SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF 9(*S*)-*N*,*N*-DIMETHYLAMINO-9-DEOXO-10,11,12,13-TETRAHYDRONIDDAMYCIN

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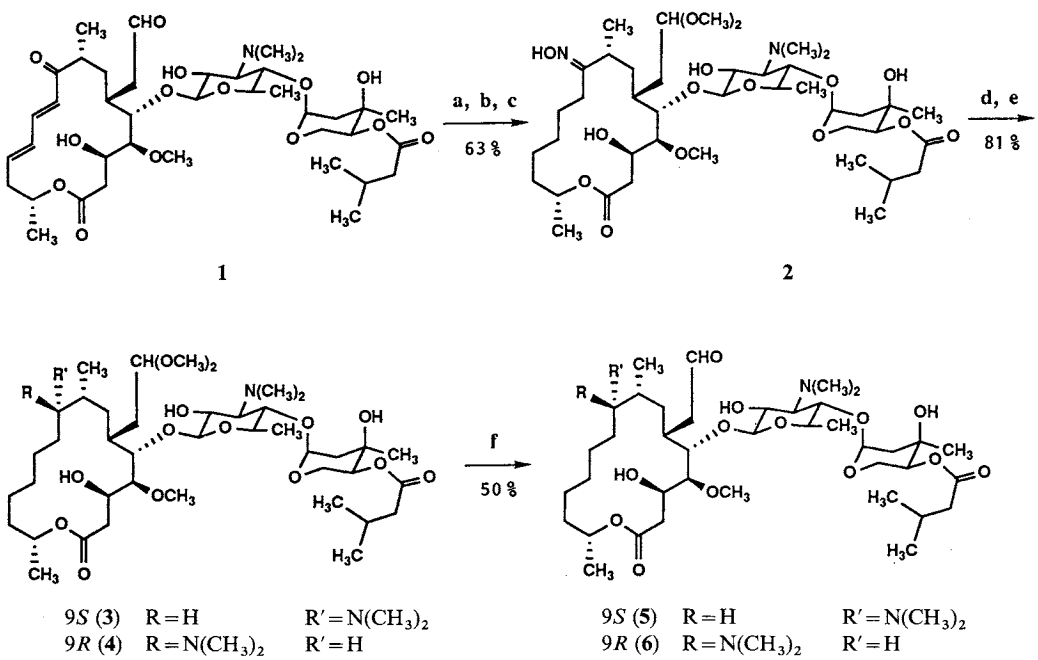
Introduction of basic amino groups at the C-9 position of the macrolide ring of 14-membered macrolide antibiotics has been an important strategy to improve the potency and spectrum of activity of these antibiotics. For example, reductive amination of the 9-ketone[1,2] of erythromycin or ring expansion[3,4] at C-9 with a basic amine has resulted in a number of compounds with improved efficacy. Yet, the C-9 position of 16-membered macrolides has gone unexplored with regard to the introduction of basic amino groups. The objective of the present work is to explore the effect of basic amine substitution at the C-9 position of a 16-membered macrolide on antibacterial efficacy.

Based on the established precedents[5] that there is essentially no difference in activity between the C-9 epimers of the leucomycins and that reduction of the diene system of the leucomycins has minimal effect on activity, the 9-*N*,*N*-dimethylamino-9-deoxo-10,11,12,13-tetrahydroniddamycin derivatives (**5** and **6**) were targeted for synthesis. Introduction of the 9-amino functionality (Scheme 1) was first accomplished by reduction of a suitably protected 9-oxime (**2**) derived from niddamycin (**1**). Subsequent reductive *N*-methylation led to a separable mixture of the protected 9-*N*,*N*-dimethylamino-9-deoxo-10,11,12,13-tetrahydroniddamycin epimers **3**, and **4** in about 2:1 ratio. Deprotection of the aldehyde acetal afforded **5** and **6**. The predominant 9*S* isomer **5**, was 10-fold more active *in vitro* than the 9*R* isomer **6**.

As a consequence of the reduction of the diene system, attempts to establish the stereochemistry of the 9-dimethylamino group of **5** by ^{1}H NMR methods were unsuccessful. The diagnostic allylic

Scheme 1. Synthesis of 9-*N*,*N*-dimethylamino isomers[a].



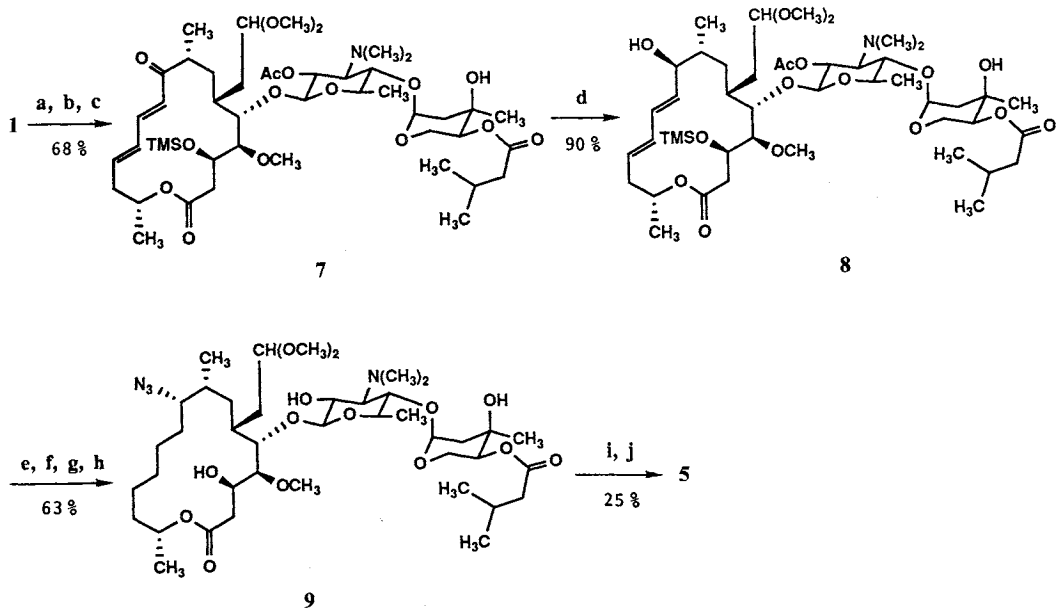
1 2

9*S* (**3**) R=H R′=N(CH$_3$)$_2$
9*R* (**4**) R=N(CH$_3$)$_2$ R′=H

9*S* (**5**) R=H R′=N(CH$_3$)$_2$
9*R* (**6**) R=N(CH$_3$)$_2$ R′=H

[a] (**a**) Acetyl chloride, MeOH, 0°C; (**b**) H_2, 5% Pd-C, MeOH; (**c**) $NH_2OH \cdot HCl$, Et_3N, MeOH, reflux; (**d**) H_2, Raney Ni, MeOH; (**e**) H_2, 5% Pd-C, formaldehyde, MeOH; (**f**) TFA, H_2O, CH_3CN.

Scheme 2. Stereospecific synthesis of 5[a].



[a] (a) Acetyl chloride, MeOH 0°C; (b) Ac_2O, CH_2Cl_2; (c) TMSCl, Et_3N, CH_2Cl_2; (d) $NaBH_4$, $CeCl_3$, MeOH −50 to −30°C; (e) H_2, Raney Ni, EtOAc; (f) MsCl, Et_3N, CH_2Cl_2; (g) LiN_3, DMF; (h) TFA, MeOH; (i) H_2, 5% Pd-C, formaldehyde, MeOH; (j) TFA (2 equiv) H_2O, CH_3CN.

Table 1. *In vitro* antimicrobial activity[a].

Organism (No. of strains)	Geometric mean MIC (μg/ml)		
	5	Niddamycin	Josamycin
Staphylococcus aureus (16)	0.24	0.40	0.84
Streptococci (9)[b]	0.03	0.08	0.17
Enterococcus faecalis (9)	0.67	8.60	10.89
Haemophilus influenzae (15)	1.00	5.20	8.40
Campylobacter jejuni (5)	0.05	0.28	0.28
Legionella pneumophila (11)	6.23	0.32	0.69
Neisseria gonorrhoeae (9)	0.14	0.30	0.58

[a] MICs determined by 2-fold agar dilution methodology recommended by NCCLS (Standard M7-A).
[b] Includes seven *Streptococcus pyogenes* and two *S. pneumoniae*.

Table 2. Mouse protection test.

Infecting organism (100 LD_{50}s)	ED_{50} (mg/kg)	
	5	Josamycin
Streptococcus pneumoniae 6303		
oral	28.2	42.2
subcutaneous	5.5	1.9
S. pyogenes C203		
oral	12.8	24.4
subcutaneous	3.9	3.1
Staphylococcus aureus NCTC 10649		
oral	237.2[a]	227.0
subcutaneous	15.1[a]	35.0

[a] Infecting dose = 10 LD_{50}s.

coupling constants used in the leucomycin series[6] for stereochemical assignments at C-9 are unavailable and the high conformational flexibility of the tetrahydromacrolide made standard NOE studies ambiguous. Therefore stereospecific synthesis of **5** from an intermediate with known stereochemistry at C-9 was undertaken.

Stereoselective reduction of the protected niddamycin derivative (**7**) (Scheme 2) using $NaBH_4$-$CeCl_3$[7] at low temperature afforded exclusively the protected *epi*-leucomycin derivative (**8**). The stereochemistry of the newly installed 9-hydroxyl group was established by deprotection of **8** to give a compound that was identical to an authentic sample of *epi*-leucomycin A_1.[8] Hydrogenation of the diene system of **8** followed by activation of the 9-hydroxyl group with methanesulfonyl chloride and displacement with lithium azide produced the azide **9**. The 2′ and 3-hydroxyl groups were deprotected followed by reduction of the 9-azide and *N*-dimethylation. Finally, hydrolysis of the dimethylacetal led to **5**.

Comparison of **5** with josamycin and niddamycin

in vitro (Table 1) against multiple strains of a number of organisms revealed **5** to be 4 to 16 times more active than josamycin and 2 to 13 times more active than niddamycin against all the organisms tested with the exception of *Legionella pneumophila*, against which it was 10~20-fold less active than josamycin and niddamycin, respectively.

Compound **5** was evaluated for *in vivo* antimicrobial activity in experimental infections in mice and compared with josamycin. The results of these experiments (Table 2) show **5** to have efficacy equivalent to that of josamycin. This is in contrast to niddamycin where efficacy in the *in vivo* mouse models could not be demonstrated.

Therefore, **5** the 9*S* epimer of 9-deoxo-9-*N*,*N*-dimethylamino-10,11,12,13-tetrahydroniddamycin demonstrates improved *in vitro* activity against most organisms, relative to niddamycin and josamycin and *in vivo* activity equal to that of josamycin.

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