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ASYMMETRIC MICHAEL REACTION USING MACROCYCLIC LACTOSE DERIVATIVES AS CHIRAL CATALYSTS.

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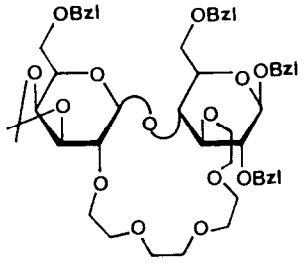
Summary. - Macrocyclic lactose derivatives complexed to potassium bases catalysed the Michael addition of phenyl- and naphthylacetic esters to methyl acrylate to give the corresponding adducts in enantiomeric excess ranging from 20 to 70%.

Asymmetric Michael reaction using chiral auxiliaries (internal asymmetric induction) has been reported[1-6]. However, the use of chiral catalysts, solvents, and complexing agents (external asymmetric induction), although highly desirable, is still far from being fully developed. There are very few examples of asymmetric Michael addition using chiral catalysts[7]. Cram et al. have reported interesting results on the use of the chiral crown ethers complexed with potassium bases[7b].

We now report our preliminary results on the use of the chiral macrocycles 1 - 4,



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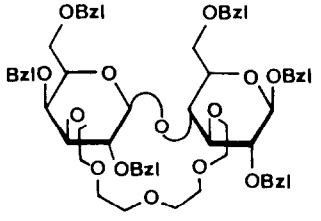

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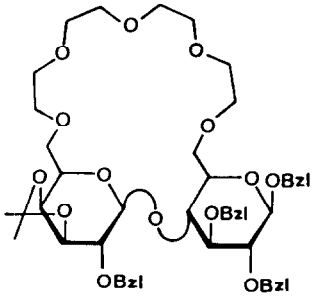

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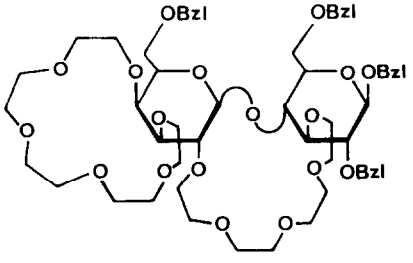

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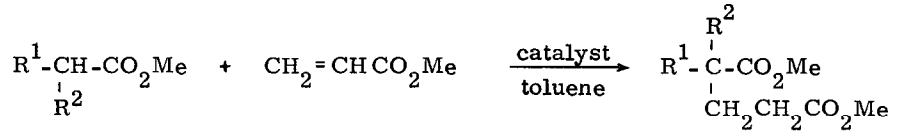
synthesised from lactose derivatives and polyethylenglycol ditosylates[8], complexed to KBu^tO or KNH_2, as catalysts in the asymmetric Michael addition of compounds 5a-c to methyl acrylate.

Methyl 1-naphthylacetate (5a), methyl phenylacetate (5b), and methyl 2-phenylpropionate (5c) were added to methyl acrylate in toluene in the presence of compounds 1 - 4 and KBu^tO or KNH_2 to give adducts 6a-c with reasonable enantiomeric excess (e.e.). Table I shows the reaction conditions and yields.

Table I. Chiral catalysis of Michael addition



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a, R^1 = Naph, R^2 = H
b, R^1 = Ph, R^2 = H
c, R^1 = Ph, R^2 = Me

Compound	Catalyst Host : Base	T °C	t / h	Yield % [a]	e.e. %
5a [b]	1 : KBu^tO	-78	5	58	21 (S) [c]
5a [b]	2 : KBu^tO	-78	5	45	63 (S) [c]
5a [b]	3 : KBu^tO	-78	5	84	37 (S) [c]
5b [d]	1 : KBu^tO	-78	1	67	26 (S) [e]
5b [d]	2 : KBu^tO	-78	1	73	70 (S) [e]
5b [d]	3 : KBu^tO	-78	1	98	36 (S) [e]
5c [f]	1 : KNH_2	-50	12	22	32 (S) [e]
5c [f]	2 : KNH_2	r.t.	2	65	16 (S) [e]
5c [f]	3 : KNH_2	-50	12	49	47 (S) [e]
5c [f]	3 : KNH_2	r.t.	1	72	39 (S) [e]

[a] The yields are based on the amount of reacted starting material. [b] Host : Base : 5a : acrylate ratio 1 : 1 : 18 : 15. [c] Enantiomeric excess was determined by ^{1}H-N.M.R. using chiral chemical shift reagents. The absolute configuration was tentatively assigned. [d] Host : Base : 5b : acrylate ratio 1 : 1 : 35 : 20. [e] Based on data from D.J. Cram and G.D.Y. Sogah, J. Chem. Soc., Chem. Comm., 1981, 625. [f] Host : Base : 5c : acrylate ratio 1 : 2.5 : 40 : 24.

Reaction of 5a and 5b with methyl acrylate in the presence of 1, 2 or 3 and KBu^tO gave 6a and 6b in 22 to 70% e.e. The best results were obtained with compound 2. Compound 5c did not react under the same conditions and was recovered unaltered from the reaction mixture. When KNH_2 was used as base, macrocycles 1 and 3 catalysed the reaction of 5c at -50° C giving 6c in 32 and 47% e.e., respectively. Reaction of 5c in the presence of macrocycle 2 in these conditions took only place at room temperature to give 6c in 16% e.e. In contrast to these results macrocycle 4 did not gave any asymmetric induction in the reaction of 5b with methyl acrylate. Similarly, no enantiomeric excess was obtained when the non-cyclic lactose derivative benzyl 2,3,6,2',6'-penta-O-benzyl-3',4'-O-isopropylidene-β-lactoside was used instead of compounds 1 - 4 in the reaction of 5a with methyl acrylate.

In a typical experiment, methyl phenylacetate (5b, 1.37 mmol) in toluene (1 mL) was added dropwise to a suspension of KBu^tO (0.035 mmol) in toluene (1 mL) under argon atmosphere at -78° C. A solution of 2 (0.037 mmol) in toluene (1 mL) was added after 15 min and the mixture was stirred for a further 15 min period. Methyl acrylate (0.68 mmol) in toluene (1 mL) was then added dropwise. After 1 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (15 mL) and extracted with toluene. The extract was dried (Na_2SO_4), evaporated, and chromatographed on a column of silica gel (6:1 hexane-ethyl acetate) to give 6b (116.8 mg, 73%), $[\alpha]_D^{20}$ +62 (c 1.6, EtOH). Compound 2 was recovered by elution with ethyl acetate and reutilised.

Further experiments using different bases and variable amounts of macrocyclic compounds are in progress.

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