a rubber septum and a stopcock. The system was reevacuated, isolated, and cooled to 0 °C. Then, 5.0 mL of 57% hydriodic acid (freshly distilled from red phosphorus) was carefully added portionwise. After degassing the system, the reaction mixture was refluxed for 3 h, and the resulting [^{14}C]methyl iodide was then isolated by vacuum transfer (twice) through a drying tower ($MgSO_4$ + KOH) in the usual manner.

A 25-mL round-bottom flask was charged with 656 mg (4 mmol) of sodium benzenesulfinate in 5 mL of dry dimethylformamide. The mixture was degassed twice, and the methyl iodide prepared above was vacuum transferred into this flask. The reaction flask was closed and allowed to stir for 4 days. The reaction mixture was then poured into 25 mL of water and extracted with 3 × 25 mL of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated, first at 70 mm and then under high vacuum, to give a brown solid, which was purified by flash chromatography[9] (230–400 mesh silica gel, 1 in. wide × 8 in. long column, 1 ethyl acetate/2 hexane) to give 328 mg (121.6 mCi) of [^{14}C]methyl phenyl sulfone (specific activity = 58.6 mCi/mmol).[10]

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(10) A typical procedure as follows: A flame-dried two-neck round-bottom flask equipped with a stirring bar and a rubber septum under nitrogen atmosphere was charged with 156 mg (1 mmol, specific activity = 6 mCi/mmol) of [^{14}C]methyl phenyl sulfone in 5 mL of dry THF. The reaction flask was cooled to 0 °C, and 0.80 mL (2.0 mmol) of *n*-butyllithium in hexane was added to yield a fine yellow precipitate of the dianion. After mixture was stirred for 10 min at 0 °C, 156 mg (1.1 mmol) of methyl cyclohexanecarboxylate (Aldrich) in 2 mL of dry THF was added in one portion. The reaction mixture was allowed to stir at 0 °C for 0.5 h and at room temperature for 0.5 h before 3 mL of 1 N hydrochloric acid was added. After the addition of 25 mL of brine, the aqueous residue was extracted with 3 × 50 mL of ether, and the combined organic extracts were washed with 25 mL of brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, concentrated, and dried under high vacuum to give 246 mg of the intermediate keto sulfones, which was carried forward without any purification. The crude keto sulfone (246 mg) was dissolved in 8 mL of dry methanol in a 25-mL round-bottom flask containing 565 mg of disodium hydrogen phosphate. Sodium amalgam (5%, 2.8 g) was added until TLC (25% ethyl acetate in hexane) indicated the disappearance of starting material (1 h). The reaction mixture was diluted with 50 mL of deionized water and extracted with 3 × 50 mL of ether. The combined organic extracts was washed with 25 mL of brine and dried over anhydrous magnesium sulfate to give 125 mg of crude ketone. The product was purified by column chromatography on 12 g of silica gel (70–230 mesh), eluting with 15% ethyl acetate in hexane to give, after removal of solvents from the appropriate fractions, 112 mg (88.9% overall yield from methyl phenyl sulfone, specific activity = 6 mCi/mmol) of the desired labeled ketone in 97% purity was determined by radiochromatographic scanner.

An Electrophile-Assisted Nonsolvent Synthesis of Alkyl Macroisocyclic Ethers: An Improved Nonsolvent Williamson Synthesis of Medium-Sized Alkyl Carbocyclic Ethers

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Received November 1, 1988

Carbon–oxygen single bond linkages are among some of the oldest and most widely used transformations in organic chemistry. The Williamson synthesis, discovered in 1850, is still one of the best methods for preparing a wide range of symmetrical and unsymmetrical ethers.[1-4] We have developed an efficient synthesis specifically for medium-sized carbocyclic ethers which utilizes alkyl halides as both the solvent and reaction electrophile. This new approach provides an excellent route to ethers that previously could not be obtained in good yield and purity.[5,6]

The well-known fragrance and surfactant potential of medium-sized carbocyclic ethers prompted us to seek a rapid, economical, high-yield synthesis for these materials.[1] We felt that an alkyl halide displacement by an alkoxide ion would provide the best route to these ethers.[1,7,8] We elected to avoid methods that required sulfate esters due to the powerful odor influence of trace amounts of sulfur-containing species.[9-11] Preparative methods such as alkyloxymercuration of alkenes or the reaction of alcohols with diazoalkanes were unattractive due to the potential presence of toxic trace contaminants and the increased reaction times required, resulting in only low yields of product.[12-18]

The five- and six-member carbocyclic alcohols have found wide use and interest in Organic chemistry. Many Williamson type ether syntheses, using these ring sizes, have been reported in the literature.[19-22] A nonsolvent ether synthesis for small ring systems was recently reported by Loupy et al.[23] In this work very reactive aromatic components were used for most of the reactions, and many of the reported products have alternatively been prepared in solvent systems with no apparent difficulties.[4,13-16,21,24] The small ring carbocyclic ethers were not of interest in our study, and many attempts to adapt literature preparations for use with the medium-sized carbocyclic ethers proceeded with only marginal success.[1,24-27] When the medium-sized carbocyclic alkoxides were reacted with primary branched or unbranched alkyl halides in solvents such as 1,2-dimethoxyethane (glyme), 2-methoxyethyl ether (diglyme), tetrahydrofuran, di-*n*-butyl ether, or toluene, elimination rather than substitution predomi-

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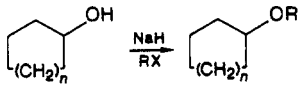
Table I. Alkyl Macroisocyclic Ethers Prepared by an Electrophile-Assisted Nonsolvent Williamson Synthesis



entry	n	R	X	distilled,[c] % yield	bp, °C/mm
1	7	benzyl	Cl	93	144–146/0.2
2	7	*n*-propyl	Br	91	68–70/0.05[a]
3	7	*n*-butyl	Br	91	84–85/0.05[b]
4	7	3-methylbutyl	Br	83	95–96/0.05
5	7	*n*-hexyl	Br	95	109–110/0.05
6	8	*n*-propyl	Br	70	82–84/0.05
7	7	*n*-propyl	I	94	68–70/0.05
8	7	n-butyl	I	96	84–85/0.05
9	7	3-methylbutyl	I	96	95–96/0.05
10	9	*n*-propyl	I	99	99–101/0.03
11	10	ethyl	I	95	105–106/0.05
12	10	*n*-propyl	I	96	114–115/0.09

[a] Literature ref 1, bp 124–7 °C (3 mm). [b] Literature ref 1 and 6, bp 127–9 °C (3 mm). [c] Satisfactory analytical data (±0.3% C, H, etc.) were obtained for all new compounds listed in the table.

nated. The best yield for entries 3 and 8 was only 29% when they were prepared in toluene.[1] These preparative difficulties are evidenced by the small number of good-yield medium-sized carbocyclic ether syntheses found in the chemical literature. Nearly complete conversion of the alcohol to the ether is important since the unreacted carbinol often co-distills with the desired product and makes the separation extremely difficult. In many cases tedious chromatographic techniques have been required to obtain uncontaminated product.[1,2,25-30]

The alkoxide is prepared and alkylated in suspension to give near quantitative conversion to the corresponding medium-sized alkyl carbocyclic ether. No special workup is required, and good to excellent yields were obtained after vacuum distillation. The product was generally greater than 99% one component by VPC, and spectra were consistent with the proposed structures.

Table I contains a summary of the reactants, distilled yields, and boiling points of the products.[1,29] These reactions were run on scales from 5 mmol to 1.7 mol.

Experimental Section

Materials and Methods. The glassware was oven-dried at 120 °C for 2 h, assembled hot, and cooled under a nitrogen or argon atmosphere. Starting materials (carbocyclic alcohols, alkyl halides, and sodium hydride) were obtained from Aldrich Chemical Co. Reaction flasks were equipped with internal thermometers, high efficiency reflux condensers, and in most cases mechanical stirrers. All reactions were carried out under an inert atmosphere.

NMR spectra were attained on a CFT-20 spectrometer. Deuterated chloroform was used as the solvent and tetramethylsilane as the internal standard. IR spectra were attained on a Beckman FTIR 1200 spectrometer. MS were recorded on a Finnigan 1050 spectrometer. Boiling points are uncorrected.

(Phenylmethoxy)cyclododecane (Entry 1). Sodium hydride (34.0 g of 60% dispersed in mineral oil, 0.85 mol) was twice washed with hexane under an argon atmosphere. The hexane was carefully decanted off, and the hydride was dried by passing argon over its surface while stirring. Next, the hydride was mixed, under an argon atmosphere and by mechanical stirring, with cyclododecanol (130.0 g, 0.71 mol) and benzyl chloride (650.0 g, 5.14 mol). The reaction mixture was heated to 125 °C. The mixture became very viscous when the temperature reached between 60 and 70 °C. A mild exotherm was observed at about 100 °C, which resulted in a marked viscosity decrease. (*Caution*: if an efficient reflux condenser is not used, some external cooling may be necessary during the mild exotherm.) The internal flask temperature increased to about 120 °C over 10 min. The reaction flask was heated at 120–125 °C for an additional hour and then it was cooled to 25 °C. The excess hydride was carefully destroyed by the addition of 100 mL of 95% ethanol under an argon atmosphere. The mixture was treated with 500 mL of aqueous saturated sodium chloride solution and extracted with three 400-mL portions of hexane. The organic layer was collected, washed with two 100-mL portions of water and two 100-mL portions of aqueous saturated sodium chloride solution. The product mixture was dried over magnesium sulfate, filtered, and concentrated at 50 °C and 15 mm. The product was distilled at 144–146 °C (0.2 mm) to give (185.7 g) 93.0% of theory, which was 99% one component by VPC: IR (neat, cm^{-1}) 2930, 2865, 1475, 1455, 1095 (C–O–C), 1070, 740; ^{13}C NMR (ppm, $CDCl_3$) 139.31, 128.17, 127.54, 127.21, 76.26 (α-ring carbon), 70.22 (α-chain carbon), 28.91, 24.75, 24.31, 23.30, 23.19, 20.81; MS *m/z* (relative intensity) 274 (M^+, 1.5), 245 (0.1), 230 (0.4), 183 (8.2), 174 (0.9), 160 (1.0), 145 (0.8), 133 (2.3), 118 (2.7), 104 (10.4), 91 (100), 81 (3.2), 65 (12.7), 56 (2.1). Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.33; H, 11.18.

***n*-Propoxycyclododecane (Entry 2).** Cyclododecanol (2.6 g, 11.14 mmol), 1-bromopropane (2.11 g, 171.73 mmol), and sodium hydride (1.13 g of 60% in mineral oil, 28.24 mmol) were reacted for 6 h and (2.9 g) 91.2% of product was isolated as above. VPC 99% one component; bp 68-70 °C at 0.05 mm.

(Entry 7). Cyclododecanol (2.6 g, 11.14 mmol), 1-iodopropane (1.74 g, 140.0 mmol), and sodium hydride (750.0 mg of 60% in mineral oil; 18.75 mmol) were strongly refluxed for 3 h. A 3.0-g sample (94.0%) was isolated as in entry 1. VPC indicated 99% one component bp 69–71 °C (0.09 mm); IR (neat, cm^{-1}) 2955, 2882, 1485, 1460, 1350, 1105 (C–O–C); ^{13}C NMR (ppm, $CDCl_3$) 77.02 (α-ring carbon), 70.32 (α-chain carbon), 29.18, 24.94, 24.49, 23.39, 20.98, 10.82. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.55; H, 13.42.

***n*-Butoxycyclododecane (Entry 3).** Cyclododecanol (184.3 g, 1.00 mol), sodium hydride (65.0 g of 60% NaH in mineral oil, 1.63 mol), and 1-bromobutane (500.0 g, 3.65 mol) were refluxed for 4 h. A 221.3-g sample (92.1%) was isolated as in entry 1. VPC indicated 99% one component, bp 83–84 °C (0.08 mm).

(Entry 8). Cyclododecanol (184.3 g, 1.00 mol), sodium hydride (50.0 g of 60% NaH in mineral oil, 1.25 mol), and 1-iodobutane (500.0 g, 2.72 mol) were reacted as in entry 1. A 230.7-g sample (96.0%) was isolated. VPC indicated 99% one component: bp 84–85 °C (0.05 mm); IR (neat, cm^{-1}) 2960, 2880, 1470, 1450, 1340 (C–O–C), 1105, 720; ^{13}C NMR (ppm, $CDCl_3$) 76.95 (α-ring carbon), 68.28 (α-chain carbon), 32.48, 29.08, 24.82, 24.36, 23.26, 20.87, 19.55, 13.97; MS *m/z* (relative intensity) 240 (M^+, 3), 197 (2), 166 (9), 141 (2), 138 (4), 137 (2), 127 (3), 124 (5), 123 (5), 113 (16), 97 (11), 96 (26), 95 (18), 82 (50), 81 (25), 68 (25), 67 (32), 57 (70), 55 (47), 43 (26), 41 (100), 39 (20). Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 80.06; H, 13.44.

3-Methylbutoxycyclododecane (Entry 4). Cyclododecanol (200.0 g, 1.09 mol), sodium hydride (72.0 g of 60% in mineral oil, 1.8 mol), and 1-bromo-3-methylbutane (500.0 g, 3.31 mol) were reacted for 2 h according to entry 1. A 228.3-g sample (82.7%) of theory was collected. VPC indicated 98% one component, bp 128–130 °C (0.05 mm).

(Entry 9). Cyclododecanol (25.0 g, 0.14 mol), 1-iodo-3-methylbutane (125.0 g, 0.63 mol), and sodium hydride (21.5 g of 60% in mineral oil, 0.54 mol) were refluxed for 2 h. A 34.2-g sample (96%) was isolated as in entry 1. VPC indicated 99% one component: bp 97–98 °C (0.08 mm); IR (neat, cm^{-1}) 2925, 2860, 1465, 1440, 1350, 1090 (C–O–C), 1010; ^{13}C NMR (ppm, $CDCl_3$) 76.98 (α-ring carbon), 66.83 (α-chain carbon), 39.18, 29.05, 25.12, 22.70, 20.87, 24.77, 23.29, 24.34; MS *m/z* (relative intensity) 254 (M^+, 1.5), 239 (0.01), 211 (0.04), 197 (0.06), 183 (1.3), 138 (1.5), 127 (3.8), 124 (2.1), 110 (3.4), 96 (10.3), 82 (20.5), 68 (6.7), 43 (100.0), 41 (55.4). Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.11; H, 13.51.

(*n*-Hexyloxy)cyclododecane (Entry 5). Cyclododecanol (20.0 g, 0.11 mol), 1-bromohexane (120.0 g, 0.17 mol), and sodium hydride (5.6 g of 60% in mineral oil, 0.14 mol) were refluxed for

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2 h. The product 96% (28.4 g) of theory, was isolated as in entry 1. VPC indicated 99% one component: bp 109–111 °C (0.03 mm); IR (neat, cm^{-1}) 2838, 2868, 1470, 1452, 1354, 1100 (C–O–C); ^{13}C NMR (ppm, $CDCl_3$) 76.90 (α-ring carbon), 68.64 (α-chain carbon), 31.81, 30.31, 29.06, 26.00, 24.78, 24.31, 23.29, 22.71, 20.78, 14.10; MS m/z (relative intensity) 268 (M^+, 1.1), 225 (0.03), 211 (0.2), 197 (1.0), 183 (0.4), 138 (2.4), 124 (3.6), 111 (4.5), 110 (6.4), 97 (2.0), 96 (19.9), 83 (15.4), 82 (46.5), 69 (16.1), 68 (17.1), 55 (34.2), 54 (6.2), 43 (100.0), 41 (40.3), 39 (14.8). Anal. Calcd for $C_{18}H_{36}O$: C, 80.53; H, 13.52. Found: C, 80.77; H, 13.33.

***n*-Propoxycyclotridecane (Entry 6).** Cyclotridecanol (900.0 mg, 4.54 mmol), sodium hydride (320.0 mg of 50% in mineral oil, 6.67 mmol), and 1-bromopropane were strongly refluxed for 3 h. A 770.0-mg sample (71%) was isolated as in entry 1. VPC indicated 98% one component: bp 82–84 °C (0.05 mm); IR (neat, cm^{-1}) 2930, 2850, 1460, 1350, 1100 (C–O–C), 1025. Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 79.90; H, 13.43.

***n*-Propoxycyclotetradecane (Entry 10).** Cyclododecanol (89 g, 0.42 mol), sodium hydride (55.0 g of 60% in mineral oil, 1.38 mol), and 1-iodopropane (340.0 g, 2.0 mol) were refluxed for 4 h. A 105.8-g sample (99%) was isolated as in entry 1. VPC indicated 99% one component: bp 99–101 °C (0.03 mm); IR (neat, cm^{-1}) 2930, 2860, 1460, 1380, 1360, 1350, 1105 (C–O–C), 1020. Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.42; H, 13.33.

Ethoxycyclopentadecane (Entry 11). Cyclododecane (3.8 g, 16.79 mmol), sodium hydride (3.8 g of 60% in mineral oil, 94.98 mmol), and iodoethane were refluxed for 18 h. A 4.1-g sample (95%) was collected as in entry 1. VPC indicated 99% one component: bp 105–106 °C (0.05 mm); IR (neat, cm^{-1}) 2930, 2850, 1460, 1350, 1100 (C–O–C), 1025. Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.31; H, 13.44.

***n*-Propoxycyclopentadecane (Entry 12).** Cyclopentadecanol (25.0 g, 0.11 mol), sodium hydride (22.5 g of 60% in mineral oil, 0.56 mol), and 1-iodopropane (186.9 g, 1.10 mol) were reacted at reflux for 4 h. A 28.3-g sample (96%) was isolated as in entry 1. VPC indicated 99% one component: bp 114–115 °C (0.09 mm); IR (neat, cm^{-1}) 2925, 2850, 1460, 1362, 1092 (C–O–C), 1030; ^{13}C NMR (ppm, $CDCl_3$) 78.62 (α-ring carbon), 70.30 (α-chain carbon), 32.17, 31.19, 29.75, 28.91, 28.54, 28.35, 27.45, 26.94, 26.75, 23.37; MS m/z (relative intensity) 268 (M^+, 4.5), 239 (0.3), 225 (1.0), 211 (0.6), 197 (0.5), 183 (0.4), 138 (3.1), 124 (5.5), 111 (4.0), 110 (7.4), 97 (13.6), 96 (26.8), 83 (19.5), 82 (86.0), 69 (20.4), 68 (20.1), 55 (100.0), 54 (9.4), 43 (94.3), 41 (93.4). Anal. Calcd for $C_{18}H_{36}O$: C, 80.52; H, 13.52. Found: C, 80.70; H, 13.50.

Acknowledgment. We greatly acknowledge analytical support of this work by R. W. Slaven and J. M. Johnson of the Lorillard Research Center.

Total Synthesis of Purpurosamine B from D-Alanine

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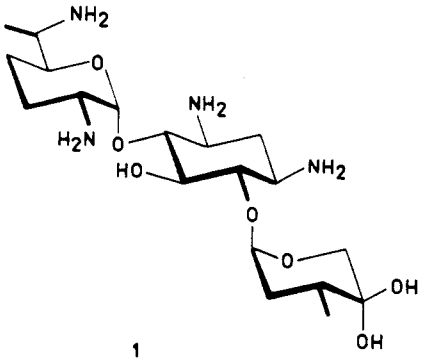
Received December 11, 1988

Purpurosamine B (**2**) is one of the two sugar components of the aminoglycosidic antibiotic gentamycin C_2 (**1**).[2]

The N-protected derivatives of purpurosamine B have been prepared in both racemic[3] and optically active[4,5] forms. The latter syntheses were based on multistep



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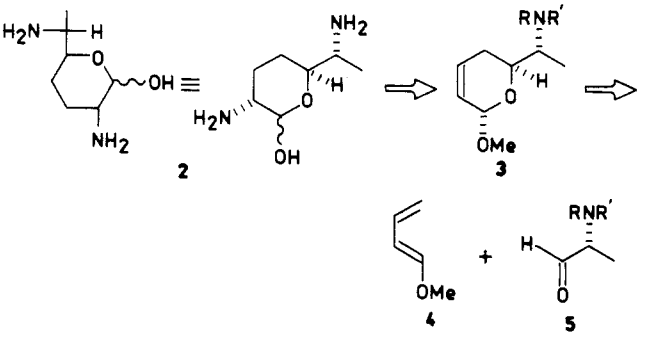
transformations of naturally occurring sugars. The key step, in our approach, is the high-pressure Diels–Alder reaction of 1-methoxybuta-1,3-diene (**4**) with the N-protected α-amino aldehyde **5**.[6]



2 **3**

4 **5**

It is obviously most important in this strategy that the major product obtained in the cycloaddition step has the correct configuration.[7] We have selected *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-D-alaninal (**5a**) as an efficient heterodienophile on the basis of our recent results.[7,8]

The Eu(fod)$_3$-mediated[9] high-pressure reaction of **4** with **5a** was carried out in the presence of 2% catalyst in ethyl ether at 15 kbar and 50 °C to afford, after acidic isomerization, a mixture of diasteroisomers **3a** and **3b** in a 16:1 ratio (80% yield).

A mixture of adducts **3a** and **3b** was subjected to hydroboration with thexylborane.[10] After oxidative workup, we obtained alcohol **6** as a major product, which was debenzylated with sodium in liquid ammonia[11] to produce alcohol **7** in a 70% overall yield after chromatographic separation. Functionalization of alcohol **7** was carried out as in our total syntheses of purpurosamine C,[10] and 6-epi B,[12] to afford methyl 2,6-di-*N*-acetyl-α-D-purpurosaminide B (**8**) in a 6% overall yield based on D-alanine (Scheme I).

This total synthesis is a practical alternative to known procedures based on monosaccharides as starting materials.[4,5] Moreover, it exemplifies the usefulness of N-protected α-amino aldehydes in the synthesis of natural products.

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