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A STEREOCONTROLLED TOTAL SYNTHESIS OF (±)-RENIERAMYCIN A

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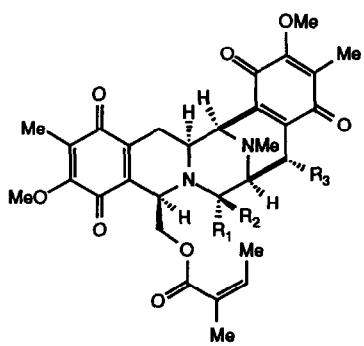
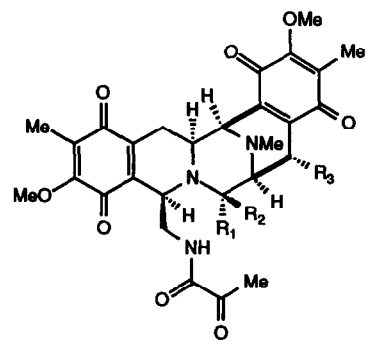
Abstract: The first total synthesis of (±)-renieramycin A (**1a**) is described. The stereochemistry of the angelate side chain was unequivocally determined by X-ray crystallographic analysis of the penultimate intermediate.

The renieramycins (**1**) were isolated in minute quantities from the bright blue marine sponge *Reniera* sp. by Faulkner and co-workers.[1] These antimicrobial metabolites belong to a growing family of isoquinolinequinone antibiotics, that includes the more notable saframycin A (**2a**) which shows potent antitumor activities.[2] Although limited supply of the renieramycins precludes extensive biological testing, structural similarities to the saframycins suggest the potential for antitumor activity. The stereochemistry of the angelate side chain of renieramycins was originally assigned as α based on difference NOE studies.[1a] However, striking resemblance of the high-field ^{1}H NMR spectrum of saframycin C (**2c**) to that of renieramycin A (**1a**) strongly suggests that both antibiotics share the same β-configuration at the side chains,[3] as revised recently by Faulkner.[1b] As a part of our ongoing synthetic endeavor in the area of saframycins,[4] we have been pursuing a total synthesis of renieramycin A (**1a**). Herein we report the first total synthesis of **1a**, that unambiguously proved the stereochemistry of the side chain.



Renieramycin

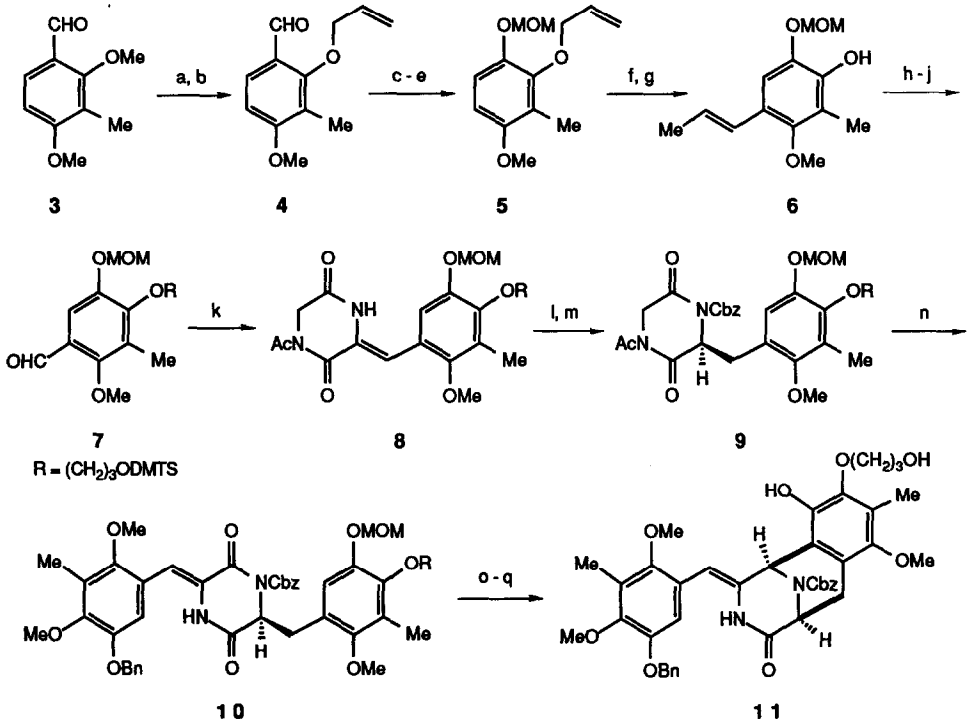


Saframycin

A: (**1a**) $R_1 = R_2 = H$ $R_3 = OH$
B: (**1b**) $R_1 = R_2 = H$ $R_3 = OEt$
C: (**1c**) $R_1, R_2 = O$ $R_3 = OH$
D: (**1d**) $R_1, R_2 = O$ $R_3 = OEt$
E: (**1e**) $R_1 = OH$ $R_2 = R_3 = H$
F: (**1f**) $R_1 = OH$ $R_2 = H$ $R_3 = OMe$

A: (**2a**) $R_1 = CN$ $R_2 = R_3 = H$
B: (**2b**) $R_1 = R_2 = R_3 = H$
C: (**2c**) $R_1 = R_2 = H$ $R_3 = OMe$
S: (**2s**) $R_1 = OH$ $R_2 = R_3 = H$

The present synthesis followed closely the pathway established for saframycin A (**2a**)[4a,b] except that the specially protected benzaldehyde **7** was employed to set up the critical benzylic oxidation. As shown in Scheme 1, **7** was prepared from the readily available aldehyde **3**[5] in 55% overall yield. Selective demethylation of **3** with BCl_3 followed by allylation gave **4**. Baeyer-Villiger oxidation of aldehyde **4** was effected by 30% H_2O_2 and a catalytic amount of SeO_2 to avoid epoxidation of the olefin. Methanolysis of the resultant formate and protection of the phenol as MOM ether furnished **5**. Claisen rearrangement of **5** at 210 °C, followed by base-catalyzed isomerization of the olefin, gave the conjugated olefin **6**. The phenol **6** was then protected as sturdy 3-hydroxypropyl ether. Further protection of the primary alcohol as dimethythexylsilyl (DMTS) ether and subsequent ozonolysis of the olefin yielded the aldehyde **7**. Condensation of **7** with N,N'-diacetylpiperazinedione was achieved by treatment with *t*-BuOK/*t*-BuOH in THF at 0 °C, giving exclusively the *Z*-isomer **8** (86%).[6] After catalytic

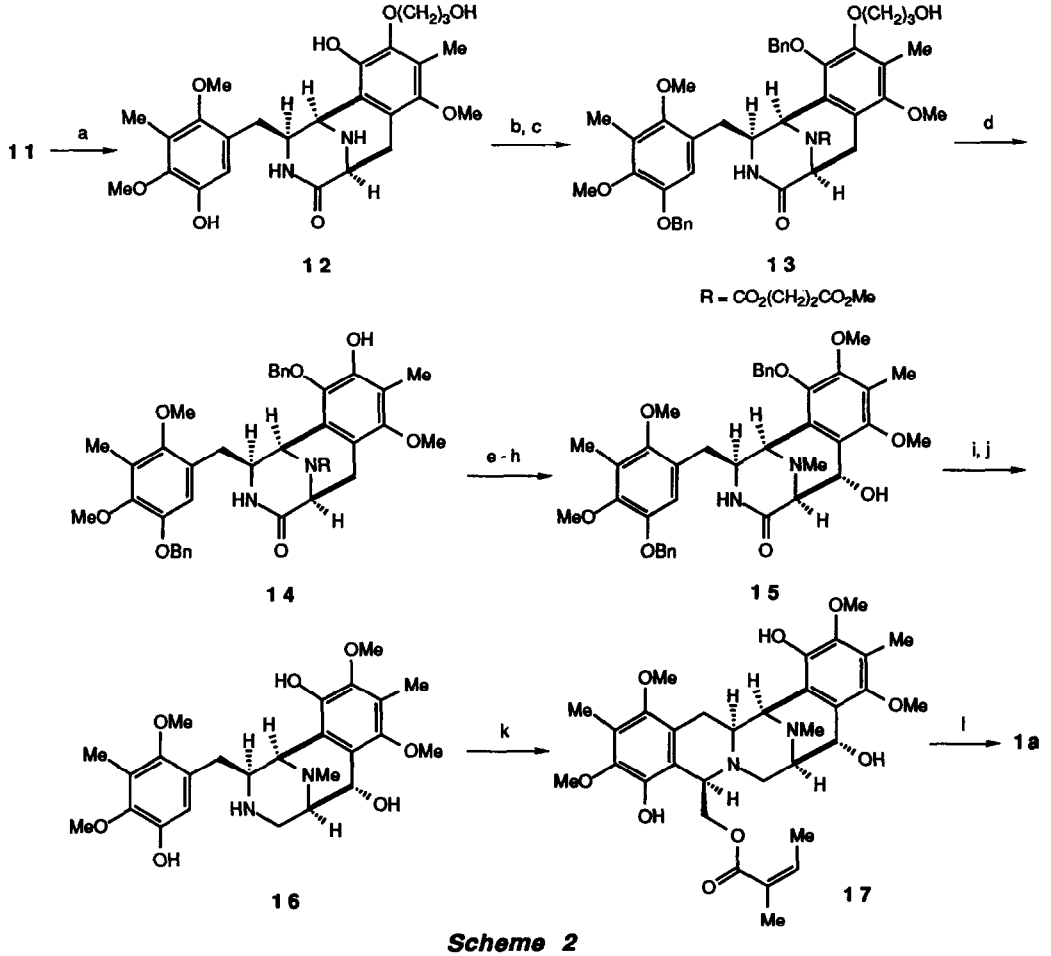


Scheme 1

(a) BCl_3, CH_2Cl_2, 0 °C. (b) allyl bromide, K_2CO_3, DMF, 80 °C. (c) 30% H_2O_2, cat. SeO_2, *t*-BuOH, 40 °C. (d) Et_3N, MeOH, 23 °C. (e) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 80 °C. (f) $PhNEt_2$, 210 °C. (g) KOH, DMSO, 105 °C. (h) $Br(CH_2)_3OH$, NaI, K_2CO_3, DMF, 70 °C. (i) DMTSCl, *i*-Pr_2NEt, DMF, 70 °C. (j) O_3, MeOH, -78 °C; Me_2S. (k) N,N'-diacetylpiperazinedione, *t*-BuOK, THF, 0 °C. (l) H_2, Pd/C, EtOAc. (m) CbzCl, Et_3N, DMAP, CH_2Cl_2, -30°C. (n) 5-benzyloxy-2,4-dimethoxy-3-methylbenzaldehyde, *t*-BuOK, THF, -78 °C; DBU, 0 °C. (o) $NaBH_4$, AcOH, EtOH, 0 °C. (p) HCO_2H, 55 °C. (q) NaOH, MeOH, 23 °C.

hydrogenation of olefin **8**, the piperazinedione ring was activated again by introduction of a carbobenzoxy group. Condensation of **9** with 5-benzyloxy-2,4-dimethoxy-3-methylbenzaldehyde[4b] furnished **10** in 68% yield from **8** (*t*-BuOK, THF, -78 °C, then DBU, 0 °C). Selective reduction of the ring carbonyl with $NaBH_4$, acyliminium ion-mediated cyclization in formic acid, and hydrolysis of the resulting formate gave the desired cyclized product **11** in 68% yield.

Catalytic hydrogenation of olefin **11** over Raney nickel took place from the less hindered exo side to give the desired endo-compound **12** as the sole product (70%) (Scheme 2). Since benzylic oxidation of **14** with DDQ gave an intractable mixture when R was methyl, we



Scheme 2

(a) H_2 (1200 psi), Ra-Ni (W2), EtOH, 80 °C. (b) $ClCO_2(CH_2)_2CO_2Me$, $PhNMe_2$, CH_2Cl_2, 23 °C. (c) BnBr, K_2CO_3, DMF, 23 °C. (d) Swern oxid. (e) DDQ, THF/H_2O (8:1), 23 °C. (f) MeI, K_2CO_3, DMF, 23 °C. (g) DBU, MeOH, 23 °C. (h) HCHO, $NaBH_3CN$, TFA, MeOH, 23 °C. (i) AlH_3, THF, 23 °C. (j) H_2, Pd/C, EtOH, 23 °C. (k) glycolaldehyde angelate, CH_3CN, 50 °C. (l) DDQ, acetone/H_2O (20:1), 23 °C.

protected the bridgehead amine of **12** as the base-sensitive urethane ($ClCO_2(CH_2)_2CO_2Me$,[7] $PhNMe_2$). Subsequent benzylation of the phenols gave **13** (58% from **12**). Swern oxidation[8] of the primary alcohol **13** provided directly the desired phenol **14** in 78% yield, setting the stage for the critical oxidation. Upon treatment with DDQ in aqueous THF, **14** gave exclusively the desired alcohol.[9] Methylation of the phenol, deprotection of the urethane with DBU through retro-Michael reaction, and reductive methylation of the resultant amine afforded **15** in 45% overall yield from **14**. Reduction of lactam **15** with AlH_3 followed by hydrogenolysis of the benzyl ethers gave amino phenol **16** (64%). Pictet-Spengler reaction of **16** with glycolaldehyde angelate[10] in CH_3CN at 50 °C furnished a 5:1 mixture of **17** and its minor α-epimer in 66% yield. The structure of **17** was determined by a single crystal X-ray analysis. Finally, **17** was oxidized with DDQ to give (±)-renieramycin A (**1a**) in 48% yield. The ^1H NMR spectrum of the synthetic renieramycin A was identical with that of the authentic sample.[11]

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11. We are indebted to Prof. D. J. Faulkner, Scripps Institution of Oceanography, for kindly providing us a copy of ^1H NMR spectrum of natural renieramycin A.

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