A Novel 13-Membered Erythromycin Analog *via* DAST-Induced Ring Contraction

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Synthesis of a number of 8,9-anhydroerythromycin-6,9-hemiacetals of general structure **1** have been reported.[1−4] Unlike erythromycin, these derivatives lack antibacterial activity, but are selective agonists of motilin receptors[5] and hence potent stimulants of gastrointestinal motility. Compound **2** (ABT-229), is one such derivative[3] which is currently under development for the treatment of diabetic gastroparesis, irritable bowel syndrome, and gastroesophageal reflux disease. In our quest to understand the SAR of this class of compounds, we decided to investigate the feasibility of substituting the 11-hydroxy group of **2** with a fluorine atom. The approach was to protect **2** so as to allow selective substitution of the 11-hydroxy group by fluorine upon treatment with the selective fluorinating agent (diethylamido)sulfur trifluoride (DAST).[6]

Results

As shown in Scheme 1, treatment of **2** with acetic anhydride under neutral conditions led to selective acetylation of the 2′-OH to provide **3**. Subsequent treatment of **3** with DAST in CH_2Cl_2 did not lead to simple nucleophilic displacement of the 11-OH with fluoride, as was expected, but instead afforded the novel 13-membered macrolactone **4** in excellent yield. No other fluorine-substituted products were observed in this reaction. Stirring **4** in methanol at room temperature led to removal of the 2′-*O*-acetate to provide compound **5**.

The initial characterization of the DAST reaction product as a fluorine-substituted, but ring-contracted, derivative was *via* NMR experiments performed on **5**. The presence of fluorine in **5** was evident from the molecular weight and a fluorine resonance at δ −171.2 (downfield from $CFCl_3$) in the ^{19}F- NMR spectrum. The ^{1}H and ^{13}C resonances were assigned from the COSY, ROESY, HMQC, and HMBC spectra. The two sets of ^{13}C resonances for C-9 (146.1 and 146.2), C-10 (52.3 and 52.5), C-19 (88.9 and 91.2), C-20 (19.5 and 19.8), and C-11 (34.0 and 34.1) suggested fluorine substitution at C-19. The corresponding ^{1}H resonances for C-10, C-19, and C-20 were also in two sets: 2.43, 2.40; 4.88, 4.78 and 1.41, 1.36, respectively. Other salient features of these spectra included a long range ^{1}H−^{13}C correlation in the HMBC spectrum between the C-21 protons and the C-9 carbon, indicating a ring contraction. A large coupling constant (J = 25 Hz) for C-20 was also indicative of its attachment to the carbon bearing a fluorine atom, rather than to the original C-10 position as in **2**. Compound **4** was subsequently crystallized from CH_3CN, which enabled a single crystal X-ray structure to be obtained.[13] Figure 1 shows the molecular structure, confirming the ring contraction and the presence of the exocyclic fluorine atom. Figure 1 also establishes the configurations of the new stereocenters at C-10 and C-19.

Discussion

A number of DAST-induced rearrangements[7] and functional group migrations[8,9] have been reported. A transitory (diethylamido)difluorosulfur intermediate such as **6** is invoked in the normal substitution reaction as well as in all the reported rearrangements and migrations. In proposing a mechanistic explanation for the formation of **4**, we considered neighboring group participation by the double bond of the dihydrofuranyl ring system. This would lead to formation of the nonclassical homoallylic carbocation **7**. The apparent stereospecificity of the reaction leads us to propose an intramolecular attack of fluorine at C-10 resulting in fluorine substitution, migration of C-9 to C-11, and hence ring contraction. The configurations of C-10 and C-19 support the proposed mechanism.

Naturally occurring analogs of erythromycin contain an even number of atoms[10] in the macrolactone ring. Thus, 12, 14, and 16-membered ring compounds have been isolated. Modifications of erythromycin have led to ring expansion to provide 15-membered macrocycles called azalides.[11] Ring contraction to 12-membered analogs (pseudoerythromycins) have also been reported.[12] This communication reports the first erythromycin ring contraction to provide a 13-membered macrolactone, for which we propose the semitrivial name erythromycin dodecalide. The biological activity of **5** is under investigation.

Experimental Section

NMR spectra were recorded at 500 MHz for ^{1}H, at 470.9 MHz for ^{19}F and at 125.87 MHz for ^{13}C. Mass spectra were recorded using a chemical ionization (DCI/NH_3) source. X-ray data was collected at ambient temperature, using Ni filtered Cu Kα radiation. Optical rotations were measured at 25 °C. Flash chromatography was with silica gel (230−400 mesh) using the solvent system; 0.5% NH_4OH/5% MeOH in $CHCl_3$. Compound **2** was synthesized as previously described.[3]

2′-*O*-Acetyl-8,9-anhydro-4″-deoxy-3'-*N*-desmethyl-3′-*N*-ethylerythromycin B-6,9-Hemiacetal (3). Compound **2** (3.01 g, 4.31 mmol) was dissolved in CH_2Cl_2 (23 mL). Acetic anhydride

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(13) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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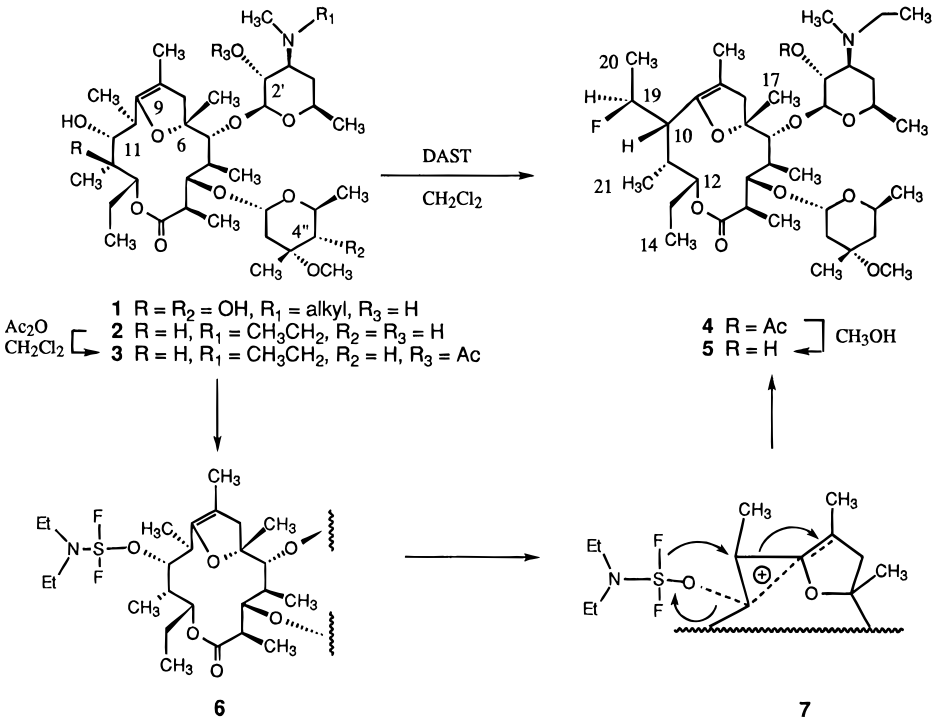
Scheme 1



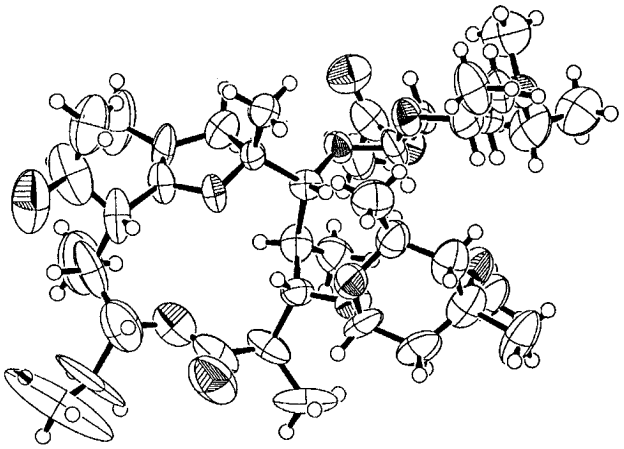


Figure 1. Molecular structure of **4**.

(0.8 mL, 8.5 mmol) was added via syringe and the mixture stirred under N_2 for 4 h at room temperature. The mixture was diluted with CH_2Cl_2 (150 mL) and extracted sequentially with saturated $NaHCO_3$, H_2O, and brine (40 mL each). The organic phase was dried over Na_2SO_4 and solvent removed *in vacuo* to give a solid which was purified by chromatography to afford 2.60 g (81%) of **3**: $[\alpha]_D$ −30.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, *J* = 12.5), 0.90 (t, 3H, *J* = 12.5, 12.5), 0.96 (d, 3H, *J* = 13.0), 1.01 (t, 3H, *J* = 11.8, 11.8), 1.06 (d, 3H, *J* = 11.5), 1.15 (s, 3H), 1.16 (d, 3H, *J* = 12.0), 1.17 (d, 3H, *J* = 9.0), 1.18 (d, 3H, *J* = 10.0), 1.25−1.54 (m, 4H), 1.34 (s, 3H), 1.56 (s, 3H), 1.68 (m, 4H), 1.93 (m, 3H), 2.0 (s, 3H), 2.24 (s, 3H), 2.25−2.80 (m, 7H), 3.32 (s, 3H), 3.42 (m, 1H), 3.62 (m, 1H), 3.82 (d, 1H, *J* = 11.0), 4.0 (m, 1H), 4.34 (m, 1H), 4.65 (m, 2H), 5.15 (m, 1H), 5.19 (d, 1H, *J* = 7.0); ^{13}C-NMR ($CDCl_3$) δ 8.7, 10.4, 11.9, 13.3, 14.1, 14.4, 21.1, 21.4, 21.7, 25.0, 25.4, 26.4, 31.9, 33.3, 33.6, 36.7, 42.1, 42.7, 43.0, 44.5, 45.9, 47.9, 49.2, 61.4, 62.3, 67.8, 70.7, 71.9, 76.8, 77.2, 80.0, 85.7, 95.6, 100.2, 101.4, 151.5, 169.9, 178.2; MS *m*/*e* 740 (M + H$^+$). Anal. Calcd for $C_{40}H_{69}NO_{11}$: C, 64.92; H, 9.39; N, 1.89. Found: C, 64.97; H, 9.79; N, 2.12.

(19*S*)-2′-*O*-Acetyl-8,9-anhydro-4″-deoxy-3'-*N*-desmethyl-3′-*N*-ethyl-19-fluoroerythromycin B Dodecalide-6,9-hemiacetal (4). Compound **3** (0.50 g, 0.68 mmol) was dissolved in CH_2Cl_2 (20 mL). DAST (0.3 mL, 2.27 mmol) was added via syringe. The mixture was stirred at room temperature and under N_2 for 4 h, diluted with CH_2Cl_2 (50 mL), and extracted sequentially with saturated $NaHCO_3$, H_2O, and brine (10 mL each). The organic phase was dried over Na_2SO_4 and solvent removed *in vacuo* to give a mixture which was purified by chromatography to afford 0.37 g (73%) of 4: $[\alpha]_D$ −24.1° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H, *J* = 7.5, 7.5), 0.85 (d, 3H, *J* = 8.0), 0.88 (d, 3H, *J* = 7.5), 0.94 (t, 3H, *J* = 7.5, 7.5), 1.09 (d, 3H, *J* = 7.5), 1.10 (s, 3H), 1.12 (d, 3H, *J* = 6.0), 1.19 (d, 3H, *J* = 6.0), 1.25 (m, 3H), 1.30 (s, 3H), 1.32 (dd, 3H, *J* = 5.5, 24.3), 1.36 (m, 2H), 1.50 (s, 3H), 1.60 (m, 3H), 1.85 (d, 1H, *J* = 16.5), 1.98 (m, 1H), 1.99 (s, 3H), 2.15 (s, 3H), 2.24 (dd, 1H, *J* = 7.5, 14.8), 2.30 (m, 2H), 2.48 (m, 1H), 2.55 (m, 1H), 2.64 (m, 1H), 2.75 (d, 1H, *J* = 15), 3.22 (s, 3H), 3.40 (m, 1H), 3.58 (d, 1H, *J* = 8.5), 3.88 (m, 1H), 4.20 (m, 1H), 4.45 (d, 1H, *J* = 8.0), 4.59 (m, 1H), 4.70 (m, 2H), 4.80 (m, 1H), 4.86 (d, 1H, *J* = 4.5); ^{13}C-NMR ($CDCl_3$) δ 9.4, 9.4, 10.2, 13.0, 13.6, 14.1, 19.5, 19.8, 21.1, 21.4, 21, 25.5, 25.6, 27.0, 31.9, 33.9, 34.0, 34.1, 36.7, 42.5, 44.2, 45.7, 47.9, 49.4, 52.2, 52.5, 61.1, 62.5, 68.4, 70.7, 71.5, 77.3, 81.4, 82.2, 86.2, 88.9, 91.1, 96.5, 101.2, 146.0, 146.2, 169.9, 177.2; MS *m*/*e* 742 (M + H$^+$). Anal. Calcd for $C_{40}H_{68}FNO_{10}$: C, 64.75; H, 9.23; N, 1.88. Found: C, 64.81; H, 9.48; N, 1.75.

(19*S*)-8,9-Anhydro-4″-deoxy-3'-*N*-desmethyl-3′-*N*-ethyl-19-fluoroerythromycin B Dodecalide-6,9-hemiacetal (5). Compound **4** (0.072 g, 0.097 mmol) was dissolved in CH_3OH (10 mL) and the mixture stirred overnight at room temperature. Solvent was removed *in vacuo* and the residue chromatographed to afford 0.06 g (90%) of **7**: $[\alpha]_D$ −20.5° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 7.5, 7.5), 1.00 (d, 3H, *J* = 6.5), 1.08 (t, 3H, *J* = 3.5, 3.5), 1.09 (d, 3H, *J* = 7.5), 1.12 (d, 3H, *J* = 7.5), 1.14 (s, 3H), 1.19 (d, 3H, *J* = 6.5), 1.20 (d, 3H, *J* = 6.0), 1.26 (s, 1H), 1.32 (m, 1H), 1.36−1.47 (m, 8H), 1.59 (s, 3H), 1.64 (m, 1H), 1.65 (m, 1H), 1.76 (m, 1H), 1.96 (d, 1H, *J* = 15.5), 2.08 (m, 1H), 2.24 (s, 4H), 2.33−2.38 (m, 2H), 2.43 (dd, 1H, *J* = 10.5, 15.3), 2.50−2.64 (m, 3H), 2.97 (d, 1H, *J* = 16.5), 3.21 (m, 1H), 3.28 (s, 3H), 3.51 (m, 1H), 3.70 (d, 1H, *J* = 8.0), 4.00 (m, 1H), 4.31 (m, 1H), 4.45 (d, 1H, *J* = 7.0), 4.64−4.95 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 9.0, 9.4, 10.2, 12.9, 13.6, 13.9, 19.5, 19.8, 21.3, 21.6, 25.4, 25.6, 27.1, 29.8, 33.8, 34.0, 34.1, 36.2, 42.8, 44.2, 45.7, 45.7, 47.6, 49.4, 52.3, 52.5, 61.1, 64.7, 68.8, 70.4, 70.6, 77.2, 81.5, 82.2, 86.2, 88.9, 91.2, 96.5, 103.3, 104.1, 146.1, 146.2, 177.3; MS *m*/*e* 700 (M + H$^+$). Anal. Calcd for $C_{38}H_{66}FNO_9 \cdot 2H_2O$: C, 62.01; H, 9.58; N, 1.90. Found: C, 62.24; H, 9.21; N, 1.75.

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