thio]-2-azetidinone (35) (26.4 g, 60.1 mmol) was treated with 2-chloroallyl oxalofluoride (31) (13.0 g, 78.3 mmol) and *N,N*-diisopropylethylamine (13.6 mL, 78.3 mmol) in 300 mL of dry methylene chloride at −60 °C as described in the preparation of oxalimide 5 to afford 33.2 g of intermediate oxalimide which was converted (according to the procedure described for the conversion of 5 to penem 32) to 11.3 g of crude penem. Crude product was tritrated with 200 mL of diisopropyl ether to afford, after filtration, 9.8 g (50.4%) of penem 36; mp 122–125 °C dec; $[\alpha]_D$ = +158.13° (c = 1, $CHCl_3$); IR (KBr) ν_{max} 1784, 1681, 1492, 1324, 1198, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 250.1 MHz) δ 0.03 (s, 6 H, Me_2Si), 0.83 (s, 9 H, tBuSi), 1.20 (d, J = 6.3 Hz, 3 H, CH_3), 2.64–2.78 (m, 4 H, CH_2, CHSO, CHSO), 3.08–3.10 (m, 1 H, CHSO), 3.61–3.82 (m, 3 H, CHS, CHSO, CHCO), 4.21–4.23 (m, 1 H, CHO), 4.61 (d, J = 14.1 H, 1 H, $CHCO_2$), 4.79 (d, J = 14.1 Hz, 1 H, $CHCO_2$), 5.34 (d, J = 1.9 Hz, 1 H, $=CH_2$), 5.61 (m, 2 H, $=CH_2$ NCHS); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ −5.44, −4.54, 17.54, 21.64, 25.52, 32.98, 46.44, 51.99, 60.52, 64.08, 64.56, 65.13, 70.89, 115.09, 115.58, 134.84, 155.22, 158.23, 173.07; HRMS (EI) calcd for $C_{17}H_{23}ClNO_5S_3Si$ (*p*-tBu) 480.0426, found 480.0451.

2-Chloroallyl (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (37). Employing the procedure utilized for the conversion of 32 to 33, 2-chloroallyl (5*R*,6*S*)-6-[1(*R*)-[(Dimethyl-*tert*-butylsilyl)oxy]-ethyl]-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (36) (6.0 g, 11.2 mmol) was converted to 4.0 g (84%) of 37; mp 156–158 °C dec; $[\alpha]_D$ = +186.7 (c = 0.35 in DMSO); IR (KBr) ν_{max} 3184, 1765, 1684, 1490, 1319, 1200, 1123, 994 cm^{-1}; ^1H NMR (DMSO-d_6, 250.1 MHz) δ 1.18 (d, J = 6.3 Hz, 3 H, CH_3), 2.38–3.00 (m, 5 H, CH_2, CH_2SO, CHSO), 3.66 (dd, J = 14.6, 8.9 Hz, 1 H, CHSO), 3.85–4.01 (m, 3 H, CHO, CHCO, CHS), 4.69 (d, J = 14.1 Hz, 1 H, $CHCO_2$), 4.64 (d, J = 14.1 Hz, 1 H, $CHCO_2$), 5.22 (d, J = 4.6 Hz, 1 H, OH), 5.46 (m, 1 H, =CH), 5.71 (d, J = 1.6 Hz, 1 H, NCHS), 5.77 (d, J = 1.2 Hz, 1 H, =CH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 21.39, 32.93, 46.35, 51.95, 60.50, 63.72, 64.71, 65.07, 71.36, 115.17, 115.17, 134.90, 155.30, 158.22, 173.60. Anal. Calcd for $C_{15}H_{18}ClNO_5S_3$: C, 42.49; H, 4.28; N, 3.30. Found: C, 42.48; H, 4.35; N, 3.24.

(5*R*,6*S*)-6-(1(*R*)-1-Hydroxyethyl)-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylic Acid (2). As described in the conversion of 33 to 34, 2-chloroallyl (5*R*,6*S*)-6-(1(*R*)-hydroxyethyl-2-[(1(*S*)-oxo-3(*R*)-thiolanyl)thio]-2-penem-3-carboxylate (37) (4.24 g, 10 mmol) was converted to its corresponding sodium salt, mp 120–123 °C dec; $[\alpha]_D$ = +115.29 (c = 0.21, DMSO). The sodium salt was treated with 3 N HCl as described in the conversion of 34 to 1 to afford 2.6 g (75%) of CP-81,032 (2): mp 185–187 °C dec; $[\alpha]_D$ = +128.67 (c = 1, DMSO); IR (KBr) ν_{max} 3472, 3434, 1778, 1747, 1502, 1299, 1232, 991 cm^{-1}; ^1H NMR (DMSO-d_6, 250.1 MHz) δ 1.14 (d, J = 6.3 Hz, 3 H, CH_3), 2.34–3.02 (m, 5 H, CH_2, CH_2SO, CHSO), 3.66 (dd, J = 14.6, 8.8 Hz, 1 H, CHSO), 3.78–4.01 (m, 3 H, CHO, CHCO, SCH), 5.19 (bs, 1 H, OH), 5.70 (s, 1 H, NCHS); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 21.40, 33.07, 46.19, 52.00, 60.60, 63.85, 64.17, 71.09, 117.87, 151.10, 160.66, 173.15. Anal. Calcd for $C_{12}H_{15}NO_6S_3$: C, 41.24; H, 4.33; N, 4.01. Found: C, 41.14; H, 4.33; N, 3.97.

Acknowledgment. We gratefully acknowledge discussions with Professors E. J. Corey, Stuart Schreiber, and Dan Kemp and in particular wish to acknowledge E. J. Corey for suggesting the use of oxalofluorides. In addition, stimulating discussions with Mike Kellogg and with Brian O'Neill concerning the synthesis of CP-70,429 (1) and interactions with Frank Busch, Tom Crawford, and other colleagues in the Chemical Process Group concerning process scaleup are also acknowledged. We especially are grateful to Dave Hageman for his pioneering experiments with chloroazetidinone 4b, to Jeff Kiplinger, Dick Ware, and Phil Reiche for mass spectrometry support, and to Diane Rescek and Steve Maginess for NMR assistance.

Supplementary Material Available: ^{13}C or ^1H NMR spectrum of each compound (32 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

New Macrolide Antibiotics: Synthesis of a 14-Membered Azalide

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The first example of a 14-membered azalide antibiotic (5) has been prepared. The key steps are sequential oxidative cleavage processes converting furanone 12 to aldehyde 14 and the subsequent reductive rearrangement of oxime 15 to amine 20.

Introduction

The erythromycin family of antibiotics has been known for 40 years.[1] Erythromycin A has provided effective and, above all, safe antibiotic therapy for much of that time. However, the last few years have seen something of a macrolide renaissance, ostensibly as a result of the emergence of a number of new semisynthetic erythromycin A derivatives—particularly clarithromycin[2,4] (2) and azithromycin (3).[3,4] Each of these addresses some of the shortcomings of the parent—notably poor oral bioavailability[5] as a result of acid instability, together with the

(1) (a) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiotic Chemother. (Washington, D.C.)* **1952**, *2*, 281. (b) Crystal structure of erythromycin A: Harris, D. R.; McGeachin, S. G.; Mills, H. H., *Tetrahedron Lett.* **1965**, 679.

(2) Synthesis of clarithromycin: Morimoto, S.; Takahashi, Y.; Watanabe, Y.; Omura, S. *J. Antibiot.* **1984**, *37*, 187. Watanabe, Y.; Adachi, T.; Asaka, T.; Kashimura, M., Morimoto, S. *Heterocycles* **1990**, *31*, 2121. Recent reports relating to biological evaluation are contained in: *J. Antimicrob. Chemother.* **1991**, *27*, Suppl. A.

(3) Synthesis of azithromycin: (a) Djokic, S.; Kobrehel, G.; Lazarevski, G.; Lopotar, N.; Tamburasev, Z.; Kamenar, B.; Nagl, A.; Vickovic, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1881. (b) Djokic, S.; Kobrehel, G.; Lopotar, N.; Kamenar, B.; Nagl, A.; Mrvos, D.; *J. Chem. Res. Miniprint* **1988**, 1239. (c) Bright, G. M.; Nagel, A. A.; Bordner, J.; Desai, K. A.; Dibrino, J. N.; Nowakowska, J.; Vincent, L.; Watrous, R. M.; Sciavolino, F. C.; English, A. R.; Retsema, J. A.; Anderson, M. R.; Brennan, L. A.; Borovoy, R. J.; Cimochowski, C. R.; Faiella, J. A.; Girard, A. E.; Girard, D.; Herbert, C.; Manousos, M.; Mason, R. *J. Antibiot.* **1988**, *41*, 1029. Recent reports relating to biological evaluation are contained in *Am. J. Med.* (**1991**, *91*, Suppl. 3A) and include many references to earlier studies.

(4) Clarithromycin (Biaxin) received FDA approval on Oct. 31, 1991. Azithromycin (Zithromax) initially received FDA approval on Nov 1, 1991.

(5) This can be allayed to some extent by using enterically coated formulations or 2′-ester prodrugs.

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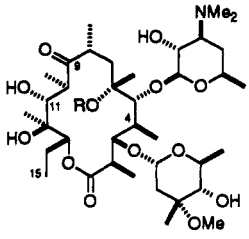
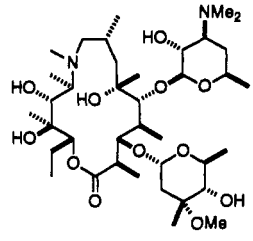
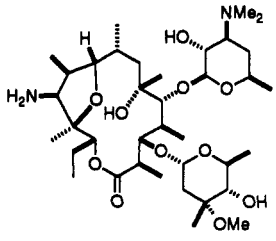
related GI disturbances[6] and poor tissue and serum half-lives. However, azithromycin provided an additional microbiological breakthrough. For the first time a macrolide antibiotic was imparted *significant* activity against Gram-negative bacteria.[7,8] The demonstration that macrolides possessed such potential has clearly seeded a number of new programs, including our own.



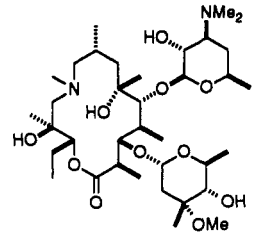
(1) R=H, Erythromycin A
(2) R=Me, Clarithromycin



(3) Azithromycin



(4) A-69334

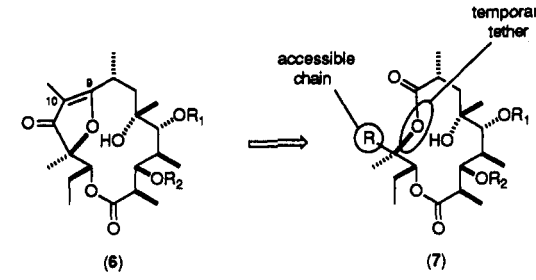


(5)

The chemistry that had been performed on erythromycin A (1) in the past comprised, for the most part, of modifications to peripheral functionality that had served to broadly define the structure–activity relationship[9] and effect limited pharmacokinetic improvements. Some of the more recent biological successes have featured transformations affecting the aglycon scaffold (see, for example, azithromycin (3)[3] and A-69334 (4)[10]). As part of a broad program in the macrolide area we set out to find a route to a new nucleus—14-membered azalides[11] (for example, 5). We cannot claim to have made such a target selection on the basis of detailed structural or conformational analyses, but rather it simply represents an empirically logical blend of erythromycin A (a 14-membered neutral aglycon) and azithromycin (a 15-membered basic aglycon). The new azalide should retain, as far as possible, the structural characteristics of erythromycin A. In the case of a 10-aza compound the conceptually optimal azalide 5 necessarily lacks the 11-hydroxy group. It is the preparation of this class that is reported here.

Scheme I

R_1 = desosamine
R_2 = cladinose



(6) (7)

Planning

Two fundamental steps are required in order to generate a 14-membered azalide from erythromycin A; a carbon atom must be excised from the framework and a nitrogen atom must be inserted into it. This, of course, necessitates that the original macrocyclic ring be broken and reclosed in some way. In early studies with the erythromycin nucleus we had been exploring ways to internally retether the macrocycle and release part of the ring as a pendant chain on which we would be free to perform the excision/insertion surgery before reannealing the full macrolide. This would avoid potential difficulties that may arise in fully rupturing the ring system. In some excellent work disclosed by a group working at Abbott Laboratories[10] furanone (6) had been formed as an intermediate in the synthesis of A-69334 (4). We perceived an opportunity to employ such a compound to generate a temporarily retethered system 7. Oxidative cleavage of the 9,10-double bond of the furanone would release carbons 10 and 11 (erythromycin A numbering) while holding the macrocycle together through the 12-hydroxy group (Scheme I). C-10 was targeted for excision.

An initial problem is revealed by this analysis. Oxidative cleavage would be incompatible with the dimethylamino functionality on the desosaminyl residue (this was subsequently confirmed). An amino-protected version of the furanone was required. The 2′,3′-bis(Cbz) derivative of erythromycin A introduced by Flynn and co-workers in 1955[12] was, to our knowledge, the only existing, chemically viable choice in this regard. However, the presence of rotamers about the 3′-N–CO bond complicates the NMR spectra to such an extent that it is not ideally suited for use in multistep sequences. We chose therefore to develop the 3′-*N*-demethyl-3′-*N*-phenylsulfonamide as an alternative. This blocking group retains the benefits of Cbz (defuses N-basicity, provides a UV chromophore, installed and removed under mild conditions) without producing the complicating effects on the NMR spectra—indeed, in addition, its NMR profile does not overlap with any of the erythromycin ^1H or ^{13}C signals.

Results and Discussion

3′-*N*-Demethylerythromycin A (8) is readily available from erythromycin A.[13] Reaction of the secondary amine with benzenesulfonyl chloride produced the requisite sulfonamide 9. The proposed deprotection conditons (i.6%Na/Hg; ii. HCHO, H_2, Pd) were tested at this stage

(6) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* 1971, *27*, 362. For lead references to GI effects see: Tsuzuki, K. Sunazuka, T.; Marui, S.; Toyoda, H.; Omura, S.; Inatomi, N.; Itoh, Z. *Chem. Pharm. Bull.* 1989, *37*, 2687.

(7) Other derivatives, notably erythromycylamine, show some improvement in Gram-negative activity but not to the same extent as azithromycin. Azithromycin is also notable for its ability to concentrate in tissue but this need not necessarily be considered a required feature of new agents.

(8) Retsema, J.; Girard, A.; Schelkly, W.; Manousos, M.; Anderson, M.; Bright, G.; Borovoy, R.; Brennan, L.; Mason, R.; *Antimicrob. Agents Chemother.* 1987, *31*, 1939.

(9) See, for example: Sakakibara, H. and Omura, S. In *Macrolide Antibiotics, Biology and Practice*; Omura, S.; Ed.; Academic Press: Orlando, FL, 1984; Chapter 3.

(10) Frieberg, L. A.; Klein, L. L.; Yeung, C. M.; Wards, C. M.; Bacino, D. J. WO 90/11288. Frieberg, L. A.; Edwards, C. M.; Bacino, D. J.; Seif, L.; Lartey, P. A.; Whittern, D. Presented at 29th Interscience Conference on Antimicrobial Agents & Chemotherapy, 1989. Freiberg, L. A.; Edwards, C. M.; Bacino, D. J.; Klein, L. L.; Stephens, R.; Spanton, S.; Kim, K. Presented at 29th Interscience Conference on Antimicrobial Agents & Chemotherapy, 1989.

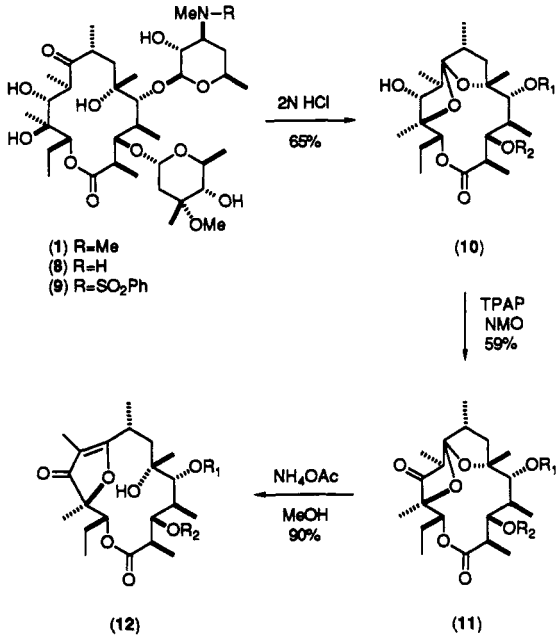
(11) The term *azalide* was originally coined for the 15-membered aza-macrolides. See ref 3c.

(12) Flynn, E. H.; Murphy, H. W.; McMahon, R. E. *J. Am. Chem. Soc.* 1955, *77*, 3104.

(13) Freiberg, L. A. US 3,725,385.

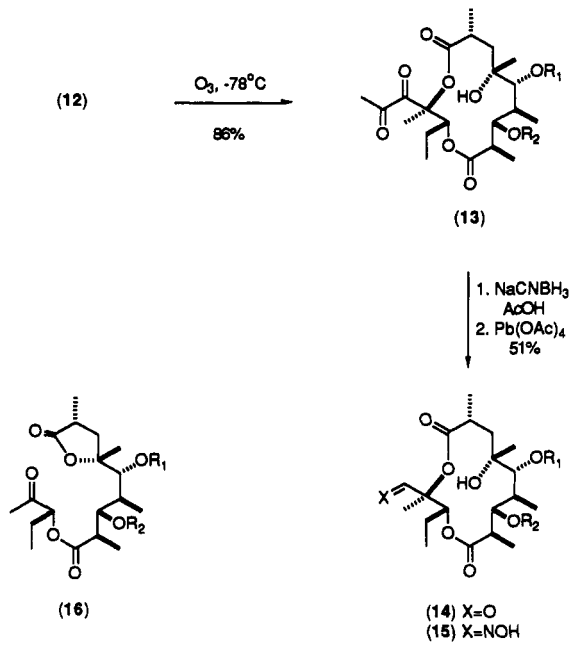
Scheme II

R_1 = 3'-N-demethyl-3'-N-phenylsulphonyl desosamine
R_2 = cladinose



Scheme III

R_1 = 3'-N-demethyl-3'-N-phenylsulphonyl desosamine
R_2 = cladinose



and proved viable even for the somewhat sensitive erythromycin A molecule itself. We have subsequently used the sulfonamide protecting group in a number of schemes involving erythromycin and further extended it as a protecting group for the desosamine and/or aglycon amino groups of the azalides, and it has proven to be eminently suitable.[14] While the 2'-hydroxy group is formally unprotected (cf. 2',3'-bis(Cbz)) the loss of anchimeric activation by the basic 3'-amine and, presumably, a certain degree of steric shielding by the arylsulfonamide alter the selectivity of hydroxyl functionalizing reactions and frequently renders such protection unnecessary (for example, vide infra).

The N-protected erythromycin A could be carried through a sequence of steps essentially identical to those employed in the unprotected series[10] (Scheme II). Two minor differences should be noted. Firstly, the spiroketalization was carried out in an aqueous/organic mixture rather than wholly aqueous to ensure dissolution of this less polar substrate. Secondly, while the 2'-hydroxyl group required protection in the dimethylamino series to ensure chemoselectivity in the subsequent oxidation,[10] it was not a requirement in this series. By this process the requisite N-protected furanone **12** was made available.

Ozonolysis of the furanone **12** in 1:1 methylene chloride/pyridine proceeded relatively slowly, but cleanly, to afford the diketone **13** (Scheme III). This set the stage for the key C-excision step. Initial attempts to reduce the diketone ($NaBH_4$, *i*PrOH) and subsequently oxidatively cleave the crude diol ($Pb(OAc)_4$), produced γ-lactone **16** as a result of participation of the 6-hydroxy group. However, the offending tertiary alcohol could be effectively neutered by performing the reduction under acidic conditions ($NaCNBH_3$, AcOH).[15] In this way the excision process proceeded smoothly to provide aldehyde **14**. The second fundamental step, introduction of nitrogen functionality, could then be simply achieved by formation of the corresponding oxime **15**. What remained at this stage was to reform the full macrocycle, incorporating the new component, and release the temporary tether.

Oxime **15** proved surprisingly resistant to reduction. Nonetheless, high-pressure hydrogenation in the presence of 0.5 wt equiv of platinum oxide over 48 h effected partial conversion. The process was complicated by slow reduction of the phenylsulfonamide to a cyclohexyl sulfonamide. If this unwanted reduction were allowed to proceed the utility of the sulfonamide as a protecting group would be compromised. Consequently, these reactions were always halted before complete consumption of the oxime. In this way the isolated products contained only trace amounts of the corresponding, generally inseparable, cyclohexyl derivatives. In addition to recovering unreacted oxime, three components were isolated—lactam[16] **17** (5–30%), imino ether[16] **19** (5–10%), and secondary amine **20** (15–35%),[17] see Scheme IV. Primary amine **21** was never observed even given the acidic conditions of the reduction. It is likely that the pivotal intermediate is the hemiorthoamide **22** which collapses to generate both lactam **17** and imino ether **19**. The imino ether is rapidly reduced to amine **20** under the prevailing reaction conditions and is consequently only observed as a minor component. Resubjection of purified imino ether **19** to the reduction conditions produced amine **20** as the only product. Re-

(14) Acton, J. J.; Jones, A. B. Unpublished results.

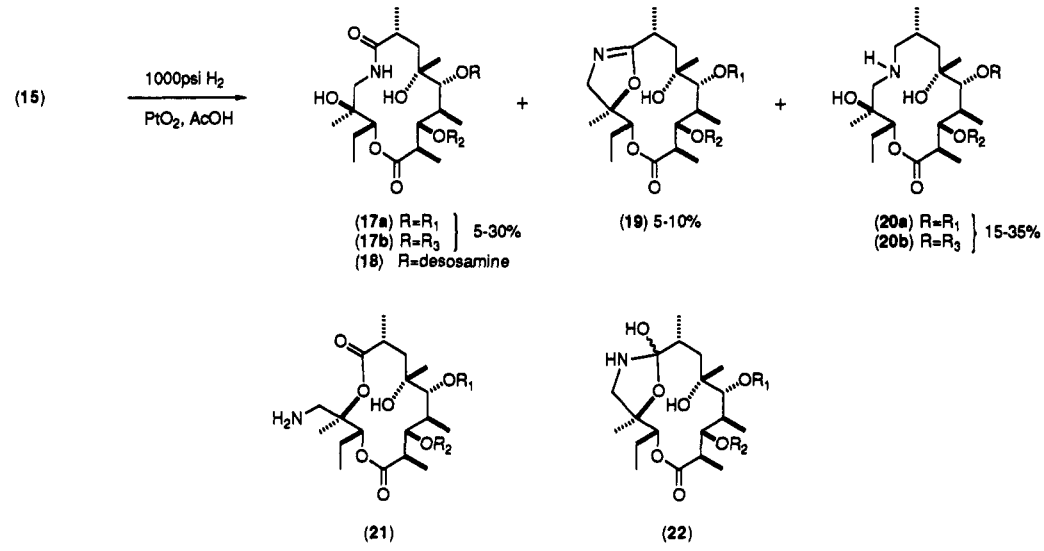
(15) Sodium borohydride in acetic acid (T. E. A. Nieminen and T. A. Hase, *Tetrahedron Lett.* **1987**, *28*, 4725) was used initially but was found to be inefficient for larger scale processes.

(16) Potenital isomeric structures arising from lactamization to the C-1 carbonyl were not observed. In the case of lactam **17** a compound arising from lactamization at C-1 followed by translactonization of the released secondary alcohol to C-9 would not be readily distinguishable. Unambiguous structural assignment in this case was provided by analysis of long range ^1H–^{13}C connectivities observed in an HMBC experiment (A. Bax and M. F. Summers, *J. Am. Chem. Soc.* **1986**, *108*, 2093). I thank Dr. G. Doss for this determination. In the case of imino ether **19** an isomeric structure arising from transimidation of the 6-hydroxy group was ruled out by the observation of a small H-7 to 6-OH coupling in the ^1H COSY.

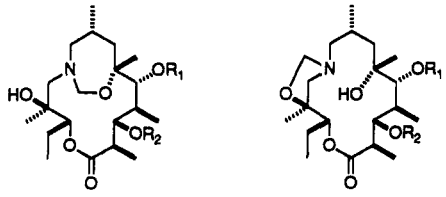
(17) Yields are based on recovered oxime. Some variability was observed over the given ranges. An "average" representation would be oxime **15** 30%, lactam **17** 20%, imino ether **19** 5%, and amine **20** 30%. The Experimental Section records one of the more favorable examples in terms of selective production of amine **20**. The influencing factors have not been examined.

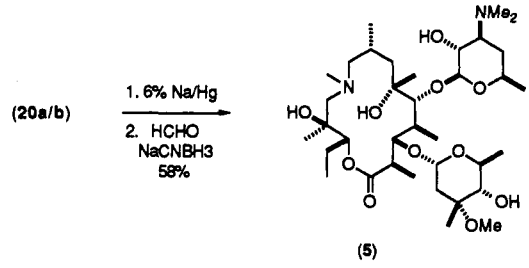
Scheme IV

R_1 = 3'-N-demethyl-3'-N-phenylsulphonyl desosamine
R_2 = cladinose
R_3 = 3'-N-demethyl-3'-N-cyclohexylsulphonyl desosamine



subjection of the lactam **17** to the reduction conditions induced only slow reduction of the phenylsulfonamide.





Subjection of these materials to reductive desulfonylation resulted in cleavage of the phenylsulfonamide, while the cyclohexylsulfonamide impurities remained unmoved. Subsequent reductive methylation provided the corresponding dimethylamino compounds. In this manner protected lactam **17** was converted (i. Li naphthalenide,[21] ii. HCHO, HCO_2H) to the biologically required dimethylamino form (**18**). Under similar conditions the more interesting amine **20** produced an acid-labile product, identified as an aminal derivative which could be formulated as involving the 6-hydroxy group (**23**) or the 12-hydroxy group (**24**).[18] NMR data indicate 10-N-12-O-aminal **24** to be the correct assignment—regioisomer **23** is ruled out by the observation of an apparent H-7 to 6-OH coupling in the ^1H COSY. Under more rigorous reduction conditions (i. 6% Na/Hg, ii. HCHO, $NaCNBH_3$) the desired bis-methylation occurred smoothly to provide the ultimate target compound, 10-aza-9-deoxo-11-deoxyerythromycin A (**5**). This then is the first example of a new class of macrolide antibiotic, the 14-membered azalides, and relative to erythromycin A, is the most structurally conserved member of the 10-aza type that could be constructed.

Preliminary in vitro microbiological screening against a panel of both Gram-positive and Gram-negative organisms indicate that the parent 10-aza compound **5** is approximately 2-fold less active against the Gram-positive organisms and 4–8-fold less active against the Gram-negative organisms than azithromycin (**3**). Relative to erythromycin A this corresponds to an approximate 2–4-fold drop in activity against Gram-positive organisms and an approximate 2-fold increase in activity against Gram-negative organisms.[19]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. ^1H NMR were recorded on a Varian XL-400 spectrometer. ^{13}C NMR were recorded at 100 MHz. Mass spectra were recorded on a MAT-731 or JOEL HX-110 mass spectrometer. Microanalyses were performed by Robertson Laboratories, Inc. Erythromycin A was obtained from Aldrich Chemical Co., Inc. All reaction solvents were anhydrous and were obtained from Aldrich Chemical Co., Inc., except for THF which was dried by distillation under nitrogen from sodium benzophenone ketyl. All reactions were performed under dry nitrogen unless otherwise stated. Chromatography was performed on EM Science silica gel 60 (230–400 mesh ASTM) or Fisher Scientific Sorbosil C60 40/60H. Thin-layer chromatography was performed on Merck silica gel 60/Kieselguhr F-254.

3'-*N*-Demethyl-3'-*N*-(phenylsulfonyl)erythromycin A (9). Erythromycin A (1) (50.0 g, 0.068 mol) was dissolved in 80:20 MeOH/H_2O (500 mL, 0.14 N) and NaOAc (28.0 g, 5.0 equiv) added. The mixture was warmed to 45–50 °C and iodine (17.3 g, 1.0 equiv) added in one portion. The pH was monitored and maintained in the 8–9 range by addition of 2.5 N NaOH solution,

(18) This product was also obtained using the reductive methylation conditions employed for the deprotection of 3'-*N*-demethyl-3'-*N*-(phenylsulfonyl)erythromycin A (HCHO, H_2, Pd).

(19) MIC's were determined in a standard broth microdilution assay. I thank Ms. C. Herbert and Dr. A. Graham for these measurements. A more detailed account of the in vitro antibacterial activities of this compound and related derivatives is in preparation.

as required. After 2.5 h (TLC 90/10/1 CH_2Cl_2/MeOH/NH_4OH), the clear solution was poured into water containing NH_4OH and extracted at pH 10–11 with CH_2Cl_2. The extracts were dried over sodium sulfate, filtered, and concentrated. The crude residue was dissolved in CH_2Cl_2 (500 mL) and Et_3N (28.5 mL, 3.0 equiv) added, followed by dropwise addition of benzenesulfonyl chloride (8.7 mL, 1.0 equiv). After 2 h (TLC 90/10/1 CH_2Cl_2/MeOH/NH_4OH) the mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (40–60% EtOAc/$PhCH_3$) to give the sulfonamide **9** as a white foam (47 g, 80%):[20] ^1H NMR (400 MHz, $CDCl_3$ + 1% py-d_5) data for keto form δ 7.84 (2 H, d, J = 7.6 Hz, o-SO_2Ph), 7.57–7.44 (3 H, m, m/p-SO_2Ph), 5.03 (1 H, dd, J = 10.8, 2.0 Hz, H-13), 4.87 (1 H, d, J = 4.8 Hz, H-1″), 4.43 (1 H, d, J = 7.2 Hz, H-1′), 4.02–3.85 (4 H, m, H-3, H-3′, H-5″, OH), 3.78 (1 H, s, H-11), 3.56–3.46 (2 H, m, H-5, H-5′), 3.33 (3 H, s, OMe), 3.27 (1 H, m, H-2′), 3.09 (1, H, s, OH), 3.08–2.98 (2 H, m, H-10, H-4″), 2.84 (1 H, m, H-2), 2.75 (3 H, s, NMe), 2.66 (1 H, m, H-8), 2.38–2.29 (3 H, m, H-2″, 2′-OH, 4″-OH), 1.99–1.86 (2 H, m, H-4, H-14), 1.82 (1 H, dd, J = 14.7, 11.4 Hz, H-7), 1.64–1.53 (2 H, m, H-7, H-2′), 1.52–1.38 (5 H, m, H-14, H-4′, Me), 1.26–1.23 (6 H, m, 5″-Me, Me), 1.19–1.09 (16 H, m, H-4″, 2-Me, 8-Me, 10-Me, 5′-Me, Me), 1.03 (3 H, d, J = 7.6 Hz, 4-Me), and 0.82 (3 H, t, J = 7.3 Hz, 3H-15) ppm;^{13}C ($CDCl_3$ + 1% py-d_5) data for keto form δ 221.0, 175.6, 139.6, 132.4, 128.8, 127.2, 103.3, and 96.2 ppm; data for hemiketal tautomers δ 179.2, 176.1, 139.7, 131.8, 128.3, 127.8, 110.3, 107.2, 106.4, 103.1, 99.0, and 95.4 ppm; IR ($CHCl_3$) 3600, 3520 and 1730 cm^{-1}; FABMS (Li spike) m/z 866 (M^+ + Li). Anal. Calcd for $C_{42}H_{69}NO_{16}S$: C, 58.65; H, 8.09; N, 1.63. Found: C, 58.70; H, 7.98; N, 1.49.

Deprotection of 3′-*N*-Demethyl-3′-*N*-(phenylsulfonyl)-erythromycin A (9). Protected erythromycin A **9** (110 mg, 0.13 mmol) was dissolved in 1/1 THF/MeOH (2.0 mL, 0.06 N) and cooled to −20 °C. KH_2PO_4 (522 mg, 30 equiv) was added, followed by freshly ground 6% sodium amalgam (1.28 g, 25 equiv). After 45 min a further 30 equiv of KH_2PO_4 and 25 equiv of sodium amalgam were added. After a further 1 h (TLC 90/10/1 CH_2Cl_2/MeOH/NH_4OH) the mixture was decanted into aqueous K_2CO_3 solution and the amalgam residue washed several times with EtOAc, combining each time with the aqueous portion. The resulting mixture was partitioned, and the organics were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in EtOH (2.0 mL) and formaldehyde (21 μL of 37% aqueous solution, 2.0 equiv) added, followed by palladium black (1.4 mg, 0.1 equiv). The mixture was hydrogenated (1 atm, room temperature), for 36 h (TLC 90/10/1 CH_2Cl_2/MeOH/NH_4OH) before filtering through Celite, eluting with CH_2Cl_2, and concentrating. The residue was chromatographed (95/5/1 CH_2Cl_2/MeOH/NH_4OH) to give erythromycin A (1) (52 mg, 55%).

3′-*N*-Demethyl-3′-*N*-(phenylsulfonyl)anhydro-erythromycin A (10). Protected erythromycin A **9** (47.0 g, 0.055 mol) was dissolved in 5/1 THF/H_2O (1.0 L, 0.05 N) at room temperature and the pH adjusted to 3.0 by addition of 2 N HCl. After ~9 h (TLC 60% EtOAc/$PhCH_3$) the mixture was poured into water containing NH_4OH and extracted at pH 10–11 with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (20–50% EtOAc/$PhCH_3$) to give the spiroketal **10** as a white foam (30 g, 65%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.58–7.46 (3 H, m, m/p-SO_2Ph), 5.14 (2 H, m, H-13, H-1″), 4.29 (1 H, dd, J = 7.0, 3.4 Hz, H-3), 4.25 (1 H, d, J = 7.2 Hz, H-1′), 3.97 (2 H, m, H-3′, H-5″), 3.48 (2 H, m, H-11, H-5′), 3.41 (1 H, d, J = 5.2 Hz, H-5), 3.27 (4 H, m, H-2′, OMe), 3.12 (1 H, m, H-2), 2.98 (2 H, m, H-10, H-4″), 2.75 (3 H, s, NMe), 2.38 (1 H, d, J = 2.6 Hz, 2′-OH), 2.35–2.21 (3 H, m, H-8, H-2″, 4″-OH), 2.10–1.88 (3 H, m, H-4, H-14, 11-OH), 1.64 (1 H, m, H-14), 1.50 (1 H, dd, J = 15.4, 4.8 Hz, H-2″), 1.45 (1 H, dd, J = 11.4, 5.5 Hz, H-7), 1.41–1.36 (4 H, m, H-4′, Me), 1.28–1.15 (13 H, m, H-4′, 10-Me (1.22, d, J = 7.3 Hz), 5″-Me (1.18, d, J = 6.9 Hz), Me (1.26 s), Me (1.19 s)), 1.12 (3 H, d, J = 6.1 Hz, 5′-Me), 1.10–1.00 (10 H, m, H-7, 2-Me (1.05, d, J = 7.7 Hz), 4-Me (1.08, d, J = 7.4 Hz), 8-Me (1.02, d, J = 6.7 Hz)), and 0.81 (3 H, t, J = 7.3 Hz, 3H-15) ppm; ^{13}C ($CDCl_3$) δ 178.6, 139.5, 132.6, 129.0, 127.3, 115.8, 102.9, and 95.2 ppm; IR (film) 3440, 2970, 2935, 2880, and 1730 cm^{-1}; FABMS (Li spike) m/z 848 (M^+ + Li). Anal. Calcd for $C_{42}H_{67}NO_{14}S.H_2O$: C, 58.67; H, 7.80; N, 1.63. Found: C, 58.70; H, 7.98; N, 1.49.

3′-*N*-Demethyl-11-oxo-3′-*N*-(phenylsulfonyl)anhydro-erythromycin A (11). The spiroketal **10** (27.0 g, 0.032 mol) was dissolved in CH_2Cl_2 (320 mL, 0.1 N) at room temperature. *N*-Methylmorpholine *N*-oxide (4.5 g, 1.2 equiv) was added, followed by tetrapropylammonium perruthenate (1.0 g, 0.09 equiv). After 30 min (TLC 40% EtOAc/$PhCH_3$) the mixture was filtered through silica gel (50% CH_2Cl_2/Et_2O) to remove the catalyst. The filtrate was concentrated and chromatographed (20–30% EtOAc/$PhCH_3$) to give ketone **11** as a white foam (16 g, 59%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.60–7.45 (3 H, m, m/p-SO_2Ph), 5.23 (1 H, d, J = 4.8 Hz, H-1″), 5.07 (1 H, dd, J = 11.3, 3.3 Hz, H-13), 4.45 (1 H, dd, J = 9.8, 1.8 Hz, H-3), 4.29 (1 H, d, J = 7.2 Hz, H-1′), 3.95 (2 H, m, H-3′, H-5″), 3.54–3.45 (2 H, overlapping m and d (J = 2.4 Hz), H-5, H-5′), 3.34 (1 H, q, J = 7.5 Hz, H-10), 3.25 (3 H, s, OMe), 3.24–3.11 (2 H, m, H-2, H-2′), 2.96 (1 H, t, J = 10.3 Hz, H-4″), 2.74 (3 H, s, NMe), 2.45–2.35 (2 H, m, H-8, H-7), 2.26 (1 H, d, J = 10.3 Hz, 4″-OH), 2.22 (1 H, d, J = 15.1 Hz, H-2″), 2.18 (1 H, d, J = 2.4 Hz, 2′-OH), 2.09 (1 H, m, H-4), 1.60–1.43 (4 H, m, H-7, 2 H-14, H-2″), 1.42 (3 H, s, Me), 1.37–1.26 (2 H, m, 2 H-4′), 1.24–1.19 (6 H, overlapping s and d, Me, 10-Me), 1.18–1.10 (12 H, overlapping s and 3xd, Me, 4-Me, 5′-Me, 5″-Me), 0.97 (6 H, d, J = 7.3 Hz, 2-Me, 8-Me), and 0.76 (3 H, t, J = 7.0 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 216.2, 178.4, 139.3, 132.8, 129.1, 127.2, 114.9, 102.2, and 94.2 ppm; IR (film) 3520, 2970, 2935, 2880, and 1740 cm^{-1}; FABMS (Li spike) m/z 846 (M^+ + Li). Anal. Calcd for $C_{42}H_{65}NO_{14}S$: C, 60.05; H, 7.80; N, 1.67. Found: C, 59.55; H, 7.92; N, 1.65.

9,10-Didehydro-3′-*N*-demethyl-9-deoxo-12-deoxy-9,12-epoxy-11-oxo-3′-*N*-(phenylsulfonyl)erythromycin A (12). 11-Keto spiroketal **11** (16.0 g, 0.019 mol) was dissolved in MeOH (190 mL, 0.1 N) and NH_4OAc (8.8 g, 6.0 equiv) added. The mixture was heated to reflux. After 90 min (TLC 40% EtOAc/$PhCH_3$) the mixture was allowed to cool to room temperature and poured into dilute aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was filtered through silica gel (50% Et_2O/CH_2Cl_2) to give the furanone **12** as a white foam (14.5 g, 90%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.52–7.41 (3 H, m, m/p-SO_2Ph), 5.00 (1 H, dd, J = 10.8, 3.1 Hz, H-13), 4.83 (1 H, br s, 6-OH), 4.71 (1 H, dd, J = 4.5, 2.0 Hz, H-1″), 4.51 (1 H, d, J = 7.3 Hz, H-1′), 4.05 (2 H, m, H-3′, H-5″), 3.98 (1 H, d, J = 3.2 Hz, 2′-OH), 3.94 (1 H, dd, J = 6.4, 2.9 Hz, H-3), 3.71 (2 H, m, H-5, H-5′), 3.32 (1 H, ddd, J = 10.3, 7.3, 3.4 Hz, H-2′), 3.25 (3 H, s, OMe), 3.00 (1 H, t, J = 9.0 Hz, H-4″), 2.90 (1 H, m, H-8), 2.74 (3 H, s, NMe), 2.49 (1 H, d, J = 9.4 Hz, 4″-OH), 2.43 (1 H, m, H-2), 2.31 (1 H, dd, J = 15.0, 2.2 Hz, H-2″), 2.14 (1 H, m, H-7), 2.02 (1 H, m, H-14), 1.82–1.73 (2 H, m, H-7, H-14), 1.70 (3 H, s, 10-Me), 1.63–1.48 (4 H, m, H-4, 2 H-4′, H-2″), 1.34 (3 H, s, Me), 1.32 (3 H, d, J = 7.1 Hz, 8-Me), 1.23 (3 H, s, Me), 1.28–1.21 (9 H, m, Me, 5′-Me, 5″-Me), 1.16 (3 H, d, J = 7.0 Hz, 2-Me), 0.95 (3 H, d, J = 7.3 Hz, 4-Me), and 0.88 (3 H, t, J = 7.4 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 204.9, 192.7, 175.6, 139.9, 132.1, 128.5, 127.5, 108.4, 105.2, and 96.6 ppm; IR (film) 3450, 2970, 2930, 2880, 1735, and 1690 cm^{-1}; FABMS (Li spike) m/z 846 (M^+ + Li). Anal. Calcd for $C_{42}H_{65}NO_{14}S$: C, 60.05; H, 7.80; N, 1.67. Found: C, 59.97; H, 7.85; N, 1.65.

3′-*N*-Demethyl-12-(1,2-dioxopropyl)-9,12-epoxy-10,11-nor-3′-*N*-(phenylsulfonyl)erythromycin A (13). Furanone **12** (14.5 g, 0.017 mol) was dissolved in 1/1 CH_2Cl_2/pyridine (175 mL, 0.1 N) and cooled to −78 °C. A stream of ozone in oxygen was passed through the mixture. After 2 h (TLC 40% EtOAc/$PhCH_3$) the ozone was turned off and oxygen passed through the solution for a further 5 min. Dimethyl sulfide (6.3 mL, 5.0 equiv) was added dropwise and the mixture allowed to warm to room temperature. After 5 min at room temperature the mixture was concentrated and then reconcentrated three times from CH_2Cl_2/heptane (to remove pyridine). The residue was filtered through silica gel (50%

(20) Like erythromycin A, this compound exists in solution as a mixture of the keto form and the two stereoisomers of the 6,9-hemiketal. It proved to be fairly sensitive to acid, degrading to the 6,9-enol ether. Consequently, NMR spectra were obtained in pyridine-d_5-doped deuteriochloroform. Erythromycin A itself is acid labile in the same manner[6] but is less sensitive by virtue of the internal buffering effect of the 3′-dimethylamine.

CH_2Cl_2/Et_2O) to give the diketone **13** as a pale yellow foam (12.9 g, 86%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.55–7.40 (3 H, m, m/p-SO_2Ph), 5.08 (1 H, dd, J = 7.9, 5.7 Hz, H-13), 4.74 (1 H, d, J = 4.3 Hz, H-1″), 4.50 (1 H, d, J = 7.2 Hz, H-1′), 4.24 (1 H, dd, J = 5.7, 1.9 Hz, H-3), 4.03–3.97 (3 H, m, OH, H-3′, H-5″), 3.69 (1 H, d, J = 5.4 Hz, H-5), 3.62 (1 H, m, H-5′), 3.37 (1 H, br, OH), 3.34–3.24 (4 H, m, OMe, H-2′), 2.97 (1 H, t, J = 9.5 Hz, H-4″), 2.76–2.62 (5 H, m, NMe, H-2, H-8), 2.39–2.32 (2 H, m, H-2″, 4″-OH), 2.29 (3 H, s, MeCOCO–), 2.14–2.02 (2 H, m, H-4, H-7), 1.66–1.42 (8 H, m, Me, 2 H-14, 2 H-4′, H-2″), 1.34 (1 H, dd, J = 15.1, 6.0 Hz, H-7), 1.23 (3 H, s, Me), 1.21 (3 H, d, J = 7.0 Hz, 8-Me), 1.20–1.14 (12 H, m, Me, 2-Me, 5′-Me, 5″-Me), 1.01 (3 H, d, J = 7.0 Hz, 4-Me), and 0.85 (3 H, t, J = 7.2 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 196.2, 193.9, 177.1, 176.1, 139.7, 132.2, 128.6, 127.4, 104.2, and 96.8 ppm; IR (film) 3480 (br), 2980, 2940, and 1725 cm^{-1}; FABMS (Li spike) m/z 877 (M^+ + Li). Anal. Calcd for $C_{42}H_{65}NO_{16}S$: C, 57.85; H, 7.51; N, 1.61. Found: C, 57.63; H, 7.56; N, 1.52.

3′-*N*-Demethyl-9,12-epoxy-12-formyl-10,11-nor-3′-*N*-(phenylsulfonyl)erythromycin A (14). Diketone **13** (10.5 g, 0.012 mol) was dissolved in AcOH (120 mL, 0.1 N) at room temperature. Sodium cyanoborohydride (2.3 g, 3.0 equiv) was added in portions over ~5 min. After 30 min (TLC 40% EtOAc/$PhCH_3$) the mixture was diluted with water and extracted once with CH_2Cl_2. The aqueous portion was adjusted to pH 10 with 5 N NaOH solution and extracted with CH_2Cl_2. The acidic extract was washed with dilute aqueous NaOH and combined with the alkaline extracts. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (120 mL) and lead tetraacetate (5.3 g, 1.0 equiv) added in one portion. After 30 min (TLC 40% EtOAc/$PhCH_3$) the mixture was poured into dilute aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organics were washed three times with water then once with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (20–30% EtOAc/$PhCH_3$) to give aldehyde **14** as a white foam (5.1 g, 51%): ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (1 H, s, CHO), 7.85 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.58–7.40 (3 H, m, m/p-SO_2Ph), 5.13 (1 H, dd, J = 10.3, 2.6 Hz, H-13), 4.87 (1 H, d, J = 4.4 Hz, H-1″), 4.55 (1 H, d, J = 7.3 Hz, H-1′), 4.28 (1 H, br s, H-3), 4.07–3.92 (2 H, m, H-3′, H-5″), 3.67 (1 H, d, J = 5.9 Hz, H-5), 3.62 (1 H, m, H-5′), 3.52 (1 H, br, s, 6-OH), 3.35–3.24 (4 H, m, OMe, H-2′), 3.03 (1 H, t, J = 9.5 Hz, H-4″), 2.81 (1 H, m, H-8), 2.75 (3 H, s, NMe), 2.72 (1 H, d, J = 2.5 Hz, 2′-OH), 2.66 (1 H, m, H-2), 2.41 (1 H, d, J = 9.9 Hz, 4″-OH), 2.39 (1 H, d, J = 15.8 Hz, H-2″), 2.04–1.94 (2 H, m, H-4, H-7), 1.72–1.35 (9 H, m, Me, H-7, 2 H-14, 2 H-4′, H-2″), 1.28 (3 H, d, J = 6.7 Hz, 8-Me), 1.26 (3 H, s, Me), 1.24 (3 H, d, J = 6.5 Hz, 5″-Me), 1.19 (6 H, m, Me, 2-Me), 1.15 (3 H, d, J = 6.1 Hz, 5′-Me), 1.04 (3 H, d, J = 7.0 Hz, 4-Me), and 0.85 (3 H, t, J = 7.3 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 197.7, 176.6, 176.1, 139.6, 132.4, 128.8, 127.3, 103.3, and 96.3 ppm; IR (film) 3500 (br), 2975, 2940, and 1735 cm^{-1}; FABMS (Li spike) m/z 836 (M^+ + Li) (also 868 (M^+ + K) and 990 (M^+ + dithioerythritol)). Anal. Calcd for $C_{40}H_{63}NO_{15}S$: C, 57.89; H, 7.65; N, 1.69. Found: C, 57.92; H, 7.78; N, 1.64.

3′-*N*-Demethyl-9,12-epoxy-10,11-nor-12-(oximinoformyl)-3′-*N*-(phenylsulfonyl)erythromycin A (15). Aldehyde **14** (6.1 g, 7.4 mmol) was dissolved in pyridine (70 mL, 0.1 N) and hydroxylamine hydrochloride (2.6 g, 5.0 equiv) added. The mixture was heated to 60 °C. After 90 min (TLC 40% EtOAc/$PhCH_3$) it was allowed to cool to room temperature and poured into dilute aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated. The residue was reconcentrated three times from CH_2Cl_2/heptane (to remove pyridine) and filtered through silica gel (50% CH_2Cl_2/Et_2O) to give the oxime **15** as a white foam (5.8 g, 93%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.05–7.90 (1 H, br, –NOH), 7.83 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.56–7.41 (4 H, m, m/p-SO_2Ph, HONC*H*–), 5.17 (1 H, dd, J = 10.0, 2.6 Hz, H-13), 4.87 (1 H, d, J = 4.7 Hz, H-1″), 4.52 (1 H, d, J = 7.1 Hz, H-1′), 4.17 (1 H, br d, J = 4.9 Hz, H-3), 4.04–3.92 (2 H, m, H-3′, H-5″), 3.65–3.55 (2 H, m, H-5, H-5′), 3.38–3.24 (5 H, m, OMe, H-2′, 6-OH), 3.03 (1 H, t, J = 9.6 Hz, H-4″), 2.74 (3 H, s, NMe), 2.72–2.62 (3 H, m, H-2, H-8, 2′-OH), 2.44 (1 H, d, J = 10.0 Hz, 4″-OH), 2.39 (1 H, d, J = 15.1 Hz, H-2″), 2.00 (1 H, m, H-4), 1.93 (1 H, dd, J = 14.9, 5.1 Hz, H-7), 1.66–1.36 (9 H, m, Me, H-7, 2 H-14, 2 H-4′, H-2″), 1.28–1.10 (18 H, m, Me, Me, 2-Me, 8-Me, 5′-Me, 5″-Me), 1.03 (3 H, d, J = 7.0 Hz, 4-Me), and 0.86 (3 H, t, J = 7.3 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 176.1, 175.8, 150.4, 139.7, 132.4, 128.8, 127.4, 103.3, and 96.3 ppm; IR (film) 3450 (br), 2975, 2940, and 1735 cm^{-1}; FABMS (Li spike) m/z 851 (M^+ + Li). Anal. Calcd for $C_{40}H_{64}NO_{15}S$: C, 56.86; H, 7.63; N, 3.32. Found: C, 56.45; H, 7.70; N, 3.15.

10-Aza-3′-*N*,10-didemethyl-11-deoxy-3′-*N*-(phenylsulfonyl)erythromycin A (17a/b), 10-Aza-3′-*N*,10-didemethyl-9,10-didehydro-9-deoxo-11,12-dideoxy-9,12-epoxy-3′-*N*-(phenylsulfonyl)erythromacin A (19), and 10-Aza-3′-*N*,10-didemethyl-9-deoxo-11-deoxy-3′-*N*-(phenylsulfonyl)erythromycin A (20a/b). Oxime **15** (3.75 g, 4.4 mmol) was dissolved in AcOH (40 mL, 0.1 N) and platinum oxide (1.8 g, 0.5 wt equiv) added. The mixture was hydrogenated at room temperature under 1000 psi hydrogen pressure for 48 h. The mixture was filtered through a pad of Celite, eluted with CH_2Cl_2, and concentrated. The residue was reconcentrated three times from CH_2Cl_2/heptane (to remove acetic acid). The resulting white foam was carefully chromatographed (80% EtOAc/$PhCH_3$; EtOAc; 95/5 CH_2Cl_2/MeOH; 95/5/1–90/10/1 CH_2Cl_2/MeOH/NH_4OH) to give recovered aldoxime (1.56 g, 42%), lactam **17a/b** (100 mg, 5% on recovered **15**, impure imino ether **19** and amine **20a/b** (700 mg, 33% on recovered **15**). Further careful chromatography (EtOAc) or PLC (triple elution, EtOAc) gave clean imino ether **19** (90 mg, 4% on recovered **15**), a process which, in this case, successfully removed the cyclohexylsulfonamide contaminant (see main text). The lactam and amine were contaminated with traces (~5%) of the cyclohexylsulfonamide analogues which precluded adequate microanalysis. **Lactam 17a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.77–7.44 (3 H, m, m/p-SO_2Ph), 6.79 (1 H, br d, J = 9.5 Hz, NH), 4.78 (1 H, br d, J = 11.1 Hz, H-13), 4.71 (1 H, d, J = 4.4 Hz, H-1″), 4.64 (1 H, d, J = 7.3 Hz, H-1′), 4.27 (1 H, d, J = 2.6 Hz, H-3), 4.15 (1 H, ddd, J = 13.8, 10.3, 1.6 Hz, H-11), 4.05 (2 H, m, H-3′, H-5″), 3.85 (1 H, d, J = 5.1 Hz, H-5), 3.75 (1 H, s, 6-OH), 3.61 (1 H, m, H-5′), 3.41 (3 H, s, OMe), 3.37 (1 H, ddd, J = 10.6, 7.6, 2.1 Hz, H-2′), 3.09 (1 H, t, J = 9.7 Hz, H-4″), 2.74 (3 H, s, NMe), 2.64 (1 H, d, J = 14.5 Hz, H-11), 2.50 (2 H, m, H-2, H-8), 2.38 (1 H, d, J = 15.4 Hz, H-2″eq), 2.30 (1 H, br s, 2′-OH), 2.27 (1 H, d, J = 9.9 Hz, 4″-OH), 2.13 (1 H, d, J = 1.9 Hz, 12-OH), 1.98 (1 H, m, H-14), 1.81 (2 H, m, H-4, H-7), 1.60 (1 H, d, J = 15.6 Hz, H-7), 1.55 (1 H, dd, J = 15.5, 4.7 Hz, H-2″ax), 1.45 (3 H, m, H-14, 2H-4′), 1.39 (3 H, d, J = 6.6 Hz, 8-Me), 1.31 (3 H, d, J = 6.2 Hz, 5″-Me), 1.26 (3 H, s, Me), 1.20 (6 H, m, Me, 2-Me), 1.14 (3 H, d, J = 6.2 Hz, 5′-Me), 1.05 (6 H, m, Me, 4-Me), and 0.82 (3 H, t, J = 7.2 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 177.9, 176.7, 139.4, 132.6, 128.9, 127.3, 101.8, and 95.0 ppm; IR (film) 3500, 3360, 2980, 2940, 1725, and 1655 cm^{-1}; FABMS (Li spike) m/z 837 (M^+ + Li); FABHRMS calcd for $C_{40}H_{66}LiN_2O_{14}S$ (M^+ + Li) 837.4395, found 837.4401. **Imino ether 19**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.58–7.41 (3 H, m, m/p-SO_2Ph), 4.88–4.80 (2 H, m, H-13, H-1″), 4.65 (1 H, d, J = 7.4 Hz, H-1′), 4.44 (1 H, br s, 6-OH), 4.15–4.05 (2 H, m, H-3′, H-5″), 3.99 (1 H, br s, H-3), 3.94 (1 H, d, J = 13.8 Hz, H-11), 3.76 (1 H, d, J = 3.4 Hz, H-5), 3.65 (1 H, m, H-5′), 3.38–3.31 (2 H, m, H-11, H-2′), 3.28 (3 H, s, OMe), 3.11 (1 H, t, J = 7.7 Hz, H-4″), 2.79–2.72 (4 H, m, NMe, 4″-OH), 2.62 (1 H, m, H-8), 2.53 (1 H, m, H-2), 2.34 (1 H, dd, J = 14.7, 3.5 Hz, H-2″eq), 2.18 (1 H, br d, J = 14.6 Hz, H-7), 1.80–1.40 (7 H, m, H-4, H-7, 2 H-14, 2 H-4′, H-2″ax), 1.35 (3 H, s, Me), 1.33 (3 H, d, J = 7.0 Hz, 8-Me), 1.28–1.24 (6 H, m, Me, 5″-Me), 1.17 (6 H, d, J = 6.3 Hz, coincident 2-Me, 5′-Me), 1.13 (3 H, s, Me), 0.98 (3 H, d, J = 7.0 Hz, 4-Me), and 0.94 (3 H, t, J = 7.4 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 176.4, 172.9, 139.9, 132.2, 128.7, 127.5, 104.9, and 96.1 ppm; IR (film) 3450, 2970, 2935, 1730, and 1665 cm^{-1}; FABMS (Li spike) m/z 820 (M^+ + Li). Anal. Calcd for $C_{40}H_{64}N_2O_{13}S$: C, 59.11; H, 7.88; N, 3.45. Found: C, 59.12; H, 8.06; N, 3.31. **Amine 20a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (2 H, d, J = 7.3 Hz, o-SO_2Ph), 7.57–7.42 (3 H, m, m/p-SO_2Ph), 4.94 (1 H, d, J = 11.0 Hz, H-13), 4.79 (1 H, d, J = 7.2 Hz, H-1′), 4.64 (1 H, br s, H-3), 4.54 (1 H, d, J = 4.7 Hz, H-1″), 4.03 (1 H, m, H-3′), 3.90 (2 H, m, H-5, H-5″), 3.67 (1 H, m, H-5′), 3.40–3.32 (4 H, m, OMe, H-2′), 3.07 (1 H, t, J = 9.2 Hz, H-4″), 3.01 (1 H, d, J = 12.5 Hz, H-11), 2.74 (3 H, s, NMe), 2.51 (1 H, q, J = 7.0 Hz, H-2), 2.44 (1 H, t, J = 10.6 Hz, H-9), 2.38–2.25 (4 H, m, H-9, H-11, H-2″eq, 4″-OH), 1.95 (1 H, br s, H-8), 1.83 (1 H, br s, H-4),

1.67–1.31 (6 H, m, H-7, 2 H-14, 2 H-4′, H-2″ax), 1.28–1.16 (10 H, m, H-7, Me, 2-Me, 5″-Me), 1.14 (6 H, m, Me, 5′-Me), 1.09 (6 H, m, Me, 8-Me), 1.04 (3 H, d, J = 7.3 Hz, 4-Me), and 0.86 (3 H, t, J = 7.1 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 175.7, 139.5, 132.5, 128.8, 127.3, 100.9, and 94.4 ppm; IR (film) 3480, 2930, and 1730 cm^{-1}; FABMS (Li spike) m/z 823 (M^+ + Li), 817 (M^+ + 1); FABHRMS calcd for $C_{40}H_{68}LiN_2O_{13}S$ (M^+ + Li) 823.4602, found 823.4623.

10-Aza-10-demethyl-11-deoxyerythromycin A (18).[21] Naphthalene (0.5 g, 3.9 mmol) was dissolved in THF (3.9 mL, 1.0 N) at room temperature, and freshly cut lithium pieces (55 mg, 2 equiv) were added. The mixture was sonicated for 45 min. Portions of this solution of lithium naphthalenide were added dropwise to a solution of the sulfonamide 17 (80 mg, 96 μmol) in THF (1.0 mL, 0.1 N) maintained at −78 °C, until the deep green color of the reagent was no longer quenched. The mixture was allowed to stir for a further 10 min before quenching with aqueous $NaHCO_3$ solution and allowing to warm to room temperature. K_2CO_3 solution was added and the mixture extracted with CH_2Cl_2. The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was crudely chromatographed (95/5 CH_2Cl_2/MeOH; 90/10/1 CH_2Cl_2/MeOH/NH_4OH) to remove naphthalene. The resulting clear oil was dissolved in $CHCl_3$ (2 mL, 0.05 N). Formaldehyde (31 μL of 37% aqueous solution, 4 equiv) was added followed by formic acid (7.3 μL, 2 equiv) and the mixture heated to 60 °C. After 90 min (TLC 90/10/1 CH_2Cl_2/MeOH/NH_4OH) it was cooled to room temperature, diluted with aqueous K_2CO_3 solution, and extracted with CH_2Cl_2. The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (95/5/1–90/10/1 CH_2Cl_2/MeOH/NH_4OH) to give the lactam 18 (21 mg, 31%) as a clear oil (which could be lyophilized from benzene to give a white powder): ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (1 H, d, J = 9.1 Hz, NH), 4.78 (1 H, d, J = 11.3 Hz, H-13), 4.72 (1 H, d, J = 4.5 Hz, H-1″), 4.61 (1 H, d, J = 7.2 Hz, H-1′), 4.30 (1 H, d, J = 2.9 Hz, H-3), 4.16 (1 H, ddd, J = 14.4, 10.5, 1.9 Hz, H-11), 4.06 (1 H, dq, J = 9.5, 6.2 Hz, H-5″), 3.90 (1 H, br s, OH), 3.86 (1 H, d, J = 5.5 Hz, H-5), 3.56 (1 H, m, H-5′), 3.34 (3 H, s, OMe), 3.30 (1 H, dd, J = 10.2, 7.2 Hz, H-2′), 3.01 (1 H, t, J = 9.8 Hz, H-4″), 2.66 (1 H, d, J = 14.4 Hz, H-11), 2.60–2.40 (3 H, m, H-2, H-8, H-3′), 2.36 (1 H, d, J = 15.4 Hz, H-2″eq), 2.30 (6 H, s, NMe_2), 2.17 (1 H, d, J = 10.3 Hz, 4″-OH), 2.13 (1 H, d, J = 2.0 Hz, 2′-OH), 2.00 (1 H, m, H-14), 1.85 (1 H, dd, J = 15.3, 10.5 Hz, H-7), 1.81 (1 H, m, H-4), 1.68 (1 H, br d, J = 12.5 Hz, H-4′), 1.62 (1 H, d, J = 15.4 Hz, H-7), 1.54 (1 H, dd, J = 15.3, 5.0 Hz, H-2″ax), 1.48 (1 H, m, H-14), 1.41 (3 H, d, J = 6.4 Hz, 8-Me), 1.32 (3 H, d, J = 6.2 Hz, 5″-Me), 1.28–1.18 (13 H, m, H-4′, Me, Me, 2-Me, 5′-Me), 1.13–1.08 (6 H, m, Me, 4-Me), and 0.83 (3 H, t, J = 7.3 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) δ 178.3, 176.9, 101.9 and 94.9 ppm; IR (film) 3465, 3370, 2970, 2940, 1715, and 1660 cm^{-1}; FABMS (Li spike) m/z 711 (M^+ + Li). Anal. Calcd for $C_{35}H_{64}N_2O_{12}$: C, 59.64; H, 9.15; N, 3.97. Found: C, 59.36; H, 9.13; N, 3.78.

(21) While the sodium amalgam procedure is perfectly adequate for the desulfonylation an alternative general procedure is also available and is illustrated here.

10-Aza-9-deoxo-11-deoxyerythromycin A (5). Protected azalide **20a/b** (160 mg, 0.2 mmol) was dissolved in 1/1 THF/MeOH (4.0 mL, 0.05 N), and KH_2PO_4 (933 mg, 35 equiv) was added. The mixture was cooled to −20 °C and freshly ground 6% sodium amalgam (1.88 g, 25 equiv) was added in one portion. After 45 min an additional 35 equiv of KH_2PO_4 and 25 equiv of amalgam were added. After a further 45 min (TLC 95/5/1 CH_2Cl_2/MeOH/NH_4OH) the mixture was decanted into aqueous K_2CO_3 solution. The amalgam residue was washed several times with EtOAc, decanting into the aqueous mixture. This mixture was partitioned and the aqueous portion reextracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in MeOH (4.0 mL, 0.05 N) and formaldehyde (79 μL of a 37% aqueous solution, 5 equiv) added. Sodium cyanoborohydride (124 mg, 10 equiv) was added in one portion. After 90 min a further 5 equiv of formaldehyde and 10 equiv of the borohydride were added and the mixture stirred for a further 12 h (TLC 95/5/1 CH_2Cl_2/MeOH/NH_4OH). Aqueous K_2CO_3 was added and the mixture extracted with CH_2Cl_2. The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (95/5 CH_2Cl_2/MeOH; 97.5/2.5/0.5–95/5/1 CH_2Cl_2/MeOH/NH_4OH) to give the azalide 5 (80 mg, 58%) as a clear oil (which could be lyophilized from benzene to give a white powder): ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (1 H, dd, J = 10.6, 2.6 Hz, H-13), 4.71 (1 H, br d, J = 2.7 Hz, H-1″), 4.54 (1 H, d, J = 7.3 Hz, H-1′), 4.48 (1 H, br s, H-3), 4.02 (1 H, dq, J = 8.7, 6.5 Hz, H-5″), 3.68 (1 H, d, J = 5.1 Hz, H-5), 3.56 (1 H, m, H-5′), 3.30 (3 H, s, OMe), 3.27 (1 H, dd, J = 12.2, 4.8 Hz, H-2′), 3.04 (1 H, d, J = 3.8 Hz, H-4″), 2.79 (1 H, d, J = 13.4 Hz, H-11), 2.59 (1 H, dq, J = 7.3, 2.2 Hz, H-2), 2.52 (1 H, m, H-3′), 2.33 (3 H, s, -NMe), 2.29 (6 H, s, $-NMe_2$), 2.28–2.15 (4 H, m, 2 H-9, H-11, H-2″), 1.92 (2 H, m, H-4, H-8), 1.79 (1 H, dd, J = 14.2, 4.4 Hz, H-7), 1.65 (1 H, br d, J = 11.3 Hz, H-4′), 1.58 (1 H, dd, J = 15.0, 4.8 Hz, H-2″), 1.53 (1 H, m, H-14), 1.33 (1 H, m, H-14), 1.25 (3 H, d, J = 6.4 Hz, 5″-Me), 1.23–1.15 (17 H, m, H-4, H-7, 2-Me, 6-Me, 12-Me, 5′-Me, 3″-Me), 1.08 (3 H, d, J = 7.3 Hz, Me), 1.03 (3 H, d, J = 6.6 Hz, Me), and 0.84 (3 H, t, J = 7.3 Hz, 3 H-15) ppm; ^{13}C ($CDCl_3$) 176.6, 103.0, and 95.2 ppm; IR (film) 3460, 2975, 2940, and 1730 cm^{-1}; FABMS m/z 705 (M^+ + H). Anal. Calcd for $C_{36}H_{68}N_2O_{11}$: C, 61.34; H, 9.72; N, 3.97. Found: C, 61.11; H, 9.81; N, 3.81.

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Supplementary Material Available: Full listings of ^{13}C and IR data for all compounds included in the Experimental Section, ^1H NMR spectra for compounds **9**, **17a/b**, and **20a/b**, ^{13}C NMR spectrum for compound **9**, and full data for compounds **16** and **24** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Molecular Structure of Phosphonium Ylides

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The structures of 12 phosphonium ylides were completely optimized at the HF/6-31G* level. Use of larger basis sets and electron correlation in optimizing the structures of methylenephosphorane and phosphorane cyclopropylide resulted in little geometric change. The phosphonium ylides can be grouped into two classes: (1) nonstabilized ylides and (2) stabilized ylides. All examples of the nonstabilized ylides have nonplanar ylidic carbon geometries, while the stabilized ylides have planar ylidic carbons. These structures are used to support the concept that the dominant resonance structure is the ylide form.

The question of the nature of the bonding in phosphonium ylides involves the relative contribution of the two resonance structures **A**, the *ylide* form, and **B**, the *ylene* form.[1] The short P-C distance (1.66–1.70 Å) of most ylides

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