.9g (80%) from 1.8g of 8 with PbO_2 and BF_3[9] in THF/H_2O (5/1), 20°C, 3h, N_2 atmosphere; more than 95% pure by GLC on column C[10].

10: waxy solid; 50mg (35%) from 140mg of 9 in 15ml of THF added during 5h to a refluxing suspension obtained from 1.0g of Zn-Cu and 0.55ml of $TiCl_4$ in 20ml of THF in an argon atmosphere; the GLC on column C[10] shows the presence of 4 diastereomers in a 2:8:8:1 ratio.

11: (S,S)-grahamimycin A_1 (data of natural product from ref.2 in brackets): m.p. 91°C |91-92|; $|\alpha|_D^{20}$ = 14.8°(C = 0.3, $CHCl_3$)|-14.7|; UV(EtOH): λ = 428nm, ε = 22 |426/16|; ^{13}C-NMR($CDCl_3$) 19.8|19.9|, 20.6|20.7|, 28.4|28.5|, 31.3|31.5|, 38.2|38.3|, 39.5|39.7|, 68.7|68.9|, 70.5 |70.6|, 123.5|123.7|, 144.8|144.9|, 164.3, 171.0, 196.3, 197.1 ppm; 15mg (20%) from 74mg of 10 with PDC in DMF, 4°C, 20h; the GLC analysis on column C[10] shows the presence of a single peak while the GLC of the corresponding product obtained by the same sequence of reactions starting with racemic 3 and 4 shows two peaks of equal intensity for the two expected diastereomers.

clized in a 70% yield into a three to one mixture of cis- and trans-1,2-cyclododecandiol[8] by a reaction medium prepared by reduction of $TiCl_4$ with a zinc-copper couple in refluxing THF.

The new chiral building block 3 was converted into the phosphonium bromide 7 by reaction with bromoacetylbromide and than with triphenylphosphine and into the aldehyde 6b through trans-acetalization, esterification with the acyl chloride 5c and hydrolysis of the acetal group. The aldehyde 6b and the phosphorane from 7 were joined to give the trans alkene 8. Oxidative hydrolysis[9] of the two dithiane groups of 8 led to the dialdehyde 9.

When the dialdehyde 9 was subjected to pinacolic coupling the cyclic diol 10 was obtained in a 35% yield. The oxidation by pyridinium dichromate of 10 gave a product having physico-chemical properties identical with those reported for natural grahamimycin A_1 (except for the sense of rotation), and for synthetic (S,S)-(+)-grahamimycin A_1[1].

Aknowledgment: the author is indebted to Mrs. Rosanna Bernardi for GLC analyses.

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4 - Method 1: the alcohol 3 was acylated with acetic anhydride and pyridine, the dithiane group was oxidatively hydrolyzed with PbO_2 and BF_3[9] and the resulting 3-acetoxybutanal reduced by LAH to (S)-1,3-butandiol $|\alpha|_D^{20} = 29.0°$(C = 1, EtOH); $|\alpha|_D = 29°$ was reported for (S)-1,3-butandiol (H.Gerlach, H.Oertle and A.Thalmann, Helv. Chim. Acta 59, 755(1976)).
Method 2: (R)-(+)-α-methoxy-α-trifluoromethylphenylacetate of 3 and of the racemate were made and their ^{1}H-NMR compared in presence of $Eu(fod)_3$(S.Yamaguchi, F.Yasuhara and K.Kabuto, Tetrahedron 32, 1363(1976)). Only the signal from the OMe group of the (R,S)- diastereomer was present in the spectrum of (R)-(+)-MTPA ester of 3. The GLC analysis on column C[10] shows two peaks for the (R)-(+)-MTPA ester of the racemic alcohol and only one peak for the (R)-(+)-MTPA ester of 3.

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10 - GLC analyses were carried out on: DANI 3800 (FID) using 2m x 3mm Pyrex columns packed with: column A - 5% SP1000 on 100-120 Supelcoport; column B - 10% UCC-W-982 on 100-120 Chrom. W-DMCS; C.ERBA Fractovap 4160(FID), column C - 25m WCOT glass capillary OV-1 film, 0.4μm th.

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