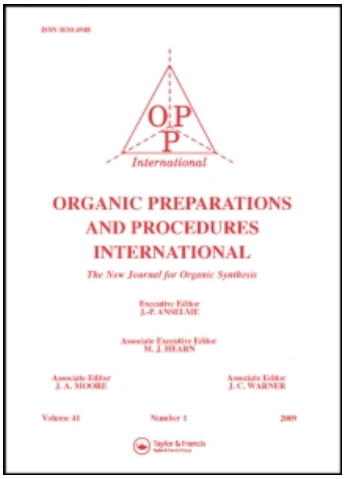

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PREPARATION OF 11-HYDROXYMETHYL-2,3-NAPHTHO-18-CROWN-6 AND ITS CONVERSION INTO A HIGHLY LIPOPHILIC CROWN CARBOXYLIC ACID†

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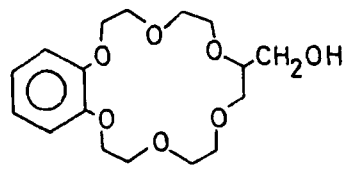
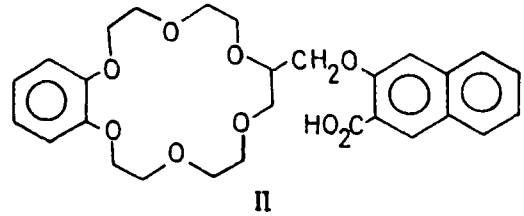
Hydroxymethyl crown ethers[1-7] are versatile synthetic intermediates for the preparation of crown compounds which bear functionalized sidearms. In our research, the crown ethers alcohols have been converted into highly lipophilic crown carboxylic acids[8-10] which are novel reagents for the solvent extraction and liquid membrane transport of alkali and alkaline earth cations.[11,12]

Recently, we reported the synthesis of 11-hydroxymethyl-2,3-benzo-18-crown-6 (I)[7] and its transformation into 11-[(3'-carboxy-2'-naphthoxy)methyl]-2,3-benzo-18-crown-6 (II).[9] We now describe the preparation of the more lipophilic 11-hydroxymethyl-2,3-naphtho-18-crown-6 (III)



I



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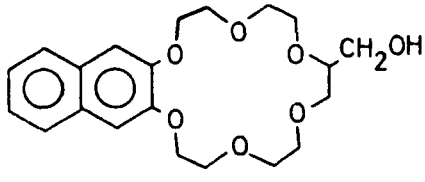

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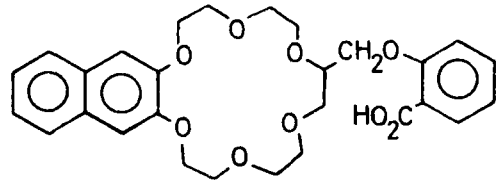


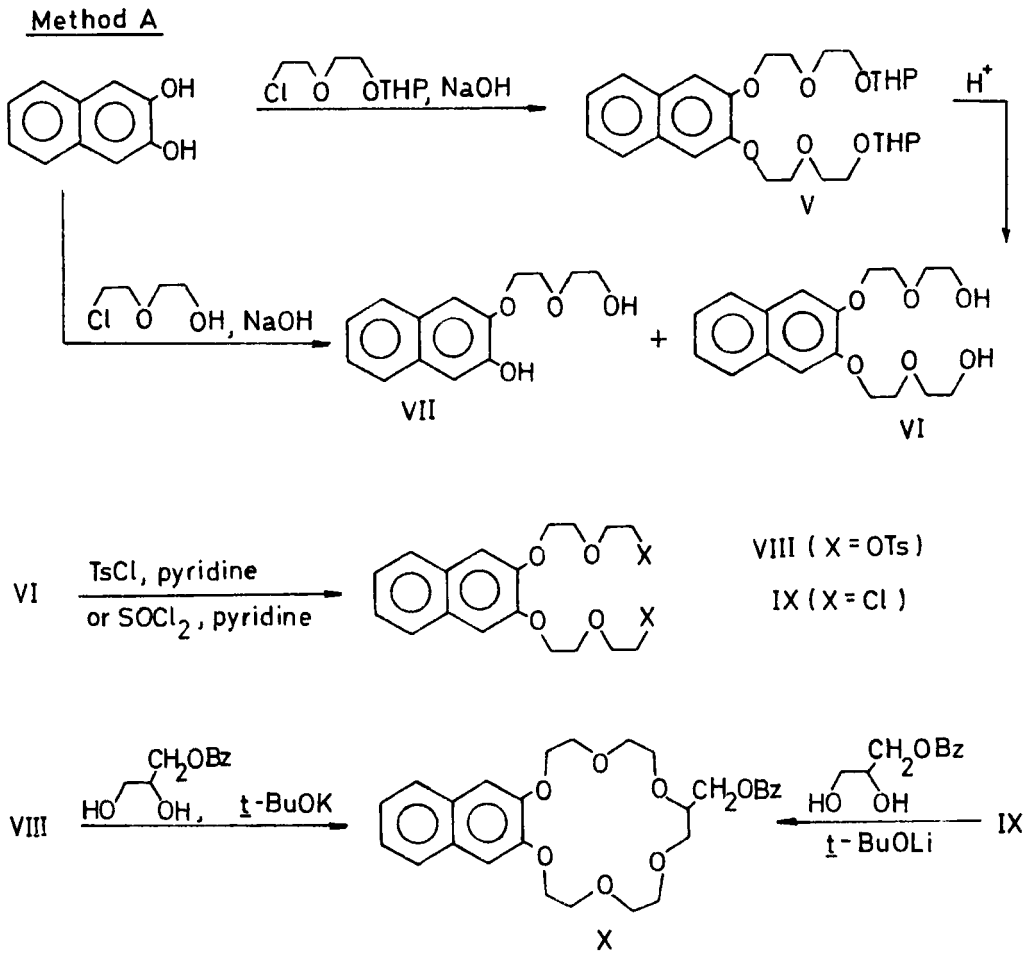
IV

by two independent routes and its conversion into 11-[(2'-carboxyphenoxy)-methyl]-2,3-naphtho-18-crown-6 (IV), which is a structural isomer of II.

The two independent synthetic routes to 11-hydroxymethyl-2,3-naphtho-18-crown-6 (III) are summarized in Scheme 1. In Method A, commercially-available 2,3-dihydroxynaphthalene was treated with tetrahydropyranyl ether-protected 2-(2-chloroethoxy)ethanol and sodium hydroxide by a procedure reported by Cram et al. for an analogous reaction[13] to give the bis-tetrahydropyranyl ether V which, after deprotection, gave diol VI in an overall yield of 57%. Direct treatment of 2,3-dihydroxynaphthalene with unprotected 2-(2-chloroethoxy)ethanol using a method described by Smid and coworkers[14] produced a complicated mixture of products from which the expected diol VI and the mono-substitution product VII were isolated by column chromatography in yields of 17 and 13%, respectively.

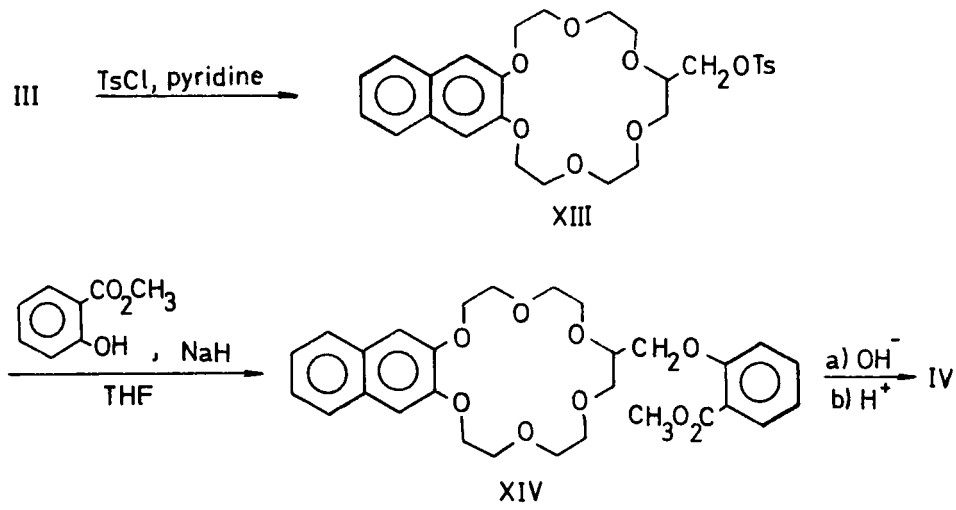
Reaction of diol VI with p-toluenesulfonyl chloride produced ditosylate VIII in 95% yield. Alternatively, treatment of diol VI with thionyl chloride yielded 76% of dichloride IX. Cyclization of ditosylate VIII with 3-(O-benzyl)glycerol[15,16] in the presence of potassium tert-butoxide afforded a 20% yield of the benzyl-protected hydroxymethyl crown X. A similar reaction of dichloride IX and 3-(O-benzyl)glycerol in the presence of lithium tert-butoxide using the Okahara procedure[17] gave only a very low yield of crown ether X.

In Method B, the reaction of 2,3-dihydroxynaphthalene with 2-chloroethanol and sodium hydroxide as described by Montanari and coworkers for the analogous reaction with catechol,[18] yielded 36% of diol XI which was converted into the corresponding ditosylate XII in 95% yield. Treatment of ditosylate XII with 3,6-dioxa-4-(benzyloxymethyl)-1,8-octanediol[7] and potassium hydroxide in aqueous THF provided a 46% yield of the benzyl-protected hydroxymethyl crown X.



Hydrogenolysis of the protected crown X for 5 days with palladium on carbon gave the title hydroxymethyl crown III in 64% yield.

An illustration of the utility of III in the synthesis of highly lipophilic ionizable crown ethers is presented in Scheme 2. The hydroxymethyl crown III was converted into tosylate XIII. Reaction of this compound with methyl salicylate and sodium hydride produced an isolated 73% yield of crown ester XIV which was readily hydrolyzed in 93% yield to the lipophilic crown ether carboxylic acid IV.



EXPERIMENTAL SECTION

PMR spectra were measured in $CDCl_3$ (unless noted otherwise) with a Varian EM-360A spectrometer and shifts are reported in δ units from the internal standard TMS. IR spectra were obtained using a Nicolet S-MX spectrophotometer and are given in cm^{-1}. Elemental analyses were performed by Galbraith Laboratories of Knoxville, Tennessee.

2,3-Bis(5-hydroxy-3-oxa-1-pentyloxy)naphthalene (VI). Method A.- A solution of 2,3-dihydroxynaphthalene (4.05 g, 0.025 mole) in n-BuOH (75 ml) was bubbled with nitrogen for 0.5 hr and sodium hydroxide (2.05 g,

0.05 mole) was added in one portion. The stirred mixture was brought to reflux under nitrogen and a solution of tetrahydropyranyl-protected 2-(2-chloroethoxy)ethanol (16.69 g, 0.08 mole) in n-BuOH (40 ml) was added dropwise. The resulting mixture was stirred and refluxed for 15 hrs and an additional portion of NaOH (0.72 g, 0.018 mole) was added. After an additional 15 hrs at reflux, the cooled reaction mixture was filtered, the solvent was removed in vacuo and the residue was subjected to column chromatography (neutral alumina, EtOAc) to give 11.10 g (88%) of bis-tetrahydropyranyl ether V as a viscous, slightly yellow liquid. The tetrahydropyranyl ether-protected diol V (11.00 g. 0.022 mole) was dissolved in a 1:1 (v/v) mixture of CH_2Cl_2-CH_3OH (100 ml) and 1 ml of concentrated HCl was added. After stirring for 1 hr at room temperature, 5 g of $NaHCO_3$ was added. An hour later the mixture was filtered, solvents were evaporated in vacuo from the filtrate and the residue was purified by short column chromatography (alumina, EtOAc-MeOH) to yield 4.78 g (65%) of diol VI as a white amorphous solid, mp 55-56°C after recrystallization from EtOAc. IR (deposit): 3379 (O-H), 1120 (C-O). PMR: 3.30-4.40 (m,18H), 6.98-7.75 (m,6H).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.04; H, 7.25.

Method B.-To a nitrogen purged solution of 2,3-dihydroxynaphthalene (80 g, 0.5 mole) in 1500 ml of n-BuOH, NaOH (40 g, 1.0 mole) was added and the mixture was brought to reflux. Then 2-(2-chloroethoxy)ethanol (125.0 g, 1.0 mole) was added dropwise with stirring and the mixture was refluxed for 20 hrs. After washing, acidification with 6 N HCl, and concentration in vacuo, the residue was vacuum distilled to give a main fraction of 86 g and bp 210-250°/0.3 torr which solidified on storage. This fraction was chromatographed on a silica gel column using EtOAc as eluent. The

first fraction 16.5 g, 13% was identified as 2-hydroxy-3-[2'-(2"-hydroxyethoxy)ethoxy]naphthalene (VII), white crystals, mp. 122-124°C. IR (deposit): 3450 (O-H), 1134 (C-O). PMR [$(CD_3)_2CO$]: 3.00 (s,2H,H_2O). 3.65 (br s,5H), 3.90-4.27 (2 x t,4H), 7.06-7.41 (m,4H), 7.41-7.77 (m,2H), 8.18 (s,1H).

Anal. Calcd for $C_{14}H_{18}O_5$ (anhydrous form): C, 67.73; H, 6.49. Found: C, 67.95; H, 6.44.

The second eluted fraction of 28.2 g (17%) was the title diol VI.

2,3-Bis(5-hydroxy-3-oxa-1-pentyloxy)naphthalene ditosylate (VIII).-A solution of the diol VI (6.75 g, 0.02 mole) in pyridine (10 ml) was cooled below 0°C and a solution of tosyl chloride (8.5 g, 0.044 mole) in pyridine (10 ml) was added dropwise with stirring at a rate which kept the temperature of the reaction mixture below -2°C. The reaction mixture was kept overnight at 4°C and then poured over ice. Extraction with CH_2Cl_2 followed by washing with cold 6 N HCl and water, drying over anhydrous $MgSO_4$ and evaporation of the solvent in vacuo afforded 12.2 g (95%) of pure product as a white amorphous solid, mp 90-91°C (from Et_2O-EtOH). IR (deposit): 1354, 1176 (SO_2), 1134 (C-O). PMR: 2.35 (s,6H), 3.65-4.35 (m,16H), 7.05-7.95 (m,14H).

Anal. Calcd for $C_{32}H_{36}O_{10}S_2$: C, 59.61; H, 5.63. Found: C,59.52; H, 5.78.

2,3-Bis(5-chloro-3-oxa-1-pentyloxy)naphthalene (IX).-To a stirred and refluxing solution of the diol VI (9.30 g, 0.028 mole) in 100 ml of dry C_6H_6 and 5.0 g (0.06 mole) of pyridine, $SOCl_2$ (7.5 g, 0.06 mole) was added dropwise. The mixture was refluxed for 20 hrs. After cooling, the reaction mixture was acidified with 10% HCl (25 ml). The C_6H_6 layer was separated, the aqueous solution was extracted with C_6H_6 (30 ml) and the combined extract was washed with H_2O. After evaporation of

benzene in vacuo, the crude product was purified by column chromatography (silica gel, pet.ether, bp 30-60°C-EtOAc, 1:1). A brown solidifying oil was decolorized by boiling with decolorizing carbon in an EtOH solution to give, after recrystalization from EtOH, 8.0 g (76%) of the dichloride IX as slightly yellow crystals, mp 66-68°C. IR (mull): 1130 (C-O). PMR: 3.50-4.40 (m.16H), 7.10-7.75 (m,6H).

Anal. Calcd for $C_{18}H_{22}Cl_2O_4$: C, 57.92; H, 5.94. Found: C,57.74; H, 5.94.

11-(Benzyloxymethyl)-2,3-naphtho-18-crown-6 (X). Method A.-A solution of 2,3-bis-(5-hydroxy-3-oxa-1-pentyloxy)naphthalene ditosylate VIII (11.3 g, 0.0175 mole) in dry THF (45 ml) was added dropwise to a vigorously stirred mixture of 3-(O-benzyl)glycerol[15,16] (3.2 g, 0.0175 mole) and t-BuOK (4.3 g, 0.038 mole) in THF (175 ml) under nitrogen at 40°C. The mixture was stirred for 24 hrs at 50°C and refluxed for an additional 48 hrs. After cooling, the solvent was removed in vacuo, CH_2Cl_2 was added (50 ml) and the mixture was filtered to remove the salts. The filtrate and washings were combined and washed with water. After evaporation of the solvent in vacuo, the residue was chromatographed (silica gel, pet. ether, bp 30-60°C-EtOAc, 1:1) to yield 1.5 g (19.5%) of the expected product as a heavy yellowish oil which slowly solidified during storage, mp 60-65°C. IR (neat) 1118 (C-O). PMR: 3.35-4.33 (m,21H), 4.48 (s,2H), 7.00-7.75 (m,11H).

Anal. Calcd for $C_{28}H_{34}O_7$: C, 69.69; H, 7.10. Found C,69.43; H, 7.23.

2,3-Bis(2-hydroxyethoxy)naphthalene (XI).-To a solution of 2,3-dihydroxynaphthalene (80 g, 0.5 mole) in 1.5 ℓ of n-butanol which was purged with nitrogen, NaOH (40 g, 1.0 mole) was added and the mixture was brought to reflux. Under nitrogen 2-chloroethanol (80.5 g, 1.0 mole) was added dropwise and reflux was continued for 16 hrs. After the reaction mixture was cooled, acidified with 6 N HCl and concentrated in vacuo, the crude

product was purified by two recrystallizations from EtOH to give 53.7 g (40%) of the monohydrate of diol XI as white crystals, mp 144-146°C. IR (mull): 3288 (O-H), 1120 (C-O). PMR: (pyridine-d_5-D_2O): 4.32 (br s,8H), 5.55 (br s,4H), 7.20-8.05 (m,6H).

Anal. Calcd for $C_{14}H_{16}O_4 \cdot H_2O$: C, 63.15; H, 6.81. Found: C, 63.50; H, 6.94.

2,3-Bis(2-hydroxyethoxy)naphthalene ditosylate (XII).-To a solution of the anhydrous diol XI (8.6 g, 0.035 m) in pyridine (40 ml) which had been cooled below 0°C, a solution of tosyl chloride (14.7 g, 0.077 mole) in pyridine (20 ml) was added with stirring at a rate which kept the reaction mixture temperature below 2°C. The reaction mixture was kept overnight at 4°C and then poured over ice. The precipitated solid was filtered and washed with H_2O. Recrystallization from EtOH afforded 18.6 g (95%) of white crystals, mp 111-112°C. IR (mull): 1361, 1176 (SO_2), 1113 (C-O). PMR: 2.35 (s,6H), 4.10-4.55 (m,8H), 6.95-7.90 (m,14H).

Anal. Calcd for $C_{28}H_{28}O_8S_2$: C, 60.42; H,5.07. Found: C,60.35; H, 5.18.

11-(Benzyloxymethyl)-2,3-naphtho-18-crown-6 (X).Method B.-Under nitrogen a solution of 3,6-dioxa-4-(benzyloxymethyl)-1,8-octanediol[7] (4.6 g, 0.017 mole) and KOH (2.4 g, 0.043 mole) in 20 ml of THF which contained 2 ml of H_2O was brought to reflux and a solution of ditosylate XII (9.5 g, 0.017 mole) in THF (20 ml) was added dropwise with stirring. The mixture was refluxed for 3 days. After cooling, the solvent was removed in vacuo, CH_2Cl_2 (25 ml) was added and the mixture was filtered. The solvent was evaporated from the filtrate in vacuo and the residue was chromatographed (alumina, EtOAc) to yield 3.8 g (46%) of the benzyl-protected crown ether X.

11-Hydroxymethyl-2,3-naphtho-18-crown-6 (III).-Hydrogen gas was bubbled through a stirred and warmed (50°C) solution of the benzyl-protected crown ether X (3.8 g, 0.008 mole) in dioxane (100 ml) which contained a catalytic

amount of p-toluenesulfonic acid and 0.4 g of 10% Pd-C. Hydrogenolysis was conducted for 5 days. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was chromatographed (alumina, EtOAc-MeOH, 10:1) to give 2.0 g (64.5%) of the hydroxycrown III as a white amorphous solid, mp 80-82°C (from MeOH). IR (deposit): 3330 (O-H), 1114 (C-O). PMR: 2.37 (br s, 1H), 3.38-4.35 (m,21H), 7.02-7.80 (m,6H).

Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C,64.05; H, 7.40.

11-Hydroxymethyl-2,3-naphtho-18-crown-6 tosylate (XIII).-A solution of the hydroxycrown III (1.2 g, 0.003 mole) in pyridine (10 ml) was cooled below 0°C and a solution of tosyl chloride (0.85 g, 0.0045 mole) in pyridine (10 ml) was added dropwise. The reaction mixture was kept overnight in a refrigerator, then poured over ice, acidified with ice-cold 6 N HCl and extracted with CH_2Cl_2 (3 x 20 ml). The combined extract was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product which was purified by column chromatography [silica gel, CH_2Cl_2-EtOH (2% v/v)] affording 0.70 g (43%) of the tosylate XIII as a very viscous oil. IR (neat): 1359, 1176 (SO_2), 1120 (C-O). PMR: 2.25 (s, 3H), 3.20-4.20 (m,21H), 6.85-7.70 (m,10H).

11-[(2'-Methoxycarbonylphenoxy)methyl]-2,3-naphtho-18-crown-6 (XIV).-nitrogen, sodium hydride (50% suspension in mineral oil, 0.08 g, 1.6 mmole) was washed with n-pentane and suspended in dry THF (5 ml). To this suspension a solution of methyl salicylate (0.2 g, 1.3 mmole) in THF (5 ml) was added dropwise. After 1 hr, a solution of the tosylate XIII (0.70 g, 1.3 mmole) in THF (10 ml) was added. The reaction mixture was stirred and refluxed for 72 hrs. After cooling, the solvent was removed in vacuo and

the crude product was purified by chromatography on alumina using a pet. ether (30-60°C)-EtOAc, 2:1 mixture as eluent to give 0.5 g (73%) of the ester XIV as a very viscous, colorless oil. IR (neat): 1732 (C=O), 1132, 1118 (C-O). PMR: 3.60-4.35 (m,24H), 6.65-7.80 (m,10H).

11-[(2'-Carboxyphenoxy)methyl]-2,3-naphtho-18-crown-6 (IV).-The ester XIV (0.50 g, 1 mmole) was dissolved in EtOH (10 ml) and a solution of NaOH (0.10 g, 25 mmole) in H_2O (1 ml) was added. After refluxing for 4 hr, the reaction mixture was cooled, the EtOH was removed in vacuo and 6 N HCl was used to make the mixture acidic. Extraction with CH_2Cl_2 (3 x 10 ml), followed by washing with water and drying ($MgSO_4$) afforded, after evaporation of the solvent in vacuo, 0.45 g (93%) of the expected crown ether carboxylic acid IV as a pale yellow glass. IR (neat): 3700-2300 (COOH), 1724 (C=O), 1118 (C-O). PMR: 3.50-4.55 (m,21H), 6.75-8.15 (m,10H). Anal. Calcd for $C_{28}H_{32}O_9$: C, 65.61; H, 6.29. Found: C, 65.67; H, 6.54.

REFERENCES

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1. F. Montanari and P. Tundo, Tetrahedron Lett., 505 (1979).
2. G. W. Gokel, D. M. Dishong and C. J. Diamond, Chem. Commun., 1053 (1980).
3. B. Czech, Tetrahedron Lett., 4197 (1980).
4. I. Ikeda, S. Yamamura, Y. Nakatsuji and M. Okahara, J. Org. Chem., 45, 5355 (1980).
5. K. Fukunishi, B. Czech and S. L. Regen, J. Org. Chem., 46, 1218 (1981).
6. F. Montanari and P. Tundo, J. Org. Chem., 47, 1298 (1982).

7. B. Czech, D. A. Babb and R. A. Bartsch, Org. Prep. Proc. Int., 15, 29 (1983).

8. R. A. Bartsch, G. S. Heo, S. I. Kang, Y. Liu and J. Strzelbicki, J. Org. Chem., 47, 457 (1982).

9. B. Czech, S. I. Kang and R. A. Bartsch, Tetrahedron Lett., 457 (1983).

10. B. Czech, B. Son and R. A. Bartsch, Tetrahedron Lett., 2923 (1983).

11. W. A. Charewicz, G. S. Heo and R. A. Bartsch, Anal. Chem., 54, 2094 (1982).

12. W. A. Charewicz and R. A. Bartsch, J. Membrane Sci., 12, 323 (1983).

13. E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore and D. J. Cram, J. Am. Chem. Soc., 99, 2564 (1977).

14. S. Kopolow, T. E. Hogen-Esch and J. Smid, Macromolecules, 6, 133 (1973).

15. M. Kates, J. H. Chan and N. Z. Stenzel, Biochemistry, 2, 394 (1963).

16. B. T. Bolding and P. V. Ioannou, Synthesis, 423 (1977).

17. T. Miyazaki, S. Yanagida, A. Itoh and M. Okahara, Bull. Chem. Soc. Jpn., 55, 2005 (1982).

18. D. Landini, F. Montanari and F. Rolla, Synthesis, 223 (1978).

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