Tetrahedron Vol. 40, No. 15, pp 2967 to 2970, 1984
Printed in the U S A.

0040-4020/84 $3.00 + .00
Pergamon Press Ltd

SYNTHESIS OF CHIRAL DIAZA-CROWN ETHERS INCORPORATING CARBOHYDRATE UNITS†

M. PIETRASZKIEWICZ* and J. JURCZAK
Institute of Physical Chemistry and Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

Abstract—A synthesis of a novel chiral diaza crown ethers derived from α-D-glucose, α-D-mannose, and α-D-galactose in two alternative pathways is described.

Synthetic macrocyclic molecular receptors have been the subject of investigations through years. They possess selective binding abilities toward cations either inorganic and organic anions as well as small neutral molecules. They behave as enzyme models and are useful in phase-transfer catalysis. Many excellent reviews have been published on this topic.[1]

A great number of chiral crown ethers has been synthesized.[2] They exhibit chiral recognition towards optically-active primary ammonium cations, and this feature was applied by Cram *et al.* for resolution of racemic amino acids by means of HPLC.[3]

So far a very limited number of chiral aza crown ethers has been reported.[4] This fact can be attributed to less available starting materials than in analogous preparations of "all-oxygen" crowns and synthetic problems due to protection-deprotection of the nitrogen atom. Introduction of nitrogen atoms into a macrocyclic ring offers various synthetic possibilities.

We report now full experimental data concerning the synthesis of a new chiral diaza 18-crown-6, derived from methyl 4,6-0-benzylidene-α-D-manno-, gluco-, and galactopyranoside (**1a, b, c**, respectively). We selected sugars as a cheap source of chirality. Hence, sugar can be functionalized in desirable manner, thus they are attractive because of synthetic point of view.

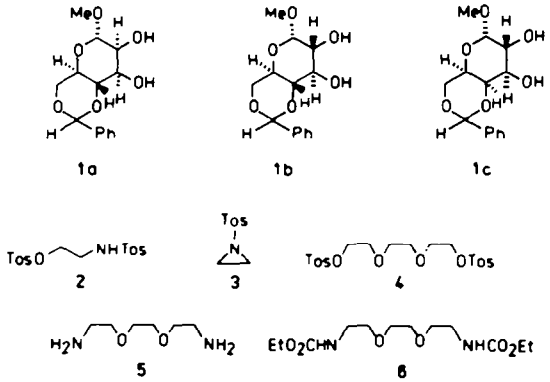
RESULTS AND DISCUSSION

There are in principal two ways leading to the same macrocyclic systems. The path I (Scheme 2) consists on a "step-by-step" synthesis. Sugars **1a–c** (Scheme 1) were O-alkylated very smoothly with t-butyl bromoacetate under phase-transfer conditions[5] in high yield to give diesters **7a–c** exclusively. Reduction of **7a–c** with lithium aluminum hydride yielded the corresponding diols **8a–c** in excellent yield. Tosylation of **8a–c** afforded bistosylates **9a–c** in good yield. Although those **9a–c** have been reported by Stoddart[6] it seems that our method possesses some advantages since it avoids the ozonolysis of the diallyl derivatives of **1a–c**. Condensations of the bistosylates **9a–c** with N,N'-bisethoxycarbonyl-1,8-diamino-3,6-dioxaoctane **6** (Scheme 1), performed according to the procedure described by Sutherland,[7] led to desired compounds **10a–c** in good yield; reduction of the obtained biscarbamates followed by lithium aluminum hydride[7] yielded N,N'-dimethyl diaza-crown ethers **11a–c**.

Apparently, the condensation of the bistosylate **9a** with 1,8-diamino-3,6-dioxaoctane **5**[8] on alumina coated with potassium fluoride[9] in acetonitrile-tetrahydrofuran mixture at elevated temperature provided diaza-crown **12a** in satisfactory yield. Although the utility of potassium fluoride on alumina has been successfully exhibited in the preparation of a simple "all-oxygen" crowns,[9] we demonstrate the first example of the formation of diaza-crowns under such conditions. However, it should be noted that the main drawback of this method is that base-sensitive groups like esters are affected by potassium fluoride on alumina.

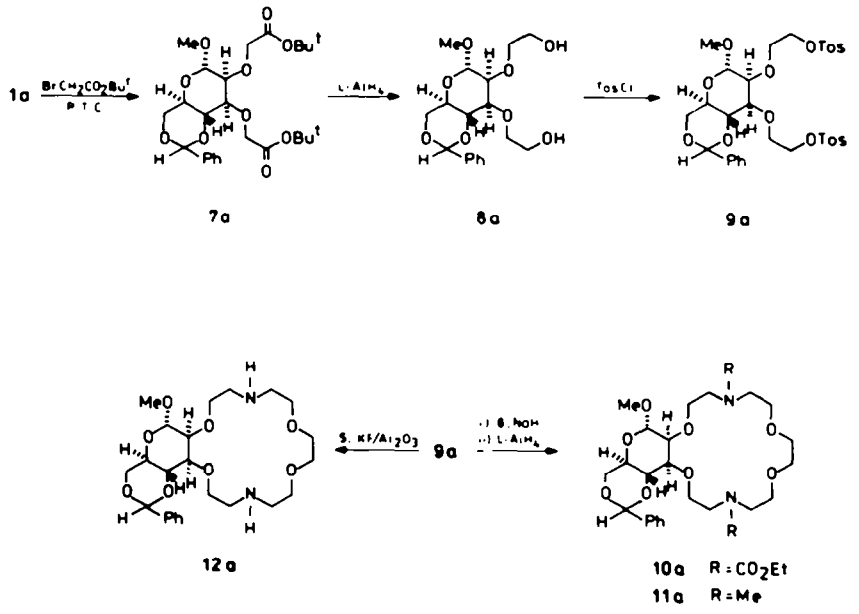
The method presented above is rather time-consuming, so this fact prompted us to investigate shorter procedures leading to the title compounds. We found two independent solutions of this problem (Scheme 3).

The path II A consists on the O-alkylation of the dianion, generated from **1a–c** by sodium hydride in dimethylformamide, with N-tosylaziridine **3**[10] to form an intermediates **13a–c**. Condensations[11] of **13a–c** with triethyleneglycol bistosylate **4** in the same reaction flask at elevated temperature (without isolation of the intermediates **13a–c**) afforded N,N'-bistosyl diaza-crowns **14a–c**. Reduction of **14a** followed by lithium aluminum hydride in boiling tetrahydrofuran[12] afforded deprotected diaza-crown **12a** in good yield.

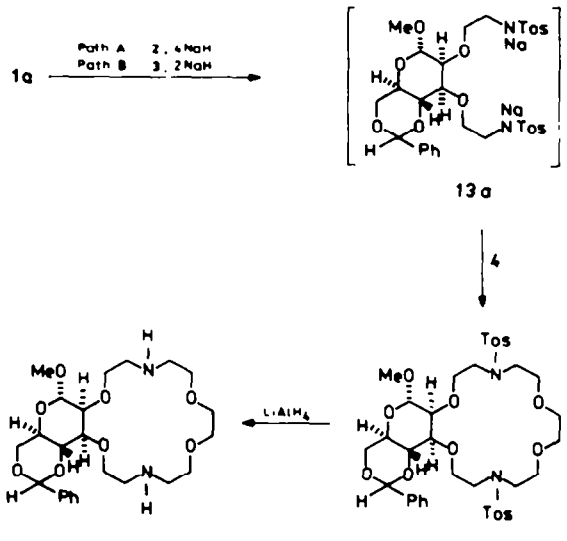


Scheme 1.

†Preliminary communication: *Idem, J. Chem. Soc.* Chem. Commun. 132 (1983).



Scheme 2.



Scheme 3.

The path II B is only a modification of II A. The difference between II A and II B consists in the fact that in II B N-tosylaziridine is formed *in situ* from N[2 - [(p - toluenesulphonyl)oxy]ethyl - p - toluenesulphonamide **2** in the presence of two additional equivalents of sodium hydride.

These two methods, "step-by-step" and "one-pot", presented herein have their advantages and drawbacks. In the first one the main drawback is the use of t-butyl bromoacetate which is relatively expensive. All the attempts to replace this reagent by ethyl chloro-, bromo-, and iodoacetates have failed because of fast ester hydrolysis under phase-transfer conditons. The second way is much shorter, and overall yields are higher than those for the pathway I.

Finally, this approach provides a simple and convenient synthesis of chiral diaza-crown ethers of potenital interest in host-guest chemistry.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Joel JNM-4H-100 spectrometer for $CDCl_3$ solutions (δ scale, TMS as internal standard). Mass spectra were obtained with a LKB 2091 spectrometer at 15 or 70 eV. All the solvents were of analytical grade. Dimethyl sulphoxide, triethyl amine, tetrahydrofuran and dimethylformamide were distilled over calcium hydride and stored over molecular sieves A–4.

Starting materials. Compounds **1a**, **1b** and **1c** were prepared according to Ref. 14. Bistosylate **2** was synthesized with the method of Ref. 13. Tosylaziridine **3** was prepared according to Ref. 10. Triethyleneglycol bistosylate **4** was obtained according to Ref. 16. Compound **5** was prepared with the methof of Ref. 17. Bisurethane **6** was synthesized according to Ref. 18.

Methyl 4,6 - *O* - *benzylidene* - 2,3 - *O* - *bis*(*t* - *butyloxycarbonylmethyl*) - α - D - *mannopyranoside* **7a**. **1a** (3.6 g, 12.8 mmol), benzene (30 ml), 50% aqueous NaOH (25 ml) and Bu_4NHSO_4 (2.1 g, 6.4 mmol) were placed in a round-bottomed flask and stirred vigorously at 10°. t-Butyl bromoacetate (7.5 g, 38.4 mmol) was added dropwise rapidly, and stirring was continued for 30 min. Water (50 ml) and hexane (100 ml) were then added, the mixture was stirred for 10 min and the organic layer was passed through a short layer of silica gel and evaporated. Yield 6.2 g (95% of oily **7a**). (Found: C, 60.75; H 7.89. $C_{26}H_{38}O_{10}$ requires: C, 61.16; H, 7.51%). MS (15 eV), *m/z* (%): 511 (M^+, 0.2), 398(21), 353(25), 187(22), 175(70), 131(18), 105 (28), 57 (100); ^{1}H NMR, δ: 7.45 (5 H, m, Ph), 5.65 (1H, s, PhCH), 5.10 (1H, s, MeOCH), 4.50–3.80 (10 H, m), 3.45 (3H, s, OCH_3), 1.52 and 1.50 (18H, 2 × s, 2 × Bu^t).

Analogously, using **1b** and **1c**, corresponding **7b** and **7c** were obtained. **7b**: 92% yield. (Found: C, 61.35; H, 7.19%) MS (15 eV), *m/z* (%): 511 (M^+, 0.5), 398(16), 353(10), 187(25), 175(67), 131(15), 105(31), 57(100); ^{1}H NMR, δ: 7.40 (5H, m, Ph), 5.60 (1H, s, PhCH, 4.92 (1H, d, MeOCH), 4.55–3.70 (10H, m), 3.50 (3H, s, OCH_3), 1.55 and 1.52 (18H, 2 × s, 2 × Bu^t). **7c**: 90% yield (Found: C, 60.83; H, 7.22%); MS (15 eV), *m/z* (%); 511 (M^+, 0.11), 398(14), 353(22), 187(27), 175(72), 131(13), 105(12), 57(100); ^{1}H NMR, δ: 7.47 (5H, m, Ph), 5.62 (1H, s, PhCH), 5.00 (1H, d,

MeOCH), 4.50–3.75 (10H, m), 3.55 (3H, s, OCH_3), 1.50 and 1.48 (18H, 2 × s, 2 × Bu^t).

Methyl 4,6 - 0 - *benzylidene* - 2,3 - 0 - *bis(p - toluenesulphonyloxyethyl)* - α - D - *mannopyranoside* **9a**. **7a** (5.1 g, 10 mmol) was reduced with lithium aluminium hydride (1.52 g, 40 mmol) in THF (20 ml). After usual work-up the viscous residue **8a** (3.32 g, 90%) was dissolved in a mixture of chloroform (50 ml) and triethylamine (10 ml), cooled down to 0° and toluene-p-sulphonyl chloride was added (3.67 g, 2.2 equiv). The mixture was kept at 4° overnight. Excess of toluene-p-sulphonyl chloride was removed by addition of a small amount of water (monitoring by TLC); organic layer was washed 3 × 20 ml of water and evaporated. Yield of **9a**: 5.06 g (85%), m.p. 127–128° (uncorrected). In analogous manner were obtained **8b** and **8c** (oils, yield 87 and 85%, respectively) and consequently **9b** and **9c** (viscous oils, yield 81 and 83%, respectively). ^1H NMR spectra of **9a–c**, were identical with those reported in the literature.[6]

N,N'-Bis(ethoxycarbonyl)diaza-crown ether **10a**. Bis(carbamate) **6** (1.46 g, 5 mmol) was dissolved in DMSO (15 ml) and added to the stirred suspension of sodium hydride (0.252 g, 10.5 mmol) and potassium bromide (1,2 g, 10 mmol) in DMSO (30 ml). After 3h the solution of bis(tosylate) **9a** (3.39 g, 5 mmol) in DMSO (20 ml) was added dropwise and the mixture was stirred at ambient temp for 3 days. The soln was diluted with water (150 ml), extracted with ethyl ether (4 × 100 ml), evaporated and chromatographed on silica gel(Merck 60, 230–400 mesh, ethyl acetate). Yield of **10a**: 2.03 g (65%). (Found: C, 56.97; H, 7.42; N, 4.54. $C_{30}H_{46}O_{12}N_2$ requires: C, 57.49; H, 7.39; N, 4.47%). MS (15 eV), *m/z* (%): 627(M^+, 0.7), 273 (28), 216(13), 169(99), 143(29), 130(100); ^1H NMR, δ: 7.45 (5H, m, Ph), 5.62 (1H, s, PhCH), 5.15 (1H, s, MeOCH), 4.50–3.30 (26H, m), 3.45 (3H, s, OCH_3), 1.27 (6H, t, CH_3CH_2O).

Analogously, using **9b** and **9c**, corresponding **10b** and **10c** were obtained, **10b**: 60% yield. (Found: C, 57.11; H, 7.19; N, 4.37%). MS (15 eV), *m/z* (%): 627(M^+, 0.5), 273(23), 169(75), 144(21), 130(100); ^1H NMR, δ: 7.40 (5H, m, Ph), 5.60 (1H, s, PhCH), 4.90 (1H, d, MeOCH), 4.40–3.30 (26H, m), 3.50 (3H, s, OCH_3), 1.30 (6H, t, CH_3CH_2O). **10c**: 51% yield. (Found: C, 57.21; H, 7.48; N, 4.52%). MS (15 eV), *m/z* (%): 627 (M^+, 0.4), 273 (15), 169(58), 143(18), 130(100); ^1H NMR, δ: 7.47 (5H, m, Ph), 5.65 (H, s, PhCH), 5.02 (1H, d, MeOCH), 4.50–3.20 (26H, m), 3.55 (3H, s, OCH_3), 1.27 (6H, t, CH_3CH_2O).

N,N'-Dimethyl diaza-crown ether **11a**. **10a** (1.25 g, 2 mmol) in THF (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g, 20 mmol) in THF (100 ml). After 3 h at ambient temperature excess $LiAlH_4$ was removed by slow quenching with 5% aqueous LiOH. Usual work-up afforded **11a** as a colourless oil. Yield 0.927 g (90%). (Found: C, 60.72; H, 8.11; N, 5.12. $C_{26}H_{42}O_8N_2$ requires: C, 61.15; H, 8.29; N, 5.49%). MS (15 eV), *m/z*(%): 511 (M^+, 3.7), 449(42), 366(44), 352(53), 229(100), 143(50), 132(45); ^1H NMR, δ: 7.45 (5H, m, Ph), 5.68 (1H, s, PhCH), 4.80 (1H, s, MeOCH), 4.40–3.50 (18H, m), 3.45 (3H, s, OCH_3), 2.75 (8H, m, NCH_2), 2.40 and 2.32 (6H, 2 × s, 2 × NCH_3).

Analogously, using **10b** and **10c**, corresponding **11b** and **11c** were obtained. **11b**: 85% yield. (Found: C, 60.81; H, 8.02; N, 5.31%). MS (15 eV), *m/z* (%): 511 (M^+, 2.8), 499(22), 366(29), 352(60), 229(100), 143(44), 132(29); ^1H NMR, δ: 7.50 (5H, m, Ph), 5.62 (1H, s, PhCH), 4.90 (1H, d, MeOCH), 4.40–3.40 (18H, m), 3.50 (3H, s, OCH_3), 2.77 (8H, m, NCH_2), 2.40 and 2.32 (6H, 2 × s, 2 × NCH_3). **11c**: 87% yield. (Found: C, 60.89; H, 8.35; N, 5.57%). MS (15 eV), *m/z* (%): 511 (M^+, 1.9), 449(31), 366(36), 352(61), 229(100), 143(39), 132(33); ^1H NMR, δ: 7.50 (5H, m, Ph), 5.65 (1H, s, PhCH), 5.02 (1H, d, MeOCH), 4,50–3.40 (18H, m), 3.50 (3H, s, OCH_3), 2.80 (8H, m, NCH_2), 2.50 and 2.35 (6H, 2 × s, 2 × NCH_3).

Diaza-crown ether **12a**. **9a** (0.678 g, 1 mmol) and diamine **5** (0.148 g, 1 mmol) were dissolved in MeCN–THF (1:1 v/v) mixture (20 ml). After addition of potassium fluoride on alumina (type B,[15] 0.37 g, 2.5 equiv. 40% KF on Al_2O_3), the suspension was stirred and refluxed for 20 h, then filtered off, washed and evaporated. The residue was dissolved in chloroform (50 ml), washed 2 × 10 ml of water and evaporated. Purification was effected by chromatography on alumina (Merck 90, 70–230 mesh, II–III activity, 2% v/v methanol in methylene chloride). Yield 0.145 g (30%). (Found: C, 58.95; H, 8.01; N, 5.67. $C_{24}H_{38}O_8H_2$ requires: C, 59.73; H, 7.93; N, 5.80%); ^1H NMR, δ: 7.47 (5H, m, Ph), 5.72 (1H, s, PhCH), 4.90 (1H, s, MeOCH), 4.40–3.50 (18H, m), 3.47 (3H, s, OCH_3), 2.87 (8H, m, NCH_2), 2.0 (2H, bs, NH).

N,N'-Bistosyl diaza-crown ether **14a**. *Pathway II A*. A soln of **1a** (0.564 g, 2 mmol) in DMF (20 ml) was stirred with sodium hydride (0.35 g 55% NaH, 8.02 mmol) for 1 h at ambient temp, and after cooling to −60° a solution of **2** (1.5 g, 4.06 mmol) in DMF (10 ml) was added dropwise. The mixture was allowed to warm for 2 h, stirred for an additional 1 h, and then heated to 90°. At this temp triethyleneglycol bistosylate **3** (0.92 g, 2 mmol) in DMF (10 ml) was added. Heating was continued until **3** disappeared (TLC). After cooling, water (100 ml) was added and the mixture was extracted with 3 × 50 ml of toluene. Evaporation yielded a glassy residue which was chromatographed on silica gel (Merck 60, 230–400 mesh, hexane–ethyl acetate 1:1 v/v). Yield of **14a** in form of glassy solid, 0.47 g (30%). (Found: C, 58.13; H, 6.64; N, 3.71. $C_{38}H_{500}O_{12}N_2S_2$ requires: C, 57.70; H, 6.37; N, 3.54%). MS (70 eV), *m/z* (%): 438(55), 155(23), 100(20), 91(100); ^1H NMR, δ: 7.67–7.26 (8H, 2 × d, 2 × Ts), 7.52–7.34 (5H, m, Ph) 5.59 (1H, s, PhCH), 4.84 (1H, s, MeOCH), 4.28–3.38 (26H, m), 3.41 (3H, s, OCH_3), 2.42 (6H, s, $C_6H_4CH_3$).

Analogously, using **1b** and **1c**, corresponding **14b** and **14c** were obtained. **14b**: 27% yield. (Found: C, 57.21; H, 6.40; N, 3.85%). MS (70 eV), *m/z* (%): 438(29), 155(37), 100(16), 91(100); ^1H NMR, δ: 8.00–7.20 (13H, m, Ph, Ts), 5.60 (^1H, s, PhCH), 4.92 (1H, d, MeOCH), 4.90–3.10 (29H, m), 2.42 (6H, s, $C_6H_4CH_3$). **14c**: 24% yield. (Found: C, 57.32; H, 6.52; N, 3.42%). MS (70 eV), *m/z* (%): 438(0.3), 198(35), 155(38), 91(100); ^1H NMR, δ: 8.00–7.20 (13H, m, Ph, Ts), 5.60 (1H, s, PhCH), 5.00 (1H, d, MeOCH), 4.50–3.10 (29H, m), 2.45 (6H, s, $C_6H_4CH_3$).

Pathway IIB. The difference in comparison with IIA is that in IIB tosylaziridine **2** (2 equiv) was added to the dianion generated from sugar of type **1** at ambient temp and the mixture was stirred for 2 days, work-up was followed in usual manner. Yields of **14a**, **14b** and **14c** were 39, 31 and 22%, respectively.

Deprotection of **14a**. N,N'-Bistosyl diaza-crown **14a** (0.41 g, 0.53 mmol) was refluxed in THF (25 ml) with lithium aluminium hydride (0.2 g, 10 equiv) under argon for 2 days. After cooling, the mixture was diluted with THF (150 ml) and quenched with 5% aqueous LiOH. Filtration and evaporation provided the residue which was purified on alumina (Merck 60, 70–230 mesh, II–III activity, 2% v/v methanol in methylene chloride). Yield of oily product 0.216 g (85%). The product was identical with **12a** obtained from **9a**.

Acknowledgements—Authors thank very much Prof. J.-M. Lehn for his valuable help and discussions. This work was supported by Polish Academy of Sciences, Grant 03.10.

REFERENCES

[1]G. W. Gokel and S. H. Korzeniowski, *Macrocyclic Polyether Syntheses*. Springer Verlag, Berlin (1982); V. K. Majestic and G. R. Newkome, *Topics Curr. Chem.* **106**, 80 (1982); D. N. Reinhoudt and F. de Jong, Crown ethers and related macrocycles with bis(methylene) aromatic or-heteroaromatic subunits: their synthesis and complexation. *Progress in Macrocyclic Chemistry*, (Edited by R. M. Izaat and J. J. Christensen), Vol. 1. Wiley, New York (1979); R. M. Izaat and J. J. Christensen, *Synthetic*

Multidentate Macrocyclic Compounds. Academic Press, New York (1978); G. W. Gokel, D. M. Dishong, R. A. Schultz, and V. G. Gatto, *Synthesis* 997 (1982).
[2]S. T. Jolley, J. S. Bradshaw, and R. M. Izaat, *J. Heterocycl. Chem.* **19**, 3 (1982).
[3]G. D. Y. Sogah and D. J. Cram, *J. Am. Chem. Soc.*, **97**, 1259 (1975); G. D. Y. Sogah and D. J. Cram, *Ibid.* **98**, 3038 (1976); L. R. Sousa, D. H. Hoffman, L. Kaplan, and D. J. Cram, *Ibid.* **96**, 100 (1974); L. R. Sousa, G. D. Y. Sogah, D. H. Hoffman, and D. J. Cram, *Ibid.* **100**, 4569 (1978); G. D. Y. Sogah and D. J. Cram, *Ibid.* **101**, 3035 (1979).
[4]F. Wudl and F. Gaeta, *J. Chem. Soc.* Chem. Commun. 107 (1972); E. P. Kyba, G. W. Gokel, F. de Jong, K. Koga, L. R. Sousa, M. G. Siegel, L. Kaplan, G. D. Y. Sogah, and D. J. Cram, *J. Org. Chem.* **42**, 4173 (1977); N. Ando, Y. Yamamoto, J. Oda, and Y. Inouye, *Synthesis* 688 (1978); J. M. Girodeau, J. M. Lehn, and J. P. Sauvage, *Angew. Chem. Int. Ed. Engl.* **14**, 764 (1975); J. P. Behr, J. M. Girodeau, R. C. Hayward, J. M. Lehn, and J. P. Sauvage, *Helv. Chim. Acta*, **63**, 2096 (1980); J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.* **101**, 2759 (1979); D. E. Fenton, D. N. Parkin, and F. Roger, *J. Chem. Soc. Perkin I* 449 (1981): N. F. Jones, A. Kumar, and I. O. Sutherland *J. Chem. Soc.* Chem. Commun. 990 (1981); J. S. Bradshaw and R. M. Izaat, *J. Heterocycl. Chem.* **19**, 551 (1982); D. A. Laidler and J. F. Stoddart, *J. Chem. Soc.* Chem. Commun. 979 (1975).
[5]M. Makosza, Two-phase reactions in organic chemistry. *Survey of Progress in Chemistry* (Edited by A. F. Scott). Academic Press, New York (1980).
[6]R. B. Pettman and J. F. Stoddart, *Tetrahedron Letters* 457, 461 (1979).
[7]L. C. Hodgkinson, M. R. Johnson, S. J. Leigh, N. Spencer, I. O. Sutherland and R. F. Newton, *J. Chem. Soc.* Perkin I 2193 (1979).
[8]S. Kulstad and L. A. Malmsten, *Tetrahedron Letters* 643 (1980).
[9]J. Yamawaki and T. Ando, *Chem. Letters* 533 (1980).
[10]A. E. Martin, T. M. Ford, and J. E. Bulkowski, *J. Org. Chem.* **47**, 412 (1982).
[11]J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.* **96**, 2268 (1974).
[12]E. Buhleier, W. Rasshofer, W. Wehner, F. Luppertz, and F. Vögtle, *Liebigs Ann. Chem.* 1344 (1977).
[13]D. B. Hope and K. C. Horncastle, *J. Chem. Soc. C* 1098 (1966).
[14]*Methods in Carbohydrate Chemistry* (Edited by R. L. Whistler and M. L. Wolfrom), Vol. II p. 307. Academic Press, New York (1963).
[15]J. Yamawaki and T. Ando, *Chem. Letters* 755 (1979).
[16]J. Dale and P. O. Kristiansen, *Acta Chem. Scand.* **26**, 1471 (1972).
[17]S. Kulstad and L. A. Malmsten, *Ibid.* **33**, 469 (1979).
[18]S. J. Leigh and I. O. Sutherland, *J. Chem. Soc.* Chem. Commun. 414 (1975).