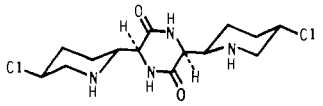
Total Synthesis of *dl*-Antibiotic 593A

Sir:

Antibiotic 593A was isolated from the soil microorganism *Streptomyces griseoluteus*[1] and has been shown to inhibit growth of the L1210 lymphocytic leukemia, Krebs 2 murine tumor systems, the rat Walker 256 carcinosarcoma, and several neoplastic cell lines.[2] Recent clinical trials have revealed that 593A is effective against certain solid tumors and leukemia.[3] An X-ray crystallographic analysis of 593A determined the structure **1** including its absolute configuration.[4] The compound is a piperazinedione composed of two identical and hitherto unknown amino acids characterized by a unique 3-chloropiperidine ring. This communication describes the first total synthesis of *dl*-593A.



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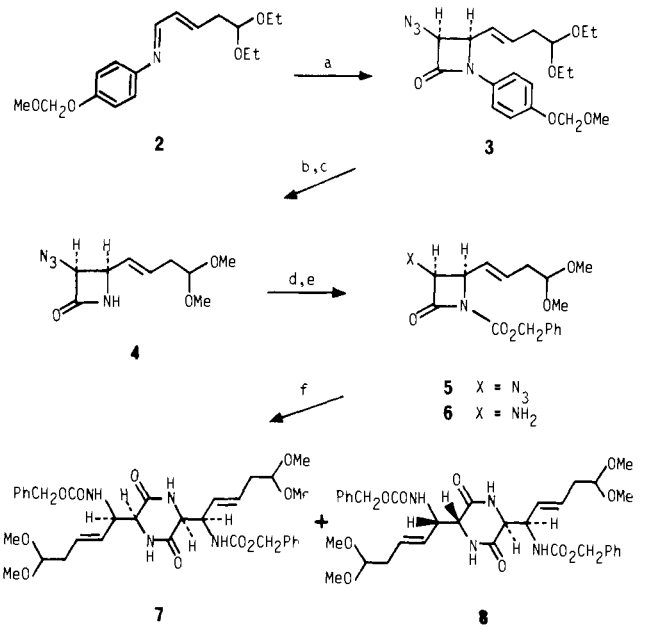
The success of our synthesis lies in the use of the β-lactam to overcome the following difficulties: (1) there are no general synthetic methods available to date for controlling the stereochemistry of α,β-diamino acids; (2) dimerization of amino acids or their derivatives generally requires drastic conditions where survival of polyfunctionalized molecules could not be expected. In fact, attempted dimerization of 2-piperidylglycine ethyl ester failed to give the corresponding piperazinediones.[5,6]

Addition of azidoacetyl chloride[7] to a mixture of triethylamine and the aldimine **2** formed from *p*-methoxymethoxyaniline[8] and 5,5-diethoxy-2-pentenal[9] at 0 °C afforded exclusively *cis*-β-lactam **3**[10,11] (Scheme I): 56%; oil; IR (CH_2Cl_2) 2105, 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (3 H, t, J = 7 Hz), 1.13 (3 H, t, J = 7 Hz), 2.43 (2 H, t, J = 6 Hz), 3.37 (3 H, s), 3.50 (4 H, m), 4.47 (1 H, t, J = 6 Hz), 4.62 (1 H, dd, J = 5, 7.5 Hz), 4.77 (1 H, d, J = 5 Hz), 5.03 (2 H, s), 5.57 (1 H, dd, J = 7.5, 15 Hz), 5.98 (1 H, dt, J = 15, 6 Hz), 6.90 (2 H, d, J = 9 Hz), 7.27 (2 H, d, J = 9 Hz). Oxidative removal of the novel amide protecting group of **3** was achieved in two steps [(1) HCl, $CH(OMe)_3$, MeOH, reflux; (2) $(NH_4)_2Ce(NO_3)_6$,[12] THF–H_2O (5:2), 0 °C, worked up with Na_2SO_3–Na_2CO_3] to give the deprotected β-lactam **4**:[10] 74% overall; mp 63–64 °C; IR (CH_2Cl_2) 3405, 2110, 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (2 H, t, J = 5.5 Hz), 3.33 (6 H, s), 4.32 (1 H, dd, J = 5, 7.5 Hz), 4.40 (1 H, t, J = 5.5 Hz), 4.70 (1 H, dd, J = 1.5, 5 Hz), 5.67 (2 H, m), 6.85 (1 H, br s). To facilitate the β-lactam ring cleavage for dimerization, **4** was activated by the introduction of a carbobenzoxy group ($PhCH_2OCOCl$, Et_3N, CH_2Cl_2, −30 °C) to give the imide **5**:[10] 93%; oil; IR (CH_2Cl_2) 2110, 1820, 1735 cm^{-1}. Reduction of **5** with zinc [Zn, AcOH, Et_2O–CH_2Cl_2 (1:9), room temperature] afforded the unstable amine **6**. Upon standing at room temperature, **6** dimerized to give a mixture of *cis*-piperazinedione **7**[10] [mp 188–189 °C; IR (CH_2Cl_2) 1723, 1683 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.25 (4 H, t, J = 5.5 Hz), 3.17 (12 H, s), 4.00 (2 H, br d, J = 4 Hz), 4.27 (2 H, t, J = 5.5 Hz), 4.43 (2 H, m), 5.52 (4 H, m)] and *trans*-piperazinedione **8**[10] [mp 186–187 °C; IR (CH_2Cl_2) 1722, 1683 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.23 (4 H, t, J = 5.5 Hz), 3.17 (12 H, s), 3.88 (2 H, br d, J = 2.5 Hz), 4.28 (2 H, t, J = 5.5 Hz), 4.40 (2 H, m), 5.47 (4 H, m)] in 80% yield, 3:2 respectively,[13] which was chromatographically separated.[14]

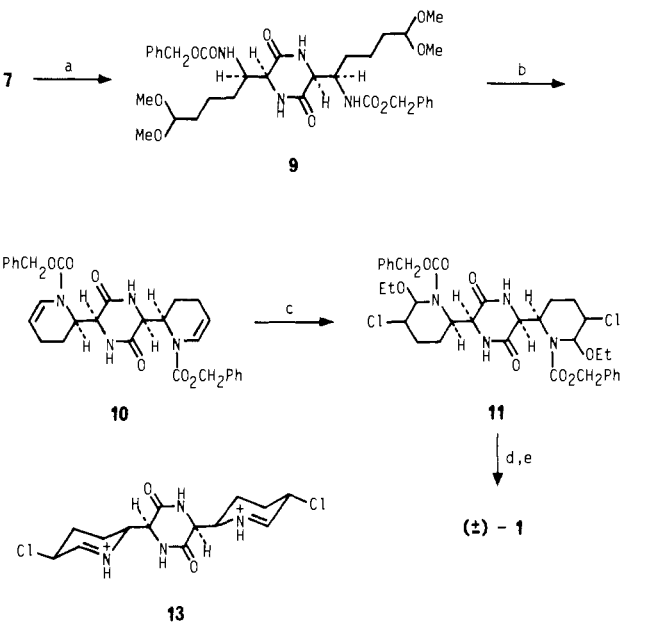
Selective catalytic hydrogenation of **7** [H_2 (1 atm)–PtO_2, MeOH, room temperature] afforded the piperazinedione **9**[10] (Scheme II), 98%, mp 153–155 °C. Facile double cyclization of **9** was effected by treatment with camphorsulfonic acid (0.3 equiv)–quinoline (0.8 equiv) in refluxing toluene–ethylene

Scheme I[a]



[a] (a) N_3CH_2COCl, Et_3N, benzene, CH_2Cl_2, 0 °C. (b) HCl, $CH(OMe)_3$, MeOH, reflux. (c) $(NH_4)_2Ce(NO_3)_6$, THF, H_2O, 0 °C. (d) $PhCH_2OCOCl$, Et_3N, CH_2Cl_2, −30 °C. (e) Zn, AcOH, ether, CH_2Cl_2, room temperature. (f) neat, room temperature.

Scheme II[a]



[a] (a) H_2 (1 atm), PtO_2, MeOH, room temperature. (b) CSA, quinoline, CH_2ClCH_2Cl, toluene, reflux. (c) Cl_2, EtOH, CH_2Cl_2, 0 °C. (d) BCl_3, CH_2Cl_2, room temperature. (e) $NaBH_3CN$, AcOH, MeOH, room temperature.

chloride (1:1) to give tricyclic compound **10**:[10] 91%; mp 267–270 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.50–2.56 (8 H, m), 3.68 (2 H, br d, J = 7 Hz), 4.67–5.27 (4 H, m), 6.63 (2 H, d, J = 8 Hz)).

Chlorination of **10** [Cl_2, EtOH–CH_2Cl_2 (2:1), 0 °C] afforded a diastereomeric mixture of chlorides **11** which, without purification, was treated with boron trichloride at room temperature to give the unstable iminium salts **12**. Reduction of **12** ($NaBH_3CN$, AcOH–MeOH, room temperature) afforded *dl*-593A **1**[10] in 62% overall yield from **10** (18% overall yield from the β-lactam **3**). This stereoselective reduction can be explained in terms of preferential formation of the thermodynamically favorable tetraquasi-equatorial iminium ion **13**

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under acidic conditions. The synthetic 593A dihydrochloride (mp 280–290 °C dec) was identical in TLC behavior and spectral (^{1}H NMR, ^{13}C NMR, and MS) properties with natural 593A dihydrochloride.[15]

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References and Notes

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(3) Benjamin, R. S.; Keating, M. J.; Valdivieso, M.; McCredie, K. B.; Livingston, R. A.; Burgess, M. A.; Rodriguez, V.; Bodey, G. P.; Gottlieb, J. A. *Cancer Treat. Rep.* **1979**, *63*, 939, and references cited therein.
(4) Pettit, G. R.; Von Dreele, R. B.; Herald, D. L.; Edgar, M. T.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 6742.
(5) Private communication from Professor R. J. Parry, Rice University
(6) In an attempt to synthesize 593A, G. R. Pettit and his co-workers tried the dimerization of L-(5-chloro-2-pyridyl)glycine unsuccessfully: Edgar, M. T.; Pettit, G. R.; Krupa, T. S. *J. Org. Chem.* **1979**, *44*, 396.
(7) Bose, A. K.; Manhas, M. S.; Anjaneyulu, B.; Bhattacharya, S. K. *Tetrahedron* **1967**, *23*, 4769.
(8) Prepared from *p*-nitrophenol in two steps [(1) P_2O_5, $CH_2(OMe)_2$, CH_2Cl_2, room temperature; (2) H_2–Pd/C, MeOH] in 89% overall yield, bp 108–110 °C (0.7 mm).
(9) Prepared from 3,3-diethoxypropanal in four steps [(1) $CH_2{=}CHCH_2MgBr$, THF, reflux; (2) MsCl, Et_3N, CH_2Cl_2, 0 °C; (3) O_3, MeOH–CH_2Cl_2 (1:9), −78 °C; (4) Me_2S, Et_3N, MeOH–CH_2Cl_2 (1:9), room temperature] in 50% overall yield, bp 68–70 °C (0.6 mm).
(10) Satisfactory spectroscopic data were obtained for this substance.
(11) Use of saturated aldehyde failed to give β-lactam under the same reaction conditions. On the other hand, α,β-acetylenic aldehyde gave a mixture of *cis*- and *trans*-β-lactams in the ratio of 3:2, respectively.
(12) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627.
(13) To obtain the desired *cis*-piperazinedione **7** as the sole product, it is necessary to resolve the racemic intermediates before dimerization. We are currently investigating the possibility of resolution.
(14) Stereochemistry of the piperazinediones was tentatively assigned based on their TLC behavior and was later confirmed by the fact that 593A was synthesized from **7**. For TLC comparison of *cis*- and *trans*-piperazinediones, see: Nitecki, D. E.; Halpern, B.; Westley, J. W. *J. Org. Chem.* **1968**, *33*, 864.
(15) We are indebted to Professor R. J. Parry, Rice University, for a sample of natural 593A dihydrochloride.

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Photochemistry and Photocatalytic Activity of a Polynuclear Metal Carbonyl Hydride: Dodecacarbonyltetrahydridotetraruthenium

Sir:

We report here our preliminary findings concerning the photochemistry and photocatalytic activity of the polynuclear hydride $H_4Ru_4(CO)_{12}$. While mononuclear hydrides and di- and trinuclear clusters have received considerable study,[1] the only other tetranuclear carbonyl species that have been the object of detailed photochemical studies are $[(\eta^5\text{-}C_5H_5)\text{-}Fe(CO)]_4$[2] and $HFeCo_3(CO)_{12-n}L_n$ (L = PPh_3; n = 0, 2)[3] which undergo metal-to-solvent charge-transfer oxidation[2] and complex, inefficient declusterification,[3] respectively. Interesting photoreactions of $H_4Os_4(CO)_{12}$ and $Ir_4(CO)_{12}$ have been reported,[4,5] but the nature of the primary chemical result from irradiation has not been established. The $H_4Ru_4(CO)_{12}$ cluster and its substituted derivatives are known catalyst precursors for olefin isomerization and hydrogenation[6-8] and thus afford us a special opportunity with respect to studying light-activated catalysis, since the actual active species may be only one step away from the precursor $H_4Ru_4(CO)_{12}$.[6-8]

The $H_4Ru_4(CO)_{12}$ complex was synthesized according to the literature procedure.[9] The yellow-orange complex exhibits an intense, near-UV absorption maximum at 362 nm (ε 17 500 M^{-1} cm^{-1}) with a tail into the visible in hydrocarbon solvents. Near-UV irradiation (355 ± 20 nm, 1.2×10^{-6} einstein/min) of the complex alone in deoxygenated isooctane solution at 25 °C and a concentration of $\sim 5 \times 10^{-4}$ M gives slow decomposition to unidentified products, but as a function of time the decomposition becomes markedly slower when the sample is sealed. Irradiation under the same conditions but in the presence of L [L = $P(OMe)_3$ or PPh_3] results in clean infrared spectral changes; data in Figure 1 are representative. The infrared bands in the CO stretching region that are associated with the product are identical with those reported[10] for $H_4Ru_4(CO)_{11}L$. Continued near-UV irradiation results in additional infrared spectral changes consistent with further functionalization of the cluster to form $H_4Ru_4(CO)_{12-n}L_n$ (n = 1, 2, 3, 4), but, as shown in Figure 1 for L = PPh_3, monosubstituted clusters can be generated essentially quantitatively before multiple substitution products appear. The 366- or 436-nm quantum yield for the photosubstitution (eq 1) is 5 ± 1 × 10^{-3} for either $P(OMe)_3$ or PPh_3 and a concentration of L = 0.01 or 0.1 M.

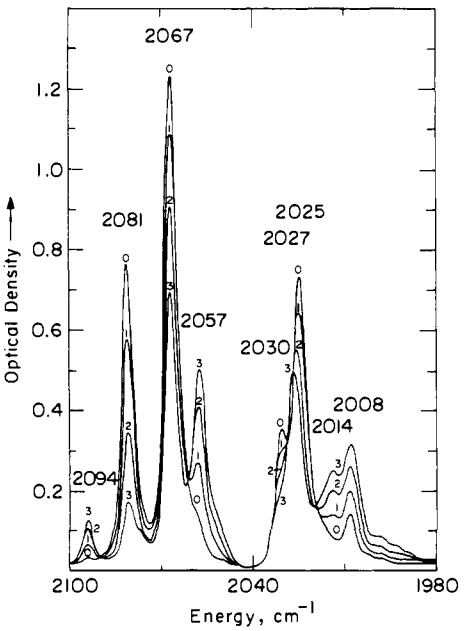

Figure 1. Infrared spectral changes accompanying near-UV (355 nm) irradiation of $H_4Ru_4(CO)_{12}$ ($\sim 5 \times 10^{-4}$ M) in the presence of PPh_3 ($\sim 10^{-1}$ M) in *n*-pentane solution at 25 °C. Bands at 2081, 2067, 2030, 2025, and 2008 cm^{-1} are due to $H_4Ru_4(CO)_{12}$ and those growing with irradiation at 2094, 2057, 2027, 2014, and 2008 cm^{-1} are due to $H_4Ru_4(CO)_{11}PPh_3$. Curves 0, 1, 2, and 3 are after 0-, 20-, 40-, and 75-s irradiation, respectively.

$$H_4Ru_4(CO)_{12} + L \xrightarrow{h\nu} H_4Ru_4(CO)_{11}L + CO \qquad (1)$$

Dinuclear, metal–metal-bonded, metal carbonyls generally undergo very efficient metal–metal bond homolysis subsequent to optical excitation,[11-13] while trinuclear complexes undergo inefficient declusterification.[3,14-16] Presumably, the trinuclear complexes may undergo efficient metal–metal bond homolysis, but low declusterification yields result from efficient recoupling of the tethered radical centers. In the tetranuclear complexes where the lowest excitations involve transitions between orbitals delocalized over four metal atoms and where each metal atom is directly bonded to three others, it is less likely that complete metal–metal bond scission obtains. Rather, the optical excitation apparently results in metal–ligand cleavage as generally obtains for mononuclear metal carbonyls having metal-centered lowest excited states.[1] At this point we cannot

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