rative TLC of this residue followed by crystallization from 30-60 °C petroleum ether then gave 36 mg (71%) of (±)-**1c** as colorless crystals, mp 69-70 °C (lit.[25c] mp 67-68 °C, for material derived from natural **1b**; (±)-**1c** previously reported as an oil[26f]). The IR and NMR spectra of (±)-**1c** thus obtained were in complete agreement with data reported for the naturally derived material.[25c]

(±)-Petasalbine (1). A flame-dried flask under a blanket of dry nitrogen was charged with 26 mg (0.10 mmol) of acetylenic alcohol **50b**, 1 mg (0.1 equiv) of hydroquinone and 5 mL of dry, freshly distilled ethylbenzene (from Na). The resulting solution was then heated under reflux, with protection from light, for a period of 32 h, during which period most of **50b** was slowly consumed (R_f 0.30, 20% acetone/hexanes) concomitant with the formation of (±)-**1** (R_f 0.5). The reaction mixture was then cooled to room temperature and concentrated under reduced pressure (bath temperature 25 °C) to afford 25 mg of a dark residue which was purified by preparative TLC (20% acetone/hexane) to give 5 mg (17%) of starting **50b** and 16 mg (69%, 84% based upon recovered **50b**) of (±)-**1** as a colorless crystalline solid. Recrystallization from 30-60 °C petroleum ether gave (±)-**1** of mp 73-74 °C (lit.[25c] mp 80-81 °C, natural; (±)-**1** previously reported as an oil.[26f] The IR, UV, ^{1}H NMR, and ^{13}C NMR spectra of (±)-**1** thus obtained were in complete agreement with data reported for the naturally occurring substance.[25c,26f,35]

(±)-Petasalbine Acetate (1d). A flame-dried flask under a blanket of dry nitrogen was charged with 24 mg (0.1 mmol) of (±)-**1**, 0.5 mL of dry pyridine (stored over molecular sieves), and 0.4 mL of acetic anhydride. After being stirred at ambient temperatures for 16 h, the resulting solution was concentrated to dryness under reduced pressure (bath temperature 25 °C), and the residue obtained was purified by flash chromatography[36] (5% acetone/hexanes) to afford 21 mg (76%) of **1d** as a colorless oil. Crystallization of this material from 30-60 °C petroleum ether then gave **1d** as a colorless crystalline solid, mp 34-35 °C (lit.[25c] mp 54-55 °C for the naturally derived material). The IR and NMR spectra of (±)-**1d** thus obtained were in complete agreement with data reported for the naturally derived material.[25c,34]

(±)-Ligularone (1b) from (±)-Petasalbine (1). A solution of 16 mg (0.08 mmol, 1.0 equiv) of $(pyr)_2CrO_3$ in 0.6 mL of dry pyridine was added dropwise and with efficient stirring to a solution of 19 mg (0.08 mmol) of (±)-**1** in 0.3 mL of pyridine.[25c] The resulting solution was stirred at ambient temperature for a period of 14 h before being quenched with 4 mL of H_2O and extracted with 5 × 10 mL of ether. The combined ethereal extracts were then washed with 2 × 10 mL of 2% aqueous HCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give, after preparative TLC, 8 mg (42%) of (±)-**1b** which was identical in all respects with the material prepared previously.

Acknowledgment. Financial support of this work by the National Science Foundation (Grant No. CHE-7800633 and CHE-8108984) and the National Institutes of Health (Grant No. CA 20483) is gratefully acknowledged. The Varian XL-200 spectrometer used in this work was financed in part by the National Science Foundation (Grant No. CHE-7908593), the Dreyfus Foundation, and Wesleyan University.

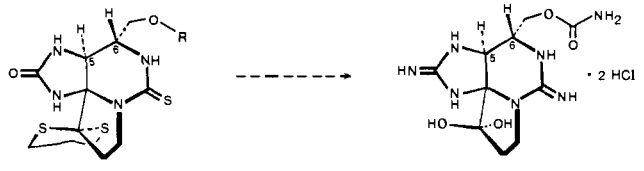
Total Synthesis of (±)-Saxitoxin†

Peter A. Jacobi,* Michael J. Martinelli, and (in part) Slovenko Polanc

Contribution from the Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06457. *Received January 23, 1984. Revised Manuscript Received March 26, 1984*

Abstract: (±)-Saxitoxin (**3**), the paralytic agent of the Alaska butter clam *Saxidomas giganteus*, has been synthesized in a totally stereospecific fashion through a sequence involving as the key steps (a) an intramolecular 1,3-dipolar addition of an azomethine imine to a 2-imidazolone, (b) a reductive cleavage of the resulting pyrazolidine ring followed by intramolecular acylation, and (c) final elaboration of a bis(pseudourea) to the requisite guanidine functionality.

Saxitoxin (**3**), the paralytic agent of the Alaska butter clam *Saxidomas giganteus*, is one of the most toxic of the non-protein poisons known and it has also found widespread use in the study of various nerve disorders.[1] Its physiological action arises from



1 (R=CH_2Ph)
2 (R=H)

Saxitoxin (3)

a disruption of the propagation of impulses in skeletal muscles and nerves, a result due chiefly to a specific interference with the increase in sodium ion permeability normally associated with excitation. The pharmacology[2] and biochemistry of **3** have been reviewed,[3] as has its isolation and purification[4] and chemical and physical properties.[5] Although initially purified in 1957,[4] however, it remained until 1975 for an X-ray analysis to conclusively reveal the molecular geometry as indicated.[6] This accomplishment was followed shortly thereafter by the elegant total synthesis of Kishi et al.,[7] who utilized the thiourea derivative **1** as a key intermediate for elaboration to **3**. In this paper we report on an alternative synthesis of **3** which proceeds through the closely related species **2**. Compound **2**, in turn, has been prepared by a route which is noteworthy for its efficiency (0.5-1.0-g scale) and the fact that no chromatographic separations are required throughout the entire reaction sequence.

Discussion and Results

The key intermediate for our synthesis of **2** was the hydrazide derivative **4** which was conveniently derived from 2-imidazolone on 5-10-g scales and larger (Scheme I).[8] This material, upon

† Dedicated to Professor Max Tishler and Elizabeth Tishler on the occasion of their 50th wedding anniversary.

(1) Takman, B. H.; Boyes, R. N.; Vassallo, H. G. "Principles of Medicinal Chemistry"; Foye, W. O., Ed.; Lea and Febiger: Philadelphia, 1974; p 316. See also: Ritchie, J. M.; Rogart, R. B. *Rev. Physiol. Biochem. Pharmacol.* **1977**, *79*, 1. Ritchie, J. M.; Rogart, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 211.
(2) Murtha, E. F. *Ann. N.Y. Acad. Sci.* **1960**, *90*, 820.
(3) Schantz, E. J. *Ann. N.Y. Acad. Sci.* **1960**, *90*, 843.
(4) Schantz, E. J.; Mold, J. D.; Stanger, D. W.; Shavel, J.; Riel, F. J.; Bowden, J. P.; Lynch, J. M.; Wyler, R. S.; Riegel, B.; Sommer, H. *J. Am. Chem. Soc.* **1957**, *79*, 5230, 5235.
(5) Schantz, E. J. *Can. J. Chem.* **1961**, *39*, 2117.
(6) (a) Schantz, E. J.; Ghazarossian, V. E.; Schnoes, H. K.; Strong, F. M.; Springer, J. P.; Pezzanite, J. O.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 1238. (b) Bordner, J.; Thiessen, W. E.; Bates, H. A.; Rapoport, H. *Ibid.* **1975**, *97*, 6008. See also: (c) Wong, J. L.; Oesterlin, R.; Rapoport, H. *Ibid.* **1971**, *93*, 7344 and references cited therein.
(7) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818. See also: (a) Kishi, Y. *Heterocycles* **1980**, *14*, 1477. (b) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.

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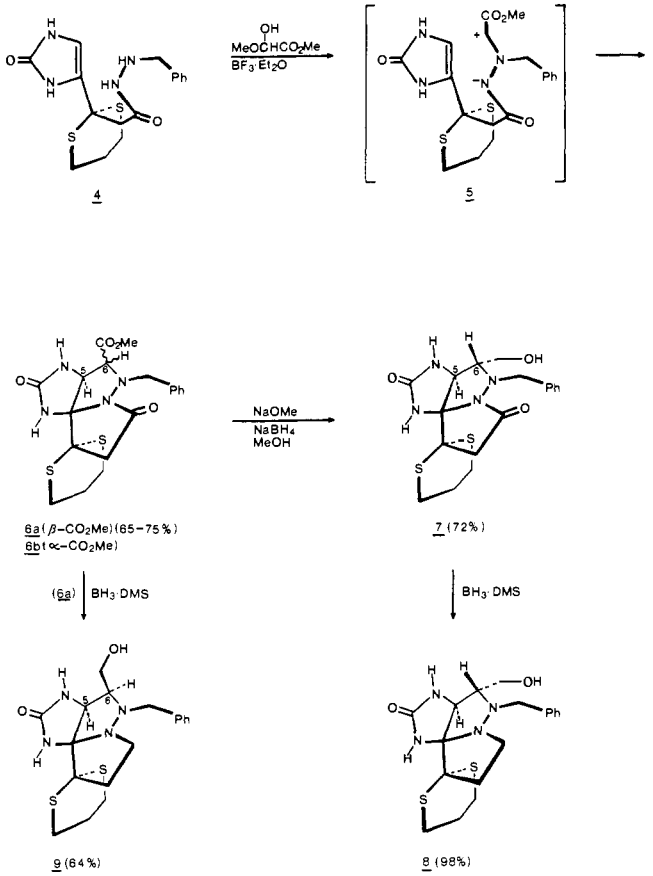
Scheme I



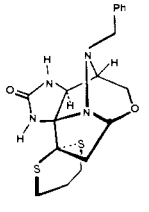
treatment with methyl glyoxylate hemiacetal[9] in the presence of $BF_3{\cdot}Et_2O$, was smoothly converted to the azomethine imine **5**, which underwent a kinetically controlled 1,3-dipolar cycloaddition[8,10] to yield the pyrazolidine derivative **6a** as the only detectable adduct (65–75%).[11] As expected, however, the stereochemical consequences of kinetic control could be readily reversed upon equilibration.[12] Thus, **6a** was next quantitatively epimerized to the α-ester **6b** (NaOMe/MeOH) which, without isolation, was cleanly reduced to the α-alcohol **7** containing all of the asymmetric centers of **3** in their proper relative configurations ($NaBH_4$/MeOH, 72% overall yield).[13,14] That **7** was indeed in hand was unequivocally demonstrated by its facile conversion to **8** ($BH_3{\cdot}Me_2S$, 98%) which was directly compared to the isomeric material **9** derived by reduction of **6a** under nonepimerizing conditions ($BH_3{\cdot}Me_2S$, 64%, $J_{5,6}$(**8**) = 3.2 Hz; $J_{5,6}$(**9**) = 6.8 Hz).

It was our intention, now, that **7** would be reductively cleaved to **10** and then further modified in such a fashion as to produce the spirocyclic pyrrolidine derivative **11** (Scheme II). This latter material appeared to be ideally suited for an eventual conversion to **2** via debenzylation and bridging with (thiocarbonyl)diimidazole.[15] In practice, however, this route could not be realized due to the highly unstable nature of derivatives of type **11** (vide infra). Thus, although **7** was easily converted to the lactam derivative **10** (Na/NH_3, −78 °C),[16] all attempts at the further reduction of **10** to **11** led to complex mixtures of products containing none of the desired material.[17] Furthermore, similarly discouraging results were obtained upon attempted reductive cleavage of **8** to give the target compound **11** directly. In this case the pyrazolidine N–N bond is not activated by acylation and a variety of reagents failed to bring about the desired transformation.

These difficulties were eventually circumvented with the findings that **8** could be smoothly debenzylated (Pd, HOAc, HCO_2H, transfer hydrogenation[18]) and selectively acylated to give a range of activated species **12** in excellent overall yield. It was our hope in this case that intermediates of type **13** might undergo an *intramolecular* acylation to afford **2** at a rate competitive with decomposition pathways, and toward this goal we examined a number of potential leaving groups L (**12a–c**). For each example the desired radical fragmentation[19] took place readily (Na/NH_3, −78 °C) and the resulting solutions were carefully examined for the presence of **2**. By way of summary, both **13a** (L = NH_2) and **13b** (L = OMe) rapidly decomposed to intractable mixtures, and no evidence was found for the desired cyclization. With the more reactive **13c** (L = OPh), however, cyclization was observed to take place at −30 °C and **2** was isolated by direct crystallization in 75% overall yield.

Once in hand the remaining steps necessary for the conversion of **2** to (±)-Saxitoxin (**3**) proceeded in a straightforward fashion as follows. Thus, **2** was cleanly acylated (Ac_2O/pyr) to give the protected derivative **14** which was directly treated with $Et_3O^+BF_4^-$/$NaHCO_3$ to afford a virtually quantitative yield of the bis(pseudourea) **15**.[7] This latter material, upon brief thermolysis with $EtCO_2^-NH_4^+$ (~130 °C, 30 min), then gave the known[7] bis(guanidine) **16** whose hexaacetate derivative was identical in all respects with an authentic sample[20] (48% overall yield). Finally, deprotection (NBS, wet CH_3CN) and treatment with chlorosulfonyl isocyanate as previously described by Kishi[7] afforded (±)-**3** as an amorphous solid indistinguishable from the natural material[21] by TLC in eight different solvent systems[22] and having the expected spectroscopic properties.[5,21,24]

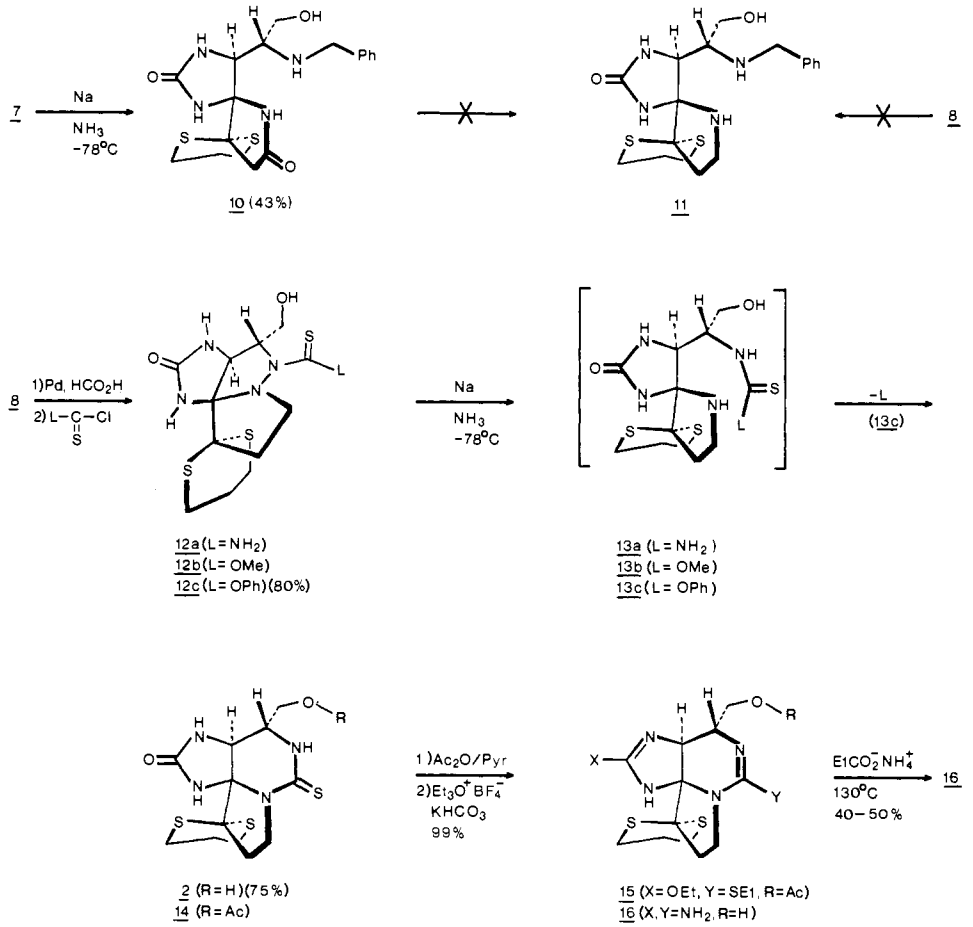
(8) Jacobi, P. A.; Brownstein, A.; Martinelli, M.; Grozinger, K. *J. Am. Chem. Soc.* **1981**, *103*, 239.
(9) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.
(10) (a) Oppolzer, W. *Tetrahedron Lett.* **1970**, 2199. (b) Oppolzer, W. *Ibid.* **1970**, 3091. (c) Oppolzer, W. *Ibid.* **1972**, 1707. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
(11) Satisfactory elemental analyses and spectral data were obtained for all new compounds reported. All yields refer to isolated and purified materials.
(12) The β-configuration at C-6 not only requires that a sterically demanding group be oriented on a highly concave surface but it also leads to strongly eclipsing interactions at positions 2, 3, and 4 of the pyrazolidine ring. See also ref 10a.
(13) Schenker, E. "Newer Methods of Preparative Organic Chemistry"; Verlag Chemie: Weinheim, 1968; Vol. 4, pp 196–335.
(14) Upon prolonged reduction with $NaBH_4$ (24 h) **7** was further reduced to the tetracyclic species **i**:



i

(15) Sharma, S. *Synthesis* **1978**, *30*, 803.
(16) Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, 3493 and references cited therein.
(17) A partial listing of reagents attempted for this transformation include $NaBH_4$, BH_3·THF, $NaBH_4/BF_3{\cdot}Et_2O$, $NaBH_4/Co(OAc)_2$, $NaBH_4/Sm_2O_3$, DIBAL-H, LAH, $NaBH_4/PrCl_3$, $LAH/AlCl_3$, $Et_3O^+BF_4^-/NaBH_4$, $NaBH_4$/HOAc, $NaBH_4$/NaOMe, $Na_2S_2O_4$/pH 7, and $Bu_4N^+BH_4^-$.
(18) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442. See also: (a) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *Ibid.* **1978**, *43*, 4194. (b) Greenstein, J. P.; Winitz, M. "The Chemistry of Amino Acids"; Wiley: New York, 1961; p 1233.
(19) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(20) We are grateful to Professor Yoshito Kishi of Harvard University for providing us with copies of spectral data (NMR, IR, UV, mass spectrum) and TLC data for compound **16** (hexaacetate) and other pertinent intermediates (cf. ref 7) as well as for providing us with experimental details for the conversion of **16** to (±)-**3**.
(21) We are grateful to Professor Allan Berlind of Wesleyan University for providing us with an authentic sample of saxitoxin.
(22) Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys. Res. Commun.* **1974**, *59*, 1219 and references cited therein.
(23) See, for example: (a) Scheuer, P. J. *Prog. Chem. Org. Nat. Prod.* **1964**, *22*, 265; **1969**, *27*, 323. (b) Premuzic, E. *Ibid.* **1971**, *29*, 417. (c) Shimizu, Y. "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 1.
(24) Ghazarossian, V. E.; Schantz, E. J.; Schnoes, H. K.; Strong, F. M. *Biochem. Biophys. Res. Commun.* **1976**, *68*, 776.

Scheme II



In closing, we might only add that conversions of the general type **12** → **2** might find further application in the synthesis of naturally occurring guanidines.[23] This possibility is currently under active investigation.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 1500 FT spectrophotometer. The 200-MHz ^{1}H NMR and 50.3-MHz ^{13}C NMR spectra were obtained on a Varian XL-200 spectrometer. Chemical shifts are expressed in parts per million relative to internal tetramethylsilane. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. All melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed at the Baron Consulting Company in Orange, CT. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionization potential of 70 eV.

(3′aα,4′β,9′a*R)-Octahydro-2′,7′-dioxo-5′-(phenylmethyl)spiro[1,3-dithiane-2,9′-[9*H*]imidazo[4,5-*c*]pyrrolo[1,2-*b*]pyrazole]-4′-carboxylic Acid (±)-Methyl Ester (6a).** A suspension of 0.91 g (2.5 mmol) of hydrazide **4**,[8] 0.60 g (5.0 mmol) of methyl glyoxylate hemimethyl acetal,[9] and 0.71 g (5.0 mmol) of freshly distilled BF_3·Et_2O in 500 mL of dry CH_3CN (from P_2O_5) was slowly brought to reflux with vigorous stirring under an inert atmosphere. Solution (pale yellow) was complete within 10 min, and after heating a total of 8 h the resulting orange-yellow solution was concentrated to approximately 150 mL, diluted with 200 mL of CH_2Cl_2, and poured into 200 mL of pH 7 buffer. After separation, the aqueous phase was extracted with an additional 2 × 200 mL of CH_2Cl_2, and the combined organic layers were washed with 200 mL of saturated brine, dried over Na_2SO_4, and concentrated to give 1.3 g of a yellow residue. Trituration with 25 mL of ice-cold CH_2Cl_2 then afforded 0.72 g (67%) of **6a** as a chromatographically homogeneous off-white powder. The analytical sample crystallized from 2-propanol in the form of colorless needles: mp 206–208 °C; R_f 0.76 (silica gel, 10% MeOH/$CHCl_3$); mass spectrum, *m/e* 434 (M^+); IR (KBr) 1710, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.86–2.12 (m, 2 H), 2.70–3.00 (m, 6 H), 3.74 (s, 3 H), 4.05 (d, 1 H, *J* = 12.8 Hz), 4.23 (d, 1 H, *J* = 4.8 Hz, collapses to a singlet upon irradiation at 5.14), 4.42 (d, 1 H, *J* = 12.8 Hz, collapses to a singlet upon irradiation at 4.05), 5.14 (dd, 1 H, *J* = 1.2, 4.8 Hz), 5.80 (br s, 1 H, exchanges with D_2O), 6.26 (br s, 1 H, exchanges with D_2O), 7.14–7.45 (m, 5 H); ^{13}C NMR (Me_2SO-d_6) δ 24.5, 26.5, 45.8, 52.2, 56.5, 56.8, 61.6, 71.2, 79.1, 89.6, 126.8, 127.7, 128.9, 137.6, 158.5, 160.0, 168.1.

Anal. Calcd for $C_{19}H_{22}N_4O_4S_2$: C, 52.52; H, 5.10; N, 12.89. Found: C, 52.22; H, 5.28; N, 13.19.

(3′aα,4′α,9a*R)-(±)-Octahydro-2′,7′-dioxo-4′-(hydroxymethyl)-5′-(phenylmethyl)spiro[1,3-dithiane-2,9′-[9*H*]imidazo[4,5-*c*]pyrrolo[1,2-*b*]-pyrazole] (7).** A solution of 2.82 g (6.5 mmol) of ester **6a** in 325 mL of anhydrous MeOH was treated with 702 mg (13 mmol) of NaOMe in one portion with vigorous stirring at room temperature. After a period of 1 h, 2.46 g (65 mmol) of $NaBH_4$ was added, and the resulting pale yellow solution was stirred for an additional 4 h. The reaction mixture was then diluted with 250 mL of CH_2Cl_2, poured into 250 mL of pH 7 buffer, and extracted with an additional 3 × 200 mL of CH_2Cl_2. The combined organic layers were then washed with 200 mL of saturated brine, dried over Na_2SO_4, and concentrated to give a slightly off-white solid. Crystallization of this material from 2-propanol then afforded 1.89 g (72%) of **7** as colorless crystals: mp 249–52 °C; R_f 0.51 (silica gel, 10% EtOH/$CHCl_3$); mass spectrum, *m/e* 406 (M^+); IR (KBr) 1730, 1694 cm^{-1}; NMR ($CDCl_3$) δ 1.82–2.12 (m, 2 H), 2.60–3.02 (m, 6 H), 3.12–3.58 (m, 4 H), 4.11 (d, 1 H, *J* = 13.0 Hz), 4.26 (d, 1 H, *J* = 13.0 Hz), 4.63 (s, 1 H), 5.22 (br s, 1 H, exchanges with D_2O), 6.06 (br s, 1 H, exchanges with D_2O), 7.00–7.46 (m, 5 H); ^{13}C NMR (Me_2SO-d_6) δ 24.4, 26.9, 27.2, 47.3, 55.7, 60.7, 62.6, 76.3, 91.5, 127.4, 128.1, 129.0, 136.9, 158.0, 166.7.

Anal. Calcd for $C_{18}H_{22}N_4O_3S_2$: C, 53.18; H, 5.46; N, 13.18. Found: C, 53.26; H, 5.74; N, 14.05.

(3′aα,4′α,9′a*R)-(±)-Octahydro-2′-oxo-4′-(hydroxymethyl)-5′-(phenylmethyl)spiro[1,3-dithiane-2,9′-[9*H*]imidazo[4,5-*c*]pyrrolo[1,2-*b*]-pyrazole] (8).** A suspension of 1.88 g (4.64 mmol) of lactam alcohol **7** and 1.32 g (9.29 mmol) of freshly distilled BF_3·Et_2O in 100 mL of dry THF was slowly brought to reflux under an inert atmosphere, and was then carefully treated with 4.65 mL of a 2 M solution of BH_3·Me_2S complex[25] in THF. Solution (pale yellow) was complete within 10 min, and after 1 h an identical 4.65-mL portion of BH_3·Me_2S was added.

(25) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

Heating was then continued for an additional 1 h before the solution was cooled to room temperature, and the resulting solution was then diluted with 200 mL of CH_2Cl_2, carefully poured into 200 mL of pH 7 buffer, and extracted with an additional 3 × 150 mL of CH_2Cl_2. The combined organic layers were then washed with 100 mL of saturated brine, dried over Na_2SO_4, and concentrated to give a white foam. Crystallization of this material from 10 mL of 2-propanol then afforded 1.78 g (98%) of **8** as short, colorless needles: mp 205–207 °C; R_f 0.55 (silica gel, 10% MeOH/$CHCl_3$); mass spectrum, *m/e* 392 (M^+); IR (KBr) 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.72–2.30 (m, 4 H), 2.60–2.98 (m, 5 H), 3.10–3.30 (m, 2 H), 3.36–3.54 (m, 3 H), 3.88 (d, 1 H, *J* = 13.0 Hz), 4.17 (d, 1 H, *J* = 13.0 Hz), 4.52 (d, 1 H, *J* = 3.2 Hz), 5.30 (br s, 1 H, exchanges with D_2O), 5.66 (br s, 1 H, exchanges with D_2O), 7.12–7.40 (m, 5 *H*); ^{13}C NMR ($CDCl_3$) δ 24.4, 27.8, 39.6, 53.4, 57.9, 62.8, 64.8, 66.0, 76.9, 98.4, 127.4, 128.4, 129.2, 138.6, 158.9.

Anal. Calcd for $C_{18}H_{24}N_4O_2S_2$: C, 55.07; H, 6.16; N, 14.27. Found: C, 54.67; H, 5.99; N, 13.84.

(3′aα,4′β,9′a*R)-(±)-Octahydro-2′-oxo-4′-(hydroxymethyl)-5′-(phenylmethyl)spiro[1,3-dithiane-2,9′-[9*H*]imidazo[4,5-*c*]pyrrolo[1,2-*b*]pyrazole] (9).** A suspension of 43 mg (0.1 mmol) of β-ester **6a** and 25 μL (0.2 mmol) of freshly distilled BF_3·Et_2O in 10 mL of anhydrous THF was slowly brought to reflux under an inert atmosphere and was then carefully treated with 150 μL (0.3 mmol) of a 2 M solution of BH_3·Me_2S complex[25] in THF. Solution (pale yellow) was complete within 1 min, and after being heated a total of 1.5 h, the reaction was cooled to room temperature, diluted with 10 mL of CH_2Cl_2, poured into 10 mL of pH 7 buffer, and extracted with an additional 3 × 10 mL of CH_2Cl_2. The combined organic layers were then washed with 10 mL of saturated brine, dried over Na_2SO_4, and concentrated to give a white foam. Crystallization of this material from 2-propanol then afforded 27 mg (64%) of **9** as colorless needles: mp 225–227 °C; R_f 0.52 (silica gel, 10% MeOH/$CHCl_3$); mass spectrum, *m/e* 392 (M^+); IR (KBr) 1707 cm^{-1}; NMR ($CDCl_3$) δ 1.86–2.06 (m, 2 H), 2.08–2.28 (m, 2 H), 2.68–3.12 (m, 7 H), 3.47 (m, 1 H), 3.56–3.92 (m, 4 H), 4.76 (d, 1 H, *J* = 6.8 Hz), 5.56 (br s, 1 H, exchanges with D_2O), 6.44 (br s, 1 H, exchanges with D_2O), 7.06–7.36 (m, 5 H).

Anal. Calcd for $C_{18}H_{24}N_4O_2S_2$: C, 55.07; H, 6.16; N, 14.27. Found: C, 54.97; H, 6.28; N, 13.71.

(3′aα,4′α,9′a*R)-(±)-Octahydro-2′-oxo-4′-(hydroxymethyl)spiro[1,3-dithiane-2,9′-[9*H*]imidazo[4,5-*c*]pyrrolo[1,2-*b*]pyrazole] (8a) (Desbenzyl 8).** A solution of 1.05 g (2.68 mmol) of pyrrolopyrazole **8** in 50 mL of 0.1 M HCO_2H/HOAc was treated with 4.0 mL of freshly prepared palladium black,[18b] and the resulting mixture was stirred vigorously at room temperature under an inert atmosphere. After a period of 1 h the reaction was gravity filtered, and the recovered catalyst was washed with several portions of glacial HOAc before concentrating to dryness. Reconcentration from 100 mL of 1:1 CH_2Cl_2/benzene, followed by drying in vacuo, then afforded **8a** as a chromatographically homogeneous white foam, R_f 0.48 (silica gel, 15% MeOH/$CHCl_3$). This material was rather unstable and was used as such for the preparation of **12c** (vide infra). An analytical sample, however, could be prepared by careful chromatography on silica gel: mass spectrum, *m/e* 302 (M^+); IR (KBr) 1697 cm^{-1}; NMR ($CDCl_3$) δ 1.84–2.08 (m, 2 H), 2.24 (t, 2 H, *J* = 7.0 Hz), 2.66–3.08 (m, 5 H), 3.28–3.70 (m, 5 H), 4.42 (s, 1 H), 4.00–4.10 (v br s, 1 H, exchanges with D_2O), 5.40 (br s, 1 H, exchanges with D_2O), 5.80 (br s, 1 H, exchanges with D_2O).

Anal. Calcd for $C_{11}H_{18}N_4O_2S_2$: C, 43.71; H, 5.96; N, 18.54. Found: C, 43.76; H, 5.79; N, 18.71.

(3′aα,4′α,9′a*R)-(±)-Octahydro-2′-oxo-4′-(hydroxymethyl)-5′-(phenoxythiocarbonyl)spiro[1,3-dithiane-2,9′-[9*H*]imidazo[4,5-*c*]pyrrolo[1,2-*b*]pyrazole] (12c).** A solution of freshly prepared debenzylated amine **8a** from above in 30 mL of dry pyridine was cooled to 0 °C under an inert atmosphere and was then treated, in dropwise fashion, with a solution of 934 mg (5.41 mmol, 2 equiv) of phenyl chlorothionoformate in 2 mL of anhydrous THF. After stirring an additional 2 h at 0 °C, the resulting bright yellow solution was diluted with 100 mL of CH_2Cl_2, poured into 100 mL of pH 7 buffer, and extracted with an additional 3 × 100 mL of CH_2Cl_2. The combined organic layers were then washed with 100 mL of saturated brine, dried over Na_2SO_4, and concentrated to give a light tan residue. Trituration of this material with 10 mL of ice-cold MeOH then afforded 941 mg (80%) of **12c** as a chromatographically homogeneous off-white solid which was used as such for the preparation of **2**. The analytical sample crystallized from MeOH in the form of a white microcrystalline solid: mp 275–276 °C; R_f 0.65 (silica gel, 15% MeOH/$CHCl_3$); mass spectrum, *m/e* 438 (M^+); IR (KBr) 1718 cm^{-1}; NMR (CD_3OD) δ 1.90–2.06 (m, 2 H), 2.26–2.62 (m, 2 H), 2.76–3.16 (m, 5 H), 3.51–4.06 (m, 3 H), 4.54–4.78 (m, 2 H), 6.94–7.40 (m, 5 H), three exchangeable protons not observed; ^{13}C NMR (Me_2SO-d_6) δ 24.4, 26.7, 27.1, 37.1, 51.9, 56.9, 57.8, 62.0, 74.4, 96.6, 122.6, 125.8, 129.2, 153.4, 159.1, 182.9.

Anal. Calcd for $C_{18}H_{22}N_4O_3S_3$: C, 49.29; H, 5.06; N, 12.78. Found: C, 49.49; H, 5.37; N, 13.07.

(3′aα,4′α,10′a*R)-(±)-Hexahydro-2′(3′*H*)-oxo-4′-(hydroxymethyl)-6′-thioxospiro[1,3-dithiane-2,10′-[1*H*,10*H*]pyrrolo[1,2-*c*]purine] (2).** A 100-mL three-neck round-bottom flask equipped with a dewar condenser was fitted with a nitrogen gas inlet and an adapter through which dry NH_3 could be distilled from a second flask containing Na. The apparatus was then flame-dried in vacuo, cooled, and purged with dry nitrogen before being charged with 910 mg (2.08 mmol) of pyrazole **12c**. After the reaction was cooled to −78 °C under nitrogen (dry ice/acetone), 65 mL of NH_3 was distilled from Na into the reaction flask and condensed with stirring to give a light tan suspension of **12c**. A total of 119 mg (5.19 mmol, 1.25 equiv) of freshly cut Na was then added in 6–8 portions over a period of 1 h at −78 °C, a deep blue color persisting for several minutes after the last aliquot was added. The resulting milky white suspension was then quenched with 400 mg (5.19 mmol) of anhydrous NH_4OAc to give a colorless solution which was stirred at reflux (−33 °C) for 1 h before the NH_3 was allowed to evaporate under a stream of dry nitrogen. The white residue thus obtained was taken up in 20 mL of 50% aqueous MeOH, and after stirring at room temperature for an additional 1 h, the resulting slurry was continuously extracted with CH_2Cl_2 for 48 h. The crude material thus obtained was recrystallized from MeOH to afford 536 mg (75%) of **2** as a colorless microcrystalline solid: mp 274–275 °C; R_f 0.43 (silica gel, 15% MeOH/$CHCl_3$); IR (KBr) 1667, 1695 cm^{-1}; UV, λ_{MeOH}^{max} 255 nm; NMR (Me_2SO-d_6) δ 1.90–2.10 (m, 2 H), 2.26–2.50 (m, 2 H), 2.68–3.10 (m, 5 H), 3.28–3.78 (m, 5 H), 4.24 (d, 1 H, *J* = 3.2 Hz), 6.95 (br s, 1 H, exchanges with D_2O), 7.66 (br s, 1 H, exchanges with D_2O), 8.26 (v br s, 1 H, exchanges with D_2O); ^{13}C NMR (Me_2SO-d_6) δ 24.6, 26.4, 26.6, 33.6, 46.8, 51.6, 57.8, 60.0, 61.8, 82.0, 158.8 180.6. Due to its extremely insoluble nature, combustion analysis of this material was performed on the acetate derivative **14** (vide infra).

(3′aα,4′α,10′a*R)-(±)-Hexahydro-2′(3′*H*)-oxo-4′-(acetoxymethyl)-6′-thioxospiro[1,3-dithiane-2,10′-[1*H*,10*H*]pyrrolo[1,2-*c*]purine] (14).** A solution of 415 mg (1.2 mmol) of thiourea **2** in 5 mL each of dry pyridine and Ac_2O was stirred at room temperature, under an inert atmosphere, for a period of 3 h. All volatiles were then removed under high vacuum (*T* ≤ 30 °C), and the residue was directly crystallized from MeOH to afford 340 mg (73%) of **14** as a colorless crystalline solid: mp 297 °C, dec, R_f 0.64 (silica gel, 15% MeOH/$CHCl_3$); mass spectrum, *m/e* 388 (M^+); IR (KBr) 1715, 1745 sh cm^{-1}; NMR (CD_3OD/$CDCl_3$) δ 1.68–1.86 (m, 2 H), 1.93 (s, 3 H), 2.24–2.39 (m, 2 H), 2.54–2.86 (m, 4 H), 3.11–3.26 (m, 1 H), 3.61–3.81 (m, 2 H), 4.01 (dd, 1 H, *J* = 8.0, 11.3 Hz), 4.11 (dd, 1 H, *J* = 6.0, 11.3 Hz), 4.34 (d, 1 H, *J* = 3.0 Hz), three exchangeable protons not observed.

Anal. Calcd for $C_{14}H_{20}N_4O_3S_3$: C, 43.28; H, 5.19; N, 14.42. Found: C, 43.10; H, 5.30; N, 14.01.

(±)-Bis(pseudourea) (15). To a suspension of 100 mg (0.26 mmol) of acetate **14** and 437 mg (5.2 mmol) of anhydrous $NaHCO_3$ in 20 mL of freshly distilled CH_2Cl_2 was added 490 mg (2.60 mmol) of freshly prepared $Et_3O^+BF_4^-$, and the resulting mixture was stirred at room temperature, under an inert atmosphere, for a period of 2 h.[7] The reaction was then diluted with 20 mL of CH_2Cl_2, poured into 30 mL of cold 20% aqueous $KHCO_3$, and extracted with an additional 3 × 30 mL of CH_2Cl_2. The combined organic layers were then dried over anhydrous K_2CO_3 and concentrated to afford a quantitative yield of chromatographically homogeneous **15** as a pale yellow, unstable oil, R_f 0.62 (silica gel, 10% EtOH/$CHCl_3$). This material could be used as such for the preparation of **16** or, alternatively, it could be purified by preparative TLC (10% EtOH/$CHCl_3$) to return 96 mg (83%) of **15**: mass spectrum, *m/e* 444 (M^+); IR ($CHCl_3$) 1597, 1625, 1737 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (t, 3 H, *J* = 7.0 Hz), 1.28 (t, 3 H, *J* = 7.0 Hz), 1.66–1.94 (m, 2 H), 2.02 (s, 3 H), 2.56–2.98 (m, 8 H), 3.21 (dt, 1 H, *J* = 5.0, 8.0 Hz, simplifies upon irradiation at 3.91), 3.48–3.83 (m, 2 H), 3.91 (d, 1 H, *J* = 8.0 Hz), 4.08 (dd, 1 H, *J* = 8.0, 11.0 Hz), 4.23–4.40 (m, 2 H), 4.50 (dd, 1 H, *J* = 5.0, 11.0 Hz), 4.70 (br s, 1 H, exchanges with D_2O); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 21.1, 25.2, 27.0, 28.2, 35.5, 45.6, 55.9, 57.4, 63.1, 65.7, 68.3, 93.2, 158.0, 165.0, 170.6.

Anal. Calcd for $C_{18}H_{28}N_4O_3S_3$: C, 48.62; H, 6.35; N, 12.60. Found: C, 48.50; H, 6.47; N, 12.40.

(±)-Descarbamoylsaxitoxin, Dithiane Derivative 16. A mixture of 94 mg (0.21 mmol) of bis(pseudourea) (**15**) and ~5 g of freshly prepared, strictly anhydrous $EtCO_2^-NH_4^+$[7a] was sealed under nitrogen in a 10-mL round-bottom flask and immersed in an oil bath maintained at 135 °C. The reaction mixture became homogeneous within 10 min (complete melt), and after a total of 30 min of heating, it was allowed to cool to room temperature. The excess salt was then sublimed off in vacuo on a hot water bath to give a yellow solid residue of crude **16**. For purification, as well as for solubility reasons, this material was directly converted to its hexaacetate derivative by being dissolved in 2.0 mL of 50:50

Ac_2O/pyr and allowed to stand at room temperature for 6-8 h. Concentration and purification by preparative TLC (silica gel, 10% MeOH/CH_2Cl_2) then afforded 59 mg (48%) of the hexaacetate derivative of **16** as a very pale yellow oil, R_f 0.70 (silica gel, 10% MeOH/CH_2Cl_2). The material thus obtained was identical in all respects with an authentic sample and was readily converted to (±)-saxitoxin (**3**) following the published procedure.[7,20]

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Stereoselection in Acyclic Systems. The Synthesis of Amino Sugars via Nitrone Cycloadditions‡

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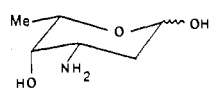
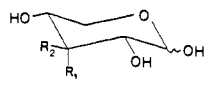
Abstract: Nitrones react with electron-rich dipolarophiles to yield isoxazolidines in which substituents have been placed in a regio- and stereoselective fashion on the periphery of the five-membered ring. Subsequent reductive cleavage of the N,O bond of these isoxazolidines results in release of a β-amino aldehyde (a Mannich system). The regioselectivity and stereoselectivity of the nitrone cycloaddition with various dipolarophiles is discussed, and the application of the method to the synthesis of the amino sugars daunosamine and 3-epigentosamine is reported.

The application of cycloaddition reactions as a means to control the stereochemistry in acyclic systems has been an area of intense activity.[1] Recently, we reported a total synthesis of the amino sugar daunosamine (**1**)[2] in which the stereochemistry of the sugar backbone was established by [3 + 2] dipolar cycloaddition of a nitrone and ethyl vinyl ether.[3] In this paper, we present full experimental details of the daunosamine synthesis and, in addition, will describe results which demonstrate that a variety of β-amino aldehyde systems can be prepared by the nitrone approach. This method is exceptionally suited for the synthesis of 3-amino-3-deoxypyranoses and has been applied to the stereoselective total synthesis of 3-epigentosamine-(*N*-methyl-3-xylosamine (**2**)).



DAUNOSAMINE **1**

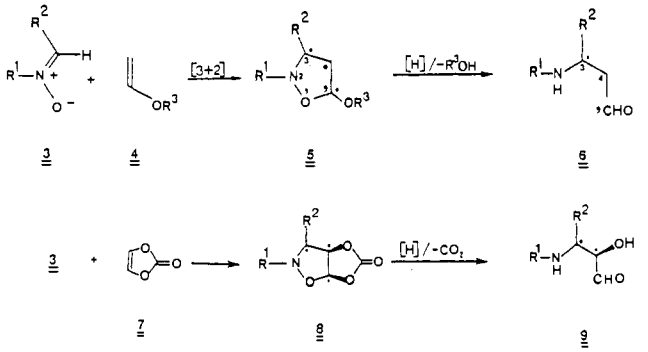


3-EPI-GENTOSAMINE, **2**: R_1 = MeNH, R_2 = H
GENTOSAMINE, : R_1 = H, R_2 = MeNH

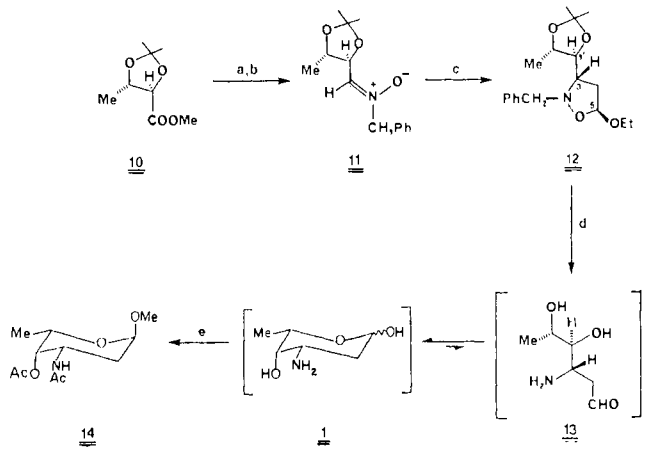
The amino sugars daunosamine (**1**) and 3-epigentosamine (**2**) are examples of the 3-amino-2,3,6-trideoxy- and 3-amino-3-deoxypyranoses, respectively, and are thus related to a wide variety of amino sugars which play critical roles in modern medicinal chemistry.[4] We decided to embark upon a project to develop a general synthetic approach to these classes of amino sugars *from non-carbohydrate precursors*. The strategy devised is shown in Scheme I and depended upon employing an isoxazolidine (**5** or **8**) as a masked form of the β-amino aldehyde moieties **6** and **9**, respectively. We had previously demonstrated[5,6] that nitrones (**3**) react with vinyl ethers and vinyl esters (**4**, R = alkyl or acyl, respectively) to produce *exclusively* isoxazolidine regioisomer **5**. Reductive cleavage of the N,O bond in isoxazolidine **5** and jettison of R^3OH liberated β-amino aldehyde **6**. Introduction of an α-hydroxyl onto **6** was to be accomplished by replacing the vinyl dipolarophile **4** with vinylene carbonate, **7**.

Traditionally, β-amino carbonyl systems are prepared by the Mannich reaction or one of its modern variants. However, the Mannich reaction fails when the systems such as **6** (or **9**) are the desired products since under Mannich conditions **6** is an effective

Scheme I



Scheme II



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