Degradative and Synthetic Approaches to the Polyhydric Array of Polyene Macrolides

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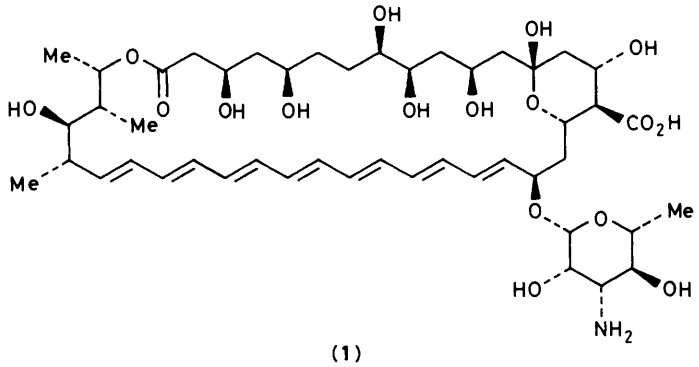
Procedures for obtaining the polyhydric array of polyene macrolides by degradation of pimaricin (natamycin) and by synthetic elaboration of a hemiacetal chiron are described.

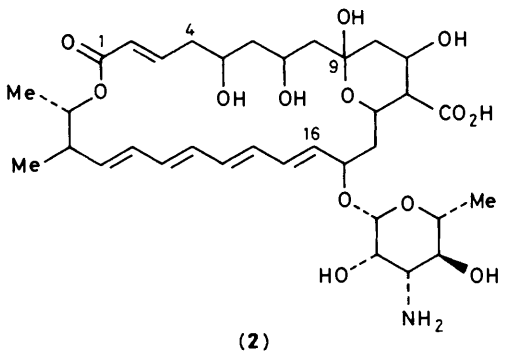
There are about 100 members of the family of polyene macrolides[1] and although several of them have been in world-wide clinical use for several years,[2] the absolute stereochemistry is known for only one member, amphotericin B (**1**).[3] The amorphous nature of the other antibiotics and/or their derivatives has precluded characterization. Judging from the recent literature,[4] there is increasing interest in the chemistry of these antibiotics and Nicolaou has recently reported a degradation–reassembly procedure for (**1**).[4c] This achievement prompts us to report some pertinent results from our laboratory, since we have been interested in developing a general degradation protocol for the polyene macrolides. In the long term, it is hoped that comparison of these degradation products with polychiral arrays assembled from suitable chirons should facilitate proof of absolute configuration. Thus, in parallel studies we have been exploring procedures for building upon the recently described hemiacetal chiron (**8**).[5] We now describe preliminary accounts of our degradation and synthetic studies.

Our degradation protocol is designed to retrieve the main polychiral arrays of the polyene macrolides, including the hemiacetal portion which is present in the majority of members, as exemplified by (**1**), (**2**), and (**3**). Our work has been carried out on pimaricin (natamycin) (**3a**), which we have been able to obtain in generous supply. In order to excise the chiral array, it was necessary to protect the various reactive functional groups and our experiments have shown that the best order is the amine, carboxylic acid, acetal, then secondary hydroxy groups. Crystalline pimaricin (**3a**) was added to a 12 : 1 mixture of MeOH and Ac_2O and when the slow process of dissolution was complete, the *N*-acetyl derivative (**3b**) was isolated in 80% yield. Attempts to esterify the carboxylic acid with diazomethane caused decomposition, but use of DCC–DMAP† afforded the ester (**3c**), in 70—80%

† *Abbreviations:* DCC = dicyclohexylcarbodi-imide; DMAP = 2-*N*,*N*-dimethylaminopyridine; PPTs = pyridinium toluene-*p*-sulphonate; TBS = t-butyldimethylsilyl; THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; AIBN = azoisobutyronitrile; OTf = trifluoromethanesulphonate.



(1)



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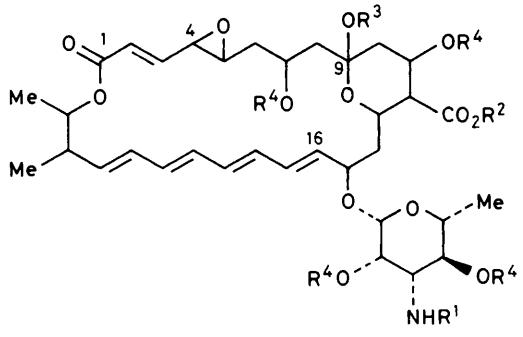
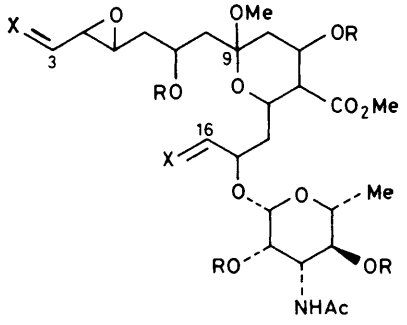


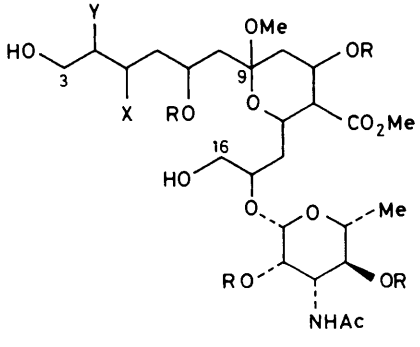
(3)

	R^1	R^2	R^3	R^4
a	H	H	H	H
b	Ac	H	H	H
c	Ac	Me	H	H
d	Ac	Me	Me	H
e	Ac	Me	Me	Ac
f	Ac	Me	Me	TBS



(4)

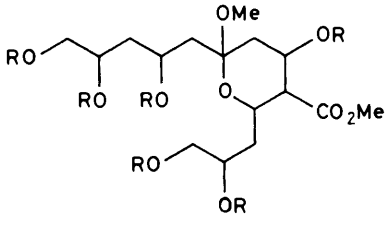
	R	X
a	Ac	O
b	TBS	O
c	Ac	H,OH
d	TBS	H,OH



(5) R = TBS

a; X = OH, Y = H

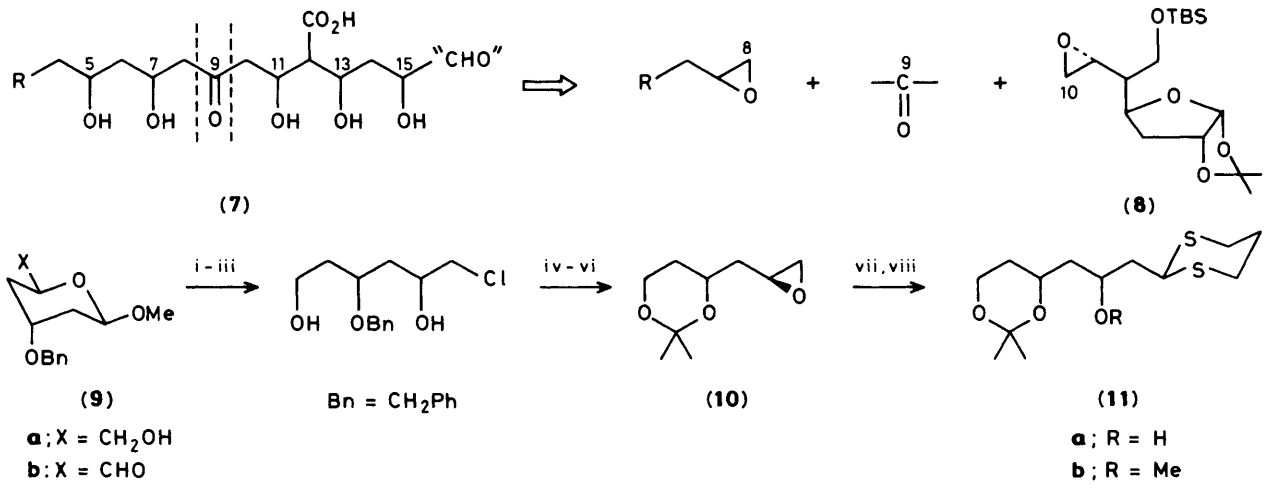
b; X = H, Y = OH



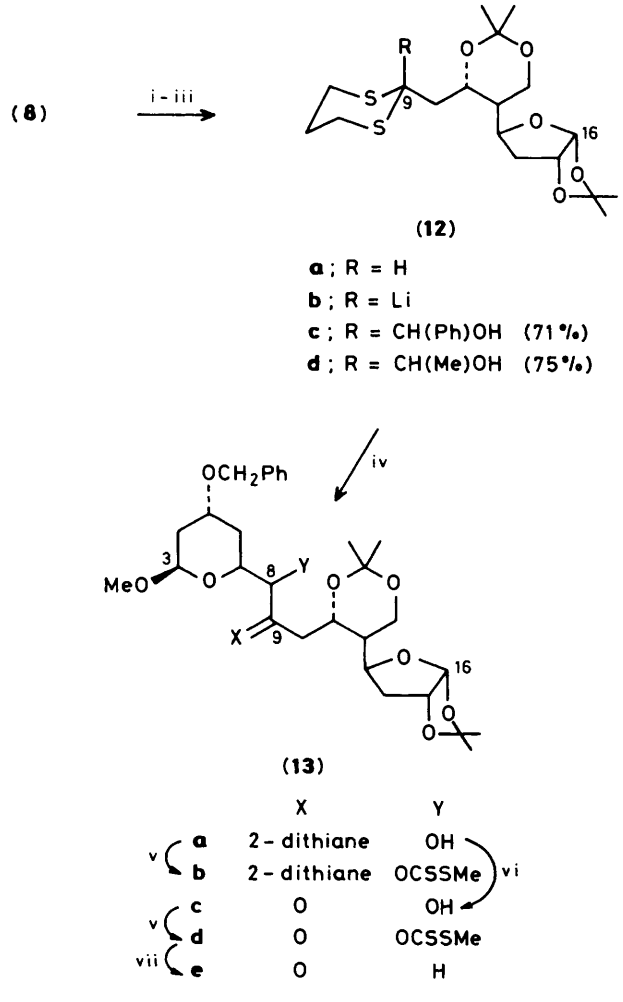
(6)

R = TBS

Scheme 1. *Reagents:* i, Ac_2O, MeOH, room temp. (80%); ii, DCC, DMAP, MeOH (80%); iii, PPTs, MeOH (70%); iv, Ac_2O, DMAP, CH_2Cl_2 (85%); v, Bu^tMe_2SiOTf, lutidine (65%); vi, O_3, MeOH, Zn, HOAc, room temp. (90%); vii, $NaBH_4$, MeOH, 0 °C (90%); viii, Redal, THF, −78 °C (65%); ix, 10% MeOH–HCl, room temp.; Bu^tMe_2SiOTf, lutidine (55%).†



Scheme 2. *Reagents:* i, Ph_3P, CCl_4, pyridine, imidazole, reflux, 1 day (95%); ii, 60% AcOH, dioxane, reflux, 45 min (100%); iii, $NaBH_4$, MeOH, 0 °C to room temp., 1 h (83%); iv, H_2, 10% Pd/C, EtOH, room temp., 4 h (100%); v, NaOMe, $CHCl_3$–MeOH, room temp., 4 h (86%); vi, 2,2-dimethoxypropane, PPTs, CH_2Cl_2, room temp., 12 h (58%); vii, NaH, MeI, Bu^n_4NI, THF, reflux, 24 h (56%); viii, 2-lithiodithiane, HMPA, THF, −78 °C.†



Scheme 3. *Reagents:* i, 2-lithiodithiane, HMPA, THF, −78 °C, 1 h; −20 °C, 6 h (75%); ii, Bu^n_4NF, THF, room temp., 2 h (88%); iii, 2,2-dimethoxypropane, PPTs, CH_2Cl_2, room temp., 12 h (97%); iv, Bu^nLi, TMEDA, THF, −20 °C, 4 h; (**12**), −78, −20 °C (50%); v, NaH, CS_2, MeI, THF, room temp., 3 h (80%); vi, Hg_2O, BF_3·OEt_2, THF–H_2O, room temp. (86%); vii, Bu^n_3SnH, AIBN, PhMe, reflux, 3 h (90%).†

yield. The acetalization was carried out most successfully with MeOH and pyridinium toluene-*p*-sulphonate,[6] the product (**3d**) being a single anomer isolated in 70% yield. The secondary hydroxy groups could then be protected as acetates (**3e**) by use of Ac_2O–DMAP in CH_2Cl_2 as solvent. Notably, Ac_2O–pyridine could not be used, since this led to decomposition. Alternatively, silylation could be effected with butyldimethylsilyl trifluoromethanesulphonate in lutidine to give (**3f**).

Ozonolysis of the fully protected compounds at −78 °C, followed by reduction with zinc in acetic acid, afforded dialdehydes (**4a**) or (**4b**), and reduction with $NaBH_4$ then gave the corresponding primary alcohols (**4c**) and (**4d**).

The oxirane ring of pimaricin (**3a**) is a unique feature of this macrolide, and comparison with tetrin A (**2**) shows that, the unknown stereochemistry notwithstanding, the skeletons of both antibiotics differ primarily in the oxidation state at C-4. It was therefore desirable to cleave the oxirane ring, and in keeping with the studies of Kishi[7] this task was achieved by use of Redal on the silylated derivative (**4d**). The regioisomeric products (**5a**) and (**5b**) were obtained in 8:1 ratio. The mycosamine moiety could now be removed from (**5a**) by treatment with MeOH–HCl and the tetraol was silylated directly to give (**6**).

The linear array (**7**) suggests that it should be possible for the oxirane (**8**) to react with a carbonyl synthon, as indicated in Scheme 2. Accordingly, the epoxide (**10**) was prepared from pyranoside (**9a**)[8] by a series of standard transformations, and reaction with 2-lithiodithiane gave the thioacetal (**11a**). However, all attempts to bring about the reaction of either (**11a**) or (**11b**) with (**8**) failed. The alternative approach involving reaction of the previously described thioacetal (**12a**)[5] with epoxide (**10**) was also unsuccessful. These failures are indicative of the general problems in the reactions of complex d^3 anions[9] with epoxides, the latter being relatively poor electrophiles and the former being capricious nucleophiles.[10—12] We tested the viability of the reaction of the lithiated derivative (**12b**) with benzaldehyde and acetaldehyde and obtained the adducts (**12c**) and (**12d**), respectively in 71 and 75% yields. In keeping with these results, the aldehyde (**9b**) was found to condense with the lithiated derivative (**12b**) at −78 °C. Compound (**13a**), obtained in 70% yield, was a single isomer, the configuration of which is currently being determined.

Removal of 8-OH from (**13a**) was next addressed. It was hoped that deoxygenation conditions could be found that would preserve the thioacetal mask for the C-9 carbonyl; however, although the xanthate (**13b**) could be prepared, subsequent reduction with tri-n-butyltin hydride[13] led to a complex mixture. Other deoxygenation procedures also failed, either because the appropriate derivatives (*e.g.*, sulphonates, halides, acetates[14]) could not be formed, or they failed to react.

Hydrolysis of the thioacetal (**13a**) proceeded best with mercury(II) oxide[15] in aqueous tetrahydrofuran (86%), and the resulting acyloin (**13c**) was subjected to the Barton–McCombie deoxygenation,[13] using the xanthate (**13d**). Compound (**13e**) was thereby obtained in 90% yield, Scheme 3.

The degradative study reported above suggests a protocol for excising the entire polyhydric array from polyene macrolides including the hemiacetal moiety, while the synthetic study shows how the hemiacetal synthon can be utilized to provide a polyhydric array of known stereochemistry.

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