



Asymmetric Diels-Alder : Monobenzylated Isosorbide and Isomannide as Highly Effective Chiral Auxiliaries

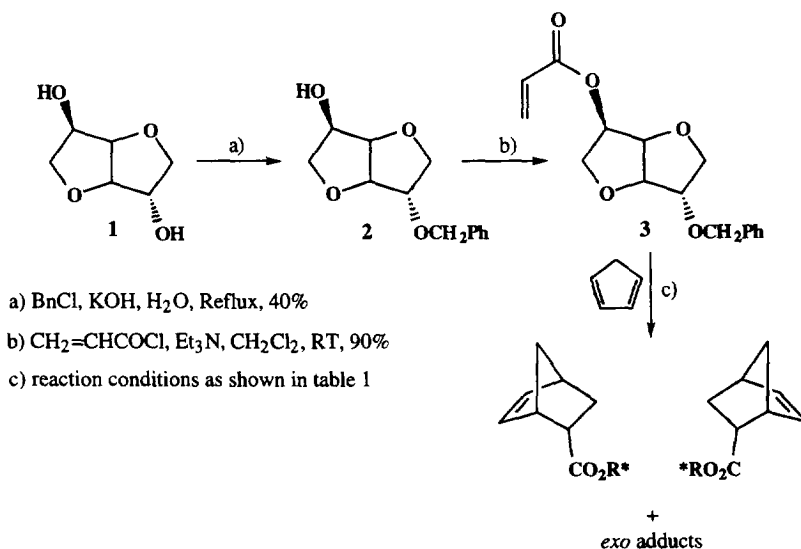
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Abstract : Lewis acid promoted Diels-Alder reactions of acrylate esters from monobenzylated isosorbide or isomannide and cyclopentadiene provided exclusively *endo*-adducts with good yields and high diastereoselectivities. The *R/S* selectivities are quasi total and opposed using either isosorbide or isomannide derivatives. Copyright © 1996 Published by Elsevier Science Ltd

1,4:3,6 dianhydro-D-glucitol (isosorbide) **1** is an important well-documented by-product of the starch industry obtained by dehydration of D-glucitol¹. It is thermally stable, of low cost, and available in large quantities. Since a few years, our laboratory bears interest on this compound and their monobenzylated derivatives in position 2 or 5^{2,3}. These chiral monoalcohols are consequently serious candidates in asymmetric synthesis⁴.

In this paper, we report the results obtained for the Diels-Alder reaction of acrylate **3** derived from *exo*-monobenzylated isosorbide **2** with cyclopentadiene (Scheme 1).



Scheme 1

Different Lewis acids were tested as well as montmorillonites which were previously shown to be efficient in this procedure^{5,6}. The Diels-Alder reaction of chiral dienophile **3** and cyclopentadiene was carried out in different solvents. The analysis of the cycloadducts was performed using ¹H NMR. The diastereomeric ratio

was determined by ^1H NMR and confirmed by visualization, after reduction with LiAlD_4 , of enantiomers in a polybenzyl L-glutamate liquid-crystal through deuterium NMR⁷ spectroscopy which also allows the determination of absolute configurations⁸.

Table 1 Diels-Alder Reactions of Acrylate Ester from Isosorbide 3 with Cyclopentadiene⁹

Entry	Catalyst (equiv.)	Solvent	Temp. °C (time)	Yield a (%)	Endo/Exo b)	R endo/S endo b) c)
1	-	CH_2Cl_2	20 (24h)	68	60:40	54:46
2	SnCl_4 (1)	"	20(45mn)	71	89:11	12:88
3	SnCl_4 (2)	"	-78 (15mn)	80	>99:1	9:91
4	"	"	20 (10mn)	77	>99:1	4:96
5	"	Et_2O	20(1h)	74	>99:1	28:72
6	"	PhMe	-78 (30mn)	92	>99:1	12:88
7	TiCl_4 (2)	CH_2Cl_2	-78 (15mn)	80	>99:1	14:86
8	EtAlCl_2 (2)	"	-78 (15mn)	80	>99:1	74:26
9	"	"	20 (15mn)	71	89:11	65:35
10	"	Et_2O	20(1h)	60	93:7	87:13
11	ZnCl_2 (2)	CH_2Cl_2	20(2h)	96	82:18	67:33
12	AlEt_3 (2)	"	20(15h)	36 f)	70:30	54:46
13	$\text{BF}_3\text{-OEt}_2$ (2)	"	20(5h)	29 f)	85:15	72:28
14	KSF d)	"	20(48h)	99	66:34	58:42
15	K10 d)	"	20(48h)	40 f)	69:31	69:31
16	ZnCl_2 /K10 d) e)	"	20(16h)	91	83:17	66:34
17	ZnCl_2 /K10 d)e) (2)	"	20 (several days)	50	>99:1	64:36

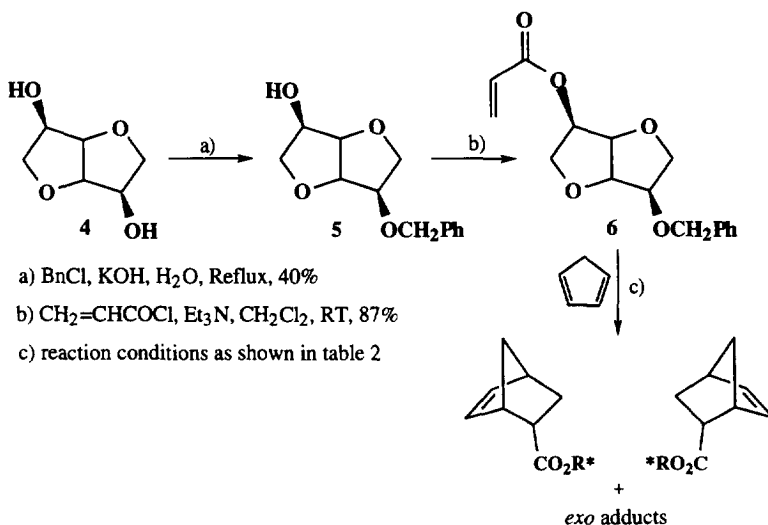
a) isolated yields b) determined by ^1H NMR c) confirmed by deuterium NMR spectroscopy
 d) 1g of microwave dried solid for 1 mmole of substrat e) ZnCl_2 /K10 is a Fluka product (0.35 mmol Zn /g)
 f) incomplete reaction

The present Diels-Alder reaction showed the following selectivity:

- 1) Lewis acid with only a single coordination site (EtAlCl_2 and $\text{BF}_3\text{,OEt}_2$) showed R-endo selectivity (entries 8-10, 13).
- 2) chelating Lewis acids (SnCl_4 and TiCl_4) showed S-endo selectivity (entries 2-7).
- 3) solid Brönsted acids (K10 and KSF clays) gave lower yields or/and selectivities (entries 14-17).
- 4) the CH_2Cl_2 is a better solvent than Et_2O or PhMe (entries 4-6).

When compared to literature¹⁰, the results we obtained show the interest of isosorbide derivatives as chiral auxiliary. Results are at least as good or even better than those using classical camphor, menthol or 8-phenyl menthol derivatives¹¹ or more recently L-quebrachitol (a cyclitol)¹², sulfonamido indanols¹³ and 9-anthrylcarbinols¹⁴.

Furthermore, we evaluated the behaviour of monobenzylated isomannide **5** as a very close parent molecule, isomannide **4** being the isomer of isosorbide where both hydroxyl groups in position 2 and 5 are endo (scheme 2).



Scheme 2

Table 2 Diels-Alder Reactions of Acrylate Ester from Isosorbide **6** with Cyclopentadiene in CH₂Cl₂

Entry	Catalyst (equiv.)	Temp.°C (time)	Yield (%)	Endo / Exo	R endo/S endo
18	SnCl ₄ (2)	-78 (30mn)	20	>99:1	60:40
19	EtAlCl ₂ (2)	-70 (1h)	79	>99:1	95:5
20	ZnCl ₂ / K10	20 (16h)	93	80:20	66:34 a)

a) absolute configuration was confirmed by optical rotation of alcohol resulting from LiAlH₄ reduction of cycloadducts ([α]_D²² + 28 (c 1.065, EtOH 95%) lit. [α]_D²² + 87 (c 1.0, EtOH 95%))¹⁵.

When compared to isosorbide derivative (Table 1, entry 8), using EtAlCl₂ as a catalyst, a significant improvement in *R-endo* selectivity is obtained (entry 19).

This result thus constitutes a noticeable complement to the SnCl₄-promoted reaction with isosorbide derivative (Table 1, entry 4) where almost complete *S-endo* selectivity is observed.

The exaltation of *R-endo* selectivity with the isomannide auxiliary can be due to a π -stacking interaction between acrylate double bond and phenyl moiety from benzylic protection. Further studies are in development to check this point.

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9. Typical procedure: 200 mg of chiral acrylate was dissolved under argon in the adequate solvent before addition of cyclopentadiene (2-5 equivalents). After cooling at the desired temperature, the catalyst is introduced. Reactions were hydrolyzed with NaHCO₃ or NH₄Cl solutions. They are monitored by tlc and analyzed by ¹H and ¹³C NMR and GC-MS. The order of reactants addition is not important.
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