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Synthetic Receptors. 3,6-Anhydro-7-benzenesulfonamido-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol: A Useful Component for the Preparation of Chiral Water-Soluble Cyclophanes Based on Carbohydrate Precursors[1]

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Contemporary interest in intermolecular interactions and biomimetic systems has created a need for new general strategies for preparing large chiral molecules that have substantial concave surfaces. In this paper, the total synthesis of a macrocyclic *C*-glycosyl compound, a chiral, water-soluble cyclophane, is described. The route to this prototypical "glycophane" relies upon the bifunctional nature of the title compound, 3,6-anhydro-7-benzenesulfonamido-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol. Two moles of this versatile structural component provide a bisalkyne, which is cyclized to afford a macrocyclic diyne. A thermal flow reactor is used to increase the efficiency of the oxidative cyclization. This new technique is an improvement over earlier approaches to oxidative cyclization. The synthetic strategy is general and is a practical contribution to the approaches available for the preparation of synthetic receptors. Future applications of this method will allow ready access to molecules containing lipophilic and hydrophilic domains.

Investigations of enzyme models and biomimetic experiments exemplify an abstractive approach to knowledge wherein the investigator attempts to identify the essential components of natural catalysts or receptors, to present a theory which explains the properties of the natural system as a consequence of these parts, and to construct and analyze systems that imitate this proposed mechanism. An important part of this process of hypothesis-and-test is the *chemical synthesis* of the target system. This paper presents a general modular approach to the chemical synthesis of large molecules related to natural receptors.

There is a need for new general synthetic strategies for preparing water-soluble binding sites for complex organic molecules. Seminal reports from Koga, Tabushi, Whitlock, and Murakami established that some water-soluble cyclophanes function as lipophilic binding sites and, in aqueous solution, will form stable association complexes with benzenoid and naphthalenoid substrates.[2-5] Diederich demonstrated that semiaqueous systems will also support such binding phenomena.[6] Work from this laboratory has explored the use of macrocyclic dibenzodiazocines (Tröger's base analogues) for the preparation of rigid water soluble cyclophanes or molecular clefts.[7,8]

One goal in this lab is to develop synthetic approaches for preparing *chiral*, water-soluble molecules that have lipophilic cavities. Studies of such synthetic receptors will be part of a rational approach to understanding organic–molecular interactions in aqueous solutions and will help

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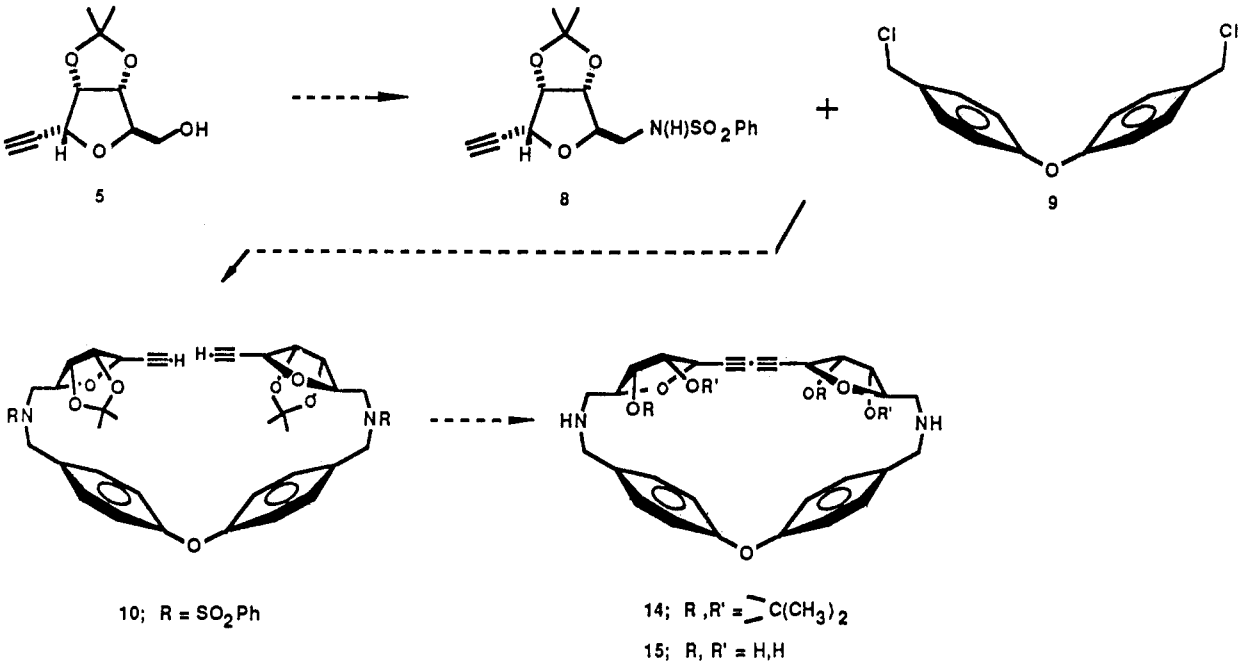
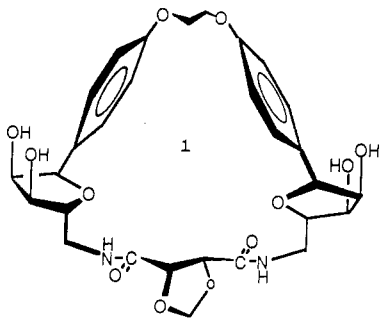


Figure 1. Synthetic strategy.

explain the forces controlling biologically important processes.

The synthesis of chiral, optically active molecules may be based on a resolution or use optically active starting materials. A common feature of prior approaches to water-soluble cyclophanes was achirality and the use of ionic charges to ensure water solubility. Wilcox and Cowart recently synthesized 1, a macrocyclic *C*-glycosyl



compound (or "glycophane"), which is soluble (no NMR evidence for micelle formation or aggregation) at up to 50 mM concentrations in D_2O.[9] Macrocycle 1 is the first macrocyclic cyclophane soluble in D_2O in neutral form. A short and efficient general synthetic approach to large chiral molecules that contain concave lipophilic regions and hydrophilic regions would allow the properties of this interesting class of molecules to be rapidly explored. These molecules will have properties similar to those of the water-soluble cyclophanes and may act as receptors in aqueous solution. The chirality and optical activity of these glycophanes may allow these molecules to be used for diastereoselective complex formation or catalysis. This paper describes a second approach to macrocyclic *C*-glycosyl compounds and introduces a practical new technique for the oxidative coupling of terminal alkynes.

Synthetic Strategy

The synthetic strategy illustrated in Figure 1 is based on the use of the versatile advanced intermediate 8. This intermediate has several important properties that suggested its potential value in an approach to water-soluble synthetic receptors. First, the molecule is a protected amino sugar derivative. Two such units in a macrocycle should render the molecule water soluble. Second, the molecule is chiral and optically active. Synthetic receptors derived in a simple way from this molecule would also be chiral. Third, the structural unit 8 (an α-*C*-glycosyl compound) has a relatively rigid and extended shape. The alternative C-3 isomer (a β-*C*-glycosyl compound) would be inappropriate for incorporation into a macrocyclic structure destined to act as a receptor because it would introduce too sharp a bend into the macrocycle. The resulting macrocycle would be unlikely to maintain an open ring structure. The extended shape of the α-*C*-glycosyl compound was therefore deemed preferable to the folded shape of the β-*C*-glycosyl compound. Finally, molecule 8 contains both a terminal alkyne and a primary amine sulfonamide. This functionality was designated to allow the straightforward incorporation of two such units into a macromolecule and a subsequent macrocyclization step based on oxidative coupling.

The synthetic route (Figure 1) was inspired by the *C*-glycosyl compound 5 first described by Buchanan and by the well-known macrocyclization technique based on oxidative coupling of terminal alkynes.[10,11] The formation

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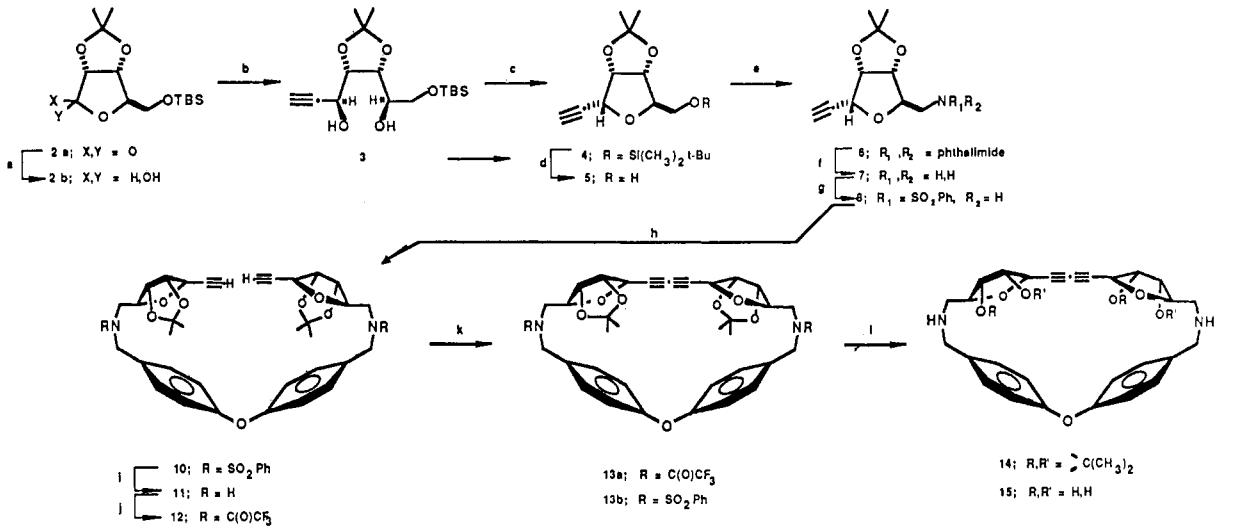
Scheme I[a]



[a] (a) DIBAL, CH_2Cl_2, −78 °C; (b) HCCLi, THF, −78 °C; (c) TsCl, pyridine, 80 °C; (d) *p*-TSA, 10% aqueous MeOH; (e) DEAD, Ph_3P, phthalimide; (f) H_2NNH_2, THF/MeOH, reflux; (g) TsCl, Et_3N, THF, 0 °C; (h) **9**, Cs_2CO_3, DMF, 80 °C; (i) sodium anthracene, THF, 0 °C; (j) $(CF_3CO)_2O$, Et_3N, THF, −78 °C; (k) $Cu(OAc)_2$, pyridine, 80 °C; (l) $NaBH_4$, EtOH.

of macrocyclic rings by oxidative coupling of alkynes is well precedented and frequently is achieved in very good yield. To create the necessary diyne, it was proposed that the *C*-glycosyl compound **5** could be easily converted by conventional procedures to sulfonamide **8**. It was proposed that sulfonamide **8**, which was intended to function as a generally useful structural subunit, could be converted to a polyhydroxylated macrocyclic molecule in just four steps. As shown for a specific case in Figure 1, the sulfonamide may be alkylated with a dihalide (**9**) and thus afford **10**, a bis-*C*-glycosyl compound. Oxidative coupling of this bisalkyne provides the macrocyclic armature and generates, after deprotection, the target water-soluble molecule **15**.

An interesting question to be addressed in this work was whether or not the functional groups present in these intermediates would be stable to the conditions required for macrocyclization and deprotection. For example, while sulfonamides are attractive reagents for forming carbon–nitrogen bonds, sulfonamides are also rather difficult to hydrolyze and are usually removed by reductive techniques. Examples of sulfonamide removal in the presence of 1,3-diynes were unknown. Would the diyne be compatible with conditions of sulfonamide removal? To test the possibility of such an approach to synthetic receptors and to evaluate the scheme proposed in Figure 1, the following study was undertaken.

Results and Discussion

Synthesis of the Diyne. Lactol **2b** (available in 99% yield of Dibal reduction of the corresponding lactone **2a**[12]) was treated with 3 equiv of lithioacetylene (prepared according[13] to Midland) in THF to provide diol **3** in quantitative yield (Scheme I). Analysis of the crude product by 90-MHz ^{13}C NMR analysis revealed that in this reaction, as in a similar reaction reported by Buchanan, only a single isomer was formed. The diol was cyclized according to Buchanan's procedure to provide *C*-glycosyl compound **4** in 96% yield. The silyl protecting group was not used by Buchanan, and it is interesting to note that this protecting group is stable to the conditions required for dehydration–cyclization. Desilylation of the C-5 hydroxyl provided primary alcohol **5**, which corresponded in all respects with the material described by Buchanan.[10]

Alcohol **5** was converted to phthalimide **6** through the Mitsunobu modification of the Gabriel procedure.[14] Hydrazinolysis of phthalimide **6** afforded the amine **7**, which was sulfonylated to provide the key intermediate **8** in a 43% overall yield from alcohol **5**.

It was expected that alkylation of this sulfonamide with a bishalide would afford the desired bissulfonamide **10**. An earlier attempt to prepare this bissulfonamide by an alternative approach had led to only small amounts of the desired material (Scheme II). This approach was based on alkylation of benzylsulfonamide **18** (prepared in three steps from chloride **9**). The terminal bromide **19** required for this approach was derived from alcohol **5**. This approach was complicated by the formation of the dehydrohalogenation product **20** and this pathway to the macrocycle was therefore abandoned. The present approach, which incorporates a nucleophilic carbohydrate derivative and a benzylic halide, was developed in an effort to avoid the problem of dehydrohalogenation.

Treatment of the bischloride **9** with 2.2 equiv of sulfonamide **8** in DMF in the presence of cesium carbonate provided the bisalkylated product **10** in nearly quantitative yield (Scheme I). This essential step in our plan provided, for the first time, a macromolecular bis-*C*-glycosyl compound, which might be cyclized via oxidative alkyne coupling. Attention was next turned to methods for this cyclization.

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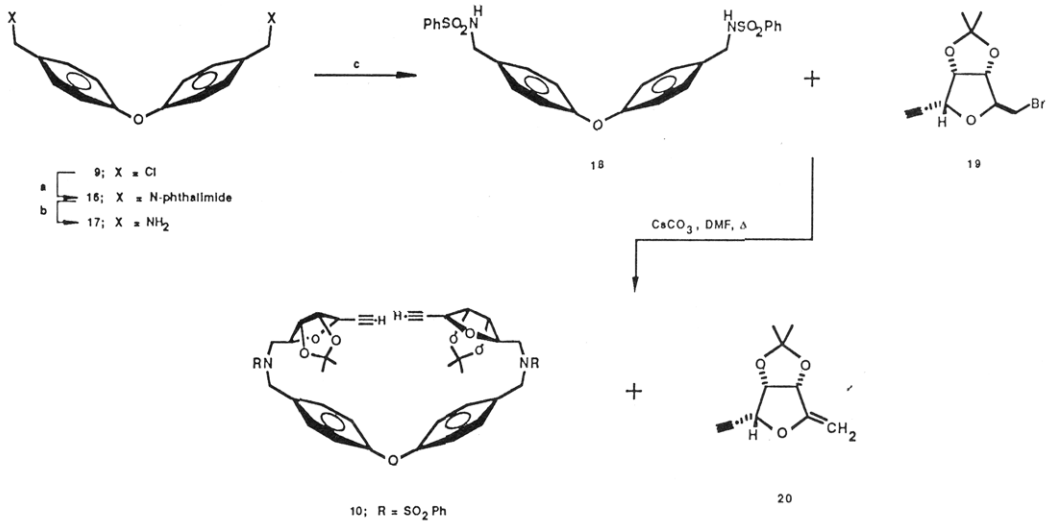
Scheme II[a]



[a] (a) Phthalimide, K_2CO_3, DMF; (b) H_2NNH_2, THF/MeOH, reflux; (c) TsCl, Et_3N, THF, 0 °C.

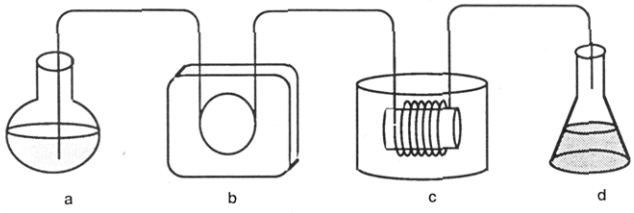


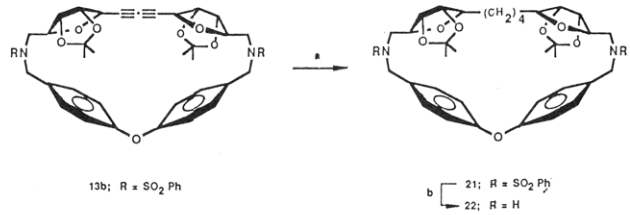
Figure 2. Thermal flow reactor schematic: (a) reservoir, (b) peristaltic pump, (c) teflon reactor coil in oil bath, (d) quench.

A New Technique for Oxidative Coupling. The cyclization of bisalkynes to provide macrocyclic 1,3-diynes is a well-known process for macrocycle synthesis.[11] The experimental process usually entails heating a preformed mixture of cuprous acetate and bisalkyne or slowly adding the bisalkyne to a solution containing the oxidant. Preliminary results revealed that the oxidative cyclization of **10** under the action of cuprous acetate in pyridine was too slow to be observed at 25 °C and was fast at 80 °C. Significantly, it was also observed that the product alkyne was not stable in the reaction mixture at 80 °C and decomposed to form a number of unidentified products.

To overcome the problem that the cyclization conditions led to the decomposition of the product soon after it was formed, an experimental procedure that allowed precise control of temperature and time of reaction was required. Optimal yields were eventually obtained in the cyclization by use of the flow reactor designed in this laboratory and illustrated in Figure 2. In this process, the oxidant and the alkyne are mixed at 25 °C under nitrogen and then pumped peristaltically through a Teflon reaction tube suspended in an oil bath. The time during which the reaction mixture contacts the bath can be conveniently and exactly controlled by changing the flow rate and/or by changing the length of the immersed Teflon coil.

An important advantage of this technique is that very precise and reproducible control of reaction conditions can be achieved. This makes optimization of the reaction conditions a more exact process. The time and temperature of heating can be better controlled for the relatively small volumes entering and leaving the bath than for large volumes, which must be heated in a batch process. Optimal product yields were obtained with heating contact times of just 1–4 min by using an oil bath at 80 °C. Immediately after leaving the reaction area, the reaction mixture can be cooled and quenched by allowing it to mix with a large volume of water and inert solvent.

Scheme III[a]



[a] (a) PtO_2, H_2, THF; (b) sodium anthracene, THF, 0 °C.

The most important advantage of this thermal flow reactor approach to oxidative cyclization (or reactions in general) is that changes in scale can be made with total confidence that the scaled up process will work under the same conditions as the smaller scale process. Changing the scale of this type of experiment is achieved simply by changing the amount of liquid pumped through the reaction coil. Because a peristaltic pump is used, no volume limitations of the type that would attend the use of a syringe pump need be considered.

Macrocyclization and Deprotection. Oxidative cyclization of **10** was achieved by use of the thermal flow reactor process (Figure 2). The reaction provided the macrocyclic bissulfonamide **13b** in 67% yield. Deprotection of this macrocyclic *C*-glycosyl compound was expected to provide the desired glycophane and establish the usefulness of intermediate **8** as a structural unit for preparing polyhydroxylated macrocycles. Unfortunately, deprotection of **13b** could not be achieved in satisfactory yield. Deprotection was attempted with sodium naphthalenide, sodium anthracenide, sodium amalgam, alkoxyaluminum hydrides, HBr/phenol, and photolysis.[15-18] In every case,

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the conditions of desulfonylation led to extensive decomposition. The reducing techniques were clearly incompatible with the diyne functional group. NMR analyses (90 MHz, ^{13}C) of the crude product from the reductions revealed new resonances corresponding to aliphatic and olefinic products and revealed that the alkynyl functional groups had undergone reaction. The HBr/phenol process also caused extensive decomposition.

To verify that the presence of the diyne was in fact preventing the successful removal of the sulfonamides, the diyne **13b** was hydrogenated to provide octahydro derivative **21** in 96% yield (Scheme III). Treatment of this perhydro derivative with sodium anthracenide in THF provided in good yield the expected perhydromacrocyclic diamine **22**. This experiment confirmed that the 1,3-diyne was indeed reactive under some conditions of desulfonylation and the deprotection of the sulfonamido carbohydrate derivatives was not difficult in the absence of the diyne. Because of the excellent yields obtained in the alkylation step, it was decided that the sulfonamide strategy should not be abandoned, and attention was therefore turned to a search for alternative routes from the bisalkyne **10** to the cyclized, deprotected target.

Desulfonylation *prior* to cyclization was an alternative route, which might avoid the problem encountered above. It was reasoned that the reduction potential of the bisalkyne was greater than that of the diyne, and therefore, the alkynes might better withstand the reagents required for desulfonylation. In fact, treatment of the bisalkyne **10** with sodium anthracenide provided a 94% yield of the desired diamine **11**.

Further experiments revealed that the bis secondary amine **11** was not a good substrate for oxidative cyclization. The diamine gave only low yields of the target macrocycle when treated with cuprous acetate in the presence or absence of triethylamine. Protection of the diamine was therefore necessary, and the diamine was converted to bis(trifluoroacetamide) **12** in 85% yield.[19] The bisamide could be cyclized and afforded the macrocycle **13a** in 35% yield by use of the flow reactor and cuprous acetate. Finally, deprotection of the bisamide **13a** was achieved with sodium borohydride in ethanol and provided the bisamine **14** in nearly quantitative yield.[20]

Conclusion

The results described here, together with other experiences in our laboratory, indicate that the incorporation of carbohydrates into cyclophanes is a difficult but not impractical approach to chiral, optically active synthetic receptors. The sulfonamide **8** is available in multigram quantities and, as shown here, can indeed be used as a key component in the synthesis of macrocyclic molecules.

We conclude that the use of the sulfonamide **8** in a general approach to macrocycles (Figure 1) is a practical synthetic strategy for preparing water soluble, chiral, symmetrical cyclophanes. In general, the use of alkynylated carbohydrates in a process involving dimerization or bisalkylation and subsequent oxidative cyclization is a promising route to polyhydroxylated macrocyclic molecules. The use of the trifluoroacetamide in the final stages of this work confirms that this functionality is useful for preparing amino diynes. The fact that trifluoroacetamides can be alkylated in high yield suggests that a final refinement of this process might be achieved by using the trifluoroacetamide analogue of **8** for the bisalkylation step. This modification would obviate the need to switch protecting groups during the process and would be a preferable path, provided the stability of the intermediates was adequate and the yield in the bisalkylation step was high. Future work will pursue the use of this sulfonamide or a trifluoroacetamide in conjunction with a larger aromatic dihalide and will result in the preparation of unique new macrocyclic synthetic receptors.

Experimental Section

Routine proton nuclear magnetic resonance (^1H NMR) spectra were recorded in $CDCl_3$ on a Varian EM-390 spectrometer. High-field NMR spectra were recorded on a Nicolet NT-200, a Nicolet NT-360, or a General Electric GN-500 multinuclear spectrometer in $CDCl_3$ unless otherwise specified. Chemical shifts were reported in parts per million (ppm) downfield from the internal standard, tetramethylsilane. Carbon magnetic resonance (^{13}C NMR) spectra were recorded in $CDCl_3$ on a Varian FT-80A, a Nicolet NT-360, a General Electric GN-300, or a General Electric GN-500 spectrometer, with chemical shifts reported in ppm and proton decoupling unless otherwise specified.

Yields are reported based on the amount of isolated material obtained following the indicated procedure. The procedures provided homogeneous material as determined by ^1H and ^{13}C nuclear magnetic resonance, and the purity of these products is therefore estimated to be greater than 95%. High-resolution mass spectra (HRMS) were calibrated by peak matching relative to a polyfluorinated alkane (PFA) standard on a Du Pont (CEC) 21-110B mass spectrometer. Low-resolution electron-impact (EI) or chemical-ionization (CI) mass spectra were collected on a Finnigan 4023 or a Bell and Howell 21-491 mass spectrometer. Data processing was conducted with an INCOS data system.

Melting points were measured on a Mel-Temp capillary melting point apparatus. Melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 298 spectrometer, using polystyrene film as the calibration standard. Optical rotations were measured in 1-dm cells of 1-mL capacity with a Perkin-Elmer Model 141 polarimeter in $CHCl_3$ filtered through neutral alumina immediately prior to use. Concentrations are reported in grams per deciliter.

Solvents were dried by distillation from the appropriate drying agent under a dry nitrogen atmosphere. Dichloromethane, toluene, benzene, triethylamine, piperidine, and pyridine were distilled from calcium hydride. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from calcium hydride under reduced pressure (ca. 10 mmHg). Tetrahydrofuran (THF), dimethoxyethane (DMF), and diethyl ether (ether) were distilled from sodium/benzophenone. Methanol (MeOH) was distilled from magnesium methoxide, and ethanol was distilled from magnesium ethoxide. Skelly B refers to a petroleum fraction with a boiling range of 60–80 °C, which was purified by stirring over concentrated sulfuric acid and then potassium carbonate and distillation. Acetylene gas was purified by passage through a −78 °C trap, concentrated sulfuric acid, and a sodium hydroxide tower. Anhydrous copper(II) acetate was prepared by refluxing the hydrate in acetic anhydride for 24 h and drying the solid under high vacuum (0.01 mmHg) at 100 °C for 24 h. Commercially available reagents were analyzed for impurities before use and then purified by crystallization or distillation when necessary.

A flow reactor (Figure 2) was constructed from 40 cm of $^1/_{16}$ in. inner diameter Teflon tubing wound around a piece of glass tubing 8 cm long × 1 cm outer diameter. This coil was suspended in a thermostated oil bath and attached to either a syringe/syringe pump or reservoir/peristaltic pump to cause the reactant solution to flow through the coil at the desired flow rate.

All reactions were conducted in oven-dried glassware under a dry nitrogen atmosphere arranged with a mercury bubbler so that the system could be alternatively evacuated and filled with ni-

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(19) (a) Quick, J.; Meltz, C. *J. Org. Chem.* **1979**, *44*, 573–578. See also: (b) Curphey, T. J. *Ibid.* **1979**, *44*, 2805–2807. (c) Newman, H. *Ibid.* **1965**, *30*, 1287–1289. (d) Imazawa, M.; Eckstein, F. *Ibid.* **1979**, *44*, 2039–2041. (e) Barrett, A. G. M.; Lana, J. C. A. *J. Chem. Soc., Chem. Commun.* **1978**, 471–472.

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trogen and left under a positive pressure unless otherwise specified.

Analytical thin-layer chromatography (TLC) was performed on Kieselgel 60 F-254 precoated plates (0.25 mm, 1.5 × 8 cm, E. Merck and Co., Darmstadt, Germany). Preparative thin-layer chromatography was accomplished on Kieselgel 60 PF_{254} plates prepared in this laboratory (0.6 mm, 20 × 20 cm, No. 7747, E. Merck and Co., Darmstadt, Germany). Column and flash chromatography[21] were conducted with Kieselgel 60 silica gel (250–400 mesh, E. Merck and Co., Darmstadt, Germany).

5-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-D-ribofuranose (2b). To a solution of lactone **2a** (29.0 g, 0.096 mol) in 500 mL of CH_2Cl_2 at −78 °C under nitrogen was added dropwise over 30 min, 134 mL of diisobutylaluminum hydride (1.0 M in hexane, 0.134 mol). After 0.5 h, methanol (20.0 mL) was added dropwise and the solution was allowed to warm to room temperature and washed with aqueous sodium tartrate (1 M, 3 × 200 mL). The organic phase was dried over $MgSO_4$, and after filtration, removal of volatile components under reduced pressure afforded **2b** as a crystalline solid. Recrystallization from Skelly B afforded **2b** as colorless crystals (23.4 g, 0.077 mol, 80%): mp 48–49 °C; R_f 0.45 (silica gel, Skelly B/EtOAc, 3:1); $[\alpha]^{23}_D$ −12.65 (*c* 0.034, $CHCl_3$); IR ($CHCl_3$) 3375, 2940, 2866, 1462, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (d, 1 H, *J* = 11.11 Hz), 4.65 (d, 1 H, *J* = 11.1 Hz), 4.56 (d, 1 H, *J* = 5.5 Hz), 4.37 (d, 1 H, *J* = 5.5 Hz), 4.18 (s, 1 H), 3.62 (s, 2 H), 1.34 (s, 3 H), 1.17 (s, 3 H), 0.78 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 111.87, 103.28, 87.35, 86.88, 81.76, 64.71, 26.38, 25.65, 24.89, 18.10, −5.79. Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.26; H, 9.21. Found: C, 55.24; H, 9.31.

7-*O*-(*tert*-Butyldimethylsilyl)-1-deoxy-4,5-*O*-isopropylidene-D-*allo*-hept-1-ynitol (3). To a solution of acetylene gas (4 × 350 mL, 0.06 mol) at −78 °C in 100 mL of THF was added dropwise over a 15-min period, 37.5 mL of *n*-butyllithium (1.6 M in hexane, 0.06 mol). After 15 min, a solution of silyl ether **2b** (6.08 g, 0.02 mol) in 10 mL of THF was added dropwise over a 10-min period. Cooling was discontinued, and the solution was allowed to warm to room temperature and stirred for 8 h. The solution was cooled to 0 °C, saturated aqueous ammonium chloride (50 mL) was added, and the organic phase was extracted with ether (3 × 30 mL). The combined ether extracts were washed with brine (20 mL) and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded a colorless oil (6.30 g, 0.019 mol, 95%): R_f 0.30 (silica gel, EtOAc/Skelly B, 3:1); $[\alpha]^{23}_D$ −4.33 (*c* 12.07, $CHCl_3$); IR (neat) 3400, 3318, 2121 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 6 H), 0.90 (s, 9 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 2.50 (d, 1 H, *J* = 2.4 Hz), 3.45 (br s, 1 H), 3.6–4.67 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 19.2, 26.24, 28.59, 26.75, 62.15, 65.23, 70.13, 74.61, 77.02, 77.25, 80.68, 83.50, 110.00; exact mass calcd for $C_{15}H_{27}O_5Si$ ($M^+ - CH_3$) 315.16276, found 315.16216.

3,6-Anhydro-7-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol (4). To a stirred solution of diol **3** (0.1980 g, 0.60 mol) in pyridine (1 mL) at 80 °C was added a solution of *p*-toluenesulfonyl chloride (0.4120 g, 2.16 mol) in pyridine (2 mL). After 4.5 h, the solution was cooled to 0 °C and poured into a separatory funnel containing ice/water (20 mL). The suspension was extracted with chloroform (3 × 10 mL) and the combined organic layers were washed with 0.25 N hydrochloride acid (2 × 10 mL) and dried over magnesium sulfate to yield, after removal of volatile components under reduced pressure, a dark crude oil. This oil was passed through a silica gel column (Skelly B/EtOAc, 10:1, eluant) to yield a clear oil (0.1477 g, 0.473 mol, 78%): R_f 0.40 (silica gel, Skelly B/EtOAc, 3:1); $[\alpha]^{23}_D$ −38.09 (*c* 16.35, $CHCl_3$); IR (neat) 3310, 3270, 2125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 6 H), 0.89 (s, 9 H), 1.38 (s, 3 H), 1.55 (s, 3 H), 2.59 (d, 1 H, *J* = 3.0 Hz), 3.78 (t, 2 H, *J* = 2.7 Hz), 4.20 (t, 1 H, *J* = 3 Hz), 4.8 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 112.8, 84.13, 82.78, 82.13, 78.29, 75.07, 73.40, 65.08, 26.24, 25.60, 25.20, 17.82; exact mass calcd for $C_{15}H_{25}O_4Si$ ($M^+ - CH_3$) 297.15220, found 297.15306.

3,6-Anhydro-1-deoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol (5). To a solution of silyl ether **4** in 10% aqueous methanol (7.170 g, 0.023 mol, 200 mL) was added a catalytic amount of *p*-toluenesulfonic acid (ca. 4 mg), and the solution was stirred for 18 h. Barium carbonate (ca. 1 g) was added, and the suspension was stirred vigorously for 0.5 h, filtered (Celite), and concentrated under vacuum to afford a thick oil. The oil was partitioned between water/Skelly B (20 mL:20 mL), and the organic layer was washed with water (2 × 10 mL). The combined aqueous layers were saturated with sodium chloride and extracted with methylene chloride (5 × 20 mL, then continuously for 24 h). The methylene chloride extracts were combined and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded **5** as a clear oil (3.75 g, 0.019 mol, 80%), which corresponded in all respects with material described by Buchanan:[10] R_f 0.30 (silica gel, EtOAc/Skelly B, 1:1); $[\alpha]^{23}_D$ −38.09 (*c* 16.35, $CHCl_3$); IR (neat) 3450, 3280, 2130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.60 (s, 3 H), 2.65 (d, 1 H, *J* = 2.0 Hz), 3.72 (m, 2 H), 4.52 (t, 1 H, *J* = 3.9 Hz), 4.83 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 113.42, 84.02, 82.08, 81.55, 77.92, 76.31, 72.22, 62.29, 26.05, 25.05; exact mass calcd for $C_9H_{11}O_4$ ($M^+ - CH_3$) 183.06573, found 183.06604.

3,6-Anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-7-phthalimido-D-*altro*-hept-1-ynitol (6). To a solution of alcohol **5** (1.25 g, 6.0 mmol), 0.947 g of phthalimide (6.60 mmol), and 1.05 mL of diethyl azodicarboxylate (6.60 mmol) in 50 mL of THF at 0 °C was added dropwise a solution of 1.74 g of triphenylphosphine in 10 mL of THF. Cooling was immediately discontinued, and the solution was allowed to warm to room temperature and stirred for 1 h. Removal of volatile components under reduced pressure afforded an oil, which was dissolved in 30 mL of CH_2Cl_2, washed with 1 N NaOH (3 × 10 mL), and dried over $MgSO_4$. Filtration and removal of volatile components under reduced pressure afforded an oil, which was stirred with dry ether (50 mL) for 1 h. The supernatant was decanted, and the solid product washed with ether (3 × 10 mL). The combined ether solutions were cooled to 0 °C overnight to deposit a solid product. The solids were combined without further purification to yield phthalimide **6** (1.36 g, 4.20 mmol, 70%): mp 149–153 °C; R_f 0.39 (silica gel, EtOAc/Skelly B, 3:2); $[\alpha]^{23}_D$ 36.39 (*c* 3.63, $CHCl_3$); IR (neat) 3310, 1775, 1772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3 H), 1.53 (s, 3 H), 2.46 (s, 1 H), 3.70 (m, 2 H), 4.19 (q, 1 H, *J* = 6.0 Hz), 4.48 (q, 1 H, *J* = 5.0 Hz), 4.69 (d, 1 H, *J* = 6.0 Hz), 4.89 (m, 1 H), 7.72 (m, 2 H), 7.84 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.86, 133.95, 131.89, 123.28, 113.75, 82.92, 81.51, 80.76, 77.21, 76.42, 71.24, 36.88, 26.21, 26.37; exact mass calcd for $C_{17}H_{14}NO_5$ ($M^+ - CH_3$) 312.0872, found 312.0886.

7-Amino-3,6-anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol (7). To a refluxing solution of phthalimide **6** (3.296 g, 0.010 mol) in THF/MeOH (1:1, 250 mL) was added anhydrous hydrazine (1.61 mL, 0.050 mol). The solution was heated at reflux for 0.5 h, and the solvent was then removed under reduced pressure. The residual white solid paste was dissolved in dichloromethane (100 mL) and washed with 1 N sodium hydroxide (3 × 20 mL). The combined aqueous layers were saturated with NaCl and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over potassium carbonate, filtered, and concentrated under reduced pressure to yield a clear oil (1.93 g, 9.80 mmol, 98%): R_f 0.23 (silica gel, CH_2Cl_2/MeOH, 10:1); $[\alpha]^{23}_D$ −35.64 (*c* 11.74, $CHCl_3$); IR (neat) 3670, 3380, 3309 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (d of d, 1 H, *J* = 5.3 + 5.3 Hz), 4.53 (m, 1 H), 4.45 (d of d, 1 H, *J* = 1.3 + 6.2 Hz), 3.96 (t, 1 H, *J* = 6.2 Hz), 2.60 (d, 2 H, *J* = 6.8 Hz), 2.54 (d, 1 H, *J* = 2.3 Hz), 1.44 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 113.80, 85.26, 82.84, 81.42, 77.84, 76.26, 71.06, 42.06, 26.12, 25.17; exact mass calcd for $C_{10}H_{15}NO_3$ 197.10518, found 197.10571.

3,6-Anhydro-7-benzenesulfonamido-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol (8). To a solution of amine **7** (2.16 g, 0.011 mol) and triethylamine (1.83 mL, 0.013 mol, 1.1 equiv) in 50 mL of THF was added dropwise a solution of benzenesulfonyl chloride (1.54 mL, 0.012 mol) in 10 mL of THF. The reaction was stirred for 2 h, and the volatile components were removed under reduced pressure. The resulting oil was dissolved in dichloromethane (30 mL), washed with 1 N sulfuric acid (3 × 20 mL), and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded a gummy solid. This solid was triturated with Skelly B (3 × 30 mL) and crystallized from ethanol to yield **8** (2.36 g, 0.007 mol, 64%): mp 106–107 °C; R_f 0.31 (silica gel, Skelly B/EtOAc, 3:2); $[\alpha]^{23}_D$ 18.28 (*c* 11.57, $CHCl_3$); IR (neat) 3350, 3310, 330, 1340, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (d, 2 H, *J* = 7.67 Hz), 7.90 (m, 3 H), 5.40

(21) Still, W. C.; Kahn, M.; Mitrai, A. *J. Org. Chem.* **1978**, *43*, 2923.

(br s, 1 H), 4.67 (t, 1 H, J = 5.43 Hz), 4.57 (d, 1 H, J = 5.6 Hz), 4.53 (m, 1 H), 4.09 (t, 1 H, J = 5.6 Hz), 2.98 (m, 2 H), 2.55 (s, 1 H), 1.47 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.49, 132.60, 129.02, 126.78, 114.12, 82.36, 81.99, 81.18, 77.35, 76.73, 71.41, 42.89, 26.11, 25.15; exact mass calcd for $C_{15}H_{16}NO_5S$ ($M^+ - CH_3$) 322.07491, found 322.07550.

Bis[4-(chloromethyl)phenyl] Ether (9). Paraformaldehyde (17.56 g, 0.590 mol) was added to a mechanically stirred solution of diphenyl ether (10.00 g, 0.059 mol) in glacial acetic acid (50 mL). Hydrogen chloride gas was bubbled into the vigorously stirred suspension for 3 h every 24 h for 3 days. The reaction mixture was poured onto ice (300 g) and extracted with 1:1 toluene/ether (3 × 100 mL). The organic layer was washed with saturated sodium bicarbonate until the aqueous layer remained basic to litmus, then washed with water (100 mL) and brine (100 mL), and dried over magnesium sulfate. Removal of volatile components under reduced pressure afforded the crude product, which was purified by distillation (170–180 °C, 0.4 mmHg) to yield **9** as a crystalline solid (8.894 g, 0.033 mol, 56%), which corresponded in all respects with reported material:[22] R_f 0.67 (silica gel, Skelly B/EtOAc, 10:1); IR ($CHCl_3$) 3020, 2960, 1905 (w), 1735 (w), 1608, 1505 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (d, 4 H, J = 10.0 Hz), 6.95 (d, 4 H, J = 10.0 Hz), 4.50 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.83, 132.49, 130.07, 118.88, 45.61; bp 160–180 °C (0.4 mmHg) [lit.[22] bp 165 °C (1.5 mmHg)].

7,7′-[Oxybis[(*p*-phenylenemethylene)(phenylsulfonyl)imino]]bis[3,6-anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol] (10). A flask charged with ribosulfonamide **8** (1.65 g, 4.9 mmol), bischloride **9** (0.595 g, 2.23 mmol), and cesium carbonate (2.91 g, 8.9 mmol) was evacuated and flushed with anhydrous nitrogen. Anhydrous dimethylformamide (30 mL) was added and the stirred suspension immersed in a 85 °C oil bath for 15 h. 1-Butanol was added (ca. 2 × 10 mL), and the product was concentrated under reduced pressure. The resulting slurry was stirred with water (ca. 50 mL) for 2 h, and the precipitated solid was filtered and dissolved in methylene chloride (50 mL). This solution was extracted with 2.5 N sodium hydroxide (3 × 10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield **10** as a light yellow foam (1.896 g, 2.28 mmol, 98%): R_f 0.25 (silica gel, Skelly B/EtOAc, 1:1); $[\alpha]^{23}_D$ 0.944 (c 7.63, $CHCl_3$); IR ($CHCl_3$) 3310, 3030–2940, 1750, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 4 H, J = 7.00 Hz), 7.55 (m, 6 H), 7.21 (d, 4 H, J = 8.3 Hz), 6.92 (d, 4 H, J = 8.30 Hz), 4.63, (t, 2 H, J = 5.2 Hz), 4.5 (m, 4 H), 4.40 (br s, 2 H), 4.28 (d, 2 H, J = 14.93 Hz), 4.05 (m, 2 H), 3.25 (d of d, 2 H, J = 5.97 + 14.9 Hz), 3.16 (d of d, 2 H, J = 8.44 + 14.93 Hz), 2.60 (d, 2 H, J = 1.30 Hz), 1.48 (s, 6 H), 1.31 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.7, 139.80, 132.66, 130.32, 130.00, 129.12, 127.13, 118.95, 113.87, 81.32, 81.11, 77.36, 76.47, 71.08, 51.41, 45.99, 26.21, 25.22; exact mass calcd for $C_{45}H_{45}O_{11}N_2S_2$ ($M^+ - CH_3$) 853.2464, found 853.2433.

7,7′-[Oxybis[(*p*-phenylenemethylene)imino]]bis[3,6-anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol] (11). To a solution of sulfonamide **10** (0.503 g, 0.580 mmol), in 20 mL of THF at 0 °C was added dropwise 14.5 mL of a solution of sodium anthracene in THF (0.2 M, 2.90 mmol). After the addition of the sodium anthracene, the solution remained blue. Water (50 mL) was added, and the suspension was extracted with dichloromethane (3 × 20 mL). The combined extracts were washed with brine (30 mL) and dried over magnesium sulfate, and the solvent was removed under reduced pressure to yield a colorless solid. This solid was triturated with methylene chloride (3 × 20 mL), and the triturate was purified by chromatography. Methylene chloride eluted the residual anthracene, and methylene chloride/MeOH (10:1) eluted the pure amine **11** (0.3217 g, 0.547 mmol, 94%): R_f 0.50 (silica gel, CH_2Cl_2/MeOH, 10:1); $[\alpha]^{23}_D$ −27.46 (c 3.30, $CHCl_3$); IR ($CHCl_3$) 3660, 3310, 1740, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.27 (d, 4 H, J = 8.18 Hz), 6.95 (d, 4 H, J = 8.18 Hz), 4.74 (m, 2 H), 4.61 (m, 4 H), 4.29 (m, 2 H), 3.81 (d, 2 H, J = 13.3 Hz), 3.75 (d, 2 H, J = 13.3 Hz), 2.67 (m, 4 H), 2.63 (d, 2 H, J = 1.24 Hz), 2.08 (br s, 2 H), 1.58 (s, 6 H), 1.36 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.46, 134.76, 129.22, 118.81, 114.12, 83.62, 83.27, 81.69, 78.17, 76.54, 71.54, 53.12, 48.93, 26.44, 25.53; exact mass calcd for $C_{34}H_{40}N_2O_7$ (M^+) 588.2835, found 588.2822.

7,7′-[Oxybis[(*p*-phenylenemethylene)(trifluoroacetyl)imino]]bis[3,6-anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol] (12). To a solution of diamine **11** (0.45 g, 0.77 mmol) and triethylamine (0.266 mL, 1.930 mmol) in 20 mL of THF at −78 °C was added dropwise trifluoroacetic anhydride (0.228 mL, 1.620 mmol). After 10 min, the cooling bath was removed, methylene chloride (20 mL) and saturated aqueous sodium bicarbonate (10 mL) were added, and, after shaking, the phases were separated. The organic phase was washed with water (10 mL), 0.5 N sulfuric acid (10 mL), and saturated aqueous sodium bicarbonate (10 mL) and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded the crude product, which was purified by column chromatography (Skelly B/EtOAc, 3:2 eluant) to yield an oil (0.4119 g, 0.528 mmol, 69%): R_f 0.36 (silica gel, Skelly B/EtOAc, 3:2); $[\alpha]^{23}_D$ 2.49 (c 0.0121, $CHCl_3$); IR ($CHCl_3$) 3310, 3025, 2940, 1690, 1600, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$, three amide conformers observed) δ 7.20 (d, 4 H, J = 9.15 Hz), 7.03 (d, 4 H, J = 10.0 Hz), 4.78–4.30 (m, 12 H), 3.37 (d, 4 H, J = 7.5 Hz), 2.68, 2.64, 2.61 (s, 2 H), 1.59, 1.55, 1.37, 1.34 (s, 12 H); ^{13}C NMR ($CDCl_3$) δ 157.50, 154.80, 134.90, 132.80, 131.74, 129.79, 128.97, 128.73; 127.58, 126.94, 119.33, 85.16, 83.16, 81.30, 80.80, 79.22, 77.84, 71.49, 50.27, 47.41, 44.02, 29.53, 26.24, 25.27; exact mass calcd for $C_{38}H_{38}N_2O_9F_6$ 780.2481, found 780.2463.

(3a*R*,4*R*,20*R*,20a*R*,23a*S*,24*R*,29*R*,29a*S*)-25,26,27,28-Tetradehydro-3a,4,5,6,7,17,18,19,20,20a,23a,24,29,29a-tetradecahydro-2,2,22,22-tetramethyl-6,18-bis(trifluoroacetyl)-4,29:20,24-diepoxy-8,11:13,16-diethenobis[1,3]dioxolo[4,5-*j*:4′,5′-*r*][1,7,22]oxadiazacycloheptacosine (13a). A flask containing bisacetylene **12** (0.560 g, 0.077 mmol) and copper(II) acetate (0.1410 g, 0.77 mmol) was carefully purged with nitrogen. Pyridine (degassed, 26 mL) was added, and the blue solution was passed through the flow reactor described in the general part of the Experimental Section and in Figure 2. The flow rate was 0.2 mL/min and the oil bath was at 80 °C; contact time was 3.5 min. The quench solution was a mixture of toluene/water (degassed, 20:20 mL) at 0 °C. After all the solution had been treated, the aqueous phase from the quench solution was extracted with toluene (2 × 20 mL), and the combined organic extracts were washed with water (2 × 20 mL) and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded the crude material, which was purified by silica gel chromatography (Skelly B/EtOAc, 5:1) to yield **13a** (0.0155 g, 0.020 mmol, 28%): R_f 0.30 (silica gel, Skelly B/EtOAc, 3:2); $[\alpha]^{23}_D$ 96.30 (c 3.54, $CHCl_3$); IR ($CHCl_3$) 1690, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6, 100 °C) δ 7.35 (d, 4 H, J = 9.0 Hz), 7.00 (br d, 4 H, J = 9.0 Hz), 4.75 (br m, 6 H), 4.58 (br m, 2 H), 4.53 (d, 2 H, J = 7.5 Hz), 4.50 (d, 2 H, J = 7.50 Hz), 4.05 (br d, 2 H), 3.83 (br d, 2 H), 1.39 (s, 6 H), 1.25 (s, 6 H); ^{13}C NMR (toluene-d_8, 100 °C) δ 157.5, 130.53, 119.21, 118.4, 116.4, 84.1, 81.8, 77.7, 75.4, 72.46, 52.36, 50.0, 48.3, 26.84, 25.83; exact mass calcd for $C_{38}H_{36}N_2O_9F_6$ 778.2325, found 778.2309.

(3a*R*,4*R*,20*R*,20a*R*,23a*S*,24*R*,29*R*,29a*S*)-25,26,27,28-Tetradehydro-3a,4,5,6,7,17,18,19,20,20a,23a,24,29,29a-tetradecahydro-2,2,22,22-tetramethyl-6,18-bis(phenylsulfonyl)-4,29:20,24-diepoxy-8,11:13,16-diethenobis[1,3]dioxolo[4,5-*j*:4′,5′-*r*][1,7,22]oxadiazacycloheptacosine (13b). By the procedure described for the preparation of **13a**, sulfonamide **10** (0.130 g, 0.15 mmol) and copper(II) acetate (anhydrous, 0.273 g, 1.500 mmol) in pyridine (50 mL) were passed through the flow reactor (0.20 mL/min, 80 °C, 3.5 min contact time) and quenched by dripping into a slowly stirred degassed water/toluene (50 mL:50 mL) mixture at 0 °C. The quenched reaction mixture was extracted with toluene (3 × 20 mL), and the combined toluene extracts were washed with water (2 × 20 mL) and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded the crude product, which was purified by passing through a short silica gel column (EtOAc/methylene chloride, 1:20) to yield a colorless solid (0.086 g, 0.010 mmol, 67%): R_f 0.2 (silica gel, Skelly B/EtOAc, 1:1); $[\alpha]^{23}_D$ 90.0 (c 5.80, $CHCl_3$); IR ($CHCl_3$) 2980, 2930, 1605, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (m, 4 H), 7.26 (m, 2 H), 7.56 (m, 4 H), 7.29 (d, 4 H, J = 8.46 Hz), 7.00 (d, 4 H, J = 8.46 Hz), 4.62 (d of d, 2 H, J = 5.21 Hz, J' = 6.60 Hz), 4.52 (d of d, 2 H, J = 6.64 Hz, J' = 3.40 Hz), 4.46 (d, 2 H, J = 14.3 Hz), 4.28 (d, 2 H, J = 5.21 Hz), 4.15

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(d, 2 H, J = 14.3 Hz), 3.90 (m, 2 H), 3.51 (d of d, 2 H, J = 14.72 + 4.95 Hz), 2.97 (d of d, 2 H, J = 8.43 Hz, J' = 14.68 Hz), 1.47 (s, 6 H), 1.32 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.4, 139.1, 132.8, 130.4, 129.2, 127.3, 118.4, 119.0, 115.5, 83.0, 82.0, 80.9, 74.3, 72.5, 71.7, 53.4, 48.9, 26.4, 25.5; MS (CI), m/e 875 (MH^+).

(3a*R*,4*R*,20*R*,20a*R*,23a*S*,24*R*,29*R*,29a*S*)-25,26,27,28-Tetradehydro-3a,4,5,6,7,17,18,19,20,20a,23a,24,29,29a-tetradecahydro-2,2,22,22-tetramethyl-4,29:20,24-diepoxy-8,11:13,16-diethenobis[1,3]dioxolo[4,5-*j*:4′,5′-*r*][1,7,22]oxadiazacycloheptacosine (14). To a solution of trifluoroacetamide **13a** (0.0712 g, 0.0915 mmol) in absolute ethanol (20 mL) was added sodium borohydride (0.0138 g, 0.366 mmol). The solution was stirred for 2.5 h, 1 mL of acetone was added, and stirring was continued for another 0.5 h. Ethanol was removed under reduced pressure, the residue was partitioned between water/methylene chloride (5 mL:5 mL), and the aqueous layer was extracted with methylene chloride (2 × 5 mL). The combined organic extracts were washed with brine (5 mL) and dried over potassium carbonate. Filtration and removal of volatile components under reduced pressure afforded a colorless oil (0.0461 g, 0.079 mmol, 86%): R_f 0.3 (silica gel, methylene chloride/MeOH, 10:1); $[\alpha]^{23}_D$ 132.4 (c 4.60, $CHCl_3$); IR ($CHCl_3$) 3320, 1670, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 4 H, J = 9.0 Hz), 6.99 (d, 4 H, J = 9.00 Hz), 8.48 (d of d, 2 H, J = 5.40 + 6.48 Hz), 8.20 (d, 2 H, J = 5.40 Hz), 8.17 (d of d, 2 H, J = 6.48 + 3.50 Hz), 7.87 (m, 2 H), 7.72 (d, 2 H, J = 13.86 Hz), 7.51 (d, 2 H, J = 13.86 Hz), 6.75 (d of d, 2 H, J = 4.68 + 12.75 Hz), 6.47 (d of d, 2 H, J = 9.36 + 12.75 Hz), 2.05 (br s, 2 H), 1.52 (s, 6 H), 1.32 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 157.2, 135.5, 131.9, 119.2, 116.4, 84.3, 83.1, 82.3, 75.4, 73.3, 72.3, 53.4, 48.9, 27.5, 26.5; MS (CI), m/e 587 (MH^+).

Bis[4-(phthalimidomethyl)phenyl] Ether (16). To a solution of phthalimide (5.91 g, 0.0402 mol) and chloride **9** (5.00 g, 0.0196 mol) in anhydrous DMF (50.0 mL) was added potassium carbonate (13.52 g, 0.098 mol), and the suspension was stirred vigorously at room temperature. Water (200 mL) was added after 18 h, and the precipitated product was filtered. The solid was then dissolved in dichloromethane (200 mL), washed with 1 N sodium hydroxide (2 × 50 mL), and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded a colorless solid (17.65 g, 0.037 mol, 92%): mp 254–258 °C; R_f 0.8 (silica gel, CH_2Cl_2/EtOAc, 10:1); IR ($CHCl_3$) 3010, 1770, 1710, 1608, 1305 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.75 (s, 4 H), 6.90 (d, 4 H), 7.37 (d, 4 H), 7.75 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 167.78, 156.66, 133.77, 132.12, 131.31, 130.11, 123.17, 118.86, 40.91. Anal. Calcd for $C_{30}H_{20}N_2O_5$: C, 71.42; H, 4.00; N, 5.55. Found: C, 71.25; H, 4.22; N, 5.32.

Bis[4-(aminomethyl)phenyl] Ether (17). Hydrazine (11.0 mL, 0.190 mol) was added to a suspension of phthalamide **16** (17.649 g, 0.037 mol) in MeOH/THF (1:1, 500 mL) heated at reflux. After 12 h, the suspension was cooled, and filtered, and the solid was washed with methanol (3 × 50 mL). The filtrate was concentrated under reduced pressure, and the resulting solid was partitioned between dichloromethane (500 mL) and 1 N sodium hydroxide (100 mL). The organic layer was extracted with 1 N sodium hydroxide (3 × 30 mL), washed with water (2 × 100 mL), and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded a colorless pasty solid (8.1 g 0.035 mol, 96%): R_f 0.50 (silica gel, $CHCl_3$/MeOH/15% NH_4OH, 1:11:0.1); IR ($CHCl_3$) 3382, 2950, 2870, 1605, 1500, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (br s, 4 H), 3.74 (s, 4 H), 6.93 (d, 4 H, J = 10.0 Hz), 7.25 (d, 4 H, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$) δ 155.46, 137.64, 127.72, 118.06, 45.14; exact mass calcd for $C_{14}H_{16}N_2O$ 228.12626, found 228.12545.

Bis(4-benzenesulfonamidomethyl) Ether (18). A solution of benzenesulfonyl chloride (7.88 mL, 0.062 mol) in THF (40 mL) was added dropwise to a mechanically stirred solution of bisamine **17** (6.400 g, 0.028 mol) and triethylamine (10.85 mL, 0.078 mol) in THF (100 mL). The reaction was stirred for 20 h and concentrated under reduced pressure. The resulting oil was dissolved in methylene chloride (200 mL), washed with 1 N sulfuric acid until the aqueous phase remained acidic to litmus, washed with water (100 mL), and dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded a crude product, which was crystallized from ethanol (ca. 200 mL) to yield cream-colored crystals (12.10 g, 0.024 mol, 85%): mp 137–138 °C; R_f 0.27 (silica gel, Skelly B/EtOAc, 1:1); IR ($CHCl_3$) 3265, 3240, 1320, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 4 H), 7.54 (m, 6 H), 7.15 (d, 4 H), 6.81 (d, 4 H), 5.1 (br s, 2 H), 4.10 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.54, 140.20, 132.39, 131.83, 129.18, 128.84, 126.86, 118.76, 46.48; exact mass calcd for $C_{26}H_{24}O_5N_2S_2$ 508.1126, found 508.1116.

3,6-Anhydro-7-bromo-1,7-dideoxy-4,5-*O*-isopropylidene-D-*altro*-hept-1-ynitol (19). Triphenylphosphine (1.359 g, 5.17 mmol) was added in small portions with stirring to a solution of alcohol **5** (0.50 g, 2.53 mmol) and *N*-bromosuccinimide (0.923 g, 5.17 mmol) in methylene chloride (10 mL) at 0 °C. Barium carbonate was added (ca. 1 g), and the suspension was heated at reflux for 20 min. The suspension was filtered (Celite), and the filtrate was washed with water (2 × 10 mL). Silica gel (ca. 1 g) was added to the filtrate, and the volatile components were removed under reduced pressure. The resulting dark powder was placed on top of a silica gel column, and the product was eluted (Skelly B/EtOAc, 3:1). Removal of volatile components from the eluate provided a clear oil (0.507 g, 1.94 mmol, 78%): R_f 0.6 (silica gel, EtOAc/Skelly B, 1:1); $[\alpha]^{23}_D$ 37.91 (c 13.00, $CHCl_3$); IR (neat) 3310, 2260, 3000–2860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.59 (s, 3 H), 2.68 (d, J = 3.0 Hz, 1 H), 3.42 (m, 2 H), 4.43 (m, 1 H), 4.85 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 114.0, 83.9, 83.0, 81.5, 77.6, 76.7, 72.2, 31.4, 26.3, 25.2; exact mass calcd for $C_9H_{10}O_3Br$ 246.97928, found 246.98009.

3,6-Anhydro-1,7-dideoxy-4,5-*O*-isopropylidene-D-*arabino*-hept-6-en-1-ynitol (20). Cesium carbonate (0.62 g, 1.91 mmol) was added to a vigorously stirred solution of sulfonamide **18** (0.487 g, 0.96 mmol) and bromide **19** (0.500 g, 1.91 mmol) in dimethylformamide (20 mL). After 24 h, additional bromide **19** (0.500 g, 1.91 mmol) and cesium carbonate (0.62 g, 1.91 mmol) were added. After a total of 30 h, 80% of the dimethylformamide was removed under reduced pressure, water was added (30 mL), and the resulting precipitate was filtered. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc, 10:1) to yield bisalkylated sulfonamide **10** (0.4921 g, 0.560 mmol, 59%), monoalkylated sulfonamide (0.128 g, 0.186 mmol, 20%) and olefin **20** (0.118 g, 0.66 mmol, 17%) as a solid: R_f 0.6 (silica gel, EtOAc/Skelly B, 1:1); $[\alpha]^{23}_D$ 30.32 (c 4.36, $CHCl_3$); IR (neat) 3300, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.55 (s, 3 H), 2.7 (d, 3 Hz, 1 H), 4.36 (m, 1 H), 4.60 (m, 1 H), 4.81 (m, 2 H), 5.08 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.08, 113.75, 87.314, 79.48, 79.06, 77.00, 76.61, 73.02, 26.47, 25.90; exact mass calcd for $C_{10}H_{12}O_3$ 180.07864, found 180.07890.

(3a*R*,4*R*,20*R*,20a*R*,23a*S*,24*R*,29*R*,29a*S*)-3a,4,5,6,7,17,18,19,20,20a,23a,24,25,26,27,28,29,29a-Octadecahydro-2,2,22,22-tetramethyl-6,18-bis(phenylsulfonyl)-4,29:20,24-diepoxy-8,11:13,16-diethenobis[1,3]dioxolo[4,5-*j*:4′,5′-*r*][1,7,22]oxadiazacycloheptacosine (21). Hydrogen gas was bubbled into a suspension of PtO_2 (0.051 g, 6.22 mmol) in THF (10 mL) for 15 min. To this suspension was added a solution of macrocyclic sulfonamide **13b** (0.226 g, 0.261 mmol) in THF (30 mL). The stirred suspension was evacuated under aspirator pressure, purged with hydrogen three times, and then exposed to a hydrogen atmosphere (790 mmHg) for 6 h until the reaction was complete (TLC). The suspension was filtered through Celite, and volatile components were removed under reduced pressure to yield a colorless solid (0.220 g, 0.252 mmol, 96%): R_f 0.42 (silica gel, EtOAc/Skelly B, 3:2); $[\alpha]^{23}_D$ 40.67 (c 1.25, $CHCl_3$); IR ($CHCl_3$) 3070–2860, 1602, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 4 H, J = 7.90 Hz), 7.53–7.43 (m, 6 H), 7.13 (d, 4 H, J = 8.13 Hz), 6.79 (d, 4 H, J = 8.49 Hz), 4.66 (d, 4 H, J = 14.21 Hz), 4.25 (d, 2 H, J = 5.90 Hz), 4.09–4.03 (m, 4 H), 3.99 (d, 4 H, J = 14.22 Hz), 3.16–3.11 (m, 4 H), 2.79 (d of d, 2 H, J = 15.1 + 9.4 Hz), 1.62 (m, 2 H), 1.48–1.05 (m, 6 H), 1.29 (s, 6 H), 1.15 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.93, 139.57, 132.66, 130.55, 129.20, 127.15, 118.7, 112.39, 83.33, 82.78, 80.24, 79.66, 51.82, 44.82, 28.53, 26.10, 25.86, 24.99; MS (CI), m/e 875 (MH^+); exact mass calcd for $C_{40}H_{49}N_2O_9S$ ($M^+ - SO_2C_6H_5$) 733.3158, found 733.3173.

(3a*R*,4*R*,20*R*,20a*R*,23a*S*,24*R*,29*R*,29a*S*)-3a,4,5,6,7,17,18,19,20,20a,23a,24,25,26,27,28,29,29a-Octadecahydro-2,2,22,22-tetramethyl-4,29:20,24-diepoxy-8,11:13,16-diethenobis[1,3]dioxolo[4,5-*j*:4′,5′-*r*][1,7,22]oxadiazacycloheptacosine (22). Preparation of 0.2 N Sodium Anthracene. Sodium (1.15 g, 0.050 mol) was stirred with a solution of anthracene (10.680 g, 0.060 mol) in THF (210 mL) until the solution became dark blue and all the sodium had been consumed (ca. 1 h).

Deprotection. To a solution of sulfonamide **21** (0.1294 g, 0.148 mmol) in 10 mL of THF at 0 °C was added dropwise a 0.2 M solution of sodium anthracene (3.70 mL, 7.40 mmol). The solution remained blue for 1 min. Water was added (5 mL), the solution was extracted with methylene chloride (3 × 20 mL), and the combined organic extracts were dried over magnesium sulfate. Filtration and removal of volatile components under reduced pressure afforded a crude product, which was purified by column chromatography to yield first anthracene (methylene chloride eluant) and then product **22** (methylene chloride/methanol eluant, 20:1, 0.05058 g, 0.085 mmol, 58%) as a clear oil: R_f 0.44 (silica gel, methylene chloride/methanol, 10:1); $[\alpha]^{23}_D$ −7.75 (*c* 0.004, $CHCl_3$); IR ($CHCl_3$) 3300, 2930, 2850, 1610, 1505, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (d, 4 H, *J* = 8.32 Hz), 6.91 (d, 4 H, *J* = 8.22 Hz), 4.46 (d of d, 2 H, *J* = 3.8 + 5.9 Hz), 4.59 (d, 2 H, *J* = 6.03 Hz), 4.23 (d of d, 2 H, *J* = 6.80 + 8.30 Hz), 4.11 (d, 2 H, *J* = 14.3 Hz), 3.62 (d, 2 H, *J* = 14.30 Hz), 3.29 (d, 2 H, *J* = 3.37 Hz), 2.37 (m, 4 H), 1.72 (m, 4 H), 1.47 (s, 6 H), 1.38 (m, 4 H), 1.29 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 156.70, 129.55, 118.81, 112.34, 83.95, 82.58, 81.28, 78.90, 52.10, 45.55, 28.53, 26.25, 25.68, 25.11; exact mass calcd for $C_{34}H_{46}N_2O_9$ 594.3305, found 594.3292.

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Structure of the Antibiotic OA-7653

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The structure of the glycopeptide antibiotic OA-7653 is assigned as **2**. Elucidation of the structure is based primarily on two-dimensional NMR experiments, analogies with other glycopeptide antibiotics of the vancomycin series, and selective degradation studies. Antibiotic OA-7653 contains a heptapeptide aglycon core in which the amino acids *N*,*N*-dimethylalanine and glutamine are encountered as the G and F components of this unit. Mild acid hydrolysis of the antibiotic effects the conversion of the δ-carboxamide of the glutamine residue to yield the carboxylic acid **3** in a reaction that is shown to proceed without rearrangement. This latter conversion to **3** proceeds without effecting cleavage of the β-glycosidic link between the aglycon and glucose. The ^1H spectra of OA-7653 and its derivatives in DMSO at pH 4.0 are shown to represent major and minor conformers that are exchanging at rates comparable to the NMR time scale.

Introduction

Glycopeptide antibiotics are a class of compounds that have received considerable attention recently. The interest, in part, stems from the dramatic increase in the use of vancomycin, the sole clinical representative of this class, for the treatment of methicillin-resistant staphylococcal infections. The isolation and characterization of new members of this series have led to the recognition of four subtypes based upon the nature of the amino acids G and F in structure **1**, which is representative of the heptapeptide core present in the aglycons of all members of this series. With the exception of vancomycin,[1] which is the sole member of its subgroup where G and F represent aliphatic amino acids, all remaining glycopeptide antibiotics whose structures have been described to date belong to the ristocetin (G, F = ArOAr),[2] avoparcin (G, F = ArAr),[3] or synmonicin (G = Ar, F = aliphatic)[4] subgroups. As part of an ongoing program in seeking to identify new members of the class as potential therapeutic agents, we report the results of the elucidation of the structure of the glycopeptide antibiotic OA-7653. The isolation and preliminary characterization of this antibiotic from a strain of *Streptomyces hygroscopicus* was first reported in 1983 by Japanese workers.[5,6] These workers found the compound to be moderately active against Gram-positive bacteria. It was presumed to be related to vancomycin on the basis of physical properties and provisional data summarized as follows. The compound was found to be soluble in aqueous base, sparingly soluble in aqueous acid, and completely insoluble in alcohols, ethyl acetate, and acetone. The isoelectric point was determined to be between 5 and 6 on the basis of paper electrophoresis. No reliable data with respect to molecular weight or elemental composition were provided. In the UV spectrum the compound gave λ_{max} (H_2O) = 278 nm (ε 1% 1 cm 56) and 0.1 N NaOH max = 298 nm (ε 1% 1 cm 100). The shift to longer wavelength in base is consistent with the presence of phenolic chromophores. Analysis of the amino acid composition and the sugar composition revealed that OA-7653 contained glutamic acid and the neutral sugar, glucose.

Experimental Section

NMR Spectroscopy. Proton spectra were obtained on a JEOL GX 500 spectrometer. All 2D NMR spectra were transferred to a VAX 11/780 via magnetic tape and processed with software developed by Hare.[7] T_1 data were determined by the inversion–recovery method using a composite population inversion pulse. The relaxation delay was set to 5 times the longest T_1 value. The T_1 parameters were obtained by nonlinear fitting of peak maxima using the standard software available on the JEOL. Details of the pulse sequences and phase cycling and other relevant details of the experimental parameters used in the various 2D NMR experiments were as described previously.[8,17] Samples for NMR experiments were dried by lyophilization and prolonged

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