Aglycon Modifications of Erythromycin A and Erythromycin B: Regiospecific Nucleophilic Ring Opening of Cyclic Thionocarbonates

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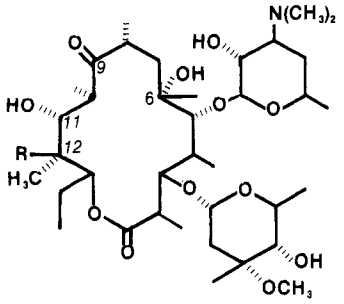
Synthetic modifications of the aglycon fragments of erythromycin A (**1**)[1] and erythromycin B (**2**)[2] have been

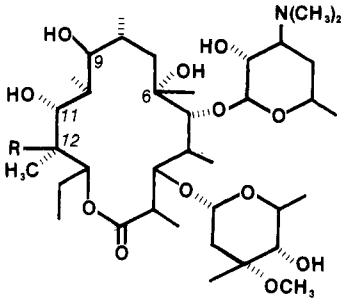


1, R = OH
2, R = H

described; however, there are no reports addressing the introduction of carbon appendages at the aglycon C-9 position. We found this intriguing, since nucleophiles having low steric requirements (such as hydride,[3] hydrazine,[4] and hydroxylamine[5]) have been incorporated into the C-9 position in both erythromycin A and erythromycin B. Thus, we sought to develop a generally useful, regiospecific, synthetic route for the introduction of carbon nucleophiles that would permit ready access to a variety of C-9 aglycon modified intermediates. This paper describes our approach.

At the outset we considered two obvious alternatives for the introduction of carbon nucleophiles at the C-9 position, namely, either direct addition of nucleophiles to the existing C-9 carbonyl center or reduction of the C-9 ketone to afford a C-9 carbinol, which would be subsequently activated toward nucleophilic displacement. Therefore, we exposed **1** and **2** to stabilized phosphonate ylides. For example, either the Emmons–Wadsworth modification of the Wittig procedure[6] or the more recent Corey modification[7] resulted in no reaction. The Peterson reaction[8] also failed, as well as the Tebbe methylenation procedure,[9] which resulted in neutral sugar cleavage or 6,9-cyclic enol ether formation. Furthermore, exposure of **1** or **2** to Grignard reagents afforded no identifiable products, and Me_3SiCN/ZnI_2[10] exposure resulted in neutral sugar cleavage or 6,9-cyclic enol ether formation.

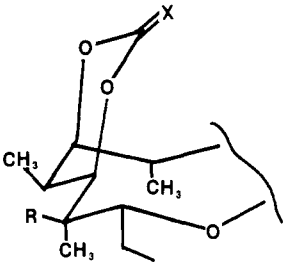
Since the more direct of the two alternatives failed, presumably as a consequence of steric factors, we attempted to activate the C-9-β-carbinols **3**[2] and **4**[2] toward nucleophilic displacement. Unfortunately, we were not



3, R = OH
4, R = H

able to *selectively* introduce activating groups such as tosylate, mesylate, or triflate into either the erythromycin A nucleus or the erythromycin B nucleus; therefore, we abandoned this approach rather than engage in a tedious synthesis of a suitably blocked intermediate. Moreover, even if we were able to prepare an activated derivative, we considered a successful displacement unlikely, since the inherent problem of steric encumbrance was still unresolved.

Since we presumed that the failure of the attempted nucleophilic additions stemmed from the severe steric environment of the C-9 position, we envisioned a solution to this problem through a conformational manipulation of the substrate. Specifically, our synthetic strategy was based on an a priori consideration of molecular models of compounds **3** and **4**, which showed that a 9,10-cyclic derivative would force the C-9 position into a *somewhat* less hindered environment. We based our considerations on the presumed conformation represented by **5**. Although



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such a strained cyclic structure might impart considerable driving force for the reaction via release of ring strain upon introduction of the nucleophile, we viewed the charge stabilization of the atom X in structure **5** as more significant.[11] Furthermore, this approach ensures the stereochemical integrity of the product, since the reaction should proceed by inversion. The intermediates that adequately fulfill the presumed requirements would be the cyclic thionocarbonates **6** and **7**.

We anticipated that a successful nucleophilic displacement on either **6** or **7** would of necessity be regiospecific for the C-9 position, since inspection of molecular models revealed that the required trajectory for an incoming nucleophile would be far more encumbered by the steric environment about the C-11 position. Thus, the synthetic problem reduced to the selective preparation of a six-membered cyclic thionocarbonate.

Preparation of the desired thionocarbonate from carbinol **4** was straightforward, since only one diol exists within the molecule. Thus, upon exposure of **4** to thio-

(1) Tadanier, J.; Martin, J.; Egan, R.; Goldstein, A.; Stanaszek, R.; Hirner, E.; Fisher, F., *J. Org. Chem.* **1974**, *39*, 2495. Tadanier, J.; Martin, J.; Goldstein, A.; Hirner, E. *Ibid.* **1978**, *43*, 2351. Hauske, J. R., Kostek, G. *Ibid.* **1982**, *47*, 1595.
(2) Perun, T. *J. Org. Chem.* **1967**, *32*, 2324.
(3) Perun, T.; Egan, R.; Martin, J. *Tetrahedron Lett.* **1969**, 4501.
(4) Massey, E.; Kitchell, B.; Martin, L.; Gerzon, K.; Murphy, H. *Tetrahedron Let.* **1970**, 157.
(5) LeMahieu, R.; Carson, M.; Kierstead, R.; Fern, L.; Grunberg, E. *J. Med. Chem.* **1974**, *17*, 953.
(6) Lombardo, L.; Taylor, R. *Synthesis* **1978**, 131.
(7) Corey, E. J.; Kang, J. *J. Am. Chem. Soc.* **1982**, *104*, 4725.
(8) Carey, F. A.; Frank, W. C. *J. Org. Chem.* **1982**, *47*, 3548.
(9) Tebbe, F.; Parshall, G.; Reddy, G. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
(10) Evans, D.; Truesdale, L.; Carroll, G. *J. Chem. Soc., Chem. Commun.* **1973**, 55.

(11) For example, exposure of the corresponding 9,11-cyclic carbonate to nucleophiles under a variety of conditions resulted in *no reaction*.

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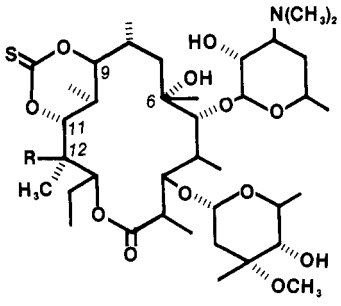
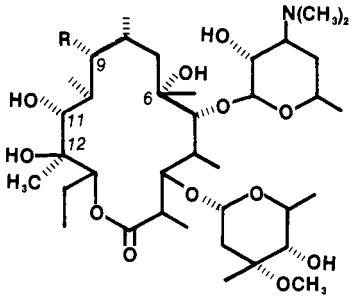


6, R = OH
7, R = H

carbonyldiimidazole, a smooth conversion to **7** ensued. Carbinol **3**, on the other hand, presents the potential complication of a 1,2-diol as well as a 1,3-diol. We were gratified, therefore, to find that treatment of **3** with thiocarbonyldiimidazole produced only *one* thionocarbonate and that it proved to be the desired intermediate **6**. The evidence consistent with this assignment derives from investigation of the ^{13}C NMR spectrum in which an H_2O/D_2O deuterium isotope shift experiment[12] supported the existence of *two* tertiary carbinolic centers as opposed to *one* tertiary carbinolic center, as would be the case for the undesired five-membered material. Furthermore, inspection of the ^1H NMR spectrum revealed a considerable chemical shift difference for the diastereotopic C-7 methylene protons, which is consistent with the conformation illustrated by **5**.

Although we felt confident that the ring opening would be regiospecific for the C-9 position, we initially prepared a well-defined C-9 modified material that would allow an unequivocal regiochemical assignment. Thus, exposure of **6** to NaN_3 in DMF solvent smoothly produced a new material, which we tentatively assigned as the corresponding α-azide (**8**). Upon treatment of **8** with Raney



8, R = N_3
9, R = NH_2
10, R = CN

Ni in ethanol under a hydrogen atmosphere a new, basic material was produced whose spectra corresponded in all respects to that of the known[13] 9α-amino erythromycin A (**9**).

Since we proved the regiospecificity as well as the stereospecificity of the procedure, all that remained was to attempt to introduce a carbon nucleophile. We chose to introduce a nitrile, since, in principle, it would be susceptible to a variety of synthetic transformations. When thionocarbonate **6** was treated with NaCN in DMF solvent, a new material was produced. Spectroscopic data substantiated the incorporation of a nitrile moiety, and by analogy to the structural correlations developed for compounds **6**, **8** and **9**, the product was assigned to be the C-9-α-nitrile **10**. This constitutes the first incorporation of a carbon moiety at the C-9 position of erythromycin A. Although we have prepared the corresponding thionocarbonate in the erythromycin B series (intermediate **7**), we have not yet attempted nucleophilic displacements; however, we anticipate little difficulty in extending the methodology to the erythromycin B series and are now pursuing the preparation of the C-9-modified materials.

In summary, therefore, we have developed a synthetic sequence that permits a regiospecific elaboration of erythromycin A derivatives at the C-9 position via nucleophilic displacement on cyclic thionocarbonates. Furthermore, this methodology should be broadly applicable to the erythromycin B series as well.

Experimental Section

General Methods. NMR spectra were obtained on a Varian XL-100 or a Bruker 250-MHz spectrometer.

Preparation of 9,11-Cyclic-Thionocarbonate Erythromycin A (6). To an acetone solution (15 mL) of 9,9-dihydroerythromycin A[2] (**3**; 30 g, 41 mmol) and anhydrous K_2CO_3 (15.0 g) was added in one portion thiocarbonyldiimidazole (8.6 g, 48.2 mmol), and the resulting solution was allowed to stir at room temperature for 2.5 h. After this period, TLC [silica/$CHCl_3$/MeOH/NH_3 (9:1:0.1)] indicated no remaining starting **3** and one, less polar UV positive material. At this point the acetone was removed in vacuo and the resulting slurry was poured into a stirring mixture of methylene chloride/water (200 mL:100 mL) and the pH stabilized at 11. The organic layer was separated, washed with water (3 × 100 mL) and aqueous saturated sodium chloride (1 × 100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The colorless solid was crystallized from hot isopropyl ether (175 mL), affording colorless, crystalline **6** (27 g, mp > 240 °C): ^1H NMR ($CDCl_3$) δ 0.95 (t), 1.15 (d), 1.20–2.00 (m), 2.30 (s), 2.35–2.55 (m), 2.70 (m), 3.05 (t), 3.25 (dd), 3.32 (s), 3.45 (br s), 3.60 (m), 3.70 (d), 3.95 (dd), 4.05 (br s), 4.35 (d), 4.60 (d), 4.90 (d), 5.05 (dd); ^{13}C NMR ($CDCl_3$) δ 190.2 (off-resonance, s), 176.0 (s), 102.3 (d), 95.4 (d), 93.4 (d), 82.5 (d), 79.5 (d), 78.3, 77.8, 77.4, 76.5, 74.1, 73.7, 72.9, 70.8 (d), 69.5 (d), 68.4 (d), 66.3 (d), 65.3 (d), 49.2 (q), 44.1, 42.9, 40.4 (q), 36.6, 34.8, 33.5, 28.6, 27.8, 25.6, 22.8, 21.8, 18.2, 18.1, 16.2, 14.5, 13.5, 11.0, 9.2.

Anal. Calcd for $C_{38}H_{67}O_{13}NS$: C, 58.67; H, 8.68; N, 1.80; S, 4.12. Found: C, 58.37; H, 8.57; N, 1.80; S, 4.01.

Preparation of 9,11-Cyclic-Thionocarbonate Erythromycin B (7). To an acetone solution (15 mL) of 9,9-dihydrodroerythromycin B[2] (**4**; 1.5 g, 2.08 mmol) and K_2CO_3 (750 mg) was added in one portion thiocarbonyldiimidazole (516 mg, 2.6 mmol), and the resulting solution was allowed to stir at room temperature for 3 h. After this period, TLC [silica/$CHCl_3$/MeOH/NH_3 (6:1:0.1)] indicated no remaining starting material and two new less polar, UV-positive materials [they proved to be the desired thionocarbonate **7** and the corresponding 4″-imidazoylthionocarbamate (ca. 9:1 ratio)]. The reaction mixture was poured into a stirring mixture of methylene chloride/water (200 mL:150 mL) and the pH was stabilized at 10.8. The organic layer was separated, washed with water (3 × 100 mL) and aqueous saturated sodium chloride (1 × 100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo affording a pale yellow solid (1.5 g). The crude material was crystallized from diethyl ether (ca. 10 mL), affording colorless, crystalline **7** (840 mg, mp 133–136 °C): ^1H NMR ($CDCl_3$) δ 0.92 (t), 1.10 (dd), 1.18–1.40 (m), 1.50–2.00 (m), 2.20 (d), 2.30 (s), 2.35 (br s), 2.40–2.80 (m), 3.05 (t), 3.25 (dd), 3.34 (s), 3.40 (br s), 3.60 (m), 3.65 (d), 3.95 (dd), 4.00 (br s), 4.05 (d), 4.35 (dd), 4.60 (d), 4.90 (br d), 5.20 (br t); ^{13}C NMR ($CDCl_3$) δ 189.9, 175.5, 101.8, 95.0, 91.8, 83.2, 78.9, 78.4, 77.3, 73.4, 73.3, 72.5, 70.4, 68.9, 65.8, 65.0, 48.9, 43.7, 42.2, 40.0, 36.2, 36.1, 34.4, 33.1, 28.5, 27.2, 24.8, 24.3, 21.3, 20.9, 18.0, 13.2, 12.2, 9.6, 9.0, 7.4.

Anal. Calcd for $C_{38}H_{67}O_{12}NS \cdot H_2O$: C, 58.51; H, 8.91; N, 1.80. Found: C, 58.65; H, 8.76; N, 1.86.

Preparation of 9α-Azidoerythromycin A (8). To a DMF solution (10 mL) of **6** (1.5 g, 1.92 mmol) was added in one portion sodium azide (750 mg, 9.5 mmol), and the resulting solution was allowed to stir at 90 °C for 3 h. After this period, TLC [sili-

(12) For a representative application of the deuterium isotope shift effect on the carbon spectrum of a macrocycle, see: Celmer, W.; Chmurny, G.; Moppett, C.; Ware, R.; Watts, P.; Whipple, E. *J. Am. Chem. Soc.* **1980**, *102*, 4203.

(13) Massey, E.; Kitchell, B. U.S. Patent 3652537, 1972.

ca/$CHCl_3$/diethylamine (9:1) and silica/$CHCl_3$/MeOH/NH_3 (9:1:0.1)] indicated no remaining starting material and one major, non-UV positive material. The reaction mixture was allowed to cool to room temperature and poured into a stirring mixture of methylene chloride/water (200 mL:150 mL). The organic layer was separated, washed with water (3 × 100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo, affording a pale yellow solid (1.4 g). The solid was chromatographed [silica/$CHCl_3$/MeOH/NH_3 (98:2:0.03)], affording a colorless solid (770 mg), which was crystallized from $CHCl_3$/hexane to afford colorless, crystalling **8** (715 mg, mp 125–129 °C): ^1H NMR ($CDCl_3$) δ 0.9 (t), 1.10–1.40 (m), 1.50–2.00 (m), 2.30 (s), 2.40 (d), 2.50 (m), 2.55 (br s), 2.85 (dq), 3.05 (t), 3.25 (dd), 3.35 (s), 3.40 (br s), 3.45–3.70 (m), 4.05 (dd), 4.15 (br s), 4.55 (br s), 4.70 (dd), 5.00 (br s); ^{13}C NMR ($CDCl_3$) δ 176.5 (off-resonance, s), 101.7 (d), 95.7 (d), 81.7, 79.5, 79.4, 77.5, 77.3, 74.9 (s), 74.5 (s), 74.4, 72.2 (s), 70.8 (d), 68.7 (d), 68.1 (d), 65.8 (d), 64.3 (d), 49.0 (q), 44.6, 40.0 (q), 35.8, 34.6, 33.9, 31.3, 29.2, 21.4, 21.2, 20.9, 19.8, 17.9, 15.8, 14.2, 11.6, 10.8, 8.9; IR ($CHCl_3$) 2110 (N_3) cm^{-1}.

Anal. Calcd for $C_{37}H_{68}O_{12}N_4 \cdot H_2O$: C, 57.04; H, 9.06; N, 7.19. Found: C, 57.28; H, 8.93; N, 7.05.

Preparation of 9-α-Cyanoerythromycin A (10). To a DMF solution (50 mL) of **6** (5.0 g, 6.42 mmol) was added in one portion potassium cyanide (5.0 g, 76.8 mmol) and the resulting solution was allowed to stir at 90 °C for 15 h. After this period, TLC [silica/$CHCl_3$/MeOH/NH_3 (9:1:0.1)] indicated starting material and one major non-UV-positive material (ca. 1:9 ratio). The reaction was allowed to cool to room temperature and poured into a stirring mixture of methylene chloride/water (400 mL:200 mL). The organic layer was separated, washed with water (3 × 200 mL) and aqueous saturated sodium chloride (2 × 100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo, affording a tan solid (3.9 g). The solid was chromatographed [silica (impregrated with formamide)/$CHCl_3$], affording a colorless solid (3.0 g), which was crystallized from ethanol/water to afford colorless, crystalline **10** (2.85 g, mp 142–147 °C): ^1H NMR ($CDCl_3$) δ 0.90 (t), 1.10–2.00 (m), 2.30 (s), 2.40–2.60 (m), 2.65 (br s), 2.85–2.95 (m), 3.05 (t), 3.30 (s), 3.60 (m), 3.70 (d), 4.00 (dd), 4.15 (br d), 4.45 (d), 4.65 (dd), 4.95 (br d); ^{13}C NMR (MeOH-d_4) δ 177.4 (off-resonance, s), 122.6 (s), 103.3 (d), 97.6 (d), 79.0 (d), 78.7, 78.5, 78.4, 78.0, 75.7, 75.1, 73.5, 72.1, 69.3 (d), 69.1 (d), 66.6 (d), 64.8 (d), 49.6 (q), 47.9, 45.9, 40.5 (q), 36.0, 35.8, 33.6, 31.0, 28.7, 22.2, 21.6, 21.5, 21.0, 18.8, 16.8, 13.9, 11.1, 9.9; IR ($CHCl_3$) 2225 (CN) cm^{-1}.

Anal. Calcd for $C_{38}H_{68}O_{12}N_2 \cdot H_2O$: C, 59.81; H, 9.25; N, 3.67. Found: C, 59.57; H, 9.14; N, 3.75.

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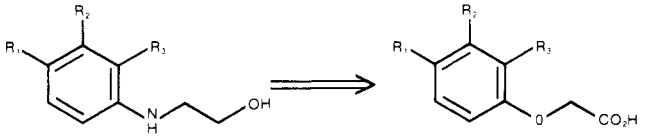
Communications

Alkoxide-Accelerated Smiles Rearrangements. Synthesis of *N*-(2-Hydroxyethyl)anilines from *N*-(2-Hydroxyethyl)(aryloxy)acetamides

Summary: The first example of an alkoxide-accelerated Smiles rearrangement is reported. The rearrangement of *N*-(2-hydroxyethyl)(aryloxy)acetamides in dimethylformamide or tetrahydrofuran–18-crown-6 and potassium hydride produces useful yields of substituted *N*-(2-hydroxyethyl)anilines.

Sir: In connection with a program directed toward the preparation of new therapeutic agents, we required a synthesis of substituted *N*-(2-hydroxyethyl)anilines from the corresponding (aryloxy)acetic acids. It occurred to



us that a potential entry into this series of compounds would be the Smiles rearrangement.[1] Turner and coworkers have described a Smiles rearrangement of 2-(aryloxy)-2-methylpropanamides.[2] They found that the rearrangement gave good yields of *N*-aryl-2-hydroxy-2-methylpropanamides when conducted in sodium hydride and dimethylformamide. Electron-withdrawing substituents on the benzene ring allowed the rearrangement to proceed at room temperature. Electron-donating groups on the ring slowed the rate of rearrangement.[3] In this paper, we report the first example of an alkoxide accelerated Smiles rearrangement. When *N*-(2-hydroxyethyl)(aryloxy)acetamides undergo a Smiles rearrangement, the rate of the reaction is accelerated by a neighboring alkoxide anion.

A series of model compounds were prepared to test the feasibility of the Smiles rearrangement. The primary amide **2** was prepared by the reaction of gaseous ammonia and the ethyl ester of the known acid **1**[4] in ethanol. The secondary amides **3** and **5** were synthesized by the condensation of ethanolamine and *n*-butylamine with the acyl imidazole derived from **1** in 98% and 87% yield, respectively. Finally, amide **4** was obtained from **3** by silylation with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane at room temperature (Scheme I). When a solution of **2** in dimethylformamide was added to suspension of 2.1 equiv of sodium hydride in dimethylformamide at room temperature for 75 min, the rearranged product **6** was obtained in 48% yield. This result parallels the findings of Turner, except that the geminal dimethyl groups were not needed in our case. We then turned our attention to the rearrangement of secondary amides. When compound **3** was subjected to the same reaction conditions as the primary amide, *a rapid and exothermic reaction resulted.* Aniline **7** was obtained in 54% yield. The direct isolation of **7** can be rationalized by acyl transfer from the nitrogen to the alkoxide. The resulting hydroxy acetate was hydrolyzed to the alcohol during aqueous workup. This result was surprising in light of literature precedent[2] and prompted us to explore the reaction further.

The rate of the rearrangement of **3** to **7** was dependent on the counterion and solvent. The relative rate of the

(1) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React. (N.Y.)* **1970**, *18*, 99.
(2) Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. *Synthesis* **1977**, 31.
(3) Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. *Synthesis* **1977**, 33.
(4) Jones, P. H.; Bariana, D. S.; Fung, A. K. L.; Martin, Y. C.; Kyncl, J.; Lall, A. U.S. Patent No. 4 166 819, 1979.

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