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SYNTHESIS AND ACTIVITIES OF 9-PYRROLO-9-DEOXO-ERYTHROMYCIN A ANALOGS

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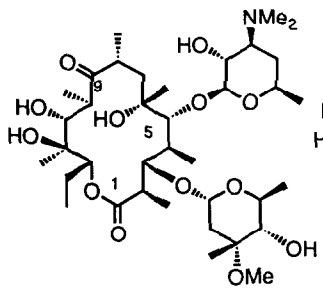
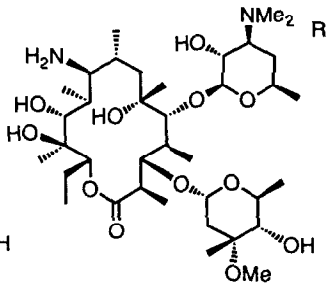
Abstract: *Preparation of novel 9-pyrrolo-9-deoxoerythromycin A analogs from 9-(S) and (R) erythromycylamines by the Clauson-Kass and Wasserman reactions is described. The biological activities of these novel analogs are also reported.*

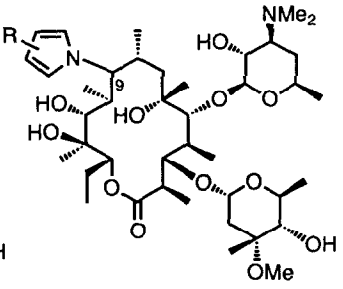
The antibiotic erythromycin A (**1**) has been a subject of intense scrutiny over many years, both by the chemical and pharmaceutical communities. Despite some shortcomings such as acid instability[1] and gastric intolerance[2] in patients, it is still a widely prescribed drug to combat bacterial infections. The semisynthetic analog 9-(S)-erythromycylamine (**2**)[3] has been known for some time and its antibacterial activity is comparable to that of erythromycin A.[4] However, 9-(S)-erythromycylamine is poorly absorbed. Modifications that enhance the oral bioavailibility of erythromycylamine have been amply reported in the literature[5] and one such analog[6] is in clinical development.



1, Erythromycin A



2, 9 -(S)-Erythromycylamine

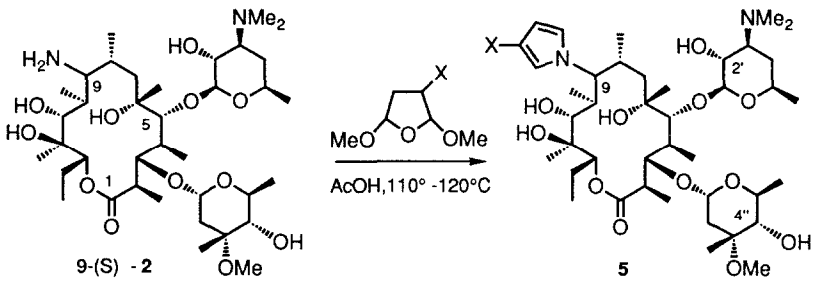


3

We report herein our initial disclosures on the preparation of a novel class of erythromycylamine derived molecules that bear substituted pyrroles at the C-9 position of the macrolide core as shown in **3**. The presence of such a ring system not only brings about structural changes, but also alters the basicity of the amine functionality at the C-9 position. We anticipated that this work might lead to erythromycin analogs with a different activity profile.

In our first approach, application of the Clauson-Kass reaction[7] to 9-(S)-erythromycylamine **2** and 2,5-dimethoxytetrahydrofuran (X=H) in acetic acid at 110°-120°C gave **5a** as illustrated by Scheme I. The structure of pyrrole **5a**[8] was determined by high field ^{1}H-NMR data wherein signals corresponding to the protons of the pyrrole ring were observed at δ 6.14 (C-3 & C-4) and δ 6.70 (C-2 & C-5). Similar reaction of **2** and 2,5-dimethoxy tetrahydrofuran 3-carboxaldehyde (X=CHO) smoothly afforded **5c**.[9] This reaction was also extended to 9-(R)-erythromycylamine **4** giving products **5b** and **5d**.[9]

Scheme I



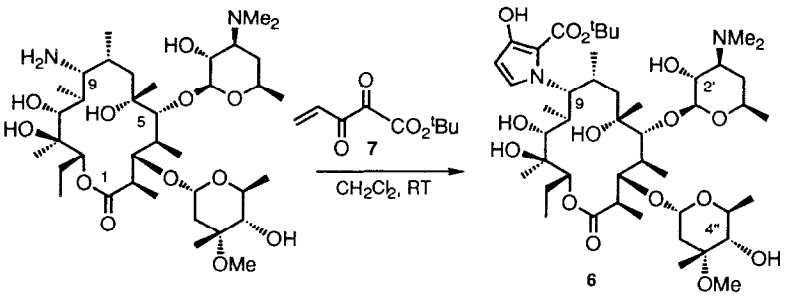
X	Configuration at C-9	Yield[a]
H	S	**5a**, 54%
	R	**5b**, 57%
CHO	S	**5c**, 41%
	R	**5d**, 41%

[a] Isolated yields.

In an effort to improve the yield of pyrroles, we also briefly explored the Chan variation[10] of the Clauson-Kass reaction, which involved the reaction of **2** with 1,4-dichloro-1,4-dimethoxybutane (a more reactive version of the reagent 2,5-dimethoxytetrahydrofuran). Unfortunately, no pyrrole was isolated and extensive decomposition of the starting material ensued.

We next turned to the Wasserman protocol[11] for the synthesis of pyrroles as shown in Scheme II. Thus, reaction of amines **2** and **4** with vinyl tricarbonyl ester **7** gave substituted pyrroles **6a** and **6b**[8]. Attempts to extend this reaction by using other terminally substituted tricarbonyl reagents[12] failed, possibly because of steric hindrance.

Scheme II



Configuration at C - 9	Yield[a]
S	**6a** , 43%
R	**6b** , 25%

[a] isolated yields

Antibacterial activity *in vitro* was determined by broth microdilution assay against several

bacterial strains as shown in Table I. As can be seen, the pyrroles **5a-5d**, **6a** and **6b** showed a significant loss of activity when compared with erythromycylamines **2** and **4** respectively. By contrast, workers from Abbott laboratories[13] noted superior *in vitro* potency with more basic 9-pyrrolidino-9-deoxoerythromycin A derived from both (9)-R and (9)-S erythromycylamines. These results illustrate the important relationship between the basicity of the nitrogen at C-9 and activity.

Table I: Minimum Inhibitory Concentration (MIC, μg/ml)

Compound[a]	*E.faec*[b]	*S.aur*	*S.epi*	*S.pne*	*S.pyog*	*H.inf*
2 (S)	1	0.5	0.5	0.13	≤0.06	128
4 (R)	64	4	2	0.5	1	128
5a (S)	64	64	32	4	4	128
5b (R)	32	128	64	2	---	>128
5c (S)	64	32	32	64	32	64
5d (R)	16	32	8	1	---	128
6a (S)	16	8	4	0.5	0.25	32
6b (R)	64	64	64	16	8	>128

[a]Configuration at C-9 is indicated in parentheses. [b]*E.fae* = *Enterococcus faecalis* (MB 5407), *S.aur* = *Staphylococcus aureus* (MB 2865), *S.epi* = *Staphylococcus epidermidis* (MB 5414), *S.pne* = *Streptococcus pneumoniae* (CL 2883), *S.pyog* = *Streptococcus pyogenes* (MB 2874), *H.inf* = *Haemophilus influenzae* (MB 5363).

In conclusion, the synthesis of novel 9-pyrrolo-9-deoxoerythromycins was achieved by two different approaches. This approach also opens up the possibility of constructing other heteroaromatics at the C-9 position of the macrolide core of erythromycin.

Acknowledgements : We are grateful to Dr. Ron Ratcliffe for helpful discussions. We thank Mr Robert Wilkening for supplying us with a sample of 9-(R)-erthromycylamine, Drs. Amy Graham, Ken Bartizal and Ms. Charmaine Herbert for performing biological assays and Ms. Amy Bernick for mass spectral determination.

References and Notes

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8. 9-(S)-Pyrrolo-9-deoxoerythromycin A (**5a**)

To a solution of 100 mg (0.136 mmol) of 9-(S)-erythromycylamine **2** in 2 ml acetic acid was added 22 mg (0.163 mmol) of 2,5-dimethoxytetrahydrofuran. The resulting mixture was heated at 110°-120°C for 10 minutes. The acetic acid was removed under vacuum and the residue was dissolved in water and 25 ml methylene chloride. The pH of the solution was adjusted to the range of 9-10 with 1N sodium hydroxide solution. The methylene chloride layer was washed with water, brine, dried (anhydrous sodium sulfate) and evaporated. Silica chromatography with CH_2Cl_2-methanol-NH_4OH, 95:5:1 afforded 58 mg (54%) of **5a**. ^{1}H-NMR ($CDCl_3$, 400 MHz, 60°C, partial data) ; δ 6.70 (2H, dd, J= 2.0 & 2.1 Hz, ArH-2, 5), 6.14 (2H, dd, J=1.9 & 2.0 Hz, ArH-3, 4), 5.14 (1H, dd, J= 4.0 & 1.6 Hz, H-1"), 4.92 (1H, dd, J =9.7 & 2.8 Hz, H-13), 4.75 (1H, d, J=7.2 Hz, H-1'), 4.02 (1H, dd, J=3.0 & 2.8 Hz H-3), 3.97 (1H, d, J =4.2 Hz, H-5), 3.93 (1H, m, H-5"), 3.60 (1H, m, H-5'), 3.54 (3,54, brs, H-11), 3.36 (3H, s, OCH_3), 3.27 (1H, dd, J=10.2 & 7.2 Hz, H-2"), 2.29 (6H, s, $N(CH_3)_2$), 0.86 (3H, t, $-CH_2-\underline{CH_3}$). ^{13}C-NMR ($CDCl_3$, 100 MHz, 60°C) δ 177.12, 120.60, 108.86, 101.31, 95.44, 79.38, 78.42, 77,92, 77.33, 75.20, 74.45, 73.43, 72.70, 70.85, 69.41, 67.76, 66.72, 65.10, 49.21, 44.41, 44.21, 40.37, 39,96, 34.64, 33.10, 32.21, 28.85, 24.97, 21,70, 21.49, 20.99, 24.50, 18.84, 18.49, 16.68, 13.41, 13.10, 11.10, 8.94 ppm. FABMS : *m/z* 785 (M^++1).

9-(R)-(2-t-Butoxycarbonyl-3-hydroxy)pyrrolo-9-deoxoerythromycin A (**6b**)

To a solution of 50 mg (0.068 mmol) of 9-(R)-erythromycylamine **4** in 1 ml methylene chloride was added 17 mg of (0.084 mmol) of the tricarbonyl compound. The resulting mixture was stirred at room temperature for one hour, at which point 200 mg of silica was added and stirred overnight. The residue obtained after filtration was purified by silica chromatography. Elution with CH_2Cl_2-methanol-NH_4OH, 97:3:1 afforded 15 mg (25%) of **6b**. ^{1}H-NMR ($CDCl_3$, 400 MHz, 60°C, partial data) ; δ 6.59 (1H, d, J= 3.1 Hz, Ar-2), 5.76 (1H, d, J= 3.1Hz, Ar-3), 4.98 (1H, d, J= 3.9 Hz, H-1"), 4.71 (1H, dd, J = 10.3 & 2.3 Hz, H-13), 4.39 (1H, d, J=7.0 Hz, H-1'), 4.32 (1H, br d, H-3), 4.02 (1H, m, H-5"),3.62 (1H, d, J= 7.7Hz, H-5), 3.29 (3H, s, OCH_3), 3.21 (1H, dd, J=10.2 & 7.1 Hz, H-2"), 2.29 (6H, s, $N(CH_3)_2$), 1.57 (9H, s, t-Bu), 0.89 (3H, t, J= 7.4 Hz, $-CH_2-\underline{CH_3}$). ^{13}C-NMR ($CDCl_3$, 100 MHz, 60°C) δ 177.35, 163.46, 155.09 124.88,124.85,109.15,103.77,97.42,97.45,96.51,83.92,83.81,81.70,81.62,78.34,78.29,77 92, 75.46, 74.92, 72.56, 70.91, 69.44, 69.14, 66.15, 65.81, 63.76, 49.29, 45.39, 40.75, 40.23, 36.74, 35.42, 34.24, 30.26, 28.89, 28.67, 21.39, 21.28, 21.13, 19.16, 18.51, 15.80, 15.51, 10.79, 9.34 ppm. FABMS . *m/z* 901 (M^+).

9. All compounds have been fully characterized by proton NMR, carbon NMR, combustion analysis and mass spectrometry.

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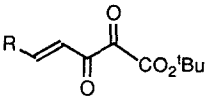
12. No pyrrole was isolated when the reaction was carried out between erythromycylamine and the tricarbonyl reagents shown below (prepared according to the reference 11).



R = Ph, Me

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