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SYNTHESIS OF POLYETHER CARBOXYLIC ACIDS WITH A BENZODIOXINIC SUBUNIT

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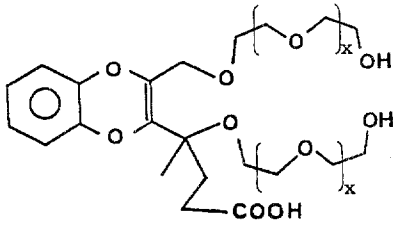
Summary : The synthesis of novel carboxylic polyethers 1 with a benzodioxinic subunit from 2-carboxy-1,4-benzodioxine is described.

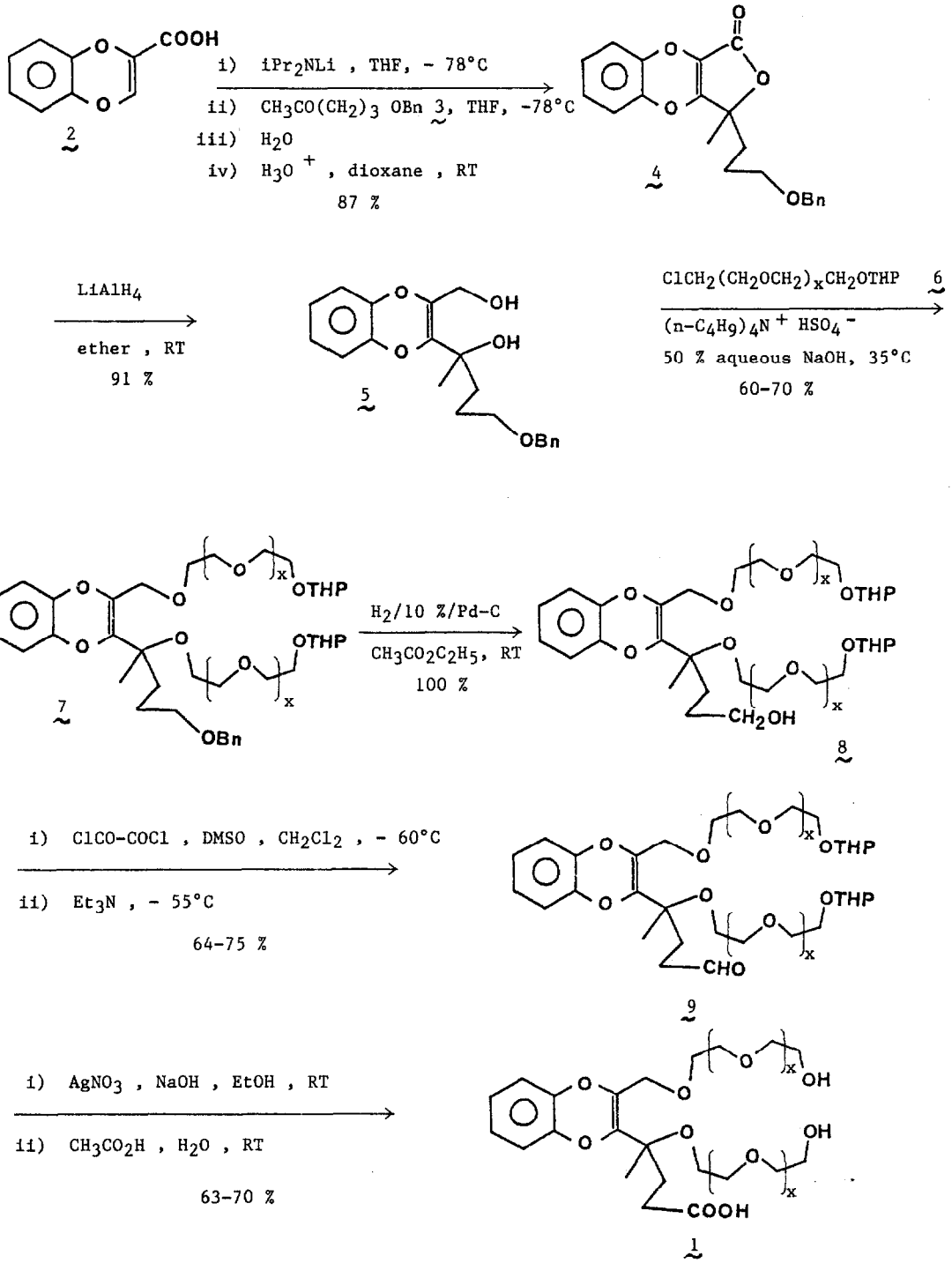
The naturally occuring carboxylic ionophores are known to mediate active ion transport through lipophilic biological membranes by formation of hydrophobic complexes with metal cations. They all have linear backbones into which oxygen-containing heterocyclic rings are inserted. They provide a variety of functional oxygen groups for cation binding including ether, carboxyl, hydroxyl and carbonyl. Carboxylic ionophores are not covalently cyclized and have as a common feature a carboxyl group at the head of the molecule and one or two hydroxyl groups at the tail. They are effectively cyclized by head-to-tail hydrogen bonding and further stabilized by the twists in the asymmetric centers and rings of the backbone[1,2].

The structure and properties of non-cyclic natural ionophores, e.g., nigericin, monensin and lasalocide, have been studied in detail, and also a number of total syntheses have been reported[3-10]. It is, however, difficult to obtain them in large quantities with a high degree of purity. Moreover, owing to the complexity of their chemical structure it is not easy to investigate the various structural and physico-chemical parameters of the complexation and cation transport processes. We believe that the intriguing possibility of designing and constructing a synthetic ligand system capable of mimicking the transport properties of these complex ionophores merits further attention[11-16] and we report herein our approach to this goal.

Some years ago we published a versatile synthesis of benzodioxinic macrocyclic polyethers[17-18]. In this paper we describe a convenient procedure for the preparation of new polyethers 1 containing both a carboxy and an hydroxy group.



1a x = 1
1b x = 2


COOH
i) iPr2NLi , THF, - 78°C
ii) CH3CO(CH2)3 OBn 3, THF, -78°C
iii) H2O
iv) H3O+ , dioxane , RT
87 %
2
4
OBn
LiAlH4
ether , RT
91 %
5
OH
OH
OBn
ClCH2(CH2OCH2)xCH2OTHP 6
(n-C4H9)4N+ HSO4-
50 % aqueous NaOH, 35°C
60-70 %
7
OTHP
OTHP
OBn
H2/10 %/Pd-C
CH3CO2C2H5, RT
100 %
8
CH2OH
i) ClCO-COCl , DMSO , CH2Cl2 , - 60°C
ii) Et3N , - 55°C
64-75 %
9
CHO
i) AgNO3 , NaOH , EtOH , RT
ii) CH3CO2H , H2O , RT
63-70 %
1
COOH

Scheme

Polyethers compounds 1 were prepared starting from readily available and inexpensive 2-carboxy-1,4-benzodioxine 2[19] according to the scheme. The dianion of 2, obtained by reaction with lithium diisopropylamide (2.2 eq.) in tetrahydrofuran, was reacted with 1.5 equivalents of the 5-benzyloxy-2-pentanone 3[20] to give, after hydrolysis and acidic treatment, the expected lactone 4. Reduction of this lactone with lithium aluminium hydride in anhydrous ether produced the diol precursor 5 (80 % overall yield from 2). Bisalkylation of 5 with chlorotetrahydropyranyl ethers 6, synthesised with quantitative yield by the method of Cram et al.[20], occurred with 50 % aqueous sodium hydroxide in the presence of tetrabutylammonium hydrogen sulfate. After hydrogenolysis with 10 % palladium on carbon in ethylacetate, compounds 7 afforded the corresponding alcohols 8 as an oil, in quantitative yield. Use of methanol or ethanol induces the destruction of the starting material. After the failure of the direct oxidation of the alcohols to the corresponding carboxylic acids, we first used the Swern oxidation[22], then we oxidised the aldehydes with silver nitrate in the presence of ethanolic sodium hydroxide[23] and obtained the corresponding carboxylic acids 9. Hydrolysis of these acids with aqueous acetic acid[24] lead to the expected compounds 1 with a fair yield[25].

Studies of cation binding properties and the transport ability of these carboxylic polyethers 1 with the benzodioxinic subunit are in progress. Preliminary results indicate that the natural non-cyclic ionophores, e.g., monensin are stronger binders for Na^+ and K^+ than the synthetic compounds 1.

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25 - 1a : viscous oil. MS m/z : 438 (M^+ - 18). IR (film) cm^{-1} : 3500 - 3400 (br, OH), 1725 (C = O). NMR (300 MHz - $CDCl_3$) δH : 1,41 (s, 3H, CH_3) ; 2.11 - 2.23 (m, 2H, CH_2); 2.39 - 2.66 (m, 2H, CH_2) ; 2.70 - 3.20 (b s, 2H, OH) ; 3.47 - 3.81 (m, 16H, OCH_2) ; 4.41 and 4.63 (2d, 2H, J = 13.9 Hz, 2H) ; 6.60 - 6.79 (m, 4H, aromatic).
1b : viscous oil. MS m/z : 526 (M^+ - 18). IR (film) cm^{-1} : 3500-3400 (br, OH), 1720 (C = O). NMR (300 MHz - $CDCl_3$) δH : 1.38 (s, 3H, CH_3) ; 2.09 - 2.20 (m, 2H, CH_2) ; 2.37 - 2.59 (m, 2H, CH_2) ; 2.70 - 3.20 (b s, 2H, OH) ; 3.49 - 3.80 (m, 24H, OCH_2) ; 4.29 and 4.41 (2d, 2H, J = 13.9 Hz, 2H) ; 6.61 - 6.80 (m, 4H, aromatic).
The intermediate products were fully characterised by spectroscopic and analytical data.

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