that **5k** consists of 100% *E* isomer.

Registry No. 1a, 79-46-9; **1b**, 600-24-8; **1c**, 66553-37-5; **1d**, 4609-91-0; **1e**, 2562-38-1; **1f**, 1122-60-7; **1g**, 10312-37-5; **1h**, 2625-30-1; **1i**, 625-74-1; **1k**, 108-03-2; **2**, 20451-53-0; (*E*)-**3**, 67652-99-7; (*Z*)-**3**, 67653-00-3; **5a**, 107-86-8; (*E*)-**5b**, 83436-87-7; (*Z*)-**5b**, 83436-90-2; **5b**-2,4-D_2, 3592-24-3; (*E*)-**5c**, 83436-88-8; (*Z*)-**5c**, 83436-89-9; (*E*)-**5d**, 82235-26-5; (*Z*)-**5d**, 82235-25-4; **5e**, 5623-82-5; **5f**, 1713-63-9; (*E*)-**5g**, 80998-56-7; (*Z*)-**5g**, 80998-57-8; (*E*)-**5h**, 37868-74-9; **5h**-2,4-D_2, 6556-91-8; (*E*)-**5i**-2,4-D_2, 19327-72-1; **5j**, 13153-14-5; **5j**-2,4-D_2, 33045-89-5; (*E*)-**5k**, 14250-96-5; **6**, 67209-90-9.

(15) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968).

Neutral Sugar Modifications of Macrolide Antibiotics. Diazo Phosphonate Mediated Intramolecular Cyclizations

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Received May 18, 1982

The ability to selectively elaborate the rather inaccessible C-3″ position of the cladinose moiety of the macrolide antibiotics erythromycin A (**1**) and 9-dihydroerythromycin A (**2**) is a challenging synthetic problem.[1a] The challenge stems from the inherent instability of the glycosidic linkage to typical dealkylation conditions. For example, the attempted demethylation of the cladinose moiety at the C-3″ position in compounds **1** or **2** by either Lewis acid or nucleophilic displacement conditions afforded only negligible quantities of the corresponding C-3″ carbinols (erythromycin C or 9-dihydroerythromycin C).[1b] Thus, we identified the fused ring derivative **5** as a useful synthetic target. Compound **5** may be viewed as a synthetic entry into C-3″-modified erythromycins, since oxidative cleavage of the resulting olefinic linkage would afford a potentially manipulatable α-hydroxy aldehyde derivative.

Our synthetic analysis of substrate **5** was based upon the hypothesis that it should be possible to carry out a controlled carbenoid insertion at the C-3″-methyl ether of the cladinose moiety. Since the macrolide presents a multitude of sites susceptible to carbenoid insertion, we chose to introduce a masked carbenoid functionality that would be preferably localized at a terminus proximate to the C-3″-methyl ether. We rationalized that, upon unmasking the carbenoid species, the favorable entropic driving force of an intramolecular cyclization would regioselectively direct the insertion to the relatively unactivated carbon–hydrogen center of the C-3″-methyl ether.

A reagent that is uniquely suited to the requirements of the proposed synthesis of **5** is the diazo phosphonate **4**.[2] For example, it is known[3] that the ylide derived from diazo phosphonate **4** nucleophilically adds to carbonyl centers in the presence of alcohols, affording a variety of substituted vinyl ethers. Although there are neither reports describing the implementation of this ylide in an intramolecular sense[4] nor the insertion of the latent carbenoid into an unactivated methyl ether carbon–hydrogen bond, it is not an unreasonable extension of the methodology. Therefore, our overall synthetic plan requires the addition of the diazo ylide derived from diazo phosphonate **4** to an appropriately substituted erythromycin precursor.

We selected 9-dihydroerythromycin A (**2**) as the macrolide substrate to attempt the synthesis of **5**, since **2** is inherently more stable than **1**.[5] Thus, intermediate **2** was converted in a straightforward manner to ketone **3** via Me_2SO–TFAA oxidizing conditions.[6] The oxidation is regiospecific for the C-4″ carbinol, and no C-9 oxidized material is isolated. Subsequent exposure of a dry tetrahydrofuran solution of ketone **3** and diazophosphonate **4** to potassium *tert*-butoxide affords carbohydrate modified derivative **5** as a crystalline material. The overall yield was 50% (Scheme I summarizes the overall sequence). The transformation of **3** to **5** is most interesting if one considers that when the reaction is carried out in the presence of a large excess of allyl alcohol,[7] *none* of the corresponding allyl vinyl ether resulting from intermolecular carbenoid insertion is observed.

Scheme II outlines our mechanistic proposal.[8] Although we have no unequivocal evidence, we believe that once the nucleophilic addition has occurred (**3** → **6**), the carbenoid moiety is unmasked and selectively inserts into the methyl ether carbon–hydrogen bond (formalized in **6** → **8**). Upon completion of the cyclization sequence, the olefin is formed by elimination (**8** → **5**) in the normal Emmons–Wadsworth fashion.

The utility of this carbenoid-mediated cyclization process may be far reaching since it allows one not only to homologate at a relatively unreactive center but also may allow formation of heterocycles[9] and fused heterocycles.

In summary, therefore, we have been able to synthesize the target erythromycin derivative **5** in 50% overall yield. The salient feature of the synthetic plan was a regioselective carbenoid insertion at a relatively unactivated carbon–hydrogen center, allowing facile ring closure.

Experimental Section

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

(1) (a) For a related study concerning the inherent instability of the cladinose moiety, see LeMahieu, R.; Carson, M.; Kierstead, R.; Fern, L.; Grunberg, E. *J. Med. Chem.* **1974**, *17*, 953. (b) Unpublished results from this laboratory.

(2) Seyferth, D.; Marmor, R. *Tetrahedron Lett.* **1970**, 2493.

(3) Gilbert, J.; Weerasooriya, U. *Tetrahedron Lett.* **1980**, 2041.

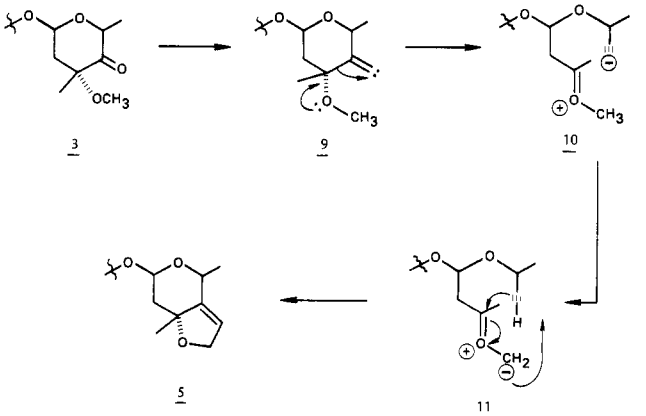
(4) After completion of this work Berson reported what is to our knowledge the first intramolecular case; Salinaro, R.; Berson, J. *Tetrahedron Lett.* **1982**, 1447.

(5) Glabski, T.; Bojarska-Dahlig, H.; Slawinski, W. *Roczniki Chem.* **1976**, *50*, 1281.

(6) Huang, S.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.

(7) Gilbert, J.; Weerasooriya, U.; Wiechman, B.; Ho, L. *Tetrahedron Lett.* **1980**, 5003.

(8) An extremely interesting alternative mechanistic possibility was proposed by Professor Jack Baldwin during informal discussions. Professor Baldwin's scheme initially involves formation of a vinyl carbene (**9**), which rearranges to dipolar intermediate **11**. Intermediate **11** then

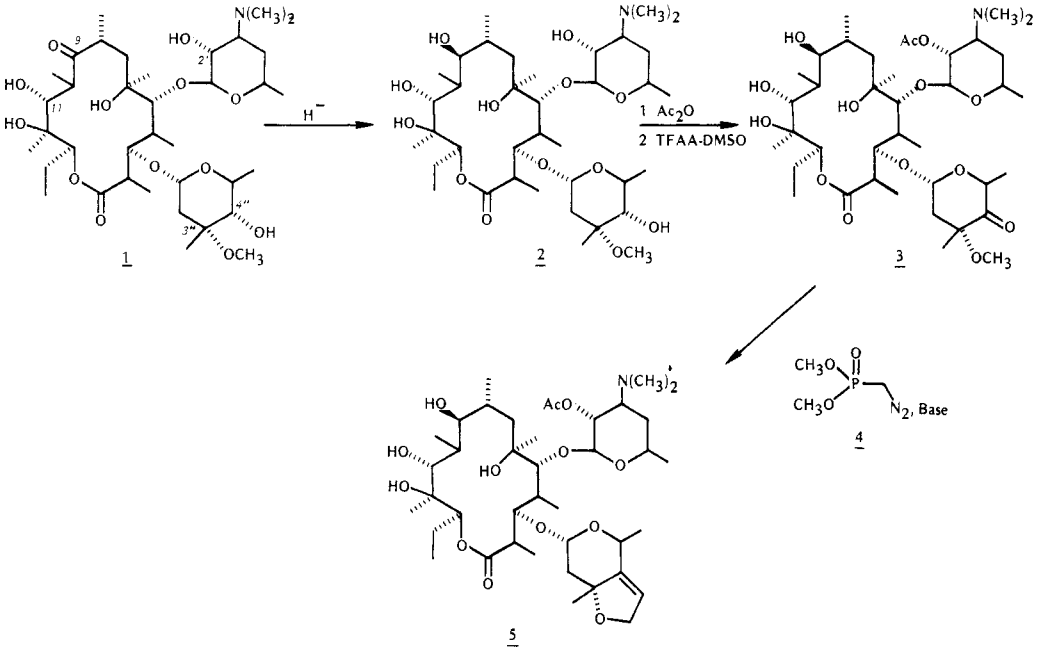


undergoes a dipolar cycloaddition to afford **5**. We thank Professor Baldwin for his contribution.

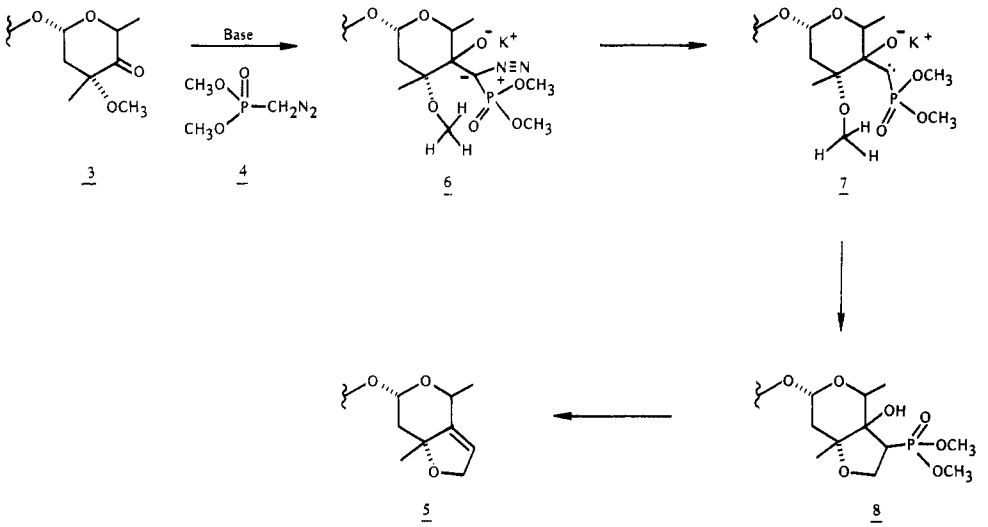
(9) It is interesting to note that addition of the diazoylide derived from **4** to *o*-methoxyacetophenone does *not* afford cyclized material; whereas similar treatment of 5-hydroxypentanal does result in the corresponding seven-membered cyclic enol ether.

0022-3263/82/1947-5019$01.25/0

Scheme I



Scheme II



was distilled from $LiAlH_4$ prior to use. All the macrolide intermdiates and reagents that were utilized are known except compounds **3** and **5**, which are fully characterized.[2,5]

Preparation of 9-Dihydro-2′-acetyl-4″-deoxy-4″-oxoerythromycin A (3). To a methylene chloride solution (80 mL) of 9-dihydroerythromycin A[5] (**2**; 20.0 g, 27.1 mmol) was added in one portion acetic anhydride (3.2 g, 3 mL, 31.7 mmol), and the resulting solution was allowed to stir under a nitrogen atmosphere for 2 h. After this period, TLC [silica/$CHCl_3$/MeOH/NH_3 (9:1:0.1)] indicated no remaining starting **2** and the solution was added to a mixture of methylene chloride/water (40 mL:150 mL), and the pH was adjusted to 11.5 with aqueous sodium hydroxide (6 N). The organic phase was separated, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 9-dihydro-2′-acetylerythromycin A (19 g) as a solid, which was used without further purification in the oxidation step.

To a methylene chloride solution (52 mL) of dimethyl sulfoxide (4.5 mL) cooled to −70 °C was added over a period of 7 min trifluoroacetic anhydride (8.3 mL), such that the temperature did not exceed −65 °C. After the mixture was stirred for 20 min at −70 °C, pyridine (5.3 mL) was added slowly over a period of 5 min, followed by the addition over 30 min of a methylene chloride solution (46 mL) of 9-dihydro-2′-acetylerythromycin A (16 g, 20.5 mmol, prepared as described above). The reaction mixture was allowed to stir for 30 min at −70 °C, after which time it was treated with triethylamine (21.7 mL) at such a rate that the temperature did not exceed −65 °C. After being stirred for 10 min, the reaction mixture was poured into a stirring mixture of methylene chloride/water (300 mL:800 mL), and the pH was adjusted to 9.5 with aqueous sodium hydroxide (6 N). The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford crude ketone **3** (16.1 g). The crude ketone was crystallized from an acetone/water mixture to afford ketone **3** hemihydrate (13.5 g, mp 183–184 °C): ^1H NMR ($CDCl_3$) δ 0.90 (t), 0.95 (d), 1.10 (s), 1.15–1.29 (multiplet), 1.40 (d), 1.45 (s), 1.70–2.00 (m), 2.05 (s), 2.25 (s), 2.30–2.85 (m), 3.35 (s), 3.45 (m), 3.70 (m), 4.10 (d), 4.30 (br s), 4.45 (q), 4.55 (d), 4.80–4.95 (m), 5.30 (br t); ^{13}C NMR ($CDCl_3$) δ 210.6 (off-resonance, s), 176.2 (s), 169.4 (s), 100.7 (d), 95.7 (d), 83.1 (d), 82.4 (d), 77.1, 74.8 (s), 74.3 (s), 72.6, 71.1, 70.0, 68.9, 63.0, 51.1 (q), 43.8, 40.7, 40.4, 38.1, 36.6, 34.3, 31.9, 30.3, 25.2, 21.4, 21.2, 20.9, 20.6, 19.0, 16.1, 15.9, 14.6, 13.8, 10.9, 8.5.

Anal. Calcd for $C_{39}H_{69}NO_{14}·0.5H_2O$: C, 59.68; H, 8.98; N, 1.79. Found: C, 59.95; H, 9.03; N, 1.82.

Preparation of 9-Dihydro-2′-acetyl-4″-deoxy-3″,4″-dihydrofuranylerythromycin A (5). To a dry tetrahydrofuran solution (8 mL) of **3** (928 mg, 1.2 mmol) maintained under a nitrogen atmosphere at 0 °C was added a dry tetrahydrofuran solution (4 mL) of dimethyl diazomethylphosphonate[2] (**4**; 269 mg, 1.79 mmol). To this solution was added over 20 min at 0 °C a

tetrahydrofuran slurry (12 mL) of potassium *tert*-butoxide (472 mg, 4.2 mmol). After 15 min, TLC [silica/$CHCl_3$/MeOH/NH_3 (9:1:.1)] indicated that starting material was consumed. The reaction mixture was added to a stirred mixture of ethyl acetate/water (40 mL:150 mL), and the pH was adjusted to 11.5 with aqueous sodium hydroxide (6 N). The organic layer was separated, washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo, affording crude **5** (900 mg). The crude material was crystallized from an acetone/water mix and recrystallized from the same solvent to afford pure **5** (800 mg, mp 132–133 °C): ^{1}H NMR ($CDCl_3$) δ 0.90 (t), 0.95 (d), 1.05 (d), 1.15–1.30 (m), 1.40 (d), 1.65 (m), 1.82 (dd, 11.9, 10.4), 2.05 (s), 2.30 (s), 2.60–2.81 (m), 3.45–3.55 (m), 3.75 (br s), 3.95 (m), 4.20 (br s), 4.30 (br s), 4.60 (AB q, J_{AB} = 12.8 Hz), 4.75–4.95 (m), 5.15 (dd, 10.1, 2.1), 5.60 (d, 1.8); ^{13}C NMR ($CDCl_3$) δ 177.2 (off-resonance, s), 169.5 (s), 143.5 (s), 118.7 (d), 99.8 (d), 94.2 (d), 85.4 (s), 83.9 (d), 80.1 (d), 78.3 (d), 76.4 (d), 74.4 (s), 73.9, 71.9, 70.8, 69.6, 68.8, 63.2, 46.2, 42.9, 41.7, 40.5, 38.4, 34.6, 32.1, 31.3, 25.7, 24.8, 21.2, 20.8, 18.5, 16.8, 15.8, 13.1, 10.9, 7.7.

Anal. Calcd for $C_{40}H_{69}NO_{13}$: C, 62.23; H, 9.01; N, 1.81. Found: C, 62.08; H, 8.94; N, 1.80.

Acknowledgment. We thank Mr. R. Ware, Dr. E. Whipple, and Dr. G. Chmurny for assistance in obtaining spectral data and invaluable discussions with regard to the interpretations.

Registry No. **2**, 63864-45-9; **3**, 83291-99-0; **4**, 27491-70-9; **5**, 83292-00-6; 9-dihydro-2′-acetylerythromycin A, 83311-47-1.

Isoquinolinium Cycloadditions: Regiospecific Synthesis of 1-Naphthaldehydes and Conversion to 1-Naphthylamines

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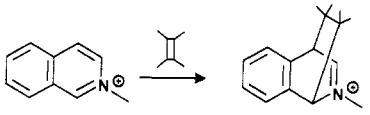
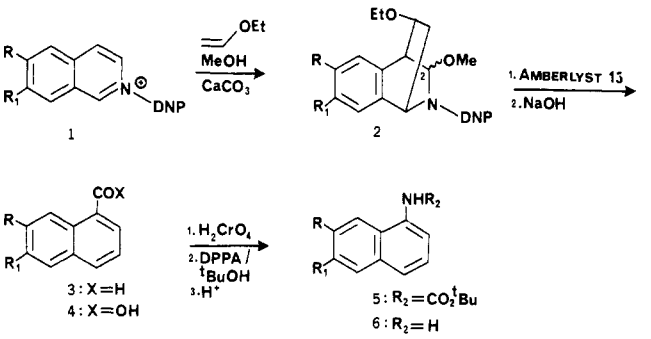
Polar cycloaddition of isoquinoline salts with electron-rich alkenes disrupts the aza aromatic ring, creating a tricyclic system containing up to four new stereocenters and an immonium ion capable of further chemistry (eq 1).



(1)

Due largely to the pioneering work of Bradsher,[1] these reactions are known to be virtually 100% regiospecific and often highly stereospecific. During our investigations into the general use of this intriguing reaction, we developed a modification that overcomes some prior synthetic limitations and gives good yields of adduct from 3-unsubstituted isoquinolines.[2] We report herein its application to a regiospecific synthesis of 1-naphthaldehydes and their conversion to 1-naphthylamines, useful benzophenanthridine alkaloid precursors.[3a,b,4]

Scheme I



a: R = R_1=OCH_2O; b: R=OCH_2Ph, R_1=OMe; c: R=H, R_1=OMe; d: R = R_1 = H

Treatment of dinitrophenyl (DNP) salt **1** (prepared from the corresponding isoquinoline[5] and 2,4-dinitrobromobenzene) in methanol with excess ethyl vinyl ether in the presence of powdered calcium carbonate for 24 h quantitatively generates adduct **2** as a mixture of C-2 epimers[1b] (Scheme I). The use of calcium carbonate is important for maximum yields. Other commonly used acid scavengers, inter alia, tertiary amines, alumina, glycidol, sodium bicarbonate, and sodium acetate, are either ineffective in preventing polymerization of the dienophile or incompatible with **1** under the reaction conditions. The foregoing epimeric mixture is hydrolyzed in tetrahydrofuran/water with Amberlyst-15 resin at 37 °C for 16 h and the isolated product immediately heated under reflux for 5 min with sodium hydroxide.[6] The entire procedure, best performed without purification of intermediates, affords naphthaldehyde **3** in 80–96% yield overall from **1** after chromatography.

Jones oxidation of **3** at 0 °C for 8 h gives naphthoic acid **4** (88–95%). Subsequent Curtius rearrangement by diphenylphosphoryl azide[7] (DPPA) and triethylamine in refluxing anhydrous *tert*-butyl alcohol leads to carbamate **5** (73–80%), which is hydrolyzed in tetrahydrofuran–water–concentrated hydrochloric acid to the easily oxidized naphthylamine (**6**; 73–86%).[8] Curtius rearrangement in dioxane with added benzyl alcohol followed by catalytic debenzylation is an equally effective alternative, e.g., **4c** to **6c** (71%).

Substituted isoquinoline methodide salts also give good yields of adduct but under more drastic contitions. For instance, 6,7-(methylenedioxy)isoquinoline methodide requires heating at 120 °C (sealed tube) for 2 days. More importantly, conversion of the adduct to naphthaldehyde proceeds in low overall yield (<30%).

Experimental Section

General Procedures. ^{1}H NMR spectra measured at 90 MHz on a JEOL FX-90Q spectrometer with tetramethylsilane as in-

(1) (a) Chen, T.-K.; Bradsher, C. K. *J. Org. Chem. 1979*, **44**, 4680–4683 and earlier references cited. (b) Intramolecular version: Gisby, G. P.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 249–255.

(2) These limitations have been recognized: Day, F. H.; Bradsher, C. K.; Chen, T.-K. *J. Org. Chem.* **1975**, *40*, 1195–1198. Day, F. H.; Bradsher, C. K. *Tetrahedron Lett.* **1971**, 409–410.

(3) Examples of 1-naphthylamine synthesis: (a) Gillespie, J. P.; Amoros, L. G.; Stermitz, F. R. *J. Org. Chem.* **1974**, *39*, 3239–3241. (b) Begley, W. J.; Grimshaw, J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2324. (c) Campbell, K. N.; LaForge, R. A.; Campbell, B. K. *J. Org. Chem.* **1949**, *14*, 346–354.

(4) Reviews: Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 223–232. Hearn, M. J.; Swanson, S. L. *Ibid.* **1981**, *18*, 207–222.

(5) For a general isoquinoline synthesis, see Falck, J. R.; Manna, S.; Mioskowski, C. *J. Org. Chem.* **1981**, *46*, 3742–3745. Also, Birch, A. J.; Jackson, A. H.; Shannon, P. V. R.; Varma, P. S. P. *Tetrahedron Lett.* **1972**, 4789–4792.

(6) For related reaction leading to ketones, consult Day, F. H., Ph.D. Dissertation, Duke University, Durham, NC, 1973.

(7) Shioiri, T.; Ninomiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.

(8) Naphthylamines are best stored as their hydrochloride salt or cold under an inert atmosphere.

0022-3263/82/1947-5021$01.25/0