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Synthesis of esters derived from c_2-symmetric chiral diols

Flavia C. M. Zacconi,[#] Liliana C. Koll[*] and Julio C. Podestá[*]

INIQO, Departamento de Química, Universidad Nacional del Sur, Avenida Alem 1253, B8000 Bahía Blanca, Argentina. E-mail: lckoll@criba.edu.ar

Introduction

Search for new chiral auxiliaries is a matter of constant interest in the field of asymmetric organic synthesis, since the choice of a suitable inductor can be crucial for achieving higher stereoselectivity.

Among the chiral organic systems that act as chiral auxiliaries in asymmetric synthesis are the C_2-symmetric diols, that is, those systems which possess a rotation axis so that the molecule appears unchanged after a $2\pi/2$ rotation around that axis.

A known example is that of TADDOL, which, within its multiple applications in stereoselective synthesis, it has been used in cyclopolymerization reactions of its diester derived from methacrylic acid, with formation of stereoregular polymers. Recently, our group has reported the synthesis of various esters derived from this chiral auxiliary (Gerbino *et al.*, 2005) and, as part of the research being carried out, studies on the synthesis of mono- and diesters were began from structural analogues of it. Therefore, diols **Ia** and **Ib** (Fig. 1) were chosen.

The synthesis of these diols was carried out following Helmchen's technique (Hartmann *et al.*, 1987) by the reaction of anthracene and *bis*-(*S*)-methyllactate fumarate as chiral dienophile.

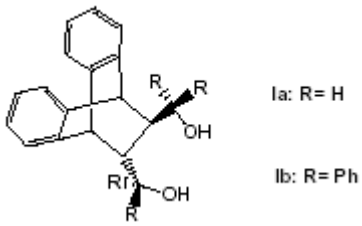
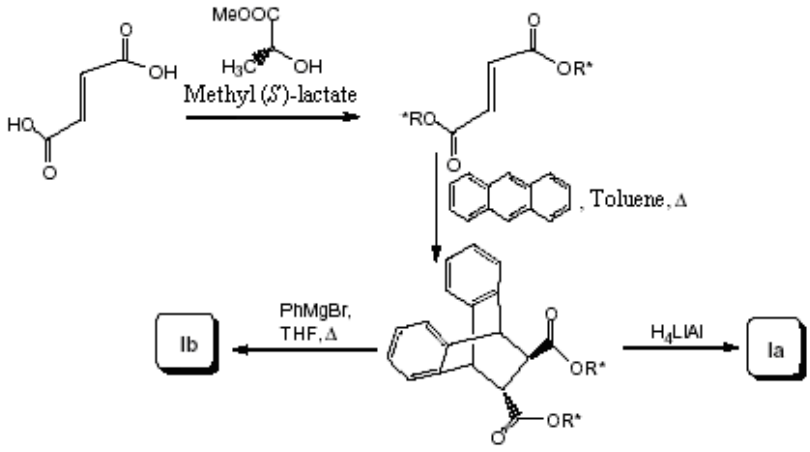


Figure 1

The product of this Diels-Alder reaction is obtained enantiomerically pure after one recrystallization. By reducing the latter with H_4LiAl the chiral diol **Ia** is obtained, while by treatment of it with PhMgBr **Ib** is obtained (Scheme 1).

From diols **Ia** and **Ib** are being carried out studies to determine the best reaction conditions that allow the synthesis of the corresponding mono- and diesters derivatives. The results shown herein were obtained in connection with the synthesis of derivatives of diol **Ia**.



Scheme 1

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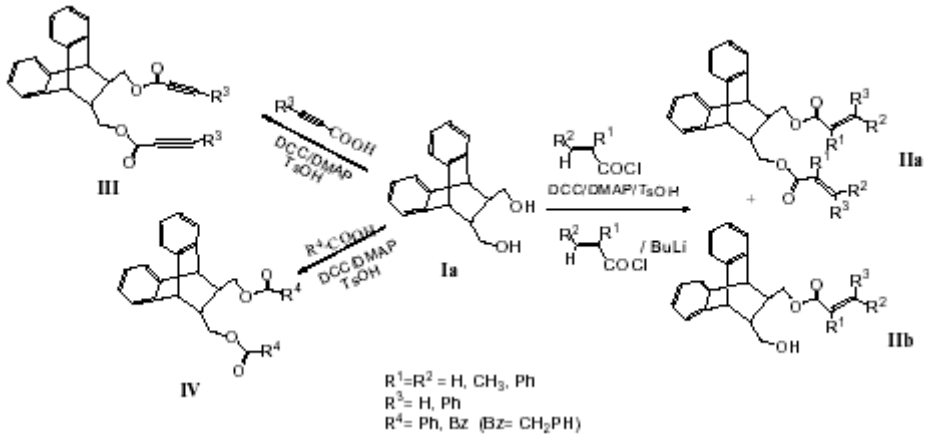
Methodology

The synthesis of esters derived from the diol **Ia** is carried out by treatment with *n*-butyllithium and the chlorides of the corresponding carboxylic acids in dry THF, or by reaction with the respective carboxylic acids in the presence of dicyclohexylcarbodiimide (DCC) as drying agent, and dimethylaminopyridine (DMAP) and *p*-toluensulfonic acid as catalysts (Lam *et al.*, 2003). The reactions are usually carried out in an inert atmosphere (nitrogen or argon), the follow-up is performed by thin layer chromatography. THF is dried by reflux with Na/benzophenone and subsequent distillation; dichloromethane is dried by distillation with phosphorus pentoxide and kept on molecular sieves. The purification of the reaction products was done by column chromatography on silica gel.

Discussion of the results

Results are summarized in Table 1.

Such studies are being initiated to determine the most suitable reaction conditions for obtaining the esters derived from the diol **Ib**. Preliminary studies in this regard provided promising results.



Scheme 2

Table 1. Synthesis of mono- and diesters derivatives of the diol **Ia**

Diol	Method	Compounds	R^1	R^2	R^3	R^4	Total yield %	% Monoester	% Diester
Ia	B	III			H		85	-	85
	B	III			Ph		87	-	87
	A	IIa y IIb	H	Ph	H		91	-	91
	B	IIa y IIb	H	Ph	H		93	-	93
	A	IIa y IIb	Me	H	H		82	11	89
	B	IIa y IIb	Me	Ph	H		90	43	57
	B	IIa y IIb	Ph	Ph	H		91	45	55
	B	IIa y IIb	Me	H	Me		93	40	60
	B	IV				Ph	98	-	100
	B	IV				Bz	85	-	100

Method A: BuLi/THF/chloride of the respective acid/0 °C/1 hr.
Method B: DCC/DMAP/TsOH/0 °C/dichloromethane/respective acid.

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Conclusions

Studies under development have shown that by these methodologies is possible to obtain diesters derived from the chiral diol **I** either exclusively or in mixture with the corresponding monoester in very good yields of the purified product. It should be noted that when using the diol **Ia** esters derived from acetylenic acids were obtained, a goal that could not be reached with TADDOL.

Fellowship of CONICET (Argentina).

∗ Research Member of CONICET (Argentina).

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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