Reaction of 1 with Diiron Nonacarbonyl in Butyl Ether. A solution of 1 (1.0 g, 8.05 mmol) in 50 mL of *n*-butyl ether was heated to reflux in the presence of 6.0 g (16.48 mmol) of diiron nonacarbonyl for 48 h under nitrogen. The workup, as previously described, gave 691 mg (5.48 mmol, 68%) of 2-(hydroxymethyl)norbornane (**3**) possessing an endo isomeric purity of 85%.

Reaction of Cyclopentadiene and Acrolein in the Presence of Carbon Tetrachloride. A solution of freshly prepared[20] cyclopentadiene (26 g, 394 mmol) in 50 mL of CCl_4 was added dropwise to a stirred solution of acrolein (22 g, 393 mmol) in 50 mL of CCl_4 at 0 °C under a nitrogen atmosphere. The contents were stirred overnight, the solvent was removed at reduced pressure, and the residue was distilled (42–43 °C/7 mmHg), giving 37 g (152 mmol, 77%) of an oil that quickly solidified upon cooling. Recrystallization from acetone gave 32 g of pure product (mp 168–171 °C), identified as a dioxetane, **13**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.62–1.52 (m, 6 H), 1.55–2.05 (m, 2 H), 2.15–2.58 (m, 2 H), 2.67–3.11 (m, 4 H), 3.88–3.99 (2 H [two isomeric doublets: 3.88–3.97, J = 2.7 Hz, minor isomer; 3.90–3.99, J = 2.7 Hz, major isomer]), 5.69–6.18 (m, 4 H); IR (CH_2Cl_2) 3060 (w), 2965 (m), 2890 (m), 1360 (m), 1339 (m), 1207 (m), 1100 (s), 1058 (m) cm^{-1}; mass spectrum, calcd mass for $C_{16}H_{20}O_2$ 244.1463, found 244.1460; other fragments at m/e 151, 122, and 93. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65, H, 8.25. Found: C, 78.76; H, 8.29.

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Registry No. *endo*-**1**, 3574-54-7; *exo*-**1**, 3574-55-8; **2**, 119337-06-3; *endo*-**3**, 13137-31-0; *exo*-**3**, 13118-79-1; **4**, 19923-87-6; **5**, 119337-07-4; *endo*-**6**, 19926-90-0; *exo*-**6**, 19926-88-6; **7**, 1218-65-1; *endo*-**8**, 15507-06-9; *exo*-**8**, 13360-81-1; **9**, 12154-95-9; **10**, 77-73-6; **13**, 119337-08-5; diiron nonacarbonyl, 15321-51-4; cyclopentadiene, 542-92-7; acrolein, 107-02-8.

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Facile Stereospecific Synthesis of Deoxyfucosyl Disaccharide Units of Anthracyclines

Joachim Thiem* and Werner Klaffke

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Orléansring 23, D-4400 Münster, Federal Republic of Germany

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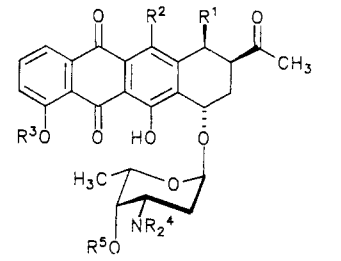
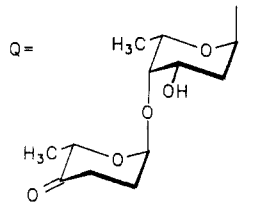
One of the main problems in the clinical application of anthracyclines like, e.g., daunorubicin (**1**) is associated with the considerable cytotoxicity which does affect neoplastic tissue but also causes severe side effects in membranes and the myocardium.[1] An enhanced therapeutic index may be achieved by the use of anthracyclines with oligosaccharide side chains, e.g., aclacinomycin A (**2**).[2] In a number of cases this led to decreased IC_{50} values for the general cytotoxicity. Furthermore, compounds of this type showed an enhanced differentiation inducing activity[3] which can be correlated with a shift of the biological effect from DNA to RNA synthesis inhibition.

Scheme I



#	R^1	R^2	R^3	R^4	R^5
1	H	OH	CH_3	H	H
2	$COOCH_3$	H	H	CH_3	Q



A survey of the data presently available supports the assumption that typical saccharide structures are required for the construction of such oligosaccharide side chains. This relates to monosaccharide configuration and substitution pattern, as well as their arrangement, and their interglycosidic linkages. Recently, some approaches to trisaccharide syntheses of anthracycline side chains have been described,[4-6] the primary drawback of which was the glycosylation step of the most unreactive axially configurated 4-hydroxy group in either of the deoxyfucose units; e.g., the Koenigs–Knorr glycosylation could be accomplished in only 40% yield.[4,5] The previously introduced *N*-iodosuccinimide glycosylation technique[7] was applied as an alternative approach. Although this procedure was successful in a variety of cases in which α-linkages have been required,[8,9] it failed in this particular case for reasons not fully understood at present. Thus, a deviation was recommended via the D-configurated precursor with an equatorial hydroxy group.[6,8,9]

The electrophilicites of both the oxocarbenium ion and the iodonium ion, the former being the intermediate in the Koenigs–Knorr or a similar type glycosylation, the latter being the one in the *N*-iodosuccinimide-mediated glycosylation, respectively, are only slightly influenced by configuration and substitution pattern. Furthermore, the reactivity in the former case may be somewhat dependent on the anomeric leaving group, a feature that does not apply to the *N*-iodosuccinimide glycosylation. Thus, an enhancement of the nucleophilicity of the donor is required for further approaches. There are reports that give evidence for increased nucleophilicites of organotin substituted oxygen derivatives,[10] and experiments along similar lines were successful in classical glycosylations.[11]

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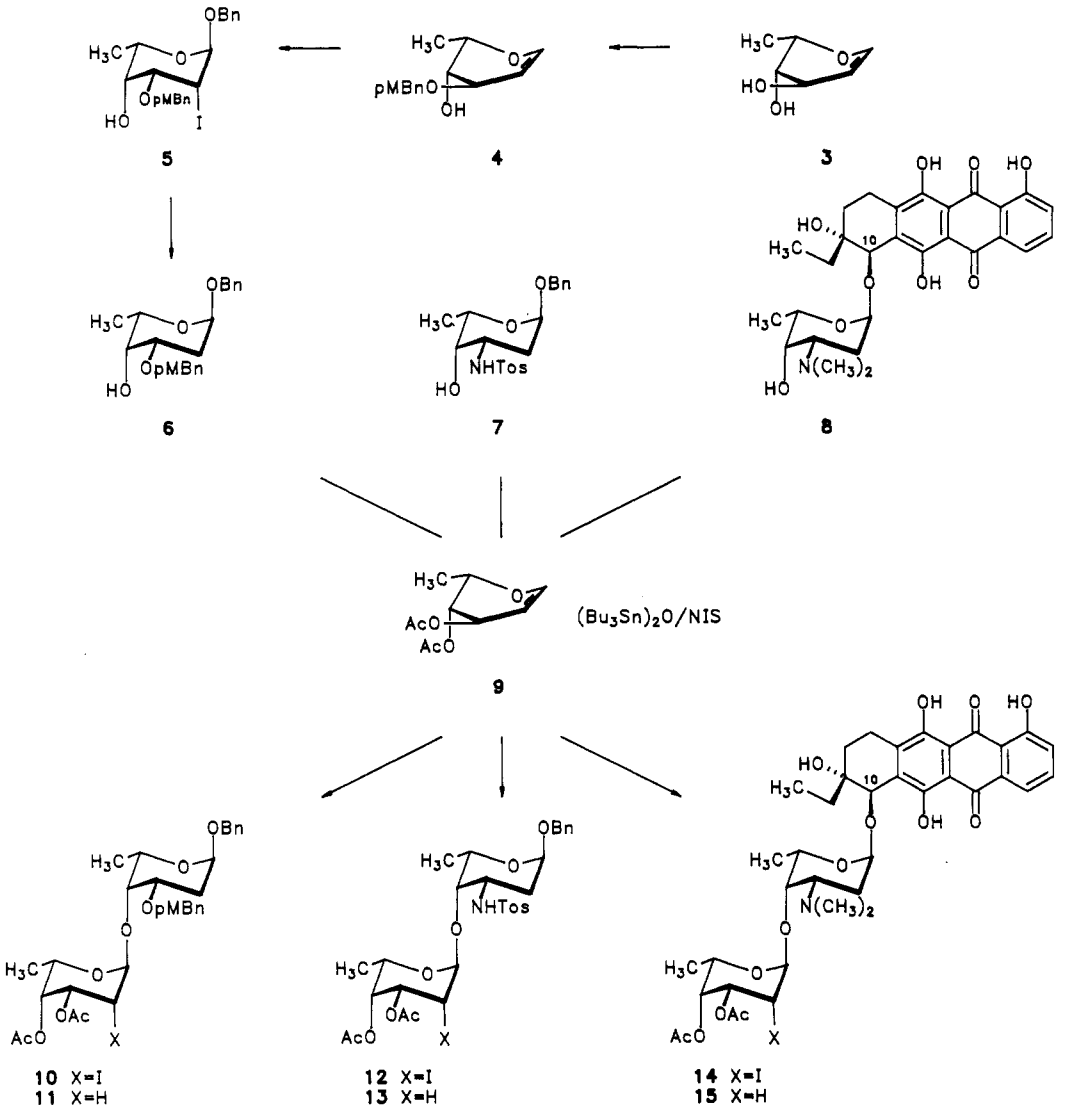
Scheme II



Results

We now report on our results using tributyltin oxide derivatives of various aglyconic sugar units (6–8) as nucleophilic donors in *N*-iodosuccinimide glycosylations of L-fucal diacetate (9).[12] Compound 7 was prepared in several steps, by either Horton's or Dyong's[13] procedures and 8 using the method described by Hermentin et al.[14] The fucoside 6 was obtained from L-fucal (3),[12] following the regiospecific alkylation via its stannylidene derivative with 4-methoxybenzyl chloride to give 4 in 75% yield. This in turn was subjected to a conventional *N*-iodosuccinimide glycosylation to yield 5 (67%), and after subsequent radical reduction, 6 was obtained in 89% yield.

In all cases, the tin oxide intermediates were obtained directly from the hydroxy components 6–8 under reflux in benzene. After workup, they were reacted in situ with *N*-iodosuccinimide and the glycal 9 in acetonitrile at room temperature in the dark. By conventional workup, the 2′-deoxy-2′-iodo disaccharides 10, 12, and 14 were obtained in yields up to 80% and characterized. The reduction step was performed most conveniently by applying the tributyltin hydride radical procedure in yields around 80% followed by extensive characterizations of the products 11, 13, and 15.

Obviously, with respect to the glycosylation of deoxyfucosyl derivatives in the construction of anthracycline oligosaccharides, this approach represents a considerable improvement. We are presently engaged in experiments to prove the enhanced nucleophilicity of trialkyltin oxide sugar derivatives and thus widen the scope of this methodology.

Experimental Section

1,5-Anhydro-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-L-*lyxo*-hex-1-enitol (4). L-Fucal[12] (1.04 g, 8 mmol) is refluxed for 1 day over 3-Å molecular sieves with dibutyltin oxide (3 g, 10.0 mmol) in 150 mL of anhydrous benzene. The mixture is concentrated to 50 mL, 4-methoxybenzyl chloride (1.2 mL, 9.0 mmol) and tetrabutylammonium bromide (2.38 g, 7.4 mmol) are added, and the mixture is refluxed for another 24 h. The mixture is diluted with 50 mL of dichloromethane, thoroughly washed with water, and dried over $MgSO_4$. The solvent is removed under reduced pressure, and the brown syrupy product is purified by flash column chromatography (silica gel 60, 40 μm, Merck; ethyl acetate–*n*-hexane, 2:3) to give a yellow oil: yield 1.5 g (75%); $[\alpha]^{20}_D$ −34.6° (*c* 1.18, C_6D_6); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 and 6.80 (m, 4 H, C_6H_5), 6.30 (dd, H-1, $J_{1,2}$ = 6.2, $J_{1,2}$ = 1.7 Hz), 4.60 (ddd, H-2, $J_{2,3}$ = 1.8, $J_{2,4}$ = 1.8 Hz), 4.35 and 4.25 (each 1 H, $C_6H_5CH_2$, J_{AB} = 11.4 Hz), 3.90 (ddd, H-3, $J_{1,3}$ = 1.7, $J_{2,3}$ = 1.8 Hz), 3.55 (mc, 2 H, H-4 and H-5, $J_{2,4}$ = 1.8, $J_{5,6}$ = 6.6, $J_{4,OH}$ = 3.5 Hz), 3.30 (s, 3 H, OCH_3), 2.50 (d, 4-OH), 1.40 (d, 3 H, H-6, $J_{5,6}$ = 6.6 Hz); MS,

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m/z (relative intensity) 250 (M^+, 57), 232 (0.5), 193 (2.5), 138 (30), 121 (100), 77 (46). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.19; H, 7.25. Found: C, 67.05; H, 7.10.

Benzyl 3-*O*-(4-Methoxybenzyl)-2,6-dideoxy-2-iodo-α-L-talopyranoside (5). To a solution of **4** (400 mg, 1.6 mmol) in 1 mL of anhydrous acetonitrile are added anhydrous benzyl alcohol (1 mL), *N*-iodosuccinimide (540 mg, 2.4 mmol), and 200 mg of powdered molecular sieves (3 Å). The crude mixture is diluted with 50 mL of dichloromethane after 12 h under argon atmosphere and light cover at room temperature. The mixture is filtered and the solution washed with 10% aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated in vacuo, to give **5** after silica gel chromatography (ethyl acetate–petroleum ether, 1:3): yield 520 mg (67%); yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 and 6.80 (m, 9 H, C_6H_5), 5.40 (s, br, H-1, $J_{1,2} < 1.0$ Hz), 4.70–4.40 (m $\approx$ 4 d, 4 H, $C_6H_5CH_2$, J_{AB} = 11.6 and 12.0 Hz), 4.30 (d, br, H-2, $J_{1,2} < 1.0$, $J_{2,3}$ = 4.4 Hz), 4.00 (q $\approx$ dq, H-5, $J_{4,5} \approx 1.3$, $J_{5,6}$ = 6.6 Hz), 3.90 (d, br, H-4, $J_{3,4}$ = 3.8, $J_{4,5} \approx 1.3$ Hz), 3.75 (s, 3 H, OCH_3), 1.70 (s, br, 4-OH), 1.30 (d, 3 H, H-6, $J_{5,6}$ = 6.6 Hz). Anal. Calcd for $C_{21}H_{25}IO_5$: C, 52.08; H, 5.20. Found: C, 52.40; H, 5.30.

Benzyl 3-*O*-(4-Methoxybenzyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (6). The reduction is carried out on **5** (500 mg, 1.03 mmol), following the general reduction procedure described for the disaccharides: yield 330 mg (89%); $[\alpha]^{20}_D$ −40.0° (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.00 and 6.80 (m, and m $\approx$ dd, 9 H, C_6H_5), 4.95 and 4.55 (each d, each 1 H, $C_6H_5CH_2$), 4.25 (m, 5 H, H-1 and $C_6H_5CH_2$), 3.40 (d, br $\approx$ dd, H-4, $J_{3,4}$ = 3.1, $J_{4,5} < 1.0$ Hz), 3.30 (s, 3 H, OCH_3), 3.10 (ddd, H-3, $J_{2e,3}$ = 5.0, $J_{2a,3}$ = 9.6, $J_{3,4}$ = 3.1 Hz), 2.95 (q $\approx$ dq, H-5, $J_{4,5} < 1.0$, $J_{5,6}$ = 6.2 Hz), 2.20 (d, 4-OH), 2.10 (ddd, H-2a, $J_{1,2a}$ = 2.1, $J_{2a,2e}$ = 12.2, $J_{2a,3}$ = 9.6 Hz), 1.95 (ddd, H-2e, $J_{1,2e}$ = 1.0, $J_{2a,2e}$ = 12.2, $J_{2e,3}$ = 5.0 Hz), 1.40 (d, 3 H, H-6, $J_{5,6}$ = 6.2 Hz). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.22; H, 7.30. Found: C, 68.91; H, 7.30.

(a) *N*-Iodosuccinimide Glycosylation of Diacetyl-L-fucal (9) with (Tributylstannyl)oxy Aglycons and (b) Reduction to Deoxyoligosaccharides of Cytostatics. (a) Typical Glycosylation Procedures. To the glycosyl donor (0.1 mmol of **6**, **7**, and **8**, respectively) dissolved in anhydrous benzene (5 mL) under an Ar atmosphere are added bis(tri-*n*-butyltin) oxide (0.05 mmol) and powdered 3-Å molecular sieves (1 g), and the solution is refluxed for 90–150 min. After filtration and evaporation, the oily residue is dried shortly in vacuo, dissolved in anhydrous acetonitrile (2 mL), mixed with L-fucal diacetate (**9**) (0.12 mmol, 25.7 mg) and *N*-iodosuccinimide (0.12 mmol, 27 mg) under an argon atmosphere at room temperature, and kept in the dark. After 3 days, the crude mixture is taken up in dichloromethane (10 mL), washed with 10% aqueous $Na_2S_2O_3$ solution (10 mL), dried ($MgSO_4$), filtered, and evaporated to a yellow syrup. Following flash chromatography on silica gel 60 (40 μM, Merck) with toluene–ethyl acetate, 2:1, colorless syrupy products are obtained.

(b) Typical Reduction Procedure. The disaccharide (0.1 mmol) is dissolved in anhydrous benzene (5 mL) at 50 °C and treated with tri-*n*-butyltin hydride (3 μL, 1.0 mmol) and α,α′-azobisisobutyronitrile (10 mg). After reflux for 1 h and evaporation, the residue is dissolved in acetonitrile (5 mL), washed three times with *n*-hexane, evaporated to a colorless oil, and flash chromatographed on silica gel 60 (40 μM, Merck) with toluene–ethyl acetate, 2:1, to yield the disaccharides.

Benzyl 4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-talopyranosyl)-3-*O*-(4-methoxybenzyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (10). Compound **6** (130 mg, 0.363 mmol) is reacted, following procedure a, to give 203 mg (82%) of colorless syrup: $[\alpha]^{20}_D$ −32.6° (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.10 (m, 8 H, C_6H_5), 6.90 (d, br, 2 H, C_6H_5), 5.45 (s, br $\approx$dd, H-1′, $J_{1,2} < 1.0$ Hz), 5.15 (d, br $\approx$ dd, H-4′, $J_{3',4'}$ = 3.0, $J_{4',5'}$ = 1.6 Hz), 4.90 (d and dd, each 1 H, H-3′, $C_6H_5CH_2$, $J_{3',4'}$ = 3.0 Hz), 4.75 (dq, H-5′, $J_{4',5'}$ = 1.6, $J_{5',6'}$ = 6.5 Hz), 4.50 (mc, 2 H, H-2 and $C_6H_5CH_2$, $J_{1,2} < 1.0$, J_{AB} = 12.6 Hz), 4.40 (d, br $\approx$ dd, H-1, $J_{1,2a}$ = 2.2, $J_{1,2e} \approx 1.0$ Hz), 3.80 (s, 3 H, OCH_3), 3.70 (d, br $\approx$ dd, H-4, $J_{3,4}$ = 3.9, $J_{4,5} < 1.0$ Hz), 3.35 (m $\approx$ dq and ddd, 2 H, H-3 and H-5), 2.20 and 2.05 (each s, each 3 H, OAc), 2.03 (ddd, H-2a, $J_{1,2a}$ = 2.2, $J_{2a,2e}$ = 12.0, $J_{2a,3}$ = 9.0 Hz), 1.90 (ddd, H-2e, $J_{1,2e} \approx 1.0$, $J_{2a,2e}$ = 12.0, $J_{2e,3}$ = 3.0 Hz), 1.30 (d, 3 H, H-6, $J_{5,6}$ = 6.6 Hz), 0.90 (d, H-6′, $J_{5',6'}$ = 6.5 Hz). Anal. Calcd for $C_{31}H_{39}IO_{10}$: C, 54.55; H, 5.76. Found: C, 54.71; H, 5.82.

Benzyl 4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-talopyranosyl)-2,3,6-trideoxy-3-[*N*-(*p*-tolylsulfonyl)amino]-α-L-*lyxo*-hexopyranoside (12). Compound **7**[13] (130 mg, 0.33 mmol) was reacted by following procedure a: yield 178 mg (74%); $[\alpha]^{20}_D$ −52.5° (*c* 0.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 and 7.30–7.00 (each m, 9 H, C_6H_5), 5.60 (d, NH, $J_{3,NH}$ = 9.0 Hz), 5.20 (t $\approx$ dd, H-3′, $J_{2',3'}$ = 3.8, $J_{3',4'}$ = 2.0 Hz), 5.10 (d, H-4′, $J_{3',4'}$ = 2.0, $J_{4',5'} < 1.0$ Hz), 4.90 (s, br $\approx$ d, H-1′, $J_{1',2'}$ = 2.0 Hz), 4.70 (s, br $\approx$ d, H-1, $J_{1,2a}$ = 2.5, $J_{1,2e} < 1.0$ Hz), 4.55 (d, $C_6H_5CH_2$, J_{AB} = 11.8 Hz), 4.35 (m $\approx$ d and dq, 2 H, H-5′ and $C_6H_5CH_2$, $J_{4',5'} < 1.0$, J_{AB} = 11.8 Hz), 4.25 (dd, H-2′, $J_{1',2'}$ = 2.0, $J_{2',3'}$ = 3.8 Hz), 3.80 (q, br $\approx$ dq, H-5, $J_{4,5} < 1.0$, $J_{5,6}$ = 6.6 Hz) 3.75 (dddd, H-3, $J_{2a,3}$ = 4.8, $J_{2e,3}$ = 5.0, $J_{3,4}$ = 1.0 Hz), 3.30 (d, br $\approx$ dd, H-4, $J_{3,4} \approx 1.0$, $J_{4,5} < 1.0$ Hz), 2.40 (s, 3 H, CH_3), 1.70 (ddd, H-2e, $J_{1,2e} < 1.0$, $J_{2a,2e}$ = 12.6, $J_{2e,3}$ = 5.0 Hz), 1.40 (dd, H-2a, $J_{1,2a}$ = 2.5, $J_{2a,2e}$ = 12.6, $J_{2a,3}$ = 4.8 Hz), 1.25 (d, 3 H, H-6′, $J_{5',6'}$ = 6.1 Hz), 1.10 (d, 3 H, H-6, $J_{5,6}$ = 6.6 Hz). Anal. Calcd for $C_{30}H_{38}INSO_{10}$: C, 49.39; H, 4.97; N, 1.92. Found: C, 49.25; H, 4.89; N, 2.05.

10-*O*-[4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-talopyranosyl)-3-(*N*,*N*-dimethylamino)-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl]-γ-rhodomycinone (14). Compound **8**[12] (60 mg, 0.114 mmol) is reacted as described in the general procedure a to give **14** in a yield of 64.2 mg (65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.00 (s, br, 11-OH), 12.68 (s, br, 6-OH), 12.04 (s, br, 4-OH), 7.90 (dd, H-1, $J_{1,2}$ = 8.5, $J_{1,3}$ = 1.0 Hz), 7.70 (t, H-2, $J_{1,2} = J_{2,3}$ = 8.5 Hz), 7.35 (dd, H-3, $J_{1,3}$ = 1.0, $J_{2,3}$ = 8.5 Hz), 5.50 (d, br, H-1′, $J_{1',2'}$ = 2.8 Hz), 5.21 (m $\approx$ dd and d, H-3″, H-4″, $J_{2'',3''}$ = 4.2, $J_{3'',4''} \approx$ 2.0, $J_{4'',5''} < 1.0$ Hz), 5.10 (d, H-10), 4.88 (d, *H*-1″, $J_{1'',2''}$ = 2.1 Hz), 4.40–4.30 (m, H-2″, H-5″), 4.05 (q, br $\approx$ dq, $J_{4',5'} < 1.0$, $J_{5',6'}$ = 6.4 Hz), 3.18 (d, br, H-4′, $J_{3',4'}$ = 1.1, $J_{4',5'}$ = 1.0 Hz), 2.69 (d, br, H-3′, $J_{2',3'}$ = 12.0 Hz), 2.30 (s, 6 H, $N(CH_3)_2$), 2.20–1.90 (m, 2 H, H-2a′, H-2e′), 1.28 (d, 3 H, H-6″, $J_{5'',6''}$ = 6.6 Hz), 1.15 (d, 3 H, H-6′, $J_{5',6'}$ = 6.4 Hz), 1.08 (t, 3 H, CH_3-14, $J_{CH_3,H\text{-}13}$ = 7.4 Hz).

Benzyl 4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-3-*O*-(4-methoxybenzyl)-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (11). Compound **10** (150 mg, 0.27 mmol) is treated with tri-*n*-butylstannyl hydride by following procedure b: yield 118 mg, 79%; $[\alpha]^{20}_D$ −56.1° (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.40–7.00 (m, 7 H, C_6H_5), 6.80 (≈dd, 2 H, C_6H_5), 5.55 (ddd, H-3′, $J_{2a',3'}$ = 12.4, $J_{2e',3'}$ = 2.6, $J_{3',4'}$ = 4.8 Hz), 5.45 (s, br $\approx$ d, H-1′, $J_{1',2a'}$ = 2.3, $J_{1',2e'} < 1.0$ Hz), 5.00 (d, br $\approx$ dd, H-4′, $J_{3',4'}$ = 4.8, $J_{4',5'} < 1.0$ Hz), 4.95 and 4.50 (each d, each 1 H, $C_6H_5CH_2$, J_{AB} = 12.0 Hz), 4.75 (dq, H-5′, $J_{4',5'} < 1.0$, $J_{5',6'}$ = 6.6 Hz), 4.35–4.20 (m, 5 H, H-1 and $C_6H_5CH_2$, J_{AB} = 11.4 Hz), 3.50 (d, br $\approx$ dd, H-4, $J_{3,4}$ = 2.9, $J_{4,5} < 1.0$ Hz), 3.30 (s, 3 H, OCH_3), 3.10 (ddd, H-3, $J_{3,4}$ = 2.9, $J_{2a,3}$ = 8.8, $J_{2e,3}$ = 3.4 Hz), 2.85 (dq, H-5, $J_{4,5} < 1.0$, $J_{5,6}$ = 6.6 Hz), 2.30–1.90 (m $\approx$ each ddd, 4 H, H-2a, H-2e, H-2a′, H-2e′, $J_{1,2a}$ = 2.2, $J_{1,2e} < 1.0$, $J_{2a,2e}$ = 12.1, $J_{2a,3}$ = 8.8, $J_{2e,3}$ = 3.4, $J_{1',2a'}$ = 2.3, $J_{1',2e'} < 1.0$, $J_{2a',2e'}$ = 11.9, $J_{2a',3'}$ = 12.4, $J_{2e',3'}$ = 2.6 Hz), 1.10 (d, 3 H, H-6, $J_{5,6}$ = 6.6 Hz), 0.90 (d, 3 H, H-6′, $J_{5',6'}$ = 6.6 Hz). Anal. Calcd for $C_{31}H_{40}O_{10}$: C, 66.90; H, 7.24. Found: C, 66.94; H, 7.21.

Benzyl 4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-2,3,6-trideoxy-3-[*N*-(*p*-tolylsulfonyl)amino]-α-L-*lyxo*-hexopyranoside (13). Compound **12** (100 mg, 0.14 mmol) is reduced by following the general procedure b: yield 68 mg (81%); colorless syrup; $[\alpha]^{20}_D$ −110.0° (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.70 and 7.30–7.00 (m, 9 H, C_6H_5), 5.90 (d, s, NH, $J_{3,NH}$ = 8.5 Hz), 5.25 (ddd, H-3′, $J_{2a',3'}$ = 12.6, $J_{2e',3'}$ = 5.0, $J_{3',4'}$ = 2.8 Hz), 5.18 (d, br $\approx$ dd, H-4′, $J_{3',4'}$ = 2.8, $J_{4',5'} < 1.0$) Hz), 4.85 (d, br $\approx$ dd, H-1′, $J_{1',2a'}$ = 2.8, $J_{1',2e'} < 1.0$ Hz), 4.80 (d, br $\approx$ dd, H-1, $J_{1,2a}$ = 2.4, $J_{1,2e} < 1.0$ Hz), 4.55 and 4.40 (each d, each $C_6H_5CH_2$, J_{AB} = 11.8 Hz), 4.20 (dq, H-5′, $J_{4',5'} < 1.0$, $J_{5',6'}$ = 6.6 Hz), 3.80 (dd, H-5, $J_{4,5} < 1.0$, $J_{5,6}$ = 6.2 Hz), 3.70 (m $\approx$ ddd, H-3, $J_{2a,3}$ = 4.8, $J_{2e,3}$ = 5.0, $J_{3,4}$ 1.0, $J_{3,NH}$ = 8.5 Hz), 3.20 (s, br $\approx$ d, H-4, $J_{3,4}$ = 1.0, $J_{4,5} < 1.0$ Hz), 2.35 (s, 3 H, $C_6H_4CH_3$), 1.90 (m, 2 H, H-2a, H-2a′), 1.60 (dd, H-2a, $J_{1,2a}$ = 2.4, $J_{2a,2e}$ = 12.0, $J_{2a,3}$ = 4.8 Hz), 1.20 (d, 3 H, H-6′, $J_{5',6'}$ = 6.6 Hz), 1.05 (d, 3 H, H-6, $J_{5,6}$ = 6.2 Hz). Anal. Calcd for $C_{30}H_{39}NO_{10}S$: C, 59.70; H, 6.18; N, 2.32. Found: C, 59.63; H, 6.14; N, 2.11.

10-*O*-[4-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-3-(*N*,*N*-dimethylamino)-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl]-γ-rhodomycinone (15). Compound **14** (40 mg, 0.054 mmol) is subjected to procedure b to give 25 mg (76%) of **15**: ^{1}H NMR (300 MHz, $CDCl_3$) (only data deviating from **14** are noted) δ 4.80 (d, br, H-1″, $J_{1'',2a''}$ = 2.5, $J_{1'',2e''}$ = 1.0 Hz), 2.20–1.90

(m, 4-H, H-2a′, H-2e′, H-2a″, H-2e″).

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Crown Ethers as a Mechanistic Probe. 1. Inhibitory Effects of Crown Ethers on the Reactivity of Anionic Nucleophiles toward Diphenyl *p*-Nitrophenyl Phosphate

Junghun Suh* and Bong Seok Mun

Department of Chemistry, Seoul National University, Seoul 151-742, Korea

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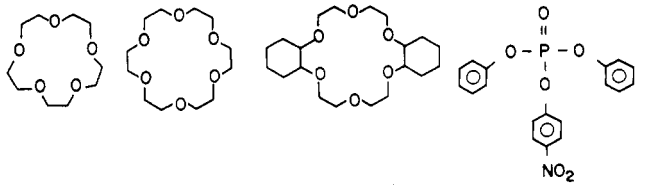
Through complex formation with cations, crown ethers affect physical and chemical behavior of both the cations and their counteranions.[1] For example, reactivities of anions are enhanced, sometimes simply due to the increased solubility of their salts in the presence of crown ethers.[1] In some cases, the intrinsic reactivity of the resultant naked anion may be raised, leading to further increases in reaction rates.[2] In addition, very close proximity between the catalytic group and the reaction site has been achieved with crown ether derivatives.[3] Furthermore, some crown ethers are able to recognize enantiomeric differences.[4]

When a metal ion is complexed by a crown ether, its effective radius is increased, reducing the charge density.[1] This would decrease the electrostatic stabilization of the anionic centers of both the transition state and the ground state, leading to a change in the overall rate. Thus, kinetic studies in the presence of crown ethers can be used as a mechanistic probe for the characterization of the distribution of negative charges in the transition state.

In order to test whether crown ethers are generally applicable as such a mechanistic probe, we have investigated the effects of 15-crown-5 (I), 18-crown-6 (II), and dicyclohexano-18-crown-6 (III) on the rates for the reaction of anionic nucleophiles with diphenyl *p*-nitrophenyl phosphate (A) in acetonitrile. In this reaction, the *p*-



I II III A

nitrophenolate of A is substituted by the nucleophiles. The anionic nucleophiles employed in the kinetic studies are phenolate (B), *p*-methoxyphenolate (C), *p*-chlorophenolate (D), 1-naphtholate (E), and ethoxide ions. The crown ethers used in the kinetic studies were chosen in view of different sizes of both the cavities and the whole molecules as well as the different inductive effects imposed by the alkyl portions.[1]

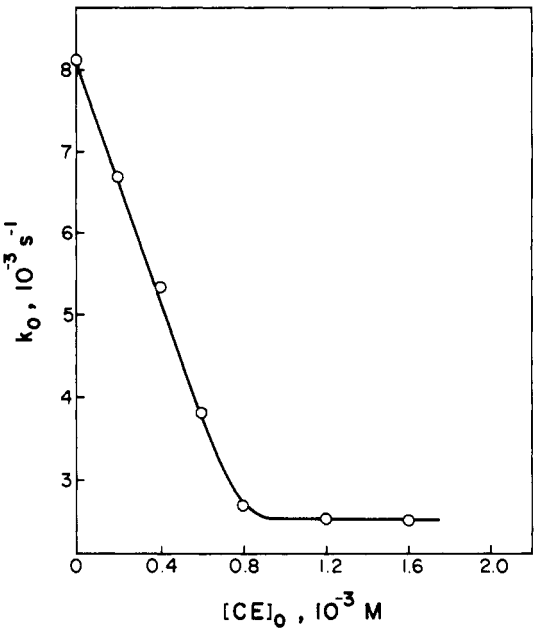


Figure 1. Dependence of the pseudo-first-order rate constant (k_0) for the reaction of 8×10^{-4} M potassium phenolate with A on the concentration of III measured in acetonitrile at 25 °C.

Table I. Parameter Values Estimated from the Kinetic Data of Nucleophilic Reactions on A in the Presence of Crown Ethers I–III[a]

countercation	nucleophile	$10^2 k_0^{sp}$, s^{-1}	$10^2 k_0^{CE}$, s^{-1} I	II	III
Na^+	B	4.7	1.2	0.86	0.79
Na^+	C	3.7	0.94	0.83	0.76
Na^+	E	1.0	0.38	0.30	0.27
K^+	B	0.81	0.54	0.38	0.25
K^+	C	1.0	0.76	0.54	0.43
K^+	D	0.88	0.50	0.43	0.26
K^+	ethoxide	13	5.3	2.8	2.7

[a] Measured at 25 °C in acetonitrile with 0.8×10^{-3} M nucleophile.

Results and Discussion

The degree of neutralization of the phenol derivatives with sodium or potassium ethoxide in acetonitrile was examined by measuring the UV–vis spectra of the substituted phenols (1×10^{-3} M) in the presence of sodium or potassium ethoxide [$(0.2–1.7) \times 10^{-3}$ M)]. The spectral titration indicated that the phenol derivatives were completely converted into the respective phenolate ions (B–E) when 1–1.1 equiv of sodium or potassium ethoxide was added. Results of the spectral titration were not affected by the addition of crown ether II.

Nucleophiles B–E were generated in the kinetic studies by mixing sodium or potassium ethoxide (0.8×10^{-3} M) and the respective phenol (1×10^{-3} M). According to the results of the spectral titration mentioned above, the ethoxide ion is to be completely protonated by the added phenol derivatives. The reaction mixtures, therefore, contain anions B–E at the concentration of 0.8×10^{-3} M. The pseudo-first-order rate constants (k_0) measured under these conditions for the release of *p*-nitrophenol from A (initial concentration: 1×10^{-5} M) decreased as the concentration ($[CE]_0$) of initially added crown ether was raised. A typical dependence of k_0 on $[CE]_0$ is illustrated in Figure 1. From the curves for the dependence of k_0 on $[CE]_0$, the pseudo-first-order rate constant (k_0^{sp}) observed

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