(36), 104 (49), 96 (60), 76 (46), 69 (52), 50 (60).

3*H*-1,2-Benzodithiol-3-one 1,1-Dioxide (12). To a stirred suspension of 3*H*-1,2-benzodithiol-3-one (**10**) (39.2 g, 0.23 mol) in trifluoroacetic acid (250 mL) was added 40 mL of a 30% aqueous solution of hydrogen peroxide within 1 min at ambient temperature (water bath). Cooling by adding ice to the water bath became necessary to maintain the internal reaction temperature at 40–42 °C. After 30 min an additional 40 mL of 30% H_2O_2 was rapidly added, and the reaction mixture was stirred at the same internal temperature for half an hour. The third and last portion of 30% H_2O_2 (40 mL) was then added, and the solution was warmed to stabilize the internal reaction temperature at 40–42 °C. The reaction was monitored by TLC ($CHCl_3$) for the disappearance of the slow moving thiosulfinate **11** (R_f = 0.27). The reaction mixture was then filtered, and the filtrate was added to 3.5 L of crushed ice. The white precipitate was filtered through a 2-L fritted-glass Buchner of coarse porosity and thoroughly washed with water until the filtrate was neutral and free of peroxides. The solid material was then transferred into a 500-mL separatory funnel to which were added dichloromethane (200 mL) and a 1% solution of sodium bisulfite (100 mL). After vigorous shaking, the organic phase was separated, washed with water (100 mL), and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the amorphous solid was dried under vacuum. The crude compound (20.8 g, 45%) was dissolved in boiling dichloromethane, treated with activated charcoal, and filtered through Celite. Hexane (ca. 50 mL) was added to the boiling filtrate (ca. 70 mL), and the solution was first allowed to cool at ambient temperature and then to 10 °C in the refrigerator. The crystalline thiosulfonate **12** (17.2 g), mp 102.5–103 °C (lit.[21] mp 98–99 °C), was collected by filtration through a sintered-glass funnel, washed with cold hexane, and dried under vacuum. ^{13}C NMR ($CDCl_3$): δ 182.9, 148.3, 136.5, 134.5, 130.0, 125.6, 121.9. MS (70 eV): *m/z* 202 (M + 2) (4), 201 (M + 1) (4), 200 (M) (45), 136 (100, base peak), 108 (41), 104 (37), 76 (92), 69 (31).

3*H*-1,2-Benzodithiol-3-one 1-Oxide (11). To a stirred suspension of 3*H*-1,2-benzodithiol-3-one (**10**) (10.1 g, 60 mmol) in glacial acetic acid (95 mL) was added 10.2 mL of a 30% aqueous solution of H_2O_2 over a period of 10 min at ambient temperature. After 14 h, TLC ($CHCl_3$) showed incomplete reaction. The mixture was then heated at 40 °C until completion of the reaction (ca. 2 h). After filtration, the filtrate was added to 1 L of crushed ice. The precipitate was collected on a fritted-glass Buchner and thoroughly washed with water. The material was dissolved in chloroform (100 mL) and extracted once with water (50 mL). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue (8.25 g) was recrystallized from CH_2Cl_2–hexane. The pure compound melted at 103.5–104 °C (lit.[21] mp 101.5–103 °C). ^{13}C NMR ($CDCl_3$): δ 190.4, 151.6, 135.6, 133.0, 130.8, 127.9, 126.7. MS (70 eV): *m/z* 186 (M + 2) (3), 185 (M + 1) (3), 184 (M) (33), 136 (100, base peak), 108 (28), 104 (13), 96 (10), 76 (31), 69 (17).

3*H*-2,1-Benzoxathiolan-3-one 1-Oxide (16). Trimethyl phosphite (1.2 mL, 10 mmol) was added, under an argon atmosphere, to a solution of **12** (2 g, 10 mmol) in 20 mL of CH_2Cl_2, dropwise over a period of 5 min at ambient temperature. The reaction mixture was stirred for 15 min and then evaporated to dryness under reduced pressure. The yellowish oil was triturated with cyclohexane (2 × 50 mL). The moisture-sensitive solid (1.5 g) was recrystallized from CH_2Cl_2–hexane, affording colorless crystals at 10 °C. The compound melted at 81–82 °C (lit.[26] mp 83 °C). ^{13}C NMR ($CDCl_3$): δ 165.3, 151.6, 136.3, 134.2, 128.5, 124.9, 123.4. MS (70 eV): *m/z* 170 (M + 2) (0.4), 169 (M + 1) (0.6), 168 (M) (7), 104 (100, base peak), 76 (72), 50 (44), 38 (12). This material was identical in all respects with that prepared by the published procedure.[26]

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Registry No. **5**, 152-18-1; **8**, 24765-75-1; **8** monooxide derivative, 127183-91-9; **10**, 1677-27-6; **11**, 127183-89-5; **12**, 66304-01-6; **16**, 127183-90-8; S-d(AACGTTGAGGGGCAT), 127279-14-5; S-d(ATGCCCCTCAACGTT), 127279-13-4; d(TACCGTAGCTAAGGTCATGCAAGTTCCG), 127279-16-7; d(TCGTCGCTGTCTCCGCTTCTTCCTGCCA), 115427-90-2; S-d(TCGTCGCTGTCTCCGCTTCTTCCTGCCA), 127279-15-6; d(T_{PS}CGTCGCTGTCTCCGCTTCTTCCTGCC$_{PS}$A), 124991-77-1; 2-mercaptobenzoic acid, 147-93-3; *o*-xylene-α,α'-dithiol, 41383-84-0.

Synthesis of Carbocyclic Analogues of 2-Deoxy-Kdo

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3(*R*),4(*S*)-Dihydroxy-5(*R*)-(1′(*S*),2′-dihydroxyethyl)-(*S*)-cyclohexanecarboxylic acid (**1**) and 3(*R*),4(*S*)-dihydroxy-5(*R*)-(1′(*S*),2′-dihydroxyethyl)-(*R*)-cyclohexanecarboxylic acid (**2**) have been synthesized as potential inhibitors of the enzyme CMP-Kdo synthetase. The key steps in the synthesis of **1** and **2** were a three-carbon chain extension at C-4 of the protected D-manno derivatives 1-*O*-(*tert*-butyldimethylsilyl)-2,3:5,6-di-*O*-isopropylidene-4-*O*-(phenoxythiocarbonyl)-D-mannitol (**5**) and 1,6-anhydro-2,3-*O*-isopropylidene-4-*O*-(phenoxythiocarbonyl)-β-D-mannopyranose (**11a**) with allyltributylstannane under radical coupling conditions and the intramolecular alkylation of 1,4-dideoxy-4-*C*-[2′-(*tert*-butoxycarbonyl)ethyl]-1-iodo-2,3:5,6-di-*O*-isopropylidene-D-mannitol (**15**) to form the protected products **1** and **2**. Two different routes leading to **1** and **2**, both starting from D-mannose, were used. The two routes converge at 4-*C*-allyl-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-mannitol (**7a**), obtained as a diastereomeric mixture in one route and as a pure isomer in the other.

Introduction

3-Deoxy-D-manno-2-octulosonic acid (Kdo)[1] is an eight-carbon sugar found in Gram-negative bacteria. It is a constituent of the core region in the outer membrane lipopolysaccharides (LPS),[2] serving as a bridge between lipid A and the polysaccharide portion. Kdo is also found in the capsular polysaccharide (K-antigen) of some Gram-negative bacteria strains,[1,3,4] some protozoans,[5] the green

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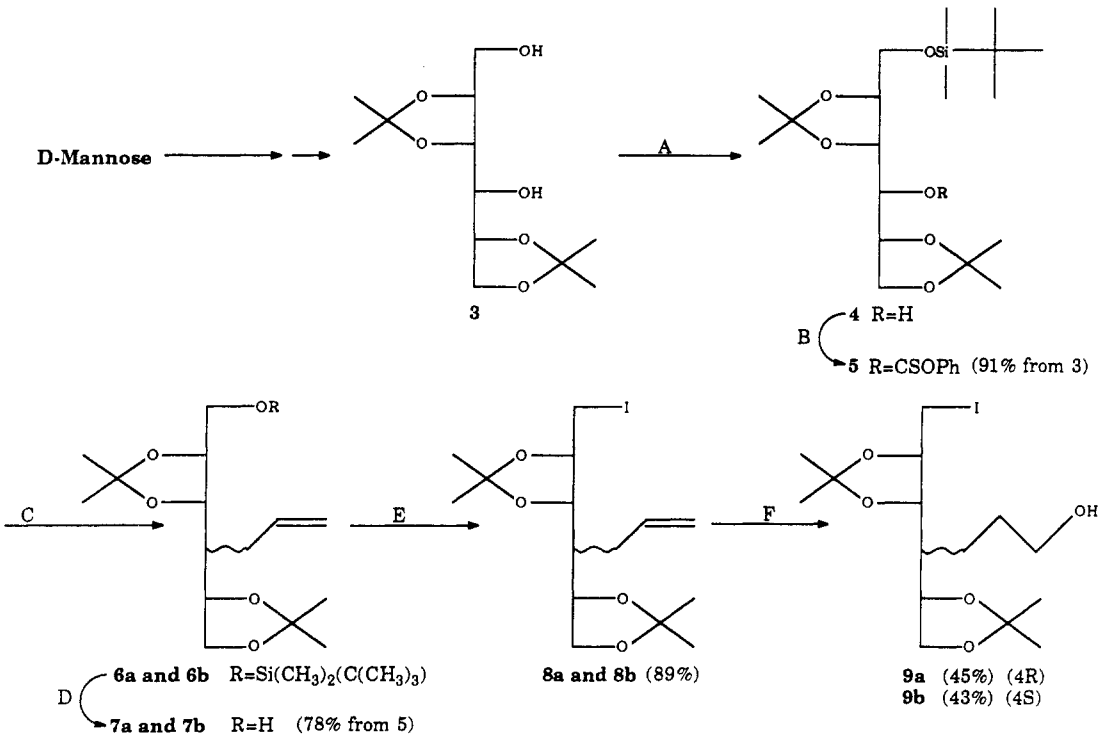
Scheme I[a]



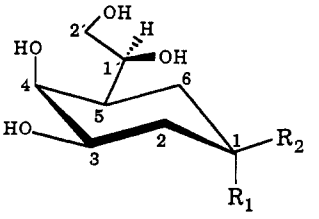
[a] Key: A, TBDMS-Cl, py; B, phenyl chlorothionoformate, py; C, allyltributylstannane, $h\nu$, toluene, 75–85 °C; D, tetraethylammonium fluoride, THF, 50 °C; E, Ph_3P, imidazole, iodine, toluene Δ; F, BH_3–SMe_2, CH_2Cl_2, then NaOH, H_2O, H_2O_2.

alga *Tetraselmis striata*,[6] and higher plants.[7-9] The enzyme CMP-Kdo synthetase catalyzes the formation of CMP-Kdo from β-Kdo and cytidine triphosphate.[10] This is believed to be the rate-limiting step in the LPS biosynthesis. It has been shown that bacteria lacking the core region no longer are viable,[11] making the CMP-Kdo synthetase an attractive target for chemotherapy. A large number of analogues of Kdo have been synthesized and tested for inhibition toward CMP-Kdo synthetase.[1,12-19] 2-Deoxy-Kdo was shown to be a potent inhibitor,[15] but exhibiting low antibacterial activity, mainly due to its inability to cross the cytoplasmic membrane.

The carbocyclic analogue of β-Kdo, synthesized by Molin and Pring starting from (-)-quinic acid,[13] showed only weak inhibitory activity toward CMP-Kdo synthetase. In view of the potent enzymatic inhibitory activity of 2-deoxy-Kdo, we decided to synthesize the carbocyclic analogue of 2-deoxy-Kdo (1) having the β-configuration (axial carboxylic group) which corresponds to the active configuration of Kdo in its interaction with CMP-Kdo synthetase.[20] A carbocyclic analogue of this type would have the added advantage of being more stable than 2-deoxy-Kdo as well as being more lipophilic, which could facilitate passage over the bacterial cell membrane.

Results and Discussion

For the synthesis of **1** and **2**, two reaction pathways (routes 1 and 2) were designed, both starting from D-mannose and employing a free-radical carbon–carbon



1 R_1=CO_2H R_2=H
2 R_1=H R_2=CO_2H

bond-forming reaction to obtain a three-carbon extension at C-4 of the mannose framework. After a number of steps, the two routes converge at the common intermediate **7a**

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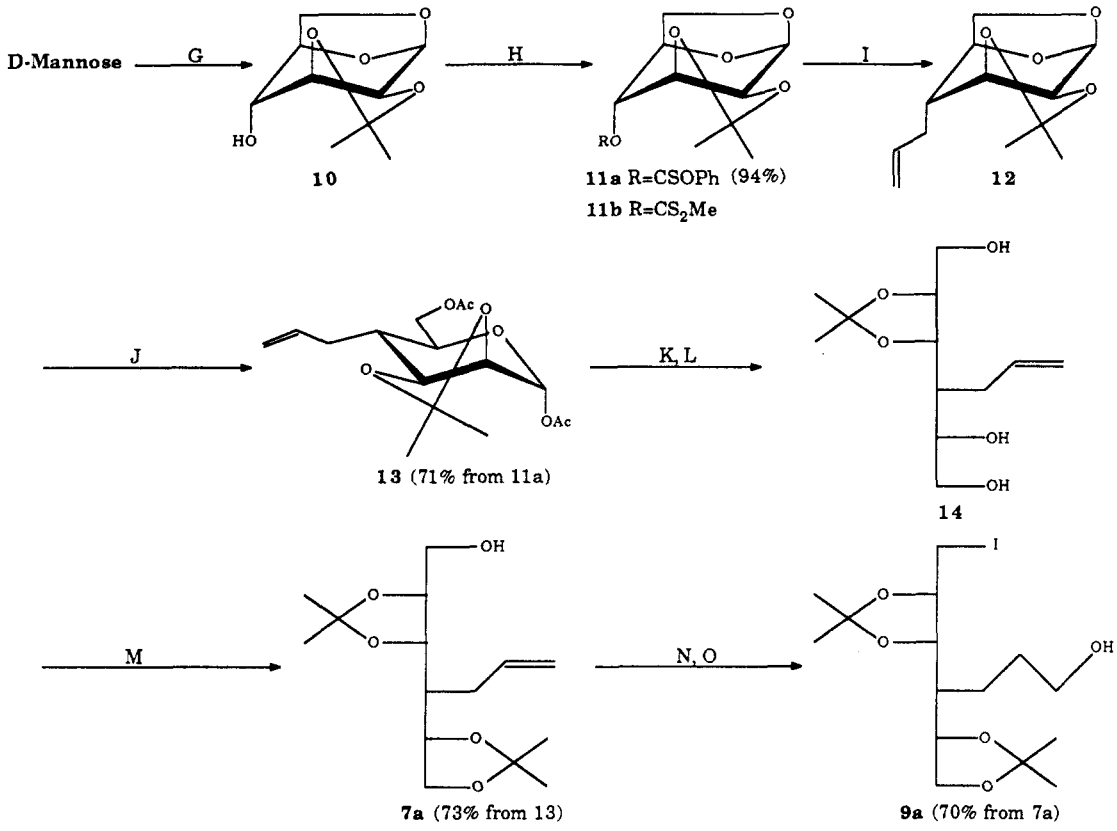
Scheme II[a]



[a] Key: G, see ref 24; H, phenyl chlorothionoformate, py; I, allyltributylstannane, $h\nu$, toluene–ethyl acetate, 75–85 °C; J, Ac_2O/TFA; K, NaOMe/MeOH; L, $NaBH_4$; M, dimethoxypropane–acetone, $CuSO_4$; N, Ph_3P, imidazole, iodine, toluene, Δ; O, BH_3–SMe_2, CH_2Cl_2, then NaOH, H_2O, H_2O_2.

obtained as a diastereomeric mixture in one route and as a pure isomer in the other. In reaction route 1 (Scheme I), D-mannose was converted to **3** in two steps.[21] Partial protection by *tert*-butyldimethylsilyl chloride gave **4**, which without chromatographic purification was reacted with phenyl chlorothionoformate to give **5** in 91% yield from **3**. By the method of Keck et al.[22] **5** was allylated at C-4 in a free-radical reaction with allyltributylstannane in toluene by irradiating the reaction mixture with a Hanovian lamp for 6 h at 75–85 °C. The stereochemistry at C-4 was completely lost in the coupling step, and a 1:1 diastereomeric mixture of **6a** and **6b** was obtained. The mixture was desilylated with tetraethylammonium fluoride to give a 1:1 mixture of **7a** and **7b** in 78% yield from **5**. Without separation of the isomers the mixture was iodinated with triphenylphosphine, iodine, and imidazole[23] to give **8a** and **8b** in 89% yield. Addition of borane–dimethyl sulfide to this mixture followed by oxidative workup gave a diastereomeric mixture of alcohols, which at this stage were separated by silica gel column chromatography to give **9a** in 45% and **9b** in 43% yields. The configuration at C-4 was determined by comparing the two isomers with the diastereomerically pure **9a** obtained from route 2.

In reaction route 2 (Scheme II) the 1,6-anhydro-D-mannose derivative **10** was obtained from D-mannose in a one-pot reaction as described by Fraser-Reid et al.[24] Reacting **10** with phenyl chlorothionoformate in pyridine gave the thiocarbonate **11a** in 94% yield. The radical coupling procedure (vide supra) with allyltributylstannane in toluene–ethyl acetate (1:1) gave the C-4 allylated mannose derivative **12** in high diastereomeric excess. The corresponding talose derivative could not be detected by NMR. Acetolysis of **12** (acetic anhydride–trifluoroacetic acid) gave **13** in 71% yield from **11a**. An NMR analysis at this point confirmed the expected structure of **13**. The large coupling constants between H-3, H-4 and H-4, H-5, respectively ($J_{3,4}$ = 8.8 Hz, $J_{4,5}$ = 10.1 Hz), strongly suggest an equatorial orientation of the allyl group at C-4 ($^4C_1$ conformation). This is also consistent with the known steric preference of radicals to attack from the sterically less shielded face in the absence of strongly directing electronic effects.[25] The other coupling constants were in accordance with the proposed structure. The use of methyl acrylate and *tert*-butyl acrylate as three-carbon synthones was initially examined in a radical coupling of the methyl xantate derivative **11b**, using azobisisobutyronitrile (AIBN) as initiator in the presence of tributyltin hydride. The expected axial coupled products were obtained, but the generation of acrylate polymers made product isolation very difficult. The corresponding deoxygenated **11b** was also formed in varying amounts. This approach was thus abandoned.

Compound **13** was deacetylated with sodium methoxide in methanol, reduced with sodium borohydride to give the *C*-allylmannitol derivative **14**, and then directly reacted with 2,2-dimethoxypropane and $CuSO_4$ in acetone to give the partially protected *C*-allylmannitol derivative **7a** in 73% yield from **13**. Compound **7a** was identical, by NMR, with one of the diastereomers obtained from route 1. Compound **7a** was then reacted in the same manner as the

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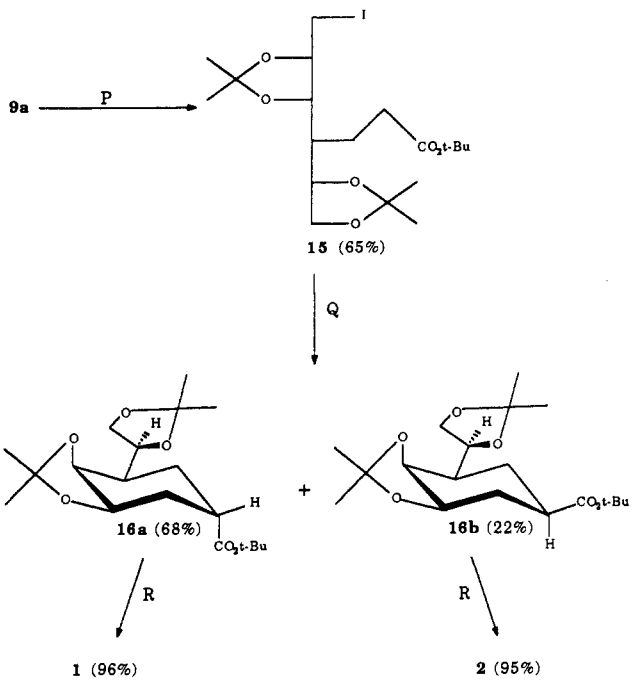
Scheme III[a]



[a] Key: P, PDC/Ac_2O, *t*-BuOH, CH_2Cl_2, Δ; Q, LDA, THF, −75 °C; R, 80% TFA.

diastereomers **7a** and **7b** (vide supra) from route 1. Iodination and hydroboration followed by oxidative workup gave **9a** in 70% from **7a**, identical, by NMR and optical rotation, with one of the separated diastereomers from route 1.

Oxidation of **9a** with pyridinium dichromate/acetic anhydride in *tert*-butyl alcohol–methylene chloride[26,27] produced the *tert*-butyl ester **15** in 65% yield (Scheme III). The corresponding carboxylic acid was obtained as a side product. Cyclization was readily accomplished by reacting **15** with lithium diisopropylamide at −78 °C, producing a C-1 epimeric mixture in a 3:1 ratio, which was separated to give **16a** and **16b** in 68% and 22% yields, respectively. A radical-induced cyclization of **8a** (Scheme IV) with bis(tributyltin)[28] to give the transposed primary iodide **17** was attempted but did not proceed to give the expected product. The main product obtained was the cyclized and reduced compound **18**.

Deprotection of **16a** and **16b** in aqueous trifluoroacetic acid (80%) gave the title compounds **1** and **2**. The configuration at C-1 was established by ^1H NMR where **2** had a large coupling constant between the axial hydrogen at C-2 and the hydrogen at C-1 ($J_{1,2_{ax}}$ = 12.6 Hz) whereas **1** only had small corresponding coupling constants (cf. carbon numbering of **1** and **2**). The NMR data of the products were consistent with the rings adopting a $^4C_1$ conformation.

Compounds **1** and **2** were screened for in vitro biological activity with the same methods described by Pring et al.[19] Compound **1** showed a weak inhibitory effect toward CMP-Kdo synthetase but had no antibacterial effect, whereas compound **2** was inactive.

Experimental Section

General Methods. Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature not exceeding 40 °C. Chemical shifts are reported (ppm) downfield from tetramethylsilane (δ 0.00, ^1H and ^{13}C) in chloroform-*d* and from 3-(trimethylsilyl)propanoate-d_4 (δ 0.00, ^1H) or dioxane (δ 67.40, ^{13}C) in deuterium oxide. All reaction were monitored by TLC with precoated silica gel plates (F 250, Merck). Spots were visualized by UV light and/or charring with 8% sulfuric acid. Column chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). The loadings were in the range 1/25–1/100. Organic phases were dried over anhydrous magnesium sulfate. Satisfactory elemental analysis for some of the noncrystalline compounds could not be obtained, but their purity and identity were established by chromatographic techniques and by NMR spectroscopy.

1-*O*-(*tert*-Butyldimethylsilyl)-2,3:5,6-di-*O*-isopropylidene-4-*O*-(phenoxythiocarbonyl)-D-mannitol (5). To a stirred solution of 1,2:4,5-di-*O*-isopropylidene-D-mannitol[21] (**3**) (6.00 g, 22.9 mmol) in pyridine (50 mL) was added a solution of *tert*-butyldimethylsilyl chloride (4.10 g, 27.2 mmol) in pyridine (20 mL) at room temperature. After 6 h methanol (1.0 mL) was added, and after another 15 min the mixture was concentrated. The residue was dissolved in diethyl ether (250 mL), washed with water, dried, and concentrated to give a colorless syrup (8.98 g). The syrup was dissolved in pyridine (70 mL), and phenyl chlorothionoformate (5.13 g, 29.7 mmol, 1.3 equiv) was added. The mixture was stirred overnight at room temperature. Methanol (2.0 mL) was added, and the mixture was concentrated. The residue was dissolved in diethyl ether (300 mL), washed with water, dried, and concentrated. Column chromatography (toluene) yielded **5** (10.68 g, 91%) as a slightly yellow syrup: $[\alpha]^{22}_D$ +18.9° (*c* 1.0 $CHCl_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.3 (CH_3Si), 18.3 ($SiC(CH_3)_3$), 25.6, 25.6, 26.5, 26.5, (4 CH_3), 25.9 (CH_3-Bu), 62.0, (C-1), 65.5 (C-6), 75.7, 75.9, 77.4, 80.0, 109.3, 109.6 (2 $C(CH_3)_2$), 122.0, 126.6, 129.5, 153.5, 194.7 (CO_2S).

Anal. Calcd for $C_{25}H_{40}O_7SSi$: C, 58.56; H, 7.86; S, 6.25; Si, 5.48. Found C, 58.23; H, 7.31; S, 6.31; Si, 5.37.

4-*C*-Allyl-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-mannitol (7a) and 4-*C*-Allyl-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-talitol (7b). Compound **5** (2.42 g, 4.72 mmol) and allyltri-*n*-butylstannane (4.70 g, 14.2 mmol, 3.0 equiv) were dissolved in dry toluene (6.0 mL) in a 12-mm NMR tube. The mixture was purged with dry nitrogen gas for 15 min before irradiation for 6 h at 75–85 °C with a Hanovian photolysis apparature. The mixture (**6a** and **6b**) was concentrated and dissolved in THF (30 mL), and tetraethylammonium fluoride (3.16 g, 21.2 mmol) was added. The mixture was stirred for 4 h at 50 °C, concentrated, and partitioned between diethyl ether and water. The organic phase was washed with water, dried, and concentrated. Column chromatography (toluene–ethyl acetate, 10:1) yielded a mixture of **7a** and **7b** (1.06 g, 78%) in a 1:1 ratio. An analytical sample of the mixture of **7a** and **7b** was separated by column chromatography. **7a**: ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 25.6, 25.7, 26.5, 28.3 (4 CH_3), 33.1 (CH_2), 40.1 (C-4), 61.9 (C-1), 69.0 (C-6), 77.2, 77.7, 78.5, 106.8, 109.0 (2 $C(CH_3)_2$), 117.6 ($CH{=}CH_2$), 134.5 ($CH{=}CH_2$). **7b**: δ 25.6, 25.8, 26.6, 28.5 (4 CH_3), 32.8 (CH_2), 40.3 (C-4), 61.7 (C-1), 69.7 (C-6), 76.8, 77.3, 77.4, 107.8, 108.1 (2 $C(CH_3)_2$), 117.4 ($CH{=}CH_2$), 135.3 ($CH{=}CH_2$).

4-*C*-Allyl-1,4-dideoxy-1-iodo-2,3:5,6-di-*O*-isopropylidene-D-mannitol (8a) and 4-*C*-Allyl-1,4-dideoxy-1-iodo-2,3:5,6-di-*O*-isopropylidene-D-talitol (8b). To the isomeric mixture of **7a** and **7b** (1.29 g, 4.50 mmol) in toluene (120 mL) were added imidazole (771 mg, 11.32 mmol, 2.52 equiv), triphenylphosphine (2.95 g, 11.25 mmol, 2.5 equiv), and iodine (2.29 g, 9.02 mmol, 2.0 equiv). The mixture was refluxed for 2 h and cooled, and saturated aqueous $NaHCO_3$ (75 mL) was added. After the mixture was stirred for 15 min, iodine was added portionwise until the toluene phase remained iodine colored. The mixture was stirred for 10 min, and then saturated aqueous $Na_2S_2O_3$ was added portionwise until the iodine color disappeared. The organic phase was washed with water, dried, and concentrated. Column chromatography (isooctane–ethyl acetate, 10:1) yielded the unseparated mixture of **8a** and **8b** (1.59 g, 89%) in a 1:1 ratio. An analytical sample of the mixture was separated by column chromatography. **8a**: ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 8.7 (C-1), 25.5, 25.8, 26.6, 28.4 (4 CH_3), 33.1 (CH_2), 41.2 (C-4), 69.2 (C-6), 76.7, 78.6, 79.3, 107.2, 109.0 (2 $C(CH_3)_2$), 117.9 ($CH{=}CH_2$), 135.1 ($CH{=}CH_2$). **8b**: δ 6.9 (C-1),

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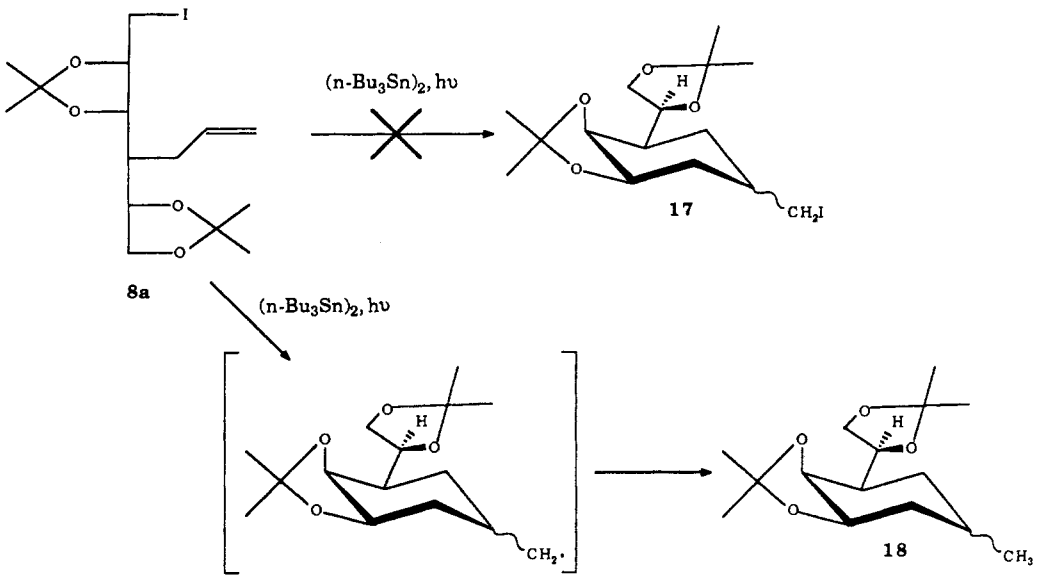
Scheme IV



25.5, 25.9, 26.6, 28.5 (4 CH_3), 32.6 (CH_2), 41.0 (C-4), 69.7 (C-6), 76.6, 77.7, 78.3, 107.9, 108.3 (2 $C(CH_3)_2$), 117.7 ($CH{=}CH_2$), 135.1 ($CH{=}CH_2$).

1,4-Dideoxy-2,3:5,6-di-*O*-isopropylidene-4-*C*-(3′-hydroxypropyl)-1-iodo-D-mannitol (9a) and 1,4-Dideoxy-2,3:5,6-di-*O*-isopropylidene-4-*C*-(3′-hydroxypropyl)-1-iodo-D-talitol (9b). To a stirred solution of a mixture of **8a** and **8b** (513 mg, 1.29 mmol) in dichloromethane (5.0 mL) was added borane–methyl sulfide complex (0.2 mL, 10 M) dropwise at room temperature under dry nitrogen. After 1.5 h, ethanol (2.0 mL) and aqueous NaOH (0.43 mL, 3 M) were added. The stirred solution was cooled on an ice bath, and 30% H_2O_2 (0.15 mL) was added. After 15 min the solution was heated on a water steam bath for 5 min. The mixture was cooled and partitioned between diethyl ether and water. The organic phase was washed with water, dried, and concentrated to yield a mixture of **9a** and **9b** (477 mg, 89%) in a 1:1 ratio. Column chromatography (toluene–ethyl acetate, 1:1) gave **9a** (240 mg, 45%) and **9b** (232 mg, 43%). **9a**: $[\alpha]^{22}_D$ +62.9° (*c* 1.58, $CHCl_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 8.6 (C-1), 24.4, 25.3, 25.9, 26.5 (4 CH_3), 28.4, 29.3 (2 CH_2), 40.8 (C-4) 62.6 (CH_2OH), 69.1 (C-6), 79.4, 79.8, 107.2, 109.3 (2 $C(CH_3)_2$). **9b**: $[\alpha]^{22}_D$ +76.2° (*c* 1.46, $CHCl_3$; δ 6.7 (C-1), 24.8, 25.6, 25.8, 26.5 (4 CH_3), 28.4, 29.6 (2 CH_2), 40.8 (C-4), 62.7 (CH_2OH), 70.0 (C-6), 77.8, 78.0, 78.5, 107.8, 108.5 (2 $C(CH_3)_2$).

Anal. Calcd for **9b** ($C_{15}H_{27}IO_5$): C, 43.49; H, 5.36. Found C, 44.05; H, 6.45.

1,6-Anhydro-2,3-*O*-isopropylidene-4-*O*-(phenoxythiocarbonyl)-β-D-mannopyranose (11a). To a solution of **10** (3.00 g, 14.8 mmol) in dry pyridine (30 mL) was added phenyl chlorothionoformate (3.33 g, 19.3 mmol, 1.3 equiv). The mixture was stirred overnight at room temperature, concentrated, dissolved in diethyl ether (250 mL), washed with water, dried, and concentrated, giving a crude crystalline product. Recrystallization from ethanol yielded **11a** (4.73 g, 94%) as slightly yellow crystals: mp 131–132 °C; $[\alpha]^{22}_D$ −62.6° (*c* 1.05, $CHCl_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 26.0, 26.0 (2 CH_3), 64.6 (C-6), 72.2, 72.7, 73.4, 76.7, 99.4 (C-1), 110.6 ($C(CH_3)_2$), 121.9, 127.0, 129.8, 153.4, 194.1 (CO_2S).

Anal. Calcd for $C_{16}H_{18}O_6S$: C, 56.79; H, 5.36; S, 9.47. Found C, 56.63; H, 5.27; S, 9.42.

1,6-Di-*O*-acetyl-4-*C*-allyl-4-deoxy-2,3-*O*-isopropylidene-β-D-mannopyranose (13). Compound **11a** (2.00 g, 5.91 mmol) and allyltributylstannane (5.87 g, 17.7 mmol, 3.0 equiv) were dissolved in toluene (4.0 mL) and ethyl acetate (4.0 mL) in a 12-mm NMR tube. The solution was purged with dry nitrogen gas for 15 min and irradiated for 6 h at 75–85 °C with a Hanovian photolysis apparature. The mixture was concentrated, and acetic anhydride (10.0 mL) and trifluoroacetic acid (0.85 mL) were added at 0 °C and stirred for 80 min. The mixture was poured into diethyl ether (150 mL). The organic phase was washed repeatedly with saturated $NaHCO_3$ until neutral, washed with water, dried, and concentrated. Silica gel column chromatography (toluene–ethyl acetate, 6:1) followed by crystallization from ethanol yielded **13** (1.38 g, 71%) as white crystals: sublimed 123–125 °C; $[\alpha]^{22}_D$ +39.5° (*c* 1.04, $CHCl_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.9, 21.0, 26.3, 28.11 (4 CH_3), 32.5, 38.4, 64.0 (C-6), 70.2, 73.0, 74.1, 91.6, 109.4, 118.2 ($CH{=}CH_2$), 134.1 ($CH{=}CH_2$), 168.7, 170.9 (2 CO_2); ^1H NMR ($CDCl_3$) δ 1.93 ($J_{3,4}$ = 8.8 Hz, $J_{4,5}$ = 10.1 Hz, $J_{4,1}$ = 5.3, H-4), 2.31 (CH_2), 3.79 (H-5), 3.99 ($J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 5.4 Hz, H-2), 4.17 (H-3), 4.18 (H-6a), 4.28 (H-6b), 5.12, 5.15 (2 $CH{=}CH_2$), 5.80 ($CH{=}CH_2$), 6.28 (H-1).

Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.53; H, 7.37. Found C, 58.39; H, 7.33.

4-*C*-Allyl-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-mannitol (7a). Compound **13** (380 mg, 1.16 mmol) in methanol containing sodium methoxide (2.9 mL, 2.9 mmol, 1.0 M, 2.5 equiv) was stirred for 30 min on an ice bath. $NaBH_4$ (88 mg, 2.32 mmol, 2.0 equiv) and H_2O (0.3 mL) were added, and the stirring was continued overnight at room temperature. The reaction mixture was neutralized by adding 80% acetic acid and concentrated, and residual acetic acid was removed by azeotropic distilation with toluene. To the residue were added 2,2-dimethoxypropane (2 mL), acetone (2 mL), and $CuSO_4$ (300 mg), and the mixture was stirred overnight at room temperature. The $CuSO_4$ was removed by filtration, and the filtrate was concentrated, leaving a colorless syrup. Silica gel column chromatography (toluene–ethyl acetate, 10:1) yielded **7a**: 242 mg, 73%; $[\alpha]^{22}_D$ +32.7° (*c* 0.99, $CHCl_3$).

1,4-Dideoxy-2,3:5,6-di-*O*-isopropylidene-1-iodo-4-*C*-(3′-hydroxypropyl)-D-mannitol (9a). Compound **7a** (210 mg, 0.73 mmol) was treated the same way as the mixture of **7a** and **7b**, yielding **8a**: 262 mg, 90%; $[\alpha]^{22}_D$ +44.1° (*c* 1.16, $CHCl_3$). Compound **8a** (230 mg, 0.58 mmol) was reacted the same way as the mixture of **8a** and **8b**, yielding **9a** (211 mg, 88%). Data are as above.

1,4-Dideoxy-4-*C*-[2′-(*tert*-butoxycarbonyl)ethyl]-1-iodo-2,3:5,6-di-*O*-isopropylidene-D-mannitol (15). To a solution of **9a** (150 mg, 0.36 mmol) in dichloromethane (6.0 mL) were added pyridinium dichromate (409 mg, 1.09 mmol, 3.0 equiv), acetic anhydride (467 mg, 5.43 mmol, 15 equiv), and *tert*-butyl alcohol (805 mg, 10.86 mmol, 30 equiv). The mixture was refluxed for 3 h, cooled, poured into ethyl acetate (30 mL), and added to a short silica gel column, eluting with ethyl acetate. The ethyl acetate eluate was concentrated, and the residue was subjected to column chromatography (toluene–ethyl acetate, 8:1), to afford **15** (114 mg, 65%) as a clear syrup: $[\alpha]^{22}_D$ +78.0° (*c* 0.95, $CHCl_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 8.6 (C-1), 24.6, 25.3, 25.9, 26.5 (4 CH_3), 28.1 (CH_3-Bu), 28.4, 32.7 (2 CH_2), 40.7 (C-4), 76.9, 79.3, 80.1, 80.3 (C-Bu), 107.3, 109.3 (2 $C(CH_3)_2$), 172.8 (CO_2).

Anal. Calcd for $C_{19}H_{33}O_6I$: C, 47.11; H, 6.87. Found C, 46.82; H 6.81.

***tert*-Butyl 3(*R*),4(*S*)-*O*-Isopropylidene-5(*R*)-((1′*S*)-3′,3′-dimethyl-2′,4′-dioxolanyl)-(*S*)-cyclohexanecarboxylate (16a) and *tert*-Butyl 3(*R*),4(*S*)-*O*-Isopropylidene-5(*R*)-**

((1′*S*)-3′,3′-dimethyl-2′,4′-dioxolanyl)-(*R*)-cyclohexanecarboxylate (16b). To a stirred solution of **15** (780 mg, 1.61 mmol) in THF (11 mL) was added lithium diisopropylamide in cyclohexane (1.5 mL, 1.5 M) under nitrogen at −75 °C. The solution was stirred overnight while the temperature was allowed to rise to room temperature. Saturated aqueous NH_4Cl (1.0 mL) was added, and the solution was partitioned between diethyl ether and water. The organic phase was washed with water, dried, and concentrated to give a colorless syrup (527 mg). Column chromatography (diethyl ether–hexane, 1:3) yielded **16a** (393 g, 68%) and **16b** (129 mg, 22%). **16a**: ^{13}C NMR δ 20.5, 24.6, 25.7, 26.5, 26.9, 28.1 (CH_3-Bu), 34.3, 38.0 (2 CH), 67.9 (CH_2O), 72.3, 72.4, 76.4, 80.2 (C-Bu), 107.7, 108.7 (2 $C(CH_3)_2$), 175.5 (CO_2). **16b**: ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 23.1, 25.7, 26.2, 26.8, 28.0 (CH_3-Bu), 28.1, 31.1, 40.0, 40.8 (2 CH_2), 67.5 (CH_2O), 72.9, 74.0, 74.0, 77.5, 80.5 (C-Bu), 108.5, 108.6 (2 $C(CH_3)_2$), 174.0 (CO_2).

3(*R*),4(*S*)-Dihydroxy-5(*R*)-(1′(*S*),2′-dihydroxyethyl)-(*S*)-cyclohexanecarboxylic Acid (1). Compound **16a** (100 mg, 0.28 mmol) was dissolved in aqueous trifluoroacetic acid (1.5 mL, 80%) and the resultant mixture stirred for 40 min at ice bath temperature. The mixture was concentrated, methanol (3.0 mL) was added, and the solution was concentrated to dryness. The residue was purified on a Biogel P-2 column with water as eluant, yielding compound **1**: 59 mg, 96%; $[\alpha]^{22}_D$ +112.5 (*c* 0.64, water); ^{13}C NMR (D_2O, 70 °C) δ 23.0, 28.5 (2 CH_2), 38.8, 40.1 (2 CH), 64.8 (C-2′), 69.4, 69.6, 72.9, 179.6 (CO_2); ^1H NMR (D_2O, 70 °C) δ 1.51 ($J_{1,6_{ax}}$ = 5.3 Hz, H-6_{ax}), 1.67 (H-5), 1.75 ($J_{1,2_{ax}}$ = 5.4 Hz, $J_{2_{ax},3}$ = 12.1 Hz, H-2_{ax}), 1.77 (H-6_{eq}), 2.03 (H-2_{eq}), 2.77 (H-1), 3.56 (H-2′), 3.69 (H-1′), 3.74 ($J_{3,4}$ = 2.8 Hz, H-3), 3.76 (H-2′), 4.13 (H-4).

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.85; H, 7.18.

3(*R*),4(*S*)-Dihydroxy-5(*R*)-(1′(*S*),2′-dihydroxyethyl)-(*R*)-cyclohexanecarboxylic Acid (2). Compound **16b** (20 mg, 0.056 mmol) was reacted the same way as **1**, yielding **2**: 12 mg, 95%; ^{13}C NMR (D_2O, 70 °C) δ 25.2, 30.9 (2 CH_2), 42.4, 43.1 (2 CH), 64.8 (C-2′), 69.1, 72.1, 72.4, 178.5 (CO_2); ^1H NMR (D_2O, 70 °C) δ 1.41 ($J_{1,6_{ax}}$ = 12.5 Hz, H-6_{ax}), 1.66 ($J_{1,6_{eq}}$ = 3.6 Hz, H-6_{eq}), 1.69 ($J_{1,2_{ax}}$ = 12.6 Hz, $J_{2_{ax},3}$ = 12.3 Hz, H-2_{ax}), 1.94 ($J_{1,2_{eq}}$ = 3.6 Hz, H-2_{eq}), 2.52 (H-1), 3.55 (H-2′), 3.65 ($J_{3,4}$ = 2.8 Hz, H-3), 3.67 (H-1′), 3.75 (H-2′), 4.11 (H-4).

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New Bastadins from the Sponge *Ianthella basta*

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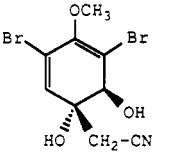
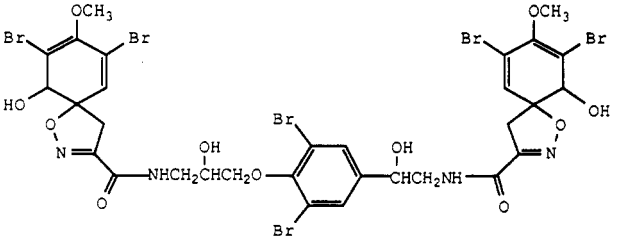
From the sponge *Ianthella basta* collected in Guam, four new bastadin type ethers, bastadin-8 (**7**), -9 (**9**), -10 (**8**), and -11 (**10**) were isolated together with the known bastadin-2 (**4**), -4 (**3**), -5 (**5**), and-6 (**6**). Structures were elucidated by extensive spectroscopic analysis and some derivative formation (methyl ethers). ^{13}C NMR assignments for bastadin-4 and -8 were made by one-bond and long-range H/C correlations. Several of the bastadins were found to exhibit cytotoxic and antiinflammatory activity.

Of the wide variety of nitrogenous natural products isolated from marine sponges, brominated tyrosine-derived metabolites have so far been found exclusively in species of the order Verongida.[1,2] Most of these metabolites consist of simple, modified tyrosines such as **1**[3] or linear combinations of tyrosine-derived units, e.g., fistularin-3 (**2**).[4] However, a unique group of macrocyclic metabolites typified by bastadin-4 (**3**) have been isolated from *Ianthella basta* collected in Australia.[5] We have examined the extracts of *Ianthella basta* collected in Guam and have isolated therefrom four new members of the bastadin series (**7**–**10**) in addition to the known bastadin-2 (**4**), -4 (**3**), -5 (**5**), and -6 (**6**).



1 Aeroplysinin-1



2 Fistularin-3

The bastadins were isolated by conventional methods as outlined in the Experimental Section. Bastadin-2, -4, -5, and -6 were identified by comparison of their ^1H and ^{13}C NMR spectral data with that reported in the litera-

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