The [2-(trimethylsilyl)ethoxy]methyl protecting group was removed from a 110-mg (0.15 mmol) sample of the above compound through contact for 4 h at 20 °C with 0.5 mL of acetonitrile containing 5% of 40% aqueous hydrofluoric acid.[19c] The product was isolated in the usual fashion and purified by preparative thin-layer chromatography with 20% ether in methylene chloride to give 64 mg (70%) of ester **7**: mp 127–130 °C; $[\alpha]^{26}_D$ +139° (*c* 1.2, chloroform); IR (neat) 3400, 3050, 3020, 2925, 1770, 1730, 1650, 1515, 1480, 1160, 1100, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.45–2.38 (m, 10 H), 3.10 (AB q, J = 11 Hz, δ_a–δ_b = 54 Hz, 2 H), 3.74 (s, 3 H), 4.71 (d, J = 2 Hz, 1 H), 4.99 (br s, 1 H), 5.29 (br s, 1 H), 5.42 (d, J = 3.5 Hz, 1 H), 5.79 (dd, J = 2.3 Hz, 9.4 Hz, 1 H), 5.84 (dd, J = 3.5, 9.4 Hz, 1 H), 6.30 (d, J = 9.4 Hz, 1 H), 6.98 (d, J = 9.4 Hz, 1 H), 7.25–7.61 (m, 8 H), 7.61–7.87 (m, 2 H); mass spectrum, *m/e* 628 (M^+ + 1), 627 (M^+). Anal. Calcd for $C_{36}H_{37}O_9N$: C, 68.88; H, 5.94; N, 2.23. Found: C, 68.68; H, 5.84; N, 2.07.

Acknowledgment. We thank Drs. Potier, Guénard, and Picot and Prof. Beriel for their helpful collaboration and Prof. Rassat and Dr. Luche for their interest in this work. Financial support from the CNRS (LA 320 and PIRMED) and fellowship awards from the CNRS to J.-N.D. and the CNPq (Brazil) to A.A.S. are gratefully acknowledged.

Registry No. **1**, 33069-62-4; **2**, 32981-85-4; **3**, 4510-34-3; **4a**, 99528-63-9; **4b**, 99528-64-0; **4c**, 99528-65-1; **5a**, 99458-15-8; **5b**, 99458-16-9; **6a** (R′ = CH_3), 99458-17-0; **6a** (R′ = H), 99458-20-5; **6a** (**8** ester), 99458-23-8; **6b** (R′ = CH_3), 99458-18-1; **6b** (R′ = H), 99458-21-6; **6b** (**9** ester), 99458-24-9; **6c** (R′ = CH_3), 99458-19-2; **6c** (R′ = H), 99458-22-7; **6c** (**10** ester), 99475-54-4; **7** (**8** ester), 99458-25-0; **7** (**9** ester), 99458-26-1; **7** (**10** ester), 99458-27-2; **8**, 1196-00-5; **9**, 4064-06-6; **10**, 510-50-9; chloromethyl 2-(trimethylsilyl)ethyl ether, 76513-69-4; phenylacetylene, 536-74-3; 3-phenyl-2-propyn-1-ol, 1504-58-1; azidotrimethylsilane, 4648-54-8; chloromethyl methyl ether, 107-30-2; benzyl chloromethyl ether, 3587-60-8.

Stereoselective Syntheses of (±)-Daunosamine, (±)-Vancosamine, and (±)-Ristosamine from Acyclic Precursors

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Stereoselective syntheses of *N*-trichloroacetyl derivatives of (±)-daunosamine (**14**) and (±)-vancosamine (**25**) from simple acyclic precursors are described. Modification of the sequence used for preparation of daunosamine resulted in a novel stereospecific total synthesis of the *N*-trichloroacetyl derivative of (±)-ristosamine (**30**).

Daunosamine[1] (**1**), the sugar fragment in the therapeutically important anticancer antibiotics daunorubicin[2] and adriamycin,[3] is the best known and most often synthesized[4] of the naturally occurring 2,3,6-trideoxy-3-aminohexoses shown in Figure 1. Though less well-known, vancosamine[5] (**2**), ristosamine[6] (**3**), and acosamine[4f] (**4**) have also been of intense synthetic interest since it was found that replacement of daunosamine (**1**) in the parent antibiotics with ristosamine (**3**) or acosamine (**4**) produced analogues, which, though somewhat less active, are significantly less toxic.[7]

In conjunction with our continuing efforts to establish new methodology for the synthesis of 2,3,6-trideoxy-3-aminohexoses from simple acyclic precursors,[4e] a general route for the stereoselective preparation of racemic daunosamine (**1**) and vancosamine (**2**) was developed. A novel stereospecific preparation of racemic ristosamine (**3**) from an intermediate in the daunosamine sequence was also accomplished.

(±)-Daunosamine. The plan devised for the synthesis of the *N*-trichloroacetyl derivative of daunosamine (Scheme I) is based, in part, on our earlier work[4e] which established that cis-hydroxylation of acyclic allyl amide systems produces predominantly the *lyxo* stereochemistry that is present in daunosamine (**1**).

Overman reaction[8] of sorbyl alcohol (**5**) (catalytic NaH, Cl_3CCN, –20 °C; xylene, reflux) furnished the deconjugated diene **6a** in quantitative yield. Initial efforts to functionalize C-1 for subsequent conversion to an aldehyde were unsuccessful; hydroboration of either the amide **6a** or the amine **6b** with 9-BBN resulted in complex mixtures of products. Ultimately, the desired functionalization was obtained through free radical addition of benzenethiol to the terminal olefin[9] (AIBN, 80–90 °C, 30 h) which regiospecifically produced the sulfide **7a** in 87% yield.

An alternate preparation of **7a** was carried out to confirm the structure of **7a** and also to explore the conceptual potential for performing optically active aminohexose synthesis from chiral allyl alcohol precursors. Wittig reaction of **8** with 3-(phenylthio)propanal[10] (**9**) furnished the

(1) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Francheschi, G.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335.
(2) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334.
(3) DiMarco, A.; Arcamone, F.; Zunio, F. In "Antibiotics"; Corcoran, J. W., Hahn, F. E., Eds.; Springer Verlag: New York, 1975; Vol. III, pp 101–128.
(4) For recent syntheses, see: (a) Hamada, A.; Kawai, A.; Shioriri, T. *Tetrahedron Lett.* **1984**, *25*, 5409. (b) Gurjar, M. K.; Yadav, J. S.; Rao, A. V. R. *Carbohydr. Res.* **1984**, *129*, 267. (c) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261. (d) Gurjar, M. K.; Yadav, J. S.; Rao, A. V. R. *Indian J. Chem., Sect. B* **1983**, *22B*, 1139. For a comprehensive list, see the following papers and references therein: (e) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236. (f) Brimacombe, J. S.; Hanna, R.; Tucker, L. C. N. *Carbohydr. Res.* **1985**, in press.
(5) Hamada, A.; Kawai, A.; Shioriri, T. *Tetrahedron Lett.* **1984**, *25*, 5113 and references therein.
(6) For a comprehensive list, see the following papers and references therein: (a) Suami, T.; Tadano, K.-I.; Suga, A.; Ueno, Y. *J. Carbohydr. Res.* **1984**, *3*, 429. (b) Brimacombe, J. S.; Hanna, R.; Saeed, M. S.; Tucker, L. C. N. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2553.
(7) (a) Arcamone, F.; Penco, S.; Vigevanti, A.; Redaelli, S.; Franchi, G.; DiMarco, A.; Soranzo, C. *J. Med. Chem.* **1975**, *18*, 703. (b) Arcamone, F.; Bargiotti, A.; Cassenelli, G.; Redaelli, S.; Hanessian, S.; DiMarco, A.; Casazzo, A. M.; Dasdia, T.; Necco, A.; Reggiani, P.; Supino, R. *J. Med. Chem.* **1976**, *19*, 733.
(8) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.
(9) Hsiao, C.-N.; Shechter, H. *Tetrahedron Lett.* **1982**, *23*, 1963.

0022-3263/86/1951-0050$01.50/0

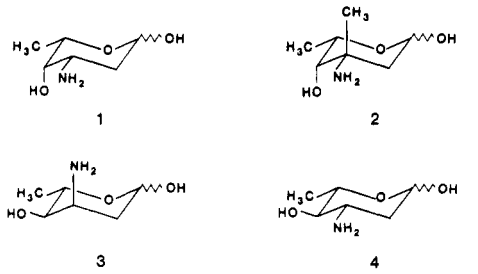
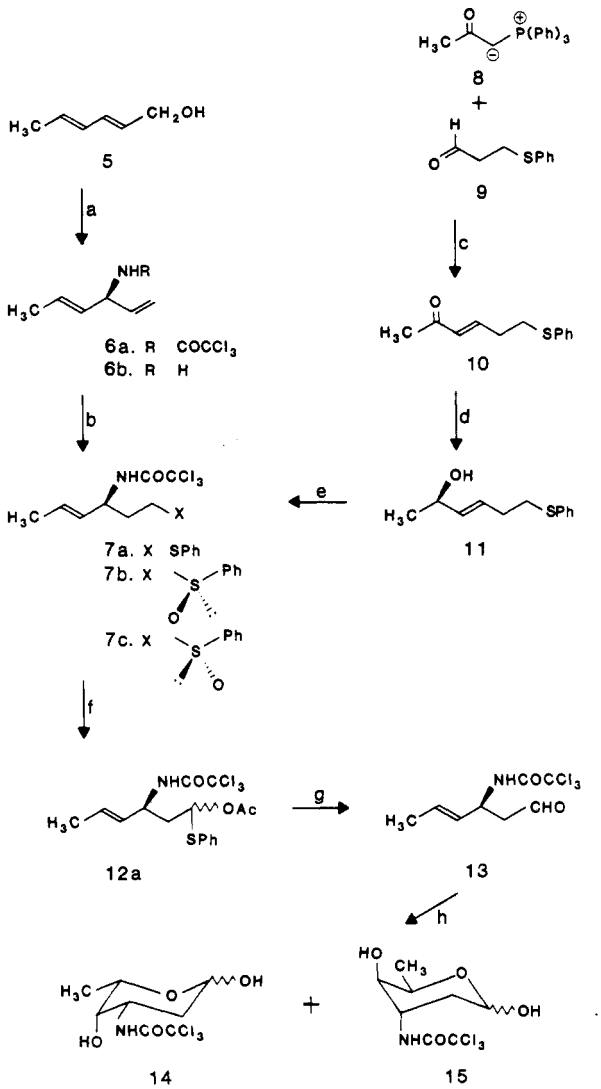


Figure 1. Some naturally occurring 2,3,6-trideoxy-3-aminohexoses.

Scheme I[a]



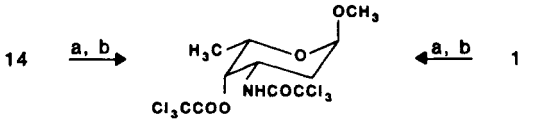
[a] (a) Catalytic NaH, CCl_3CN, Δ; 100%. (b) 1. PhSH, AIBN, Δ; 87%. 2. SeO_2, H_2O_2; 82%. (c) PhH, Δ; 80%. (d) LAH; ~100%. (e) Catalytic KH, CCl_3CN, Δ; ~100%. (f) $(CF_3CO)_2O$, Ac_2O, lutidine; 100%. (g) $CuCl_2$, H_2O, CH_3CN; 86%. (h) Catalytic OsO_4, TMNO; 86%.

unsaturated ketone **10** (80%) which was quantitatively reduced (LAH) to the alcohol **11**. Overman reaction of **11** produced material that was identical with **7a** obtained in the other sequence.

The sulfide group in **7a** was oxidized to a sulfoxide in order to use the Pummerer reaction to convert C-1 to an aldehyde functionality. Predominant production of either diastereoisomeric sulfoxide[11] (**7b** or **7c**) was determined

(10) Sirotanovic, K.; Bajlon-Rocen, M.; Galovic, D. *Glas. Hem. Drus. Beograd* **1960–61**, *25/26*, 509; *Chem. Abstr.* **1963**, *59*, 8635d.

Scheme II[a]



[a] (a) CH_3OH, HCl. (b) Cl_3CCOCl, Py.

by the choice of oxidizing agent. Reaction of **7a** with hydrogen peroxide and selenium dioxide[12] ($MeOH–H_2O$, room temperature, 5 min; 82%) gave an 82:18 ratio of **7b** to **7c**, whereas oxidation with sodium metaperiodate[13] (MeOH, 0 °C, 48 h; 87%) furnished the sulfoxides in an inverted 8:92 ratio. The isomers were readily separated through crystallization or, for purposes of quantitation, by chromatography.

As expected from the nature of the Pummerer rearrangement,[14] individual reaction ($(CF_3CO)_2O$, Ac_2O, lutidine, room temperature)[15] of the sulfoxide isomers (**7b** and **7c**) produced identical mixtures of diastereomeric acetoxy sulfides, although at different rates. The ratio of the inseparable isomers, obtained in quantitative yield, was 6:4, as determined by comparison of the acetoxyl methyl absorptions in the ^1H and ^{13}C NMR spectra.

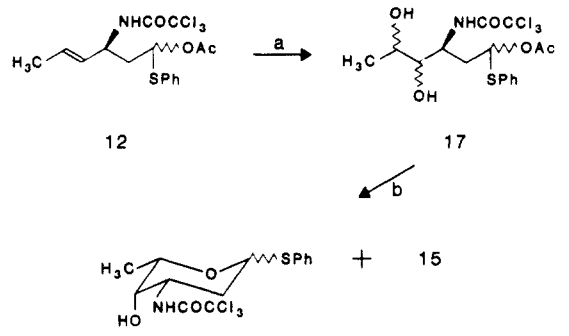
For the most expeditious handling of intermediates, the much faster selenium dioxide–hydrogen perioxide oxidation of **7a** was preferred over the periodate method. The initially received diastereoisomeric sulfoxide mixture was filtered through a short slug of silica gel to remove selenium impurities and directly subjected to Pummerer rearrangement. The overall yield of the acetoxy sulfides **12** was routinely 92–95%.

Hydrolysis of the acetoxy sulfide moiety in **12** ($CuCl_2$, CH_3CN, H_2O)[16] furnished the aldehyde **13** in 86% yield. In spite of the potential for β-elimination of the trichloroacetamide residue, **13** proved to be quite stable and was conveniently purified by chromatography on silica. Hydroxylation of the olefinic moiety in **13** with a catalytic amount of osmium tetraoxide and trimethylamine *N*-oxide[17] (TMNO) gave a 6:4 mixture (94%) of *N*-(trichloroacetyl)daunosamine (**14**) (56%) and the *xylo* isomer **15** (38%). These products were quantitatively separated through crystallization. The identity of **14** was established through conversion to methyl *N,O*-bis(trichloroacetyl)daunosaminide (**16**) (Scheme II). The ^1H and ^{13}C NMR spectra were identical with those obtained on similar conversion of an authentic sample of **1**.

Cis-hydroxylation of the olefinic acetoxy sulfides **12** (catalytic OsO_4, TMNO, 95%) and subsequent hydrolysis of the acetoxy sulfide entity ($CuCl_2$, CH_3CN, H_2O) in **17** were performed in an attempt to establish a second route to **1**. (See Scheme III.) Unexpectedly, the hydrolysis produced a mixture of the α and β anomers of the *lyxo* thioglycoside **18** and the fully hydrolyzed *xylo* sugar **15** in a 6:4 ratio. The products were readily washed apart with carbon tetrachloride since the thioglycosides were soluble and the *xylo* sugar was not. None of the fully hydrolyzed

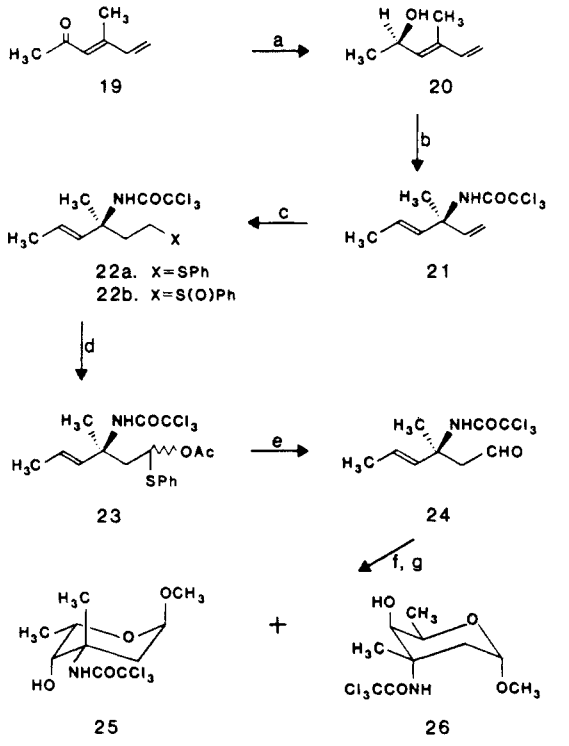
(11) The structures of the sulfoxide diastereoisomers were established in conjunction with other studies. Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458.
(12) Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1978**, *12*, 758.
(13) (a) Johnson, C. R.; Keiser, J. E. *Org. Synth.* **1966**, *46*, 78. (b) Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1109.
(14) (a) Oae, S.; Kitao, T.; Kawamura, S.; Kitaoka, Y. *Tetrahedron* **1963**, *19*, 817. (b) Oae, S.; Kise, M. *Tetrahedron Lett.* **1965**, 2261.
(15) Tanikaga, R.; Yabuki, Y.; Ono, N.; Kaji, A. *Tetrahedron Lett.* **1976**, 2258.
(16) Sugihara, H.; Tanikaga, R.; Kaji, A. *Synthesis* **1978**, *12*, 881.
(17) Ray, R.; Mateson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.

Scheme III[a]



[a] (a) Catalytic OsO_4, TMNO; 97%. (b) $CuCl_2$, H_2O, CH_3CN; 91%.

Scheme IV[a]



[a] (a) LAH, Et_2O; 100%. (b) Catalytic KH, 18-crown-6, CCl_3CN, Δ; 88%. (c) 1. AIBN, PhSH; 85%. 2. SeO_2, H_2O_2; 85%. (d) $(CF_3CO)_2O$, Ac_2O, lutidine; 89%. (e) $CuCl_2$, CH_3CN, H_2O; 99%. (f) Catalytic OsO_4, TMNO; 85%. (g) CH_3OH/HCl.

lyxo isomer **14** nor any of the phenylthio derivative of the *xylo* isomer was obtained. Apparently, under the hydrolytic conditions used, the acetoxy sulfide diastereoisomers with the *lyxo* configuration could achieve transition-state geometries leading to selective replacement of the acetoxy functionality, whereas those isomers with the *xylo* configuration could not. The structure of **18** was confirmed through conversion to the *N,O*-bis(trichloroacetyl) thioglycoside derivative and then to the methyl glycoside of daunosamine (MeOH, HCl).

(±)-Vancosamine. The preparation of vancosamine (**2**) shown in Scheme IV conceptually parallels that employed for synthesis of daunosamine. The dienone starting material **19**, prepared according to the procedure of Cookson and Gopalan,[18] was reduced with LAH to dienol **20** in

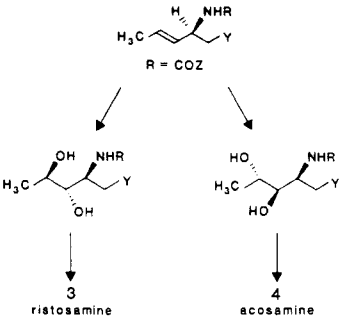
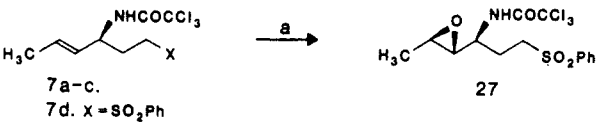


Figure 2. Aminohexoses from trans-hydroxylation of allyl amides.

Scheme V[a]



[a] (a) MCPBA, CH_2Cl_2.

quantitative yield. Overman reaction[8] of **20** proved unexpectedlay difficult, and a change in base to potassium hydride gave only a 25–30% yield of the desired deconjugated trichloroacetamide **21**. Addition of 18-crown-6 to the potassium hydride catalyzed reaction and the use of a longer reaction time gave excellent results, producing **21** in 90% yield.

Free-radical addition of benzenethiol (AIBN, 90 °C; 85%) to **21** regiospecifically furnished the sulfide **22a**, which was oxidized with selenium dioxide and hydrogen peroxide to a 1:1 mixture of the diastereoisomeric sulfoxides **22b**. Pummerer rearrangement ($(CF_3CO)_2O$, Ac_2O, lutidine, 89%), followed by hydrolysis ($CuCl_2$, CH_3CN, H_2O) of the resultant acetoxy sulfides **23** gave the aldehyde **24**. Cis-hydroxylation (catalytic OsO_4, TMNO) of **24** was even more stereoselective than the corresponding hydroxylation in the daunosamine sequence and produced a 7:3 ratio of *N*-(trichloroacetyl)vancosamine (**25**) and the *xylo* isomer **26** (85% from **24**; 52% overall). As before, the sugars were characterized as the methyl glycoside derivatives.

(±)-Ristosamine. As shown in Figure 2, trans-hydroxylation of the allyl amide intermediates used for synthesis of daunosamine would provide precursors to ristosamine (**3**) or acosamine (**4**) which have the *ribo* and *arabino* configurations, respectively. The predominant production of either stereochemistry would depend upon the stereochemical course and selectivity of the trans-hydroxylation process.

A variety of strategies based on neighboring-group participation of the amide residue have been developed for the trans-hydroxylation of allyl amide systems.[19-21] The sequence established by Roush and co-workers,[20,21] in which stereoselective epoxidation of the allyl amide system is followed by neighboring-group opening of the epoxide by the amide, was chosen for investigation. The epoxidation was initially performed on the sulfide **7a** since the expected product would be a simple mixture of diastereoisomers and thereby would provide an indication of

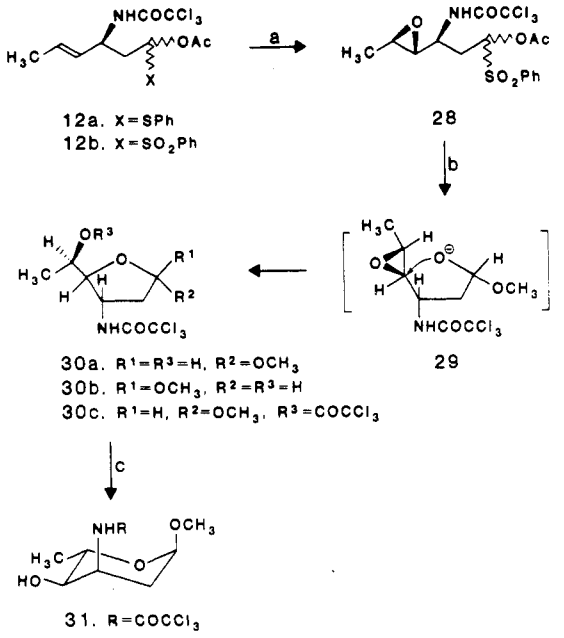
(18) (a) Cookson, R.; Gopalan, R. *J. Chem. Soc., Chem. Commun.* **1978**, 608. (b) Horner, L.; Binder, V. *Justus Liebigs Ann. Chem.* **1972**, *757*, 33.

(19) For halo-hydroxylation of olefins with neighboring amide participation, see: (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1982**, 1308. (b) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (c) Parker, K. A.; O'Fee, R.; *J. Am. Chem. Soc.* **1983**, *105*, 654.

(20) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083.

(21) Private communication from W. R. Roush: unpublished results from the thesis of Richard J. Brown, Massachusetts Institute of Technology.

Scheme VI[a]



[a] (a) MCPBA, CH_2Cl_2; 85%. (b) CH_3OH, NaOH; ~100%. (c) 1. H_3O^+. 2. CH_3OH, HCl; 80%.

the stereoselectivity of the reaction. In contrast to the expectation that epoxidation of the allyl amide system would be only stereoselective, a single epoxy sulfone (**27**) was obtained when *m*-chloroperoxybenzoic acid was used as the oxidizing agent (Scheme V).[22] Corresponding reaction of the sulfoxides **7b** and **7c** and of the sulfone **7d** produced identical results. Although it was clear from both the ^1H and ^{13}C NMR spectra that **27** was a single isomer, it was not possible to determine unequivocally the stereochemistry of the material. An X-ray analysis established the relative stereochemistry to be that shown for **27**.

The previous studies indicated that systems with this substitution pattern undergo stereospecific epoxidation; therefore, similar reaction of **12a** followed by hydrolytic cleavage of the acetoxy sulfide would provide a late-stage precursor to the aminohexoses ristosamine (**3**) and/or acosamine (**4**). Since **12a** was a 6:4 mixture of diastereoisomers, it would be necessary to subsequently remove the acetoxy sulfide functionality to determine the stereoselectivity of the epoxidation.

Attempted epoxidation of **12a** with 2 equiv of *m*-chloroperoxybenzoic acid selectively produced the acetoxy sulfone **12b**. The structure of **12b** was elucidated from its ^1H and ^{13}C NMR spectra which had olefinic absorptions at 5.65 ppm and from the IR spectrum which had an absorption at 1025 and 1154 cm^{-1} for the sulfone.

Reaction of **12a** with 3 equiv of *m*-chloroperoxybenzoic acid produced the epoxide **28** (Scheme VI) as evidenced by the absence of olefinic protons and by the presence of a multiplet at 2.88 ppm in its ^1H NMR spectrum. As expected, the diastereoisomers of **28** produced proton and carbon NMR spectra that were too complex to definitively assign the stereochemistry of the epoxide group relative to the amide.

Cleavage of the acetoxy sulfone moiety in **28** with methanolic sodium hydroxide gave a major product, isolated in 93% yield, and a trace of a second material. The ^1H NMR spectrum of the major product had a methoxyl absorption at 3.40 ppm and was otherwise consistent with that expected for the furanose **30a** with the *ribo* configuration. The presence of a furanose fragment in **30a** was demonstrated through decoupling experiments on the trichloroacetate derivative **30c**. The protons on C-4 and C-5 in the ^1H NMR spectrum are well-separated in benzene-d_6, and irradiation of the multiplet at 5.01 ppm led to collapse of the methyl doublet at 1.21 ppm to a singlet and also to simplification of the multiplet at 3.65 ppm. Rigorous assignment of the stereochemistry of **30a** and that of the anomeric carbon was made by comparison of the spectral data to that reported by Fronza and coworkers.[23] The minor product, isolated in 3% yield, was shown from its ^1H NMR spectrum to be the C-1 anomer **30b** and also to have the *ribo* configuration.

The mechanism of formation of **30a** and **30b** from **28** results from initial hydrolysis of the acetoxy sulfone group to an aldehyde which then undergoes a second addition of methoxide to give the hemiacetoxide intermediate **29**. Concomitant intramolecular ring closure of **29** through backside attack on C-4 and opening of the epoxide furnishes the furanose **30a**. In effect, the stereochemical course of the ring closure of **28** was regiospecific, and the epoxiation of **12a** was most probably stereospecific.

Another rigorous proof of the *ribo* configuration of **30a** was achieved by converting it to the methyl pyranoside **31** and comparing its ^1H NMR spectrum with that of an authentic sample; these spectra were identical.

Summary and Conclusions. The preparations of (±)-methyl *N*-(trichloroacetyl)daunosaminide, -vancosaminide (**25**), and -ristosaminide (**30a**) demonstrate that the parallel routes used can be generally applied to synthesis of these aminohexoses from simple acyclic precursors. These sequences are notable for their brevity, the absence of steps that require low temperatures, and the general ease of executation. These routes are also potentially useful for large-scale preparation and for optically active synthesis. The vancosamine and ristosamine sequences are particularly noteworthy in that they are among the shortest and highest yield routes yet reported for racemic preparations of these sugars.

Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra are expressed in reciprocal centimeters. Proton and carbon nuclear magnetic resonance spectra were measured at 90 MHz.

Analytical thin-layer chromatography (TLC) was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, 0.25-mm thickness) manufactured by E. Merck and Co. Radial preparative thick-layer chromatography was performed on a Chromatotron (Harrison Research) with rotors coated to 2- and 4-mm thickness (Merck silica gel 60, PF-254). Silica gel columns for chromatography utilized E. Merck silica gel 60, 70–230-mesh ASTM.

Tetrahydrofuran (THF) and dioxane were dried by distillation from lithium aluminum hydride (LAH). All other solvents were reagent grade and were not further purified. Trichloroacetonitrile and trichloroacetyl chloride were distilled before use. A stock solution of osmium tetraoxide (1 g in 200 mL of 3:1 *t*-BuOH–CCl_4) was used for hydroxylations. All reactions were run under a nitrogen atmosphere. Methyl L-daunosamine hydrochloride was purchased from Pfanstiehl Laboratories.

(4*E*)-3-(Trichloroacetamido)-1,4-hexadiene (6a). Sodium hydride (0.48 g, 0.10 mmol, 50% suspension) was repeatedly

(22) It is emphasized that epoxidation of acyclic allyl amide systems is usually only stereoselective.[20,21]

(23) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 885.

(24) Occasional difficulty was encountered in running this reaction. If the mixed anhydride solution turns yellow, it should be discarded. Attempted Pummerer rearrangement with the yellow solution resulted predominantly in reduction of the sulfoxide to a sulfide.[25]

(25) (a) Johnson, C. R.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 682. (b) Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266.

washed with hexanes (3 × 5 mL) to remove the mineral oil and was then suspended in ether (100 mL). Sorbyl alcohol (**5**) (10 g, 100 mmol) in ether (30 mL) was added rapidly to the magnetically stirred sodium hydride suspension, and the resultant yellow solution was stirred at ambient temperature for 15 min and then chilled at −10 to −15 °C. Trichloroacetonitrile (15.90 g, 110 mmol) in ether (35 mL) was slowly added to the reaction, and the resultant brown solution was stirred cold for 1 h and then at room temperature for 3 h. Hexanes (20 mL) and methanol (6 mL) were added to the reaction, and the resultant solution was filtered through Celite. Evaporation of the solvents at reduced pressure gave the imidate intermediate, which was taken up in xylenes (100 mL) and heated at reflux for 12 h. The progress of the reaction was followed by TLC. The solvent was removed at reduced pressure, and the residue was filtered through silica (100 g; 9:1 hexanes/ethyl acetate) to give 24.09 g (100%) of the deconjugated diene amide **6a** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.97 (br s, 1 H), 5.54 (m, 5 H); 4.85 (m, 1 H), 1.66 (d, J = 5.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.37, 131.39, 124.51,123.64, 111.89, 88.43, 50.62, 13.35; IR (film) 3350, 1710, 1522, and 820 cm^{-1}; EI mass spectrum, m/z 241 ($M^{+\cdot}$), 206.

Anal. Calcd for $C_8H_{10}Cl_3NO$: C, 39.62; H, 4.16; N, 5.78. Found: C, 39.62; H, 4.05; N, 5.71.

(*E*)-1-(Phenylthio)-3-(trichloroacetamido)-4-hexene (7a) from Diene 6a. A magnetically stirred mixture of benzenethiol (10.95 g, 99.6 mmol), AIBN (1.64 g, 10 mmol), and **6a** (24.0 g, 99.6 mmol) was heated at 80–90 °C for 12 h, then cooled, and diluted with methylene chloride (100 mL). The dark solution was washed with potassium hydroxide (0.5 M, 3 × 30 mL), and the aqueous extracts were back-extracted with methylene chloride (1 × 25 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed (silica gel, 150 g; 9:1 hexanes/ethyl acetate) to give 30.70 g (88%) of the sulfide **7a** as a gold oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5 H), 6.78 (br d, 2 H), 5.52 (m, 2 H), 4.51 (p, J = 7.2 Hz, 1 H), 2.95 (t, J = 7.4 Hz, 2 H), 1.94 (q, J = 7.2 Hz, 2 H), 1.71 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.97, 135.56, 129.55, 129.45, 128.74, 128.46, 126.24, 92.71, 52.62, 33.99, 29.98, 17.51; IR (film) 3411, 3021, 1700, and 1517 cm^{-1}; EI mass spectrum, m/z 351 ($M^{+\cdot}$), 316, 242, 206.

Anal. Calcd for $C_{14}H_{16}Cl_3NOS$: C, 47.68; H, 4.57; N, 3.97. Found: C, 48.00; H, 4.82; N, 4.01.

(*E*)-6-(Phenylthio)-3-hexen-2-one (10). A magnetically stirred mixture of 3-(triphenylphosphoranylidene)-2-propanone (**8**) (44.10 g, 138.55 mmol) and 3-(phenylthio)propanal[10] (**9**) (20 g, 120.48 mmol) in dry benzene (300 mL) was heated at reflux for 60 h, at which time analysis of a TLC indicated that the starting materials had been consumed. The reaction was cooled to ambient temperature, and water (50 mL) and ethyl acetate (50 mL) were added. The layers were separated, and the aqueous phase was extracted with additional ethyl acetate (2 × 50 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give a red-brown slushy solid. The mixture was dissolved in hot ether, chilled to effect crystallization, and then filtered in order to remove triphenylphosphine oxide. A second repetition of the crystallization procedure gave an additional small quantity of the oxide. The filtrate was evaporated, and the residue was chromatographed (silica gel, 200 g; 8:2 hexanes/methylene chloride) to give 19.86 g (80%) of the unsaturated ketone **10** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5 H), 6.80 (m, 1 H), 6.01 (m, 1 H), 3.02 (t, J = 6.59 Hz, 2 H), 2.56 (q, J = 7.01 Hz, 2 H), 2.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.48, 144.83, 135.56, 132.09, 129.44, 128.79, 126.14, 31.87, 26.56.

(*E*)-6-(Phenylthio)-3-hexen-2-ol (11). Lithium aluminum hydride (LAH) (1.00 g, 26.38 mmol) was added in small protions to a solution of the hexenone **10** (10 g, 48.54 mmol) in ether (200 mL), and the mixture was stirred for 16 h. Excess LAH was destroyed by successively adding water (1 mL), aqueous potassium hydroxide (1 mL, 15%), and water (3 mL). The mixture was filtered, and the filtrate was evaporated at reduced pressure to give a quantitative yield of **11** (10.08 g). The product, homogenous by TLC, was used in the next step without purification: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.50 (m, 2 H), 4.48 (p, J = 5.71 Hz, 1 H), 2.98 (t, J = 7.25 Hz, 2 H), 2.40 (m, 2 H), 1.46 (br s, 1 H), 1.25 (d, J = 6.37 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 127.11, 125.92, 124.18, 66.44, 31.55, 30.03, 21.58.

(*E*)-1-(Phenylthio)-3-(trichloroacetamido)-4-hexene (7a) from Dienol 11. A modification of the Overman reaction[8] used to prepare **6a** was employed. The imidate obtained from the dienol **11** (8.01 g, 38.51 mmol), potassium hydride (0.44 g of a 35% suspension in mineral oil, 3.85 mmol), and trichloroacetonitrile (5.56 g, 38.51 mmol) was heated at reflux (12 h) in ethyl acetate (100 mL) to give 13.50 g (100%) of **7a** after purification on silica. The IR and ^{1}H NMR spectra and the TLC behavior of this product were identical with the material prepared from **6a**.

(*E*)-1-(Phenylsulfinyl)-3-(trichloroacetamido)-4-hexene (7b and 7c). Predominant production of either diastereomeric sulfoxide (**7a** or **7b**) was accomplished by oxidation of the sulfide **7a** with either (A) sodium metaperiodate[13] or (B) selenium dioxide–hydrogen peroxide.[12]

(A) Sodium metaperiodate (8.94 g, 28.49 mmol) was added in small portions to a magnetically stirred solution of **7a** (10.0 g, 28.49 mmol) in methanol (75 mL) at 0 °C. The reaction was allowed to warm to room temperature and then stirred for 2–3 days, at which time, analysis of a TLC showed that the reaction was complete. The mixture was filtered to remove sodium iodate, and the filtrate was evaporated under reduced pressure to remove the methanol. The mixture was diluted with methylene chloride (75 mL), transferred to a separatory funnel, and washed with water (3 × 20 mL). The combined aqueous phases were back-extracted once with ethyl acetate (25 mL). The organic extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure.

Fractional crystallization of the residue from ethyl acetate/hexanes gave the pure diastereoisomeric sulfoxides **7b** and **7c**, the sulfone **7d** (0.82 g, 8%) as a yellow oil, and a small amount of recovered sulfide **7a**. The less polar sulfoxide diastereomer (R_f 0.52; 1:1 ethyl acetate/hexanes) was obtained as colorless needles (8.93 g, 85%) with mp 110–112 °C, ^{1}H NMR ($CDCl_3$) δ 7.59 (m, 6 H), 5.48 (m, 2 H), 4.44 (p, J = 6.1 Hz, 1 H), 2.93 (m, 2 H), 2.17 (m, 2 H), 1.73 (d, J = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.46, 143.15, 131.07, 129.28, 129.01, 128.36, 123.92, 52.57, 52.40, 26.78, 17.62; IR (KBr) 3275, 1700, 1498, and 1081 cm^{-1}; FAB mass spectrum, m/z 368 ($M^{+\cdot}$), 243, 207.

Anal. Calcd for $C_{14}H_{16}Cl_3NO_2S$: C, 45.60; H, 4.37; N, 3.80. Found: C, 45.47; H, 4.43; N, 3.81.

The more polar sulfoxide diastereomer (R_f 0.47; 1:1 ethyl acetate/hexanes) was isolated as a pale yellow, low-melting (mp <50 °C) solid (0.73 g, 7%): ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 6 H), 5.56 (m, 2 H), 4.43 (p, J = 6.2 Hz, 1 H), 2.89 (m, 2 H), 1.95 (m, 2 H), 1.72 (d, J = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.51, 144.05, 131.12, 129.33, 129.12, 128.30, 127.87, 124.08, 52.46, 29.65, 27.16, 17.68. IR ($CDCl_3$) 3419, 1709, 1507, and 1022 cm^{-1}; FAB mass spectrum, m/z 368 ($M^{+\cdot}$), 243, 207.

(B) A solution of selenium dioxide (4.95 g, 44.6 mmol) and hydrogen peroxide (30%, 1.52 g, 44.6 mmol) in methanol (32 mL) and water (8 mL) was added dropwise to a magnetically stirred solution of the sulfide **7a** (15.65 g, 44.6 mmol) in methanol (100 mL) at 0 °C. Immediately following addition of the oxidizing agent, analysis of a TLC indicated that the reaction was complete. Saturated sodium chloride solution (25 mL) was added, and the resultant mixture was extracted with methylene chloride (3 × 35 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 150 g; 6:4 hexanes/ethyl acetate) gave 2.53 g (15.5%) of the less polar sulfoxide and 11.51 g (70.5%) of the more polar diastereoisomer.

(*E*)-1-(Phenylthio)-1-acetoxy-3-(trichloroacetamido)-4-hexene (12a). Pummerer rearrangement of either the pure sulfoxide diastereoisomer (**7b** or **7c**) or of the mixture gave identical mixtures (6:4) of diastereoisomeric acetoxy sulfides **12a**. A typical procedure from a diastereoisomeric mixture of sulfoxides follows.

A solution of mixed anhydrides prepared from acetic anhydride and trifluoroacetic anhydride (2:1) was initially prepared and allowed to stand 5 h before use.[24] The diastereoisomeric sulfoxides **7b** and **7c** (10.0 g, 27.25 mmol) were dissolved in acetic anhydride (20 mL), and the solution was stirred for 15 min at ambient temperature before *slow*, dropwise addition of 2,6-lutidine (11.66 g, 109 mmol). Addition of the lutidine produced a slightly exothermic reaction, and the initially colorless solution became orange-red in color.

The reaction was stirred for 5 h and then transferred to a large Erlenmeyer flask with methylene chloride (50 mL). Saturated aqueous sodium bicarbonate (50 mL) was cautiously added, and then solid bicarbonate was added in small portions until the reaction mixture ceased foaming. The layers were separated, and the aqueous protion was extracted with methylene chloride (2 × 50 mL). The combined organic extracts were washed with 10% HCl (3 × 25 mL), then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed (silica gel, 200 g; 2:8 ethyl acetate/hexanes) to give 11.03 g (99%) of the acetoxy sulfide **12a** as a gold oil. The product, homogenous by TLC, was shown by ^1H and ^{13}C NMR to be a 6:4 mixture of diastereoisomers. Attempted separation of the isomers, using a variety of chromatography techniques, was unsuccessful: ^1H NMR (benzene-d_6) δ 7.60 (m, 2 H), 7.05 (m, 3 H), 6.32 (m, 1 H), 5.26 (m, 2 H), 4.60 (m, 1 H), 1.96 (m, 2 H), 1.73 (d, J = 10.99 Hz, 3 H), 1.42 (m, 3 H; ^{13}C NMR ($CDCl_3$) δ 169.91, 169.20, 160.86, 134.42, 133.94, 129.01, 128.68, 128.52, 127.39, 77.65, 76.57, 50.62, 39.08, 20.98, 17.68; IR (film) 3341, 1711, 1675, and 835 cm^{-1}; FAB mass spectrum, m/z 351 (M^+· − 59), 300, 216.

(*E*)-3-(Trichloroacetamido)-4-hexenal (13). A mixture of **12a** (8.0 g, 19.56 mmol), cupric chloride dihydrate (6.69 g, 39.12 mmol), acetonitrile (150 mL), and water (10 mL) was heated at reflux for 15 min. The acetonitrile was removed at reduced pressure, and the mixture was transferred to a separatory funnel with methylene chloride (50 mL). The layers were separated, and the organic phase was repeatedly washed with water (4 × 50 mL) until the aqueous extracts were no longer green in color. The organic solution was dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (150 g; 4:6 ethyl acetate/hexanes) gave 4.32 g (86%) of the aldehyde **13** as a colorless oil: ^1H NMR ($CDCl_3$) δ 9.73 (br s, 1 H), 7.55 (br s, 1H), 5.94 (m, 2 H), 5.13 (m, 1 H), 3.15 (d, J = 5.27 Hz, 2 H), 1.97 (d, J = 4.83 Hz, 3 H; ^{13}C NMR ($CDCl_3$) δ 200.03, 160.81, 129.12, 128.79, 127.60, 126.57, 92.28, 48.61, 46.99, 17.35.

(±)-*N*-(Trichloroacetyl)daunosamine (14) and (±)-*N*-(Trichloroacetyl)-3-*epi*-daunosamine (15). To a solution of the aldehyde **13** (4.00 g, 15.56 mmol) trimethylamine *N*-oxide monohydrate (3.46 g, 31.12 mmol) in acetone (50 mL), and water (5 mL) was added the osmium tetraoxide stock solution (0.5 mL), and the mixture was stirred under nitrogen at room temperature for 12 h. Methylene chloride (100 mL) and saturated sodium bisulfite (25 mL) were added, and the mixture was stirred at room temperature. After 15 min, the reaction turned dark, indicating that the osmium tetraoxide had been completely reduced to the dioxide. The layers were separated, and the aqueous phase was extracted with methylene chloride (2 × 35 mL). The combined organic extracts were successively washed with saturated sodium bicarbonate (1 × 25 mL) and brine (1 × 25 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue (4.25 g, 94%) was chromatographed on silica gel (150 g). Elution with 1:1 ethyl acetate/hexanes gave 1.70 g (38%) of the *xylo* isomer **15** (*epi*-daunosamine) with mp 142–146 °C: ^1H NMR (MeOH-d_4) δ 5.29 (m, 1 H), 4.29 (q, J = 12.75 Hz, 1 H), 3.94 (q, J = 6.37 Hz, 1 H), 3.41 (d, J = 5.27 Hz, 1 H), 2.31 (dt, J = 14.72, 3.74 Hz, 1 H), 1.66 (m, 1 H), 1.22 (d, J = 6.60 Hz, 3 H); FAB mass spectrum, m/z 292 (M^+·), 274, 257, 240, 207.

Continued elution gave 2.55 g (56%) of (±)-*N*-(trichloroacetyl)daunosamine (**14**) as a pale yellow oil: ^1H NMR acetone-d_6/D_2O) δ 5.29 (m, 1 H, 4.23 (dq, J = 1.10, 6.7 Hz, 1 H), 4.03 (q, J = 3.52 Hz, 1 H), 3.43 (m, 1 H), 2.29 (dt, J = 4.18, 14.06 Hz, 1 H), 1.61 (m, 1 H), 1.14 (d, J = 6.59 Hz, 3 H); FAB mass spectrum, m/z 292 (M^+·), 274, 240, 207.

(±)-Methyl *N*-(Trichloroacetyl)daunosaminide and (±)-Methyl *N*,*O*-Bis(trichloroacetyl)daunosaminide (16). Dry hdyrogen chloride gas was bubbled into a cold (0 °C) solution of **14** (1.0 g, 3.44 mmol) in dry methanol (10 mL) for 30 s. The colorless solution was allowed to come to room temperature and then stirred for an additonal 0.5 h. The solvent was evaporated under reduced pressure at room temperature, and the residue was chromatographed on silica gel (50 g; 6:4 ethyl acetate/hexanes) to give 1.04 g (82%) of methyl *N*-(trichloroacetyl)dauosaminide as a yellow oil: ^1H NMR (benzene-d_6) δ 7.00 (br s, 1 H), 4.41 (d, J = 3.73 Hz, 1 H), 4.22 (m, 1 H), 3.81 (m, 1 H), 3.53 (q, J = 6.60 Hz, 1 H, 3.08 (s, 3 H), 1.83 (dd, J = 5.71, 12.96 Hz, 1 H), 1.45 (dd, J = 3.29, 12.53 Hz, 1 H), 0.99 (d, J = 6.60 Hz, 3 H).

The bis(trichloroacetyl) derivative was prepared by adding pyridine (1 mL) and freshly distilled trichloroacetyl chloride (0.32 g, 1.75 mmol) to a solution of the above methyl glycoside (0.50 g, 1.64 mmol) in anhydrous ether (20 mL) at 0 °C. The mixture was stirred 0.5 h and quenched by adding saturated sodium bicarbonate solution (15 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 25 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue (silica, 50 g; 4:6 ethyl acetate/hexanes) gave 0.67 g (90%) of **16** as a golden yellow oil: ^1H NMR ($CDCl_3$) δ 6.58 (br d, 1 H), 5.29 (m, 1 H), 4.90 (m, 1 H), 4.62 (dq, J = 10.0, 1.53 Hz, 1 H), 4.14 (q, J = 6.40 Hz, 1 H), 3.39 (s, 3 H), 2.00 (m, 2 H), 1.24 (d, J = 6.59 Hz, 3 H). The IR and ^1H NMR spectra and the TLC behavior of **16** were identical with that of an authentic sample prepared by reacting methyl daunosaminide hydrochloride with trichloroacetyl chloride and pyridine in ether.

1-(Phenylthio)-1-acetoxy-3-*N*-(trichloroacetamido)hexane-4,5-diol (17). To a magnetically stirred solution of **12a** (3.62 g, 8.85 mmol) in acetone (100 mL) and water (5 mL), under nitrogen, was added 0.5 mL of the osmium tetraoxide stock solution and trimethylamine *N*-oxide monohydrate (1.97 g, 17.70 mmol). The solution was heated at reflux for 1 h and then cooled to room temperature. Methylene chloride (50 mL) and saturated sodium bisulfite (35 mL) were added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous phase was extracted with methylene chloride (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography of the residue on silica gel (50 g; ethyl acetate) gave 3.59 g (92%) of **17** (6:4 mixture of isomers) as a yellow semisolid which was used in the next step: ^1H NMR (benzene-d_6) δ 7.37 (m, 6 H), 6.46 (m, 1 H), 4.20 (m, 1 H), 3.48 (m, 1 H), 2.99 (m, 1 H), 2.15 (m, 1 H), 1.75 (d, J = 11.43 Hz, 3 H), 0.95 (d, J = 6.59 Hz, 3 H; ^{13}C NMR ($CDCl_3$) δ 169.64, 169.53, 162.25, 161.84, 134.75, 134.37, 133.83, 129.01, 128.74, 79.22, 78.41, 68.55, 66.92, 51.32, 48.99, 35.29, 34.96, 29.60, 21.15, 21.04, 19.52; FAB mass spectrum, m/z 334 (M^+·), 310, 275.

(±)-*N*-(Trichloroacetyl)-3-*epi*-daunosamine (15) and (±)-Phenyl *N*-(Trichloroacetyl)-1-thiodaunosaminide (18). A magnetically stirred mixture of the diol **17** (3.88 g, 8.76 mmol) in acetonitrile (100 mL) and water (10 mL) and cupric chloride dihydrate (3.74 g, 21.90 mmol) was heated at reflux for 2 min. The dark mixture was evaporated, and methylene chloride (25 mL) and water (10 mL) were added. The layers were separated, and the aqueous phase was successively extracted with methylene chloride (35 mL) and ethyl acetate (30 mL). The combined organic extracts were washed with water until the aqueous extracts were no longer green in color. The organic solution was dried ($MgSO_4$), filtered, and evaporated at reduced pressure.

Either of two procedures were employed to separate the mixture. Heating the mixture in carbon tetrachloride resulted in selective dissolution of the phenylthio product. The *xylo* sugar **15** was collected by filtration and then further purified by chromatography. Evaporation of the carbon tetrachloride and chromatography of the residue gave pure phenyl *N*-(trichloroacetyl)-1-thiodaunosaminide (**18**) as an anomeric mixture. Alternatively, the 4:6 mixture (2.88 g, 95%) was directly separated on silica gel (100 g). Elution with 6:4 hexanes/ethyl acetate gave 0.97 g (38%) of *N*-(trichloroacetyl)-3-*epi*-daunosamine (**15**) as colorless crystals with mp 142–146 °C. The TLC behavior and IR and ^1H NMR spectra of this product were identical with the material obtained through cis-hydroxylation of the aldehyde **13**.

Continued elution yielded an anomeric mixture of phenyl *N*-(trichloroacetyl)-1-thiodaunosaminide (**18**) (1.91 g, 57%) as a yellow solid with mp 97–103 °C: ^1H NMR ($CDCl_3$) δ 7.73 (m, 5 H), 6.90 (br d, 1 H), 5.07 (m, 1 H), 4.26 (m, 1 H), 3.12 (m, 2 H), 2.06 (d, J = 2.42 Hz, 3 H), 1.20 (d, J = 5.94 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 134.51, 130.18, 128.77, 76.87, 68.64, 53.47, 52.22, 26.87, 19.66; mass spectrum, m/z 384 (M^+·), 275.

(3*E*)-4-Methyl-3,5-hexadien-2-ol (20). Lithium aluminum hydride (5.17 g, 136.4 mmol) was added in small portions to a solution of 4-methyl-3,5-hexadien-2-one (**19**)[18] (30 g, 272.7 mmol) in ether (250 mL), and the mixture was stirred at room temperature for 12 h. The reaction was decomposed by sequentially adding water (5.2 mL), aqueous potassium hydroxide (15%; 5.2

mL), and water (15.6 mL). The mixture was filtered, and the filtrate was evaporated under reduced pressure at <30 °C. The crude material was purified by chromatography on silica gel (300 g; 8:2 hexanes/ethyl acetate) and gave 30.23 g (99%) of the dienol **20** as a colorless liquid with a pleasant odor: ^{1}H NMR ($CDCl_3$) δ 6.58 (m, 1 H), 5.06 (m, 3 H), 1.81 (m, 3 H), 1.69 (br s, 1 H), 1.26 (d, J = 6.25 Hz, 3 H).

(4*E*)-3-Methyl-3-(trichloroactamido)-1,4-hexadiene (21). A modification of the procedure employed to prepare **6a** was used. The imidate, prepared from the dienol **20** (10 g, 89.28 mmol), potassium hydride (2.04 g of a 35% suspension in mineral oil, 17.84 mmol) and 18-crown-6 (4.72 g, 17.84 mmol) and trichloroacetonitrile (13.73 g, 95.0 mmol) was heated for 12 h in xylenes (75 mL) to give 20.39 g (89%) of **21** as a yellow oil after chromatography (silica gel, 200 g; 8:2 hexanes/ethyl acetate): ^{1}H NMR ($CDCl_3$) δ 6.61 (br s, 1 H), 5.87 (m, 3 H), 5.18 (m, 2 H), 1.74 (d, J = 3.52 Hz, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.89, 140.33, 133.12, 126.08, 113.95, 69.85, 24.29, 17.73.

(*E*)-1-(Phenylthio)-3-methyl-3-(trichloroacetamido)-4-hexene (22a). The procedure employed for preparation of **7a** was used. From the diene amide **21** (10.00 g, 38.71 mmol), AIBN (1.59 g, 9.68 mmol), and benzenethiol (4.26 g, 38.71 mmol) there was obtained 12.48 g (88%) of the sulfide **22b** as a yellow oil and 1.02 g (10%) of the starting amide **22a** after chromatography (silica gel, 200 g; 8:2 hexanes/ethyl acetate): ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 5 H), 6.76 (br s, 1 H), 5.59 (m, 2 H), 2.86 (t, J = 7.91 Hz, 2 H), 2.19 (m, 2 H), 1.50 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 160.53, 148.46, 136.75, 133.72, 129.22, 128.95, 126.19, 125.32, 58.20, 38.54, 29.65, 28.35, 24.45, 17.79.

Anal. Calcd for $C_{15}H_{18}Cl_3NOS$: C, 49.13; H, 4.95; N, 3.82. Found: C, 50.01; H, 5.14; N, 3.79.

(*E*)-1-(Phenylsulfinyl)-3-methyl-3-(trichloroacetamido)-4-hexene (22b). The selenium dioxide–hydrogen peroxide procedure used for preparation of the sulfoxides **7a** and **7b** was employed. From the sulfide **22a** (6.00 g, 16.37 mmol), selenium dioxide (1.82 g, 16.37 mmol), and hydrogen peroxide (30%; 1.86 g, 16.37 mmol) there was obtained 5.32 g (85%) of **22b** as a yellow syrup after chromatography on silica gel (100 g; 6:4 hexanes/ethyl acetate). Although this product was a single spot by TLC, both the ^{1}H and ^{13}C NMR spectra of the material indicated it was a 1:1 mixture diastereoisomers: ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 5 H), 7.14 (br s, 1 H); 5.52 (m, 2 H), 2.84 (m, 2 H), 2.16 (m, 2 H), 1.69 (d, J = 4.84 Hz, 3 H), 1.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.37, 143.04, 133.29, 133.07, 131.07, 129.22, 125.54, 123.97, 57.28, 51.10, 31.01, 24.72, 24.51, 24.43, 17.79, 17.57.

(*E*)-1-(Phenylthio)-1-acetoxy-3-methyl-3-(trichloroacetamido)-4-hexene (23). The Pummerer rearrangement was conducted as previously described for the preparation of **12a**. From the sulfoxides **22b** (5.00 g, 13.08 mmol) in acetic anhydride (50 mL), a solution of the mixed anhydrides (2:1 acetic anhydride/trifluoroacetic anhydride; 16.7 mL, 5.49 g TFAA, 26.16 mmol) and 2,6-lutidine (5.60 g, 52.32 mmol), there was obtained 4.95 g (89%) of the acetoxy sulfide **23** as a yellow syrup, which was used in the next step without purification: ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5 H), 7.09 (br d, 1 H), 6.16 (m, 1 H), 5.52 (m, 2 H), 2.39 (m, 2 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.71 (m, 3 H), 1.52 (d, J = 1.75 Hz, 3 H).

(*E*)-3-Methyl-3-(trichloroacetamido)-4-hexenal (24). A mixture of the acetoxy sulfide **23** (3.00 g, 7.06 mmol) dissolved in acetonitrile (50 mL), water (10 mL), and cupric chloride dihydrate (2.41 g, 14.12 mmol) was heated on a steam bath until the initial blue-colored solution became black (2 min). The solvents were evaporated under reduced pressure, and the solid residue was directly placed on a silica gel column (150 g). Elution with 9:1 hexanes/ethyl acetate gave 1.89 g (99%) of the aldehyde **24** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 9.68 (t, J = 2.2 Hz, 1 H), 6.94 (br s, 1 H), 5.63 (m, 2 H), 2.99 (d, J = 2.42, 2 H), 1.69 (t, J = 1.98 Hz, 3 H), 1.53 (s, 3 H).

(±)-Methyl *N*-(Trichloroacetyl)-3-*epi*-vancosaminide (26) and (±)-Methyl *N*-(Trichloroacetyl)vancosaminide (25). The procedure employed for hydroxylation of **24** was used. From the aldehyde **24** (1.50 g, 5.54 mmol), trimethylamine *N*-oxide monohydrate (1.23 g, 11.08 mmol), and the osmium tetraoxide stock solution (0.5 mL) there was obtained a mixture of the *lyxo* and *xylo* configurated sugars. In order to facilitate their separation, the sugars were converted to their methyl glycosides. The mixture was dissolved in anhydrous methanol (25 mL) and chilled in an ice/salt bath for 15 min. Anhydrous hydrogen chloride gas was bubbled through the solution for 15 s, after which the reaction was allowed to warm to room temperature and stand for 1 h. The crude material, a 3:7 mixture (85%), was purified by chromatography on silica gel (100 g). Elution with 8:2 hexanes/ethyl acetate gave 0.49 g (28%) of (±)-*epi*-vancosaminide **26** as cream-colored crystals with mp 93–96 °C: ^{1}H NMR ($CDCl_3$) δ 5.13 (dd, J = 12.31, 18.02 Hz, 1 H), 4.12 (m, 1 H), 3.37 (s, 3 H), 3.04 (dd, J = 9.01, 14.72 Hz, 1 H), 2.02 (m, 2 H), 1.48 (d, J = 4.39 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.48, 104.09, 84.37, 65.03, 64.97, 55.71, 44.55, 29.71, 22.83, 20.17.

Continued elution gave 1.15 g (65%) of (±)-methyl *N*-(trichloroacetyl)vancosaminide (**25**) as light yellow crystals with mp 87–90 °C: ^{1}H NMR ($CDCl_3$) δ 8.44 (br s, 1 H), 4.78 (d, J = 3.51 Hz, 1 H), 4.06 (q, J = 6.37 Hz, 1 H), 3.46 (d, J = 6.40 Hz, 1 H), 3.35 (s, 3 H), 1.92 (m, 2 H), 1.56 (s, 3 H), 1.22 (t, J = 3.08 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.48, 97.97, 88.97, 68.50, 63.42, 55.76, 54.84, 35.12, 21.69, 16.87.

1-(Phenylsulfonyl)-3-(trichloroacetamido)-4,5-epoxyhexane (27). Oxidation of either (A) the sulfide **7a**, (B) the sulfoxides **7b** and **7c**, or (C) the sulfone **7d** with excess *m*-chloroperoxybenzoic acid (MCPBA) gave the epoxy sulfone **27**. A typical procedure from the sulfide **7a** is given below.

(A) A solution of *m*-chloroperoxybenzoic acid (80–85%) (9.22 g, 42.72 mmol) and the sulfide **7a** (5.00 g, 14.24 mmol) in methylene chloride (75 mL) was stirred at room temperature for 15 h. Saturated aqueous sodium bisulfite (35 mL) was added, and the mixture was stirred for 30 min to destroy any unreacted MCPBA. The layers were separated, and the organic phase was washed successively with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue (silica gel, 100 g; 4:6 ethyl acetate/hexanes) gave 5.39 g (95%) of pure **27** with mp 167–168 °C: ^{1}H NMR (benzene-d_6) δ 7.87 (m, 2 H), 6.99 (m, 3 H), 6.94 (br d, 1 H), 3.91 (dq, J = 2.01, 5.00 Hz, 1 H), 3.03 (m, 2 H), 2.64 (dq, J = 1.99, 5.04 Hz, 1 H), 2.16 (dd, J = 1.98, 4.18 Hz, 1 H), 1.95 (m, 2 H), 0.90 (d, J = 5.28 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.16, 138.70, 133.99, 129.49, 127.98, 59.28, 52.57, 51.70, 48.40, 26.46, 16.81; FAB mass spectrum, m/z 400 (M^+·), 365, 275.

(B) From the diastereoisomeric sulfoxides **7b** and **7c** (either individually or mixed) (2.13 g, 5.80 mmol) and *m*-chloroperoxybenzoic acid (80–85%) (2.50 g, 11.60 mmol) in methylene chloride (50 mL) there was obtained 2.22 g (96%) of the epoxy sulfone **27**.

(C) From the sulfone **7d** (0.84 g, 2.19 mmol) and *m*-chloroperoxybenzoic acid (80–85%) (0.48 g, 2.22 mmol) in methylene chloride (25 mL) there was obtained 0.85 g (97%) of the epoxy sulfone **27**.

(*E*)-1-(Phenylsulfonyl)-1-acetoxy-3-(trichloroacetamido)-4-hexene (12b). *m*-Chloroperoxybenzoic acid (1.06 g of 80–85%, 4.88 mmol) was added to a magnetically stirred solution of the acetoxy sulfide **12a** (1.00 g, 2.44 mmol) in methylene chloride (35 mL). Analysis by TLC indicated that the reaction was complete in <5 min. Saturated aqueous sodium bisulfite (10 mL) was added, and the mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous phase was extracted with methylene chloride (10 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatotron chromatography of the residue (1:1 ethyl acetate/hexanes) gave 1.02 g (95%) of the acetoxy sulfone **12b** as a gold oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (m, 5 H), 6.66 (br d, 2 H), 5.65 (m, 3 H), 4.53 (m, 1 H), 2.39 (m, 2 H), 1.96 (s, 3 H), 1.46 (d, J = 38.01 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.90, 161.97, 134.64, 129.55, 129.28, 127.82, 126.89, 82.91, 82.31, 50.29, 49.26, 31.93, 20.28, 20.17, 17.73; IR ($CDCl_3$) 3409, 1715, 1675, 1771, 1266, 1050, and 1074 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}Cl_3NO_6S$: C, 42.02; H, 3.95; N, 3.05. Found: C, 42.22; H, 4.15; N, 2.99.

1-(Phenylsulfonyl)-1-acetoxy-3-(trichloroacetamido)-4,5-epoxyhexane (28). Treatment of (A) the acetoxy sulfide **12a** or (B) the acetoxy sulfone **12b** with excess *m*-chloroperoxybenzoic acid gave the epoxide **28**.

(A) From the acetoxy sulfide **12b** (1.02 g, 2.49 mmol) and *m*-chloroperoxybenzoic acid (80–85%, 1.07 g, 49.80 mmol) in

methylene chloride (35 mL) there was obtained 1.07 g (98%) of the epoxy sulfone **28** as a colorless solid with mp 77–80 °C: ^{1}H NMR ($CDCl_3$) δ 7.76 (m, 5 H), 6.76 (br m, 1 H), 5.91 (dq, J = 3.74, 10.55 Hz, 1 H), 4.39 (m, 1 H), 2.88 (m, 1 H), 2.48 (m, 1 H), 1.98 (s, 3 H), 1.96 (s, 3 H), 1.31 (d, J = 4.84 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.55, 167.69, 161.99, 135.24, 134.69, 129.49, 129.28, 92.06, 82.31, 59.61, 58.91, 46.72, 45.80, 30.52, 30.19, 20.33, 17.08, 16.76; IR ($CDCl_3$) 3400, 1770, 1719, 1265, 1050, 1156, and 1326 cm^{-1}.

(B) From the acetoxy sulfone **12b** (0.91 g, 2.14 mmol) and *m*-chloroperoxybenzoic acid (0.46 g, 2.14 mmol) in methylene chloride (35 mL) there was obtained 0.92 g (97%) of the epoxy sulfone **28**.

(±)-Methyl 2,3,6-Trideoxy-3-(trichloroacetamido)-α-*ribo*-furanoside (30a). Sodium hydroxide (0.26 g, 3.24 mmol) was added to a solution of the acetoxysulfone **28** (1.43 g, 3.24 mmol) in methanol (25 mL) and water (2 mL). After 1 h, analysis by TLC indicated that the reaction was complete. Brine (10 mL) and methylene chloride (25 mL) were added, and the layers were separated. The aqueous phase was further extracted with methylene chloride (2 × 15 mL), and the combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The initially received material was purified on the Chromatotron (6:4 hexanes/ethyl acetate) to give 0.94 g (96%) of the furanose **30a** as a low melting yellow solid: ^{1}H NMR ($CDCl_3$) δ 7.63 (br d, 1 H), 5.19 (m, 2 H), 4.64 (t, J = 8.13 Hz, 1 H), 4.02 (t, J = 2.41 Hz, 1 H), 3.40 (s, 3 H), 2.42 (ddd, J = 13.62, 7.47, 4.39, 4.18 Hz, 1 H), 1.96 (d, J = 13.84 Hz, 1 H), 1.50 (d, J = 6.59 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.02, 104.95, 90.06, 67.97, 54.63, 50.67, 38.92, 18.55.

(±)-Methyl *N,O*-Bis(trichloroacetyl)-3-amino-α-*ribo*-furanoside (30c). From the furanoside **30a** (0.50 g, 1.64 mmol), trichloroacetyl chloride (2 mL), and pyridine (2 mL) in diethyl ether (15 mL) there was obtained the bis(trichloroacetyl) furanoside **30c** (0.70 g, 95%) as a yellow syrup: ^{1}H NMR (benzene-d_6) δ 7.56 (br d, 1 H), 5.01 (dq, J = 6.59, 2.86 Hz, 1 H), 4.63 (d, J = 4.18 Hz, 1 H), 4.43 (t, J = 8.57 Hz, 1 H), 3.65 (t, J = 2.64 Hz, 1 H), 3.06 (s, 3 H), 1.92 (ddd, J = 18.23, 4.61, 4.17, 7.69 Hz, 1 H), 1.47 (d, J = 13.63 Hz, 1 H), 1.22 (d, J = 6.81 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.95, 161.62, 105.88, 88.48, 77.65, 55.49, 51.32, 39.08, 16.32.

(±)-Methyl *N*-(Trichloroacetyl)-α-ristosaminide (31). The furanoside **30a** (0.91 g, 2.98 mmol) in aqueous acetic acid (50%; 20 mL) was heated on a steam bath for 20 min. Analysis of a TLC indicated that the hydrolysis of the methyl glycoside residue had occurred. The solvent was evaporated, and the residue was taken up in methylene chloride (25 mL) and washed with saturated aqueous sodium bicarbonate (2 × 15 mL). The organic solution was dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was dissolved in anhydrous methanol (15 mL) and chilled in an ice/salt bath, and dry hydrogen chloride gas was bubbled into the reaction for 15 s. The solution was allowed to warm to room temperature and then stand for 1 h. The reaction was transferred to a separatory funnel with methylene chloride (25 mL), and the organic solution was washed with saturated aqueous sodium bicarbonate (2 × 15 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue, a 3:1 mixture by TLC, was purified by chromatography (silica gel, 50 g). Elution with 6:4 hexanes/ethyl acetate gave 0.26 g (28%) of the methyl pyranoside **31** as a light yellow solid with mp 94–97 °C: ^{1}H NMR ($CDCl_3$) δ 8.52 (br s, 1 H), 4.74 (m, 1 H), 4.18 (m, 1 H), 3.64 (m, 1 H), 3.38 (s, 3 H), 2.57 (br s, 1 H), 2.01 (m, 1 H), 1.65 (m, 1 H), 1.28 (d, J = 5.71 Hz, 3 H). Continued elution gave 0.51 g (56%) of the furanoside **30a** which was identical with the material obtained above.

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Supplementary Material Available: A ball-and-stick drawing of the epoxysulfone **27**, a description of the X-ray analysis procedure, tables of fractional coordinates and anisotropic thermal parameters, and figures showing bond distances and bond angles (7 pages). Ordering information is given on any current masthead page.

Metabolites of the Marine Hydroid *Garveia annulata*: Garveatins B and C, 2-Hydroxygarvin A, and Garvin A Quinone

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Four antimicrobial metabolites, garveatins B (**2**) and C (**3**), 2-hydroxygarvin A (**4**), and garvin A quinone (**5**), have been isolated from the marine hydroid *Garveia annulata*. The structures of garveatin B (**2**), garveatin C (**3**), and 2-hydroxygarvin A (**4**) were inferred from their spectral data and chemical derivatization reactions. The structure of garvin A quinone (**5**) was determined by X-ray diffraction analysis of its monoacetate (**12**).

The phylum coelenterata encompasses a diverse collection of marine invertebrates that includes familiar animals such as the hard and soft corals, gorgonians, sea pens, jellyfish, and sea anemones. Hydroids are a large class of coelenterates that are less well-known because they tend to be small and somewhat inconspicuous. To date, marine natural product chemists have successfully isolated a large number of interesting secondary metabolites from soft corals, gorgonians, sea pens, and zooanthids.[1] By contrast, the hydroids have received very little attention.[2] It is not

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