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SYNTHESIS OF THE OLIGOSACCHARIDE MOIETIES OF MUSETTAMYCIN AND MARCELLOMYCIN , NEW ANTITUMOUR ANTIBIOTICS.

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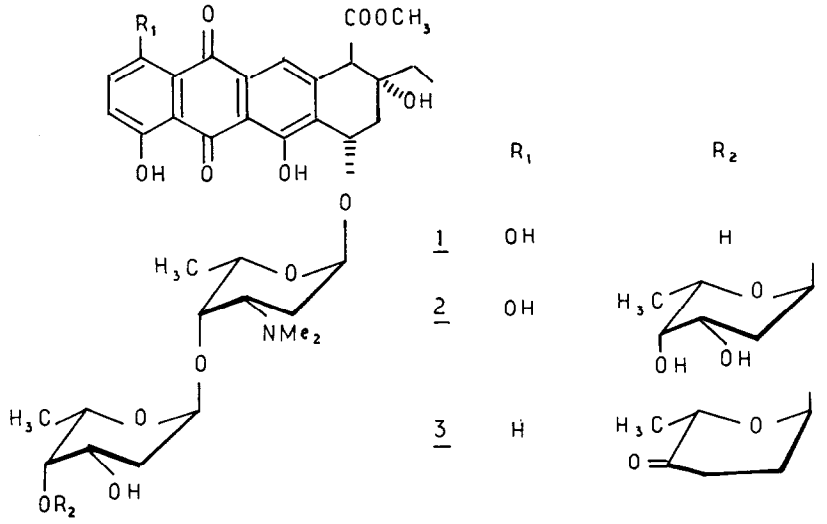
Summary : *The total syntheses of the di and trisaccharide respective sugar-moieties of musettamycin and marcellomycin are reported.*

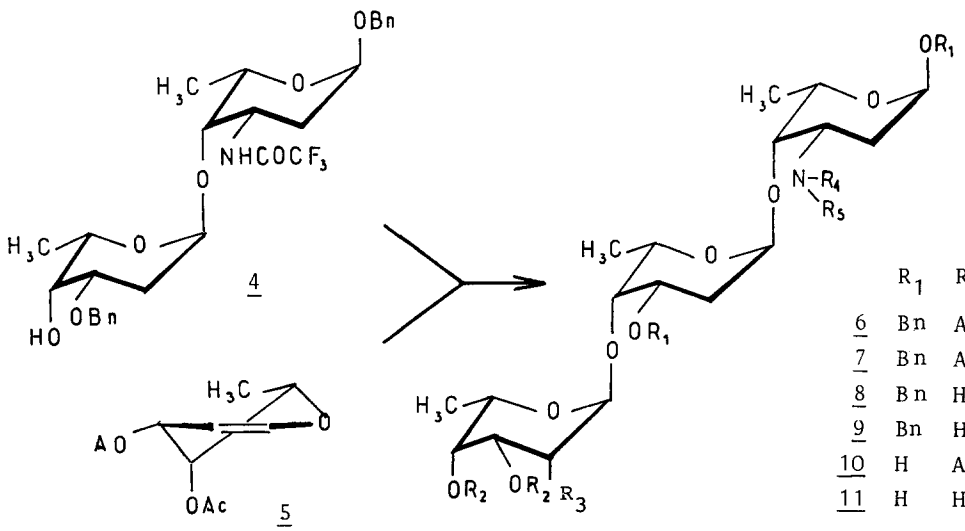
Structure analysis of Musettamycin 1 and Marcellomycin 2, new antibiotics obtained by fermentation broth of an Actinosporangium species [1], showed that these molecules were di and trisaccharide anthracycline respectively. Marcellomycin was the second class II anthracyclines introduced into clinical trials as antitumor agent after Aclacinomycin A[2] since both compounds induced little myelosuppression and are less cardiotoxic than doxorubicin[3].



Starting from the aglycons, the sugar sequence for the three oligosaccharide moieties are : L-rhodosamine (unit A) and 2-deoxy-L-fucose (unit B) for 1 with an additional 2-deoxy-L-fucose (unit C) in the case of 2 or L-cinerulose in the case of 3. In both cases, interlinkages are α-L(1 → 4).

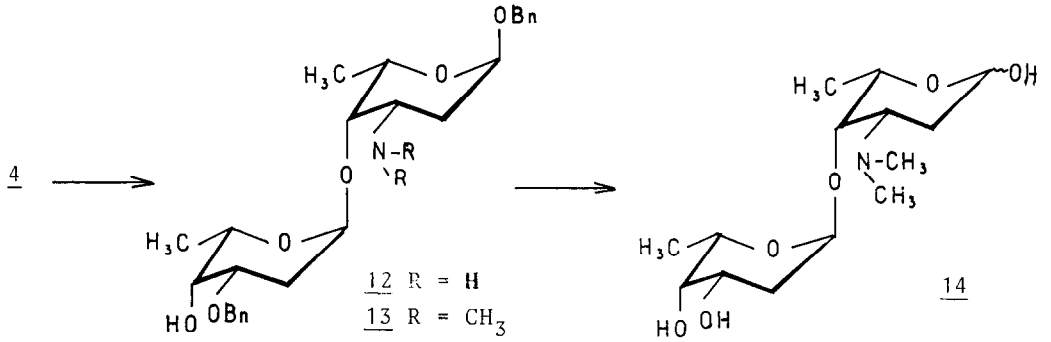
Syntheses of the methyl glycosides of the disaccharide unit A-B[4] or B-C[5] or syntheses of the methyl glycosides of disaccharides closely related to them[6] have been previously reported but none of them were suitable for complete elaboration of the trisaccharide skeletons of 2 or 3. On the other hand, we have recently published[7] the synthesis of a trisaccharide related to the sugar moiety of aclacinomycin A based upon a general strategy allowing access to various analogs. This is illustrated in this paper where we describe the synthesis of the trisaccharide moiety of marcellomycin.

Coupling of the disaccharide 4[7] with an excess of 3,4-di-O-acetyl-L-fucal 5 (2 molar equivalents) is performed in the presence of N-iodosuccinimide[8]. This affords (MeCN, 20°C, 1 h) the trisaccharide 6, stereospecifically in 70 % yield after chromatography on silica gel (hexane-EtOAc, 3:1) as a crystalline compound (m.p. 64°, $|\alpha|_D^{20}$ -145°)[9]. The α linkage between the units B and C was proved by a characteristic signal for 1''-H at δ 5.16 ppm ($J_{1'',2''}$ < 1Hz). Hydrogenolysis of the $C_{2''}$-I bond of 6 (Pd-C, EtN_3, EtOH, 2h) leading to 7 (80 %, syrup, $|\alpha|_D^{20}$ = -159°) is followed by deacylation (70 %, K_2CO_3, MeOH-H_2O, 18 h, 20°C) to give 8 as a syrup ($|\alpha|_D^{20}$ -164° in methanol). Treatment of an acetonitrile solution of 8 with formaldehyde in the presence of $NaBH_3CN$ for 18h affords the dimethylamino compound 9 (86 %) as a syrup ($|\alpha|_D^{20}$ -234°)



	R_1	R_2	R_3	R_4	R_5
6	Bn	Ac	I	H	$COCF_3$
7	Bn	Ac	H	H	$COCF_3$
8	Bn	H	H	H	H
9	Bn	H	H	CH_3	CH_3
10	H	Ac	H	H	$COCF_3$
11	H	H	H	CH_3	CH_3

While the trisaccharide 7 was easily hydrogenolyzed (Pd-C, EtOAc, H_2, 30 min.) giving 10 in 60 % yield as a mixture of anomers, difficulties to remove the benzyl groups were encountered with 9 probably due to the basic amine. Preliminary experiments were conducted with the disaccharide 4. Alkaline treatment of 4 (K_2CO_3, MeOH, H_2O, 3 h, 20°C) affords the amino derivative 12 (95 %, syrup, $|\alpha|_D^{20} = -125°$) which is immediatly N-methylated as described above for 9 leading to 13 (syrup, $|\alpha|_D^{20} = -116°$) in 85 % yield. Treatment of 13 under various conditions (H_2 and Pd-$BaSO_4$ or Pd-C, EtOH, AcOH or Pd-C, EtOH, HCOOH) resulted in either the recovery of the starting material or to the formation of many side-products. The conversion of 13 into the free disaccharide moiety of musettamycin 14 was finally conducted under H_2 (1 atm.) with Pd-C in 0.2N HCl methanolic solution for 30 min.



As for 13 the conversion of 9 into the free trisaccharide moiety of marcellomycine 11 was then conducted under H_2 with Pd-C in 0.2N HCl methanolic solution for 30 min. Compound 11 was obtained as a mixture of α and β anomers and fully characterized by chemical ionization mass spectrometry and by n.m.r. spectroscopy.

The general scheme has allowed us to synthesize for the first time the sugar moieties of anthracyclines class II such as aclacinomycin A[7,10], marcellomycin and musettamycin. However coupling of these di or trisaccharides with different aglycons can be achieved with the N-trifluoroacetyl derivatives such as 10, the dimethylamino function at C-3 being introduced later on[11].

Full details concerning these syntheses as well as those of the sugar moiety of aclacinomycin A and of other disaccharides closely related to 14 will be reported elsewhere.

References and notes.

1. D.E. Nettleton, Jr, W.T. Bradner, J.A. Bush, A.B. Coon, J.E. Moseley, R.W. Myllymaki, F.A. O'Herron, R.H. Shreiber and A.L. Vulcano, J. of Antibiotics, 30, 525 (1977).
2. T. Oki, Recent Results Cancer Res., 76, 21 (1981).
3. S.D. Reich, W.T. Bradner, W.C. Rose, J.E. Schurig, H. Madissoo, D.F. Johnson, V.H. DuVernay, S.T. Crooke in : Anthracyclines, Current Status and New Developments edited by S.T. Crooke and S.D. Reich, Academic Press, 343 (1980).
4. J. Boivin, C. Monneret and M. Pais, Tetrahedron Letters, 21, 2413 (1980).
5. J. Thiem, H.W. Kluge and J. Schwentner, Chem. Ber., 113, 3497 (1980) ; A. Martin, M. Pais and C. Monneret, Carbohydr. Res., 113, 21 (1983).
6. J. Boivin, C. Monneret and M. Pais, Tetrahedron, 37, 4219 (1981) ; H.S. El Khadem and D. Matsuura, Carbohydr. Res., 88, 332 (1981) and 101, C-1 (1982).
7. A. Martin, M. Pais and C. Monneret, JCS, Chem. Comm., 305 (1983).
8. J. Thiem, K. Karl and J. Schwentner, Synthesis, 696 (1978).
9. Analytical data of the new compounds described here, including microanalyses are in excellent agreement with the assigned structures. $(\alpha)_D$ were measured in $CHCl_3$ solution (c = 1). Selected NMR ($CDCl_3$ solution and TMS as ref. zero) and Mass in excellent agreement with the assigned structures. Selected NMR and Mass spectra (DCI/NH_3) data : 6 : δ 4.95 (bs, 1-H and 1'-H), 5.16 (bs, 1"-H), 1.17 (d, 6-Me), 1.24 (d, 6'-Me), 0.84 (d, 6"-Me), 2.18 (s, OAc), 2.08 (s, OAc) ; m/z 911 (M+18), 785 (M+18-I), 571 (unit AB+18), 351 (unit A+18, base peak) ; 7 : δ 5.00 (bs, 1-H and 1'-H), 5.16 (bs, 1"-H), 1.17 (d, 6-Me), 1.24 (d, 6'-Me), 0.84 (d, 6"-Me), 2.14 and 2.00 (s, OAc) ; m/z 785 (M+18), 571 (AB+18), 351 (A+18, b.p.) ; 8 : δ 4.92 (bs, 1-H), 4.88 (bs, 1'-H), 4.99 (bs, 1"-H), 1.08 (d, 6-Me), 1.12 (d, 6'-Me), 0.82 (d, 6"-Me) ; 9 : δ 5.22 and 5.32 (bs, 1-H and 1'-H), 5.43 (bs, 1"-H), 1.38-1.33 (3d, Me), 2.75 (bs, NMe_2) : m/z 623 (M+18), 571 (AB+18), 266 (A+18, b.p.) ; 10 : δ 4.88 (bs, 1-H), 5.01 (bs, 1'-H), 5.19 (bs, 1"-H), 2.15 (s, 2OAc), 1.23 and 1.14 (d, 6-Me and 6'-Me), 0.88 (d, 6"-Me), 5.88 (dd, 1-Hβ) ; 11 : δ 5.08 (bs, 1-He) and 5.06 (m, 1-Ha), 4.84 and 4.73 (1'-H and 1"-H), 2.15 (bs, NMe_2) 1.03-1.01 (3d, Me) ; m/z 436 ($M+H^+$, b.p.), 306 ($AB+H^+$) ; 12 : δ 5.00 and 4.95 (1-H and 1'-H), 1.28 (d, 6'-Me), 1.18 (d, 6-Me) ; 13 : δ 5.09 and 5.04 (bs, 1-H and 1'-H), 1.24 and 1.20 (d, 6-Me and 6'-Me), 2.38 (bs, NMe_2) ; m/z 486 ($M+H^+$), 266 (A+18, b.p.) ; 14 (DMSO-d_6) : δ 5.06 and 4.99 (bs, 1 and 1'-H), 1.10 and 1.08 (d, 6 and 6'-Me), 2.22 (bs, NMe_2) ; m/z 436 ($M+H^+$).
10. A. Martin, C. Monneret and M. Pais, Abstr. XIIth International Carbohydr. Symposium, A 6.3 (1984), Utrecht, July 1-7, The Netherlands.
11. D.W. Henry, G.L. Tong, A.N. Fujiwara and W.W. Lee, Am. Chem. Soc., Natl. Meet. 172nd, MEDI 90 (1976) San Francisco, Aug. 29-Sept.3 ; G.L. Tong, H.Y. Wu, T.H. Smith and D.W. Henry, J. Med. Chem., 22, 912 (1979).

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