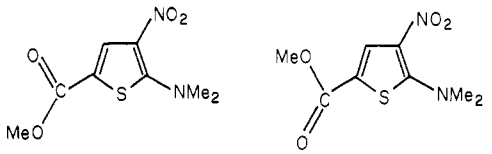
Table II. Dimethylamino Compounds[a]

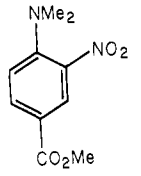
compd	crystallization solvent	mp, °C
2a	petroleum ether-benzene	32-33
2b	ligroin-benzene	83-84
2c	ethanol-dioxane	212-213
2d	ethanol	125-126
2e[b]	methanol-dioxane	150-151
2f	ethanol-dioxane	159-160
2g	methanol-dioxane	149-150
2h[c]	chloroform	153-154
4	benzene	138-139
5	ligroin-benzene	72-73

[a] Satisfactory analytical data (±0.3% for C, H, and N) were obtained for all new compounds listed in the table. The compounds are yellow or orange. [b] Cf.: Izmail'skii, V. A.; Polevshchikov, P. F. *Dokl. Akad. Nauk SSSR* **1964**, *159* (5), 1803. [c] Cf.: Hellerbach, J.; Szente, A. German Offen 2 342 931, 1974; *Chem. Abstr.* **1974**, *80*, 146002.

in ring shape could eliminate this degeneracy. Therefore, we searched for restricted rotation about the Ar–CO_2Me bond in **2d** and observed at −120 °C two well-separated ^{13}C signals for both C-4 and OCH_3, corresponding to the conformers **6a** and **6b** in nearly equal amounts. Unambigous NMR evidence for rotamers in an aromatic ester has thus been obtained; the $\Delta G^{\ddagger}$ value is shown in Table I. In order to confirm this interpretation, we examined the analogous benzene derivative 4-(methoxycarbonyl)-2-nitro-*N*,*N*-dimethylaniline (**7**). The introduction of the nitro group was expected to modify the symmetry of methyl 4-(dimethylamino)benzoate and thus the degeneracy postulated in this compound,[19] and this result was found. At −140 °C all the signals for ring carbon atoms, as well as that for the carbonyl group, were split, but with very small separations (maximum $\Delta\nu$ observed 0.64 ppm, minimum 0.16 ppm). The intensity ratio within each doublet was about 2:1, and such an effect can result only from restriction of the Ar–CO rotation, giving rise to a pair of unequally populated syn–anti conformers.



6a **6b**



7

Restricted rotation about the Ar–NMe_2 bond was also detected in **7**; this phenomenon does not affect the aromatic carbons but only makes the two *N*-methyl groups diastereotopic, with lines having an intensity ratio of 1:1. The $\Delta G^{\ddagger}$ of 6.3 kcal mol^{-1} (Table I) is lower than that for the analogous thiophene **2d**.

Experimental Section

Materials. Compounds **2a–h**, **4**, and **7** were prepared by reacting the appropriate bromonitro compound (5 mmol) with dimethylamine (15–50 mmol) in benzene (20 mL) at room temperature for a few minutes or several hours, depending on the substrate. The reaction mixtures were evaporated and the residue purified by column chromatography on silica gel (eluant petroleum ether–benzene) and/or crystallization (Table II).

NMR Measurements. NMR spectra were recorded in the FT mode on a Varian XL-100 instrument. A few hundred transients were accumulated, and an external ^{19}F lock system made it possible to lock at the very low temperatures employed. A thermocouple inserted in a dummy tube was used to monitor the temperature, and the $\Delta G^{\ddagger}$ values were obtained by determining the line-coalescence temperature. Samples were prepared by connecting the 10-mm sample tubes to a vacuum line and condensing the gaseous solvent (CHF_2Cl) in them by using liquid nitrogen. The sample tubes were then sealed under vacuum and introduced into the precooled probe of the spectrometer.

Acknowledgment. We are grateful to the Consiglio Nazionale delle Ricerche for financial support.

Registry No. 2a, 82080-40-8; **2b**, 82080-41-9; **2c**, 82080-42-0; **2d**, 82080-43-1; **2e**, 881-31-2; **2f**, 82080-44-2; **2g**, 82080-45-3; **2h**, 52431-12-6; **4**, 23631-00-7; **5**, 1670-17-3; **7**, 82080-46-4.

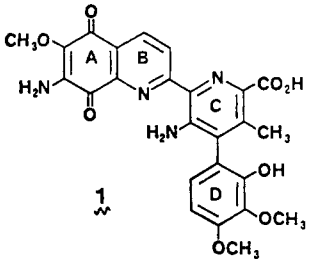
A Heterocyclic Diels–Alder Approach to the Synthesis of the Pyridine C Ring of Streptonigrin[1,2]

John C. Martin

Syntex Research, Institute of Bio-Organic Chemistry, Palo Alto, California 94304

Received February 26, 1982

Streptonigrin 1, an antitumor antibiotic with interesting biological activities, was first isolated by Rao and Cullen from *Streptomyces flocculus*.[3] The structure was determined by spectroscopic and chemical studies[4] and later confirmed by X-ray analysis.[5] Additionally, studies of the biosynthesis[6] and mechanism of action[7] of streptonigrin have been published. Although streptonigrin has been found to be effective as an antitumor agent, it is too toxic for general clinical use.[8]



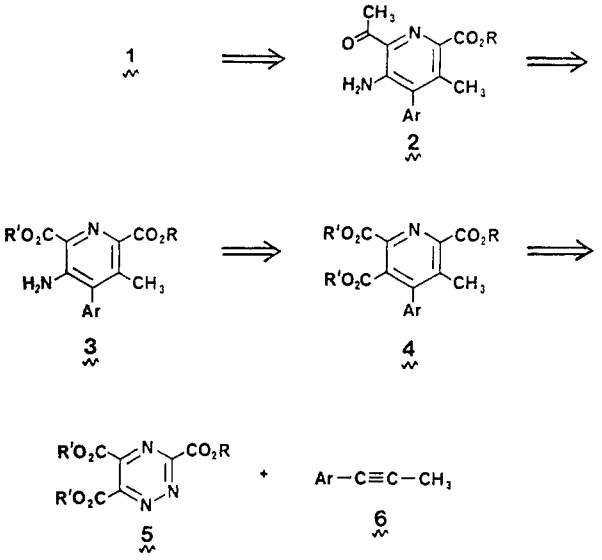
1

Because of its complex, unique structure and the need for less toxic analogues, streptonigrin has been the focus of considerable synthetic effort[9] including two total syntheses;[10] however, the regiospecific synthesis of its

(1) Contribution no. 148 from the Institute of Bio-Organic Chemistry.
(2) Presented in part at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, April 2, 1982.
(3) Rao, R. V.; Cullen, W. P. *Antibiot. Annu.* **1959–1960**, 950.
(4) Rao, R. V.; Biemann, K.; Woodward, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2532.
(5) Chiu, Y. P.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1975**, *97*, 2525.
(6) Gould, S. J.; Cane, D. E. *J. Am. Chem. Soc.* **1982**, *104*, 343.
(7) Cone, R.; Hasan, S. K.; Lown, J. W.; Morgan, A. R. *Can. J. Biochem.* **1976**, *54*, 219. Lown, J. W.; Sim, S. *Ibid.* **1976**, *54*, 446.
(8) Driscoll, J. S.; Hazard, G. F.; Wood, H. B.; Goldin, A. *Cancer Chemother. Rep.* **1974**, *4*, Part 2, 1.
(9) Hibino, S. *Heterocycles* **1977**, *6*, 1485.
(10) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271. Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.* **1982**, *104*, 536.

0022-3263/82/1947-3761$01.25/0 © 1982 American Chemical Society

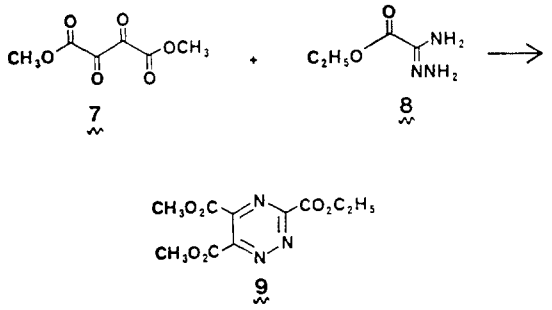
Scheme I



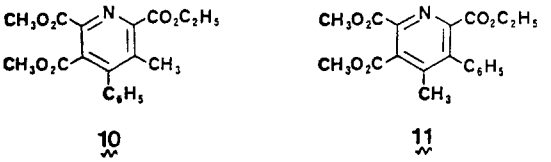
pentasubstituted pyridine C-ring moiety still presents a considerable challenge. We now report an alternative approach to the synthesis of the pyridine moiety that involves the cycloaddition of a 1,2,4-triazine with an acetylene to yield a pentasubstituted pyridine containing the appropriate functionalities for the elaboration of the streptonigrin framework. The strategy planned for the synthesis is developed in Scheme I. Methodology exists for synthesizing streptonigrin I from acetylpyridine 2,[9] which should be accessible from diester 3. Aminopyridine 3 could be prepared from triester 4 which in turn would be a potential Diels–Alder adduct of the reaction of triazine 5 with propyne 6.

The key step of this retrosynthetic analysis is the Diels–Alder reaction of an acetylene with a 1,2,4-triazine to give a pyridine of type 4. Electron-deficient triazines have been reported to undergo cycloaddition with electron-rich dienophiles such as ynamines[11] and enamines[12] to give highly substituted pyridines. However, from the literature precedent the reactivity or the regiochemistry of cycloaddition of an aryl propyne with a 1,2,4-triazine could not be predicted.

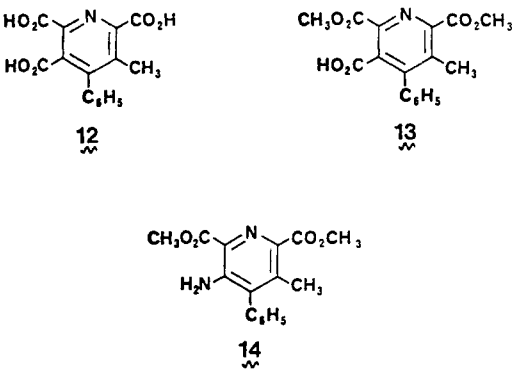
Therefore, in order to investigate the feasibility of this approach, the use of 1-phenylpropyne (6; Ar = Ph) as a model dienophile was studied. Condensation of dioxosuccinate 7[13] with amidrazone 8[14] afforded an appropriate starting triazine 9 in 67% yield. Triazine 9 was reacted



with an excess of 1-phenylpropyne at 200 °C in a Parr bomb for 12 h to give a 62% yield of a 3:2 mixture of pyridines 10 and 11, respectively, as indicated by an ^1H NMR spectrum of the chromatographically purified product mixture. Fortunately, the desired isomer 10 could be crystallized from this mixture in 18% yield. Pyridines 10 and 11 proved difficult to separate by chromatography so only a 3% yield of isomer 11 was obtained in pure form by further chromatography of the mother liquor. The structures of isomeric pyridines 10 and 11 were clearly indicated by their corresponding ^1H NMR spectra. The proton absorptions of the ester functionalities adjacent to the phenyl were strongly shielded. Thus, the proton absorption of one methyl ester of 10 was shifted upfield 0.49 ppm when compared to that of 11. Similarily, the methyl absorption of the ethyl ester for 11 exhibited an upfield shift of 0.44 ppm.



In order to further demonstrate the feasibility of this approach to the synthesis of streptonigrin, pyridine 10 was first treated with aluminum chloride in ethanethiol[15] to give triacid 12 in 76% yield. Selective esterification of 12 with methanolic hydrochloric acid furnished a 90% yield of acid 13. Finally treatment of 13 with diphenylphosphoryl azide[16] in refluxing benzene afforded a 60% yield of amine 14.



Current efforts are being directed toward applying this methodology to the total synthesis of streptonigrin. The results of these further investigations will be communicated in due course.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian A-60 (^1H NMR, 60 MHz), a Bruker WM-300 (^1H NMR, 300 MHz and ^{13}C NMR, 75.453 MHz), and a Bruker WH-90 (^{13}C NMR, 22.62 MHz), spectrometer from samples dissolved in deuteriochloroform, unless otherwise indicated, and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Infrared spectra (IR), reported in recriprocal centimeters, were recorded as KBr pellets on a Perkin-Elmer 247B instrument. Mass spectra (MS) were recorded on a Finnigan-MAT CH 7 spectrometer operating in the direct inlet mode. Spectroscopic data and elemental analyses were obtained by the Syntex Analytical Reserach Division. Melting points were determined on a hot-stage microscope and are corrected.

3-(Carboethoxy)-5,6-bis(carbomethoxy)-1,2,4-triazine (9). A solution of 8.9 g (68 mmol) of amidrazone 8 in 1 L of absolute ethanol was added dropwise with magnetic stirring over 8 h to a solution of 13.3 g (76 mmol) of dioxosuccinate 7 in 200 mL of

(11) Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2901.
(12) Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, 5171. Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.
(13) Fox, H. H. *J. Org. Chem.* **1947**, *12*, 535.
(14) Schmidt, P.; Druey, J. *Helv. Chim. Acta* **1955**, *38*, 1560.
(15) Mode, M; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991.
(16) Shiori, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1971**, *94*, 6203.

ethanol at 21 °C. After an additional 16 h at 21 °C, the solution was heated at reflux for 2 h. The solvent was then evaporated and the residue was distilled on a Kugelrohr apparatus at 190 °C (1 torr). The orange distillate was dissolved in ethyl acetate and the resulting solution washed with 10% HCl, saturated $NaHCO_3$, and brine. The organic solution was dried over sodium sulfate, concentrated, and recrystallized from ethyl acetate/hexane to give 12.2 g (67%) of **9**: mp 82–86 °C; ^1H NMR (60 MHz) δ 4.65 (q, J = 7 Hz, 2 H), 4.12 (s, 3 H), 4.10 (s, 3 H), 1.51 (t, J = 7 Hz, 3 H); ^{13}C NMR (22.62 MHz) δ 162.88, 161.25, 156.96, 149.74, 149.15, 64.04, 54.29, 14.17; IR 3000, 2970, 1740, 1450, 1390, 1290, 1220, 1185, 1100, 1020, 980; MS 269 (M^+), 238, 224, 211, 183, 111 (base). Anal. Calcd for $C_{10}H_{11}N_3O_6$: C, 44.62; H, 4.12; N, 15.61. Found: C, 44.72; H, 4.09; N, 15.54.

6-(Carboethoxy)-2,3-bis(carbomethoxy)-5-methyl-4-phenylpyridine (10) and 6-(Carboethoxy)-2,3-bis(carbomethoxy)-4-methyl-5-phenylpyridine (11). A mixture of 4.05 g (15.0 mmol) of triazine **9** and 6.0 mL (48 mmol) of 1-phenylpropyne was heated in a Parr bomb at 200 °C for 12 h. The resulting product was chromatographed (3:7 ethyl acetate/hexane) to give 3.35 g (62%) of a 3:2 mixture of pyridines **10** and **11**, respectively. Crystallization from ethyl acetate/hexane afforded 0.95 g (18%) of **10**: mp 91.5–92.5 °C; ^1H NMR (60 MHz) δ 7.6–7.1 (m, 5 H), 4.51 (q, J = 7 Hz, 2 H), 3.98 (s, 3 H), 3.56 (s, 3 H), 2.27 (s, 3 H), 1.43 (t, J = 7 Hz, 3 H); ^{13}C NMR (75.473 MHz) δ 166.75, 165.82, 164.60, 150.65, 150.35, 141.72, 135.19, 134.92, 133.27, 128.81, 128.50, 128.39 62.35, 53.33, 52.46, 16.79, 14.18; IR 3010, 2960, 1745, 1730, 1720, 1445, 1375, 1350, 1235, 1160, 1105, 1015; MS 357 (M^+), 327, 326, 314, 299, 286, 254 (base). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.68; H, 5.34; N, 3.95. Further purification of the mother liquor by column chromatography with the above solvent system followed by crystallization of selected fractions furnished by 0.17 g (3%) of **11**: mp 90–91 °C (ethyl acetate/hexane); ^1H NMR (60 MHz) δ 7.6–7.1 (m, 5 H), 4.12 (q, J = 7 Hz, 2 H), 4.05 (s, 6 H), 2.23 (s, 3 H), 0.99 (t, J = 7 Hz); ^{13}C NMR (75.473 MHz) δ 167.57, 165.61, 164.74, 150.56, 145.96, 143.29, 139.38, 135.19, 128.57, 128.38, 61.79, 53.39, 53.08, 17.25, 13.55; IR 2990, 2960, 1730, 1445, 1350, 1295, 1225, 1200, 1085, 1030; MS 357 (M^+), 327, 326, 313, 298, 285, 284 (base), 251, 241, 195, 167. Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.60; H, 5.41; N, 3.86.

5-Methyl-4-phenyl-2,3,6-tricarboxypyridine (12). The triester **10** (0.829 g, 2.32 mmol) was added to a magnetically stirred solution of 2.9 g (22 mmol) of aluminum chloride in 25 mL of ethanethiol at 0 °C. After 2 h the solution was taken up in ethyl acetate and washed with 10% HCl and then brine. The organic solution was dried over Na_2SO_4 and concentrated and the residue recrystallized from ethyl acetate/hexane to give 0.533 g (76%) of **12**: mp 196–197 °C; ^1H NMR (Me_2SO-d_6, 60 MHz) δ 7.6–7.1 (m, 5 H), 2.16 (s, 3 H); ^{13}C NMR (Me_2SO-d_6, 22.62 MHz) δ 167.03, 165.54, 150.19, 149.28, 142.52, 135.30, 133.03, 132.77, 128.41, 16.19; IR 3450 (br), 1730, 1700, 1445, 1255, 1190, 1110; MS 283 (M^+ – H_2O), 256, 239, 210, 44 (base). Anal. Calcd for $C_{15}H_{11}NO_6$: C, 59.80; H, 3.68; N, 4.65. Found: C, 59.66; H, 3.69; N, 4.62.

3-Carboxy-2,6-bis(carbomethoxy)-5-methyl-4-phenylpyridine (13). The triacid **12** (533 mg, 1.77 mmol) was treated with 100 mL of 10% methanolic HCl for 18 h at 21 °C. The solution was then concentrated, and the residue was recrystallized from ethyl acetate/hexane to give 525 mg (90%) of **13**: mp 155–157 °C; ^1H NMR (300 MHz) δ 7.42 (m, 3 H), 7.19 (m, 2 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 2.28 (s, 3 H); ^{13}C NMR (75.473 MHz) δ 169.13, 166.00, 164.44, 150.68, 149.48, 141.69, 136.03, 134.76, 132.73, 128.84, 128.56, 128.50, 53.33, 53.11, 16.91; IR 3400 (br), 2950, 1730, 1445, 1355, 1230, 1105; MS 329 (M^+), 328, 296, 284, 270, 253, 239, 227 (base), 194, 166. Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 62.00; H, 4.62; N, 4.20.

3-Amino-2,6-bis(carbomethoxy)-5-methyl-4-phenylpyridine (14). A solution of 525 mg (1.60 mmol) of acid **13**, 0.50 g (1.8 mmol) of diphenylphosphoryl azide, and 0.50 mL (3.6 mmol) of triethylamine in 30 mL of benzene was heated at reflux for 1 h, whereupon 2 mL of water was added and the heating continued for 45 min. The solution was then concentrated. A solution of the residue in ethyl acetate was washed with water and then brine, dried over Na_2SO_4, and concentrated. The product was recrystallized from ethyl acetate/hexane to yield 287 mg (60%) of **14**: mp 179–181 °C; ^1H NMR (300 MHz) δ 7.53 (t, J = 8 Hz, 2 H), 7.44 (t, J = 8 Hz, 1 H), 7.17 (d, J = 8 Hz, 2 H), 6.2–5.8 (br s, 2 H), 3.96 (s, 3 H) 3.92 (s, 3 H), 2.26 (s, 3 H); ^{13}C NMR (75.473 MHz) δ 167.61, 166.14, 146.56, 138.64, 137.32, 136.22, 134.31, 129.92, 129.07, 128.86, 124.90, 52.67, 52.49, 17.87; IR 3480, 3360, 3060, 3000, 2950, 1710, 1685, 1585, 1435, 1350, 1310, 1245, 1205, 1105; MS 300 (M^+), 285, 242, 210 (base), 182. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.93; H, 5.46; N, 9.43.

Acknowledgment. I appreciate the assistance of Dr. M. L. Maddox and Mrs. J. Nelson in the obtaining and interpreting of the NMR spectra.

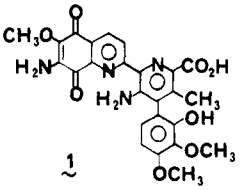
Pyridine Construction via Thermal Cycloaddition of 1,2,4-Triazines with Enamines: Studies on the Preparation of the Biaryl CD Rings of Streptonigrin

Dale L. Boger*[1] and James S. Panek

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045

Received January 18, 1982

Streptonigrin (1), an antitumor antibiotic isolated from



1

cultures of *Streptomyces flocculus*, has been the subject of extensive biological and chemical studies.[2] Its antibiotic activity against gram-positive and gram-negative bacteria and its potent antitumor activity have provided the incentive for much synthetic work[2] which has culminated recently in two separate reports of its total synthesis.[3] Herein we disclose the results of an initial investigation on the development of a convergent approach to streptonigrin based on our recent observation that 1,2,4-triazines undergo a regiospecific, inverse electron demand Diels–Alder reaction with pyrrolidine enamines to afford substituted pyridines.

A key to the synthesis of the streptonigrin carbon framework lies in the preparation of a pentasubstituted pyridine (e.g., **2**),[3] and our studies on the utility of the

(1) Chicago Community Trust Co./Searle Scholar Recipient, 1981–1984.

(2) Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Naturt.*, in press.

(3) (a) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 1271. Kende, A. S.; Naegely, P. C. *Tetrahedron Lett.* **1978**, 4775. (b) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 3962. Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *Ibid.* **1982**, *104*, 536. For previous studies on the construction of the streptonigrin CD ring system see: Kametani, T.; Ogasawara, K.; Shio, M. *Yakugaku Zasshi* **1966**, *86*, 809. Kametani, T.; Ogasawara, K.; Kozuka, A. *Ibid.* **1966**, *86*, 815. Kametani, T.; Ogasawara, A.; Kozuka, A.; Shio, M. *Ibid.* **1967**, *87*, 254, 260. Kametani, T.; Ogasawara, K.; Kozuka, H.; Nyu, K. *Ibid.* **1967**, *87*, 1189. Kametani, T.; Ogasawara, K.; Kozuka, A. *Ibid.* **1967**, *87*, 1195. Kametani, T.; Kozuka, A.; Tanaka, S. *Ibid.* **1970**, *90*, 1574; **1971**, *91*, 1068. Liao, T. K.; Wittek, P. J.; Cheng, C. C. *J. Heterocycl. Chem.* **1976**, *13*, 1283. Wittek, P. J.; Liao, T. K.; Cheng, C. C. *J. Org. Chem.* **1979**, *44*, 870. Rao, K. V.; Venkateswarlu, P. *J. Heterocycl. Chem.* **1975**, *12*, 731. Rao, K. V.; Kuo, H.-S. *Ibid.* **1979**, *16*, 1241. Martin, J. C. *Ibid.* **1980**, *17*, 1111. Kim, D.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 121, 125. Cushman, M.; Mathew, J. *Ibid.* **1981**, *46*, 4921. A related approach employing 1,2,4-triazines for the construction of the streptonigrin CD ring system has been described: Martin, J. C. 183rd National Meeting of the American Chemical Society, Las Vegas, Mar 1982; ORGN 254.

0022-3263/82/1947-3763$01.25/0 © 1982 American Chemical Society