Pergamon

Tetrahedron Letters, Vol. 38, No. 41, pp. 7259-7262, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01686-9

Chiral Azacrown Ethers Derived from D-glucose as Catalysts for Enantioselective Michael Addition

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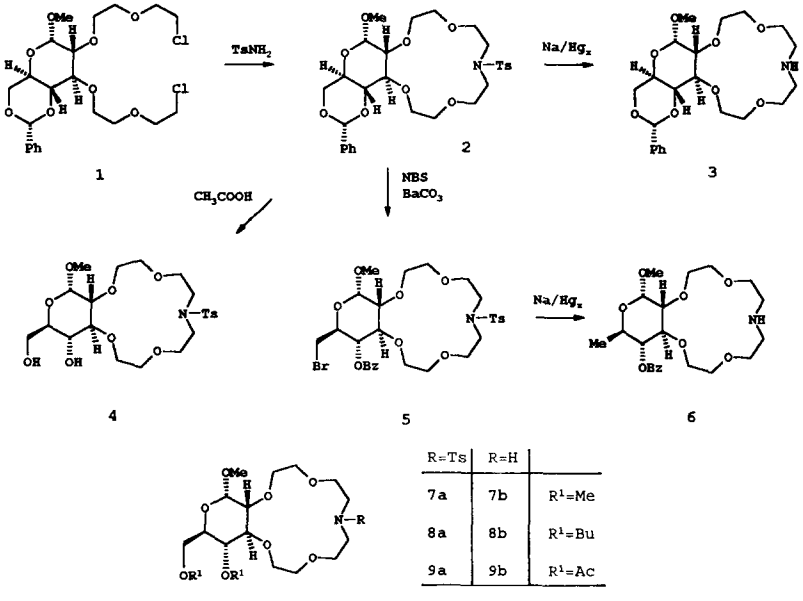
Abstracts: Chiral monoaza-crown ethers incorporating glucose units have been synthesized and applied as phase transfer catalysts in the enantioselective Michael addition of 2-nitropropane to a chalcone to give the corresponding adduct in enantiomeric excess up to 90%. © 1997 Elsevier Science Ltd.

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral catalysts. A number of chiral crown ethers have been employed as chiral catalysts in phase transfer reactions.[1] The Michael reaction is one of the most important C-C bond-forming reactions, and stereoselective variants have been extensively investigated in recent years. High asymmetric inductions have been reported in Michael addition of methyl phenylacetate to methyl acrylate catalyzed by chiral crown ethers.[2a-h] The effect of certain catalysts on the stereoselective addition of nitroalkanes to methyl vinyl ketone[2i] and to enones[2j] was studied recently. We have previously reported the synthesis of new 15-membered ring monoaza-crown ethers from glucose and galactose[3] and their application as catalysts in an asymmetric Michael addition[4,5] and in a Darzens condensation.[4] We first began investigating the addition of 2-nitropropane to a chalcone catalyzed by chiral macrocyclic polyethers under phase transfer conditions. The best result achieved in this reaction was 60% ee for the *S*-antipode.[4,5]

We now report on the synthesis of some new chiral monoaza-crown ethers incorporating glucose units (Scheme 1) and their asymmetric induction in the Michael addition mentioned above.

The chiral starting macrocycle **2** needed for the preparation of the derivatives **3-9** was obtained from the "half-crown" **1**[3,6] by treatment with 1 molar equivalents of p-toluenesulfonamide in DMF (in dilute solution 2-3%) in the presence of dry K_2CO_3 (reflux, 36 h) in 42% yield after chromatography. Compound **2** was deprotected to **3** by 4% sodium amalgam in the presence of dibasic sodium phosphate in methanol (reflux, 20 h) in a yield of 92%, as reported for similar compounds.[7] Our attempt to form **3** by reductive removal of the N-tosyl groups in **2** by $LiAlH_4$ in THF[8] was not successful and caused the macrocyclic ring to open. The benzylidene group was removed selectively from **2** with 96% aqueous acetic acid for 2 h at 100 °C, resulting in the dihydroxy compound **4** in 92% yield. Alkylation or acylation of **4** furnished compounds (**7a, 8a, 9a**), which

upon treatment with sodium amalgam gave the required crown amines (**7b, 8b, 9b**). The reaction of compound **4** with methyl iodide, in DMF, in the presence of barium oxide[9] (8 h, r.t.) resulted in the dimethyl derivative **7a**, followed by reduction to the corresponding amine **7b** in 78% overall yield. The dibutyl derivative **8a** was synthesized from **4** using butyl bromide in dry DMF containing NaH, for 40 h at 40 °C, cleavage of the tosyl group of **8a** furnished the amine **8b** in 58% overall yield. Crown ether **4** was also allowed to react with acetic anhydride in pyridine to yield the diacetyl derivative **9a**, reduction of which afforded the crown amine **9b** in 75% yield for the two steps.



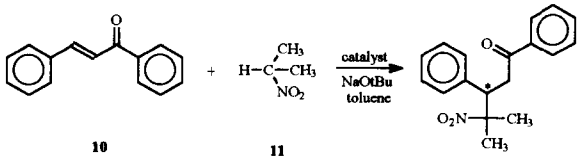
Scheme 1

The cleavage of the acetal ring in **2** can be performed in regioselective manner using Hanessian's method.[10] Treatment of **2** with boiling carbon tetrachloride containing N-bromo-succinimide, barium carbonate, and benzoyl peroxide for 3 h yielded 88% of the 4-benzoyl-6-bromo-6-deoxy derivative **5**. The structure of **5** was proved by the reduction with sodium amalgam to give the 4-benzoyl-6-deoxy derivative **6** whose ^{1}H NMR spectrum contained a doublet at δ 1.23 for the CH_3CH. All new compounds displayed satisfactory spectral and analytical data in full agreement with their structures.[11]

We examined the effect of these new compounds as chiral catalysts in the enantioselective Michael addition of 2-nitropropane **11** to chalcone **10** under solid-liquid phase transfer conditions (Scheme 2).

Our experiments were carried out in toluene employing solid sodium tert-butoxide as base in the presence of 7 mol% catalyst.[12] After preparative TLC work-up the asymmetric inductions expressed in terms of enantiomeric excess (ee) values were determined by optical rotation, the absolute configuration assigned by

comparison of specific rotation with literature value.[4,5] The results of these experiments are presented in Table 1.



10 11 12

Scheme 2

Table 1: Enantioselective Addition of 2-Nitropropane **11** to Chalcone **10** Catalyzed by Chiral Crown Ethers[a]

Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2**	26	28	4 (*S*)
2	**3**	11	73	61 (*S*)
3	**5**	24	20	6 (*S*)
4	**6**	9	77	55 (*R*)
5	**7a**	22	25	6 (*S*)
6	**7b**	15	68	34 (*S*)
7	**8a**	18	35	10 (*S*)
8	**8b**	9	82	90 (*S*)[d]
9	**9a**	28	23	5 (*S*)
10	**9b**	14	65	47 (*S*)

[a] In toluene, at room temperature, 35 mol% $NaOBu^t$ was used. [b] Based on substance isolated by preparative TLC; [c] Determined by optical rotation, absolute configuration are give in parantheses. [d] Checked by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent[5].

It can be seen that the crown ethers having tosyl groups on the N-atom (**2, 5, 7a, 8a, 9a**) resulted in a low chemical yield and very poor selectivities (entries 1, 3, 5, 7, 9). The catalytic activity and enantioselectivity dramatically increased in the presence of catalysts **3, 6, 7b, 8b, 9b** all having free NH group. It is probable that, the N-Ts amide part in the crown ring depreciates the complex-forming properties and its steric hindrance may play an essential role too. Among all the catalysts tested, the compound **8b** proved to be the best: optical purity of 90% for the *S*-antipode and a chemical yield of 82% were obtained (entry 8). It is interesting to note that, while all the catalysts, except **6**, gave the *S*-enantiomer, the 6-deoxy derivative **6** gave the product with opposite configuration ; the *R*-antipode was obtained in 55% ee (entry 4).

In conclusion, we have studied the enantioselective Michael addition of 2-nitropropane to a chalcone in the presence of glucose based monoaza-crown ethers as phase transfer catalysts. We have proved, both chemical yield and optical purity significantly depend on the substituents on the sugar part, the butyl groups proved to be the most effective (90% ee). Furthermore all of the successful catalysts have a free NH group in the cycle making probable the H-bond involvement in the transition state structures.

Further investigations including mechanistic studies are in progress.

Acknowledgements: This work was partly supported by the Hungarian Academy of Sciences and the National Science Foundation (OTKA T 015677).

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11. For instance, **2**: mp 127-29°C; $[\alpha]_D^{20}$ + 15.6 (c=2, $CHCl_3$); MS (CI): m/z 594 (MH^+); ^1H NMR ($CDCl_3$) δ (ppm): 2.35 (s, 3H), 3.4 (s, 3H), 3.47-4.0 (m, 20H), 4.25 (d, J=4.8Hz, 2H), 4.82 (d, J=3.6Hz, 1H), 5.5 (s, 1H), 7.2-7.7 (m, 9H). **3**: mp 116-17°C; $[\alpha]_D^{20}$ + 46.6 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$): 2.75 (t, 4H), 3.1 (s, 1H), 3.4 (s, 3H), 3.47-4.0 (m, 16H), 4.27 (d, J=4.8Hz, 2H), 4.86 (d, J=3.6 Hz, 1H), 5.52 (s, 1H), 7.2-7.5 (m, 5H). **6**: $[\alpha]_D^{20}$ + 19.3 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.23 (d, J=2.5Hz, 3H), 2.45 (t, 4H), 3.05 (s, br, 1H), 3.4 (s, 3H), 3.45-4.0 (m, 13H), 4.47-4.95 (m, 4H), 7.22-7.4 (m, 5H). **8b**: $[\alpha]_D^{20}$ + 58.9 (c=1, $CHCl_3$); ^1H NMR: 0.9 (t, 6H), 1.14-1.73 (m, 12H), 2.45 (t, 4H), 2.8-3.05 (m, 5H), 3.4 (s, 3H), 3.45-4.8 (m, 14H), 4.9 (d, J=3.6Hz, 1H).
12. A typical experimental procedure is as follows:Under argon atmosphere, sodium tertiary butoxide (0.5 g, 0.5 mmol) was added to a solution of chalcone **10** (0.3 g, 1.44 mmol), 2-nitropropane (0.3 mL, 3.36 mmol) and crown ether (0.1 mmol) in anhydrous toluene (3 mL) and the mixture was stirred at room temperature. After completing the reaction a mixture of toluene (7 mL) and water (10 mL) was added. The organic phase was processed in the usual manner. The product was purified on silica gel by preparative TLC with hexane-ethyl acetate (10:1) as eluent (development in UV light).

(*Received in UK* 26 *June* 1997; *revised* 8 *August* 1997; *accepted* 15 *August* 1997)