## Methyl 3,4-O-methylene- $\beta$ -D-arabinoside as a new Chiral Template for the Asymmetric Diels-Alder Reaction

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Key words : Asymmetric Diels-Alder reaction, carbohydrates, arabinose

## **Abstract** : The acrylate of the methyl 3,4-O-methylene- $\beta$ -D-arabinoside is a very stable and efficient chural dienophile for asymmetric Diels-Alder reactions with cyclopentadiene, isoprene and dimethyl butadiene.

Many chiral compounds have been developed for the asymmetric Diels-Alder reaction. Carbohydrates are continuously renewable raw materials and their use in chiral organic chemistry is increasing<sup>1</sup>. However, their use as chiral templates in the asymmetric Diels-Alder reaction has received little attention<sup>2</sup>, especially when the chiral carbohydrate moiety is attached to an acrylate<sup>3</sup>.

Chiral acrylates or acrylamides derived from chiral alcohols like phenyl menthol<sup>4</sup> and pantolactone<sup>5a</sup> or amides like proline<sup>6</sup> and sultam<sup>7</sup> have proved to be efficient dienophiles for the asymmetric Diels-Alder reaction. The preparation of the chiral dienophile is sometimes tedious, particularly for large scale synthesis, and it is often difficult to synthesize the chiral auxiliary leading to the opposite enantiomer.

Due to the variety of the configurations of their asymmetric centers, natural carbohydrates promise to constitute an important source of chiral templates for asymmetric induction.

The synthesis of the very stable 3,4-O-methyleneacetal of methyl  $\beta$ -D-arabinoside (2) has been achieved in our laboratory by a very simple, selective and efficient method starting from commercialy available methyl  $\beta$ -D-arabinoside (1) or D-arabinose<sup>8</sup>. The advantage of the methyleneacetal protection is its high stability in acidic medium and its resistance to Lewis acid cleavage<sup>9</sup>.



The acrylate 3, obtained pure in good yield, was reacted with cyclopentadiene, isoprene or dimethyl butadiene in the presence of various Lewis acids and these reactions led to the major adducts 4, 5 and 6; the results for asymmetric induction are summarized in table 1.

Diastereoisomeric excesses are good to excellent.

Due to the steric shielding of the  $OCH_3$  group of the sugar, the approach of the diene is favored on the *Re* face of the double bond. This leads to the major (2S) adduct. The side of the approach is the same with Lewis acids that have the capability of tetracoordination (EtAlCl<sub>2</sub>, BF<sub>3</sub>) as with TiCl<sub>4</sub> and SnCl<sub>4</sub>, but the de are lowered.

Table 1	
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dienes	LA, eq	Solvent	Temp°C <sup>(a)</sup>	Time h	Yield	endo/exo	%S/R	de%
	TiCl <sub>4</sub> , 1 2 TiCl <sub>4</sub> , 2 BF <sub>3</sub> , 2 EtAICl <sub>2</sub> , 2 SnCl <sub>4</sub> , 2 SnCl <sub>4</sub> , 1	$\begin{array}{c} CH_2CI_2\\ Toluene\\ CH_2CI_2\\ CH_2CI_2\\ CH_2CI_2\\ CH_2CI_2\\ CH_2Ci_2 \end{array}$	-40 -78 -78 -78 -78 -78 0	8 10 9 7 8 10	39 71 46 60 93 62	90/10 >99/1 >99/1 >99/1 98/2 98/2	72/28 100/0 80/20 73/27 96/4 95/5	44 >99 (c) 60 46 92 90
Ĺ	TıCl <sub>4</sub> , 1 2 SnCl <sub>4</sub> , 1 2	Toluene CH <sub>2</sub> Cl <sub>2</sub>	0 0	12 12	65 40	(b)	81/19 50/50	62 (d) 0
X	ТіСІ <sub>4</sub> , 1 SnCl <sub>4</sub> , 1 SnCl <sub>4</sub> , 1 SnCl <sub>4</sub> , 1	Toluene CH <sub>2</sub> Cl <sub>2</sub> Toluene CH <sub>2</sub> Cl <sub>2</sub>	0 0 0 RT	12 12 12 12	49 70 60 46		100/0 >99/1 >99/1 98/2	>99 >98 >98 96

For each adduct an authentic synthesis of the 50/50 diastereoisomeric mixture was accomplished from 2 and racemic norbornene, cyclohexene or dimethylcyclohexene carboxylic acid chloride R and S adducts from cyclopentadiene are well resolved by HPLC and 400 MHz<sup>1</sup>H NMR The R/S ratio of the adducts from isoprene and dimethyl butadiene can be only determined by <sup>1</sup>H NMR in  $C_6D_6$  as solvent<sup>10</sup> (a) and additional 12 h at room temperature (b) presence of the 1,3 isomer 20% (c)-(d) saponification of these adducts can be carried out with LiOH in THF/water under experimental conditions thorougthly described by Helmchen<sup>5b</sup>, the corresponding carboxylic acid is obtained in 93-97% and the alcohol 2 recovered in 90% yield  $[\alpha]_D^{20}$ -146 (c 1, 95% EtOH) for (c) and  $[\alpha]_D^{20}$ -60 (c 1, 95% EtOH) for (d)

In most cases reported in the literature, high levels of diastereoselectivities are a consequence of the chelation with Lewis acid, which allows an efficient differentiation of the diastereotopic faces of chiral acrylate. In the reactions reported in table 1, the steric shielding of the  $\beta$ -anomeric methoxyl group is sufficient to ensure a total differentiation of the *Re* and *Si* faces of the acrylate

To our knowledge, these results are the first reported of the use of a simple carbohydrate acrylate as chiral dienophile for asymmetric Diels-Alder reaction<sup>11</sup>. As arabinose is also available in the L form, the (R) enantiomers of the resulting acids could also be obtained.

The authors gratefully thank "Roquette Frères" for financial support References and notes

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- 9 Kunz, H., Muller, B.; Schanzenbach, D Angew Chem 1987, 99, 269-271 This is the only example where the acrylate is attached to a protected carbohydrate (glucofuranoside). In this case one or two OH groups are protected as trimethylsilyl ethers. In the presence of  $TiCl_4$ , an alkoxytitane and  $(CH_3)_3SiCl$  are produced, no uncomplexed Lewis acid and HCl are present in the reaction medium the isopropylidene acetals are not cleaved by the Lewis acid.
- 10 In CDCl<sub>3</sub>, for the 50/50 diastereoisomeric mixture, the signals of the two diastereoisomers overlap.
- 11 Very recently, Kunz, H and Stahle, W. reported the use of stable carbohydrates auxiliaries for asymmetric Diels-Alder reactions Synlett, 1991, 260-262