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TETRAHEDRON: *ASYMMETRY*

Diastereoselective *cis* to *trans* desymmetrization of dimethyl succinates

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Abstract

Meso-succinates, readily available by Diels–Alder cycloaddition of dimethyl maleate or maleic anhydride followed by esterification, can be isomerized quantitatively from the *cis* to the *trans* isomers in the presence of lithium alkoxides. The reaction performed with enantiopure chiral lithium alkoxides yields diastereomeric *trans*-succinates in good yield and selectivity. © 1999 Elsevier Science Ltd. All rights reserved.

The practice of desymmetrization of *meso* compounds is becoming quite common in modern asymmetric synthesis.[1] These reactions are usually performed on C_S-symmetric (*meso*) esters,[2] anhydrides,[3] ketones,[4] epoxides[5] or diols[6] and to a minor extent on olefins[7] and other substrates.[8] The processes leading to the desymmetrized product are, in most instances, reactions catalyzed by enzymes[9] or by enantiopure bases[10] and acids.[11] The clear advantage of this synthetic strategy is that, in principle, the yields of the desired isomer are quantitative, without any waste of material due to the disposal of the unwanted enantiomer.

Enantiopure *E*-1,2-dicarboxylic esters are valuable intermediates in the synthesis of many natural or bioactive compounds because of the versatility of the ester moiety[12] and as precursors of effective ligands of chiral catalysts.[13] As shown in Scheme 1, the synthesis of such compounds is achieved through diastereoselective Diels–Alder cycloadditions of fumarate esters of enantiopure alcohols with appropriate dienes.[14] This strategy requires the previous preparation of the chiral dienophile and usually the reactions are performed with high diastereoselectivities only at low temperatures and sometimes in the presence of Lewis acids.

Our research was aimed at defining an alternative practical strategy of synthesis of such compounds as represented for a general case in the second part of Scheme 1. This approach entails a *cis–trans* desymmetrization plus transesterification of the readily available and inexpensive Diels–Alder cycloadducts of dimethyl maleate. The final transformation leads to diastereoisomers that might be further separated for obtaining enantiopure products. Because of our interest in high-symmetry chiral reagents, this investigation was limited to succinates eventually leading to C_2-symmetric chiral products.[15]

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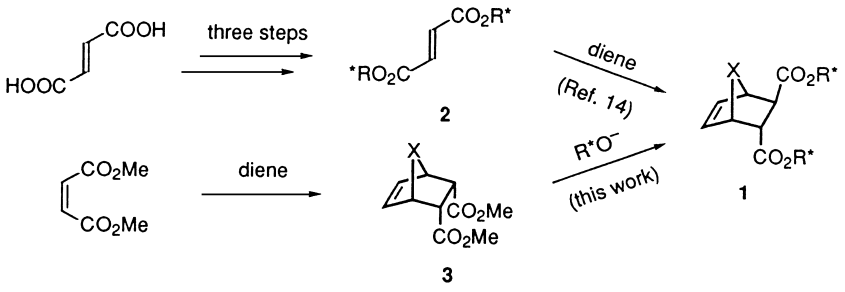


Scheme 1.

The *cis*-9,10-dihydro-9,10-ethano-anthracene-dicarboxylic acid-11,12-dimethyl ester[16] is the substrate that was selected for testing the isomerization reaction and the performance of the various enantiopure alcohols. At the outset, the reaction conditions to perform the reaction were determined. While the use of alkoxides generated by sodium bases such as sodium hydride or metallic sodium led to reaction mixtures contaminated by several by-products, the use of *n*-butyllithium, besides being more practical, afforded very clean reaction mixtures composed exclusively of the products of interest and specified below. The efficiency of lithium alkoxides in transesterification reactions is known.[17]

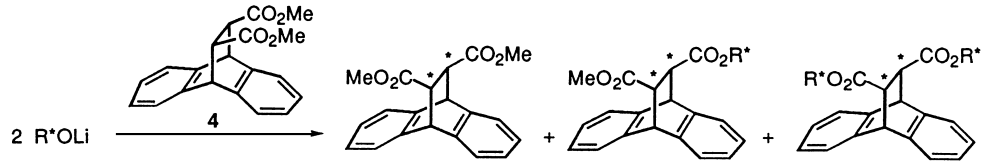
As shown in Table 1, best yields are obtained with low sterically demanding alcohols, but best selectivities were obtained with more crowded alcohols such as 8-phenylmenthol and 2-phenylcyclohexanol. These alcohols, denominated as convex chiral auxiliaries, are most often the most efficient in the transfer of the chiral information.[18] The reaction goes to completion to the final bis-transesterified product in all instances, except for 2-phenylcyclohexanol and 8-phenylmenthol where complete transesterification appears to occur with more difficulty. With these later alcohols, attempts to draw the reaction to completion led to concomitant formation of a number of uncharacterized by-products. In the cases of diacetone-D-glucose and quinine, only *cis–trans* isomerization occur, unfortunately with no selectivity.

Our concern was to determine if the *cis* to *trans* isomerization occurs before or after the transesterification reaction. For this reason the reaction of **4** with lithium mentholate was followed via ^{1}H NMR from the mixing of the reagents. It was observed that the *cis–trans* isomerization occurs almost instantaneously, while the transesterification takes about 24 h to reach completion (using a ca. 1 M lithium mentholate solution in THF). It was also observed that the *cis–trans* isomerization occurs unselectively and that the enrichment of one diastereomer over the other depends on the following transesterification reaction.

It is interesting to note that in the case of 2-phenylcyclohexanol and 8-phenylmenthol the diastereomeric ratio of the monomethyl, monomenthyl ester **6** (57:43 and 84:16) is lower than that of the completely transesterified product **7** (76:23 and 96:4). This observation may indicate an equilibration of the *trans* forms under the reaction conditions towards the thermodynamically more stable isomer or a kinetically preferred transesterification of one diastereoisomer of **6**. In order to obtain this information, a single diastereoisomer **7** derived from menthol was subjected to the same condition of the reaction (i.e. reaction with MeOLi). After a few minutes the ^{1}H NMR of the reaction mixture revealed the presence of both diastereomers in the final 6:4 ratio. It is thus concluded that the enrichment is actually thermodynamically controlled.

The reaction with diols affords *cis* to *trans* isomerization only. No transesterification was detected in these cases. While with 1,1′-binaphthalene-2,2′-diol and diacetone-D-mannitol no enantiomeric excess was observed for **5**, a fair but significant 56% ee was obtained with hydrobenzoin. The higher efficiency of this compound with respect to other diols has been noticed in other cases that have recently been reviewed.[19]

Table 1
Product distribution,[a] yield and diastereomeric ratio[b] (or enantiomeric excess)[c] in the reaction of **4** with lithium alkoxides



		5	6	7
R-1-phenylbutanol	72 h	—	—	quant.: d.r. 50 : 50
(+)-*endo*-fenchol	72 h	—	—	quant.: d.r. 65 : 35
(–)-*endo*-borneol	72 h	—	—	quant.: d.r. 54 : 35
(–)-menthol	24 h	—	—	quant.: d.r.[d] 60 : 40
(+)-isopinocanpheol	48 h	—	—	quant.: d.r. 50 : 50
(1*S*,2*R*)-2-phenylcyclohexanol	72 h	—	18%: d.r. 57 : 43	82%: d.r.[e] 76 : 23
(–)-8-phenylmenthol	72 h	—	68%: d.r. 84 : 16	32%: d.r.[d] 96 : 4
(–)-1,2:5,6-diacetone-D-glucose	72 h	quant.: ee 0%	—	—
(–)-quinine	72 h	quant.: ee 0%	—	—
(+)-1,2:5,6-diacetone-D-mannitol	24 h	quant.: ee[f] 10%	—	—
M-1,1'-binaphthalene-2,2'-diol	140 h	—	—	—
(*R*,*R*)-hydrobenzoin	48 h	quant.: ee[g] 56%	—	—

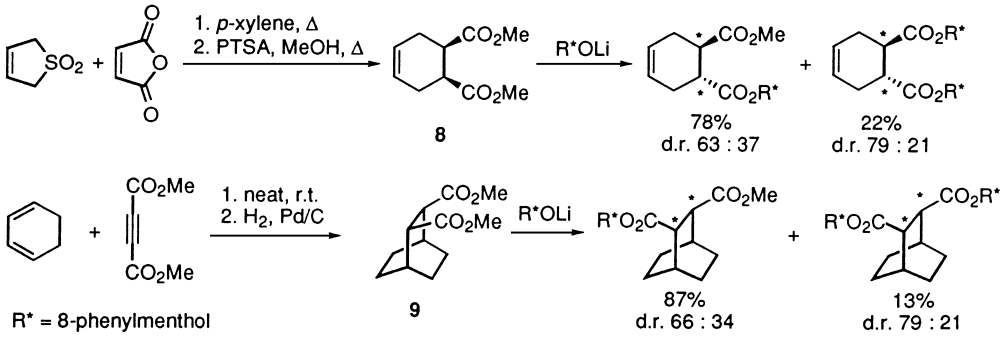
[a]**General Procedure:** To a solution of alcohol or diol (2 or 1 mmol) in dry THF (2 mL), maintained at –78 °C under argon atmosphere, was added via syringe *n*-BuLi 2.5 *M* in hexanes (2.2 mmol). After 30 min diester **4** (1 mmol) in dry THF (1 mL) was added at room temperature. The solution was stirred at r.t. for the time reported in Table 1, added of H_2O, extracted with Et_2O, dried over $MgSO_4$ and concentrated *in vacuum*. [b]Determined by ^1H NMR of the crude materials. [c]Determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent. [d]Major diastereoisomer having C(11) and C(12) of *R*,*R* configuration (determined by reduction to the diol of known absolute configuration[14e]). [e] Major diastereoisomer having C(11) and C(12) of *R*,*R* configuration (X-ray). [f]Major enantiomer having C(11) and C(12) of *R*,*R* configuration[14b]. [g]Major enantiomer having C(11) and C(12) of *S*,*S* configuration[14b].

It is important to point out that in all cases the measure of the enantiomeric excesses (or diastereomeric ratios) has been performed on the thermodynamically equilibrated reaction mixtures.

The best results obtained on substrate **4** were next transferred to other cycloadducts in order to determine the generality of the method. Other dicarboxylic methyl esters that have been tested are compounds **8** and **9** derived from 1,3-butadiene and 1,3-cyclohexadiene (Scheme 2). The synthesis of these compounds is indicative of the variety of molecules that can be submitted to the desymmetrization reaction and of the several methods available for the preparation of these substrates.

The slightly inferior results obtained both with **8** and **9** may be caused by the diminished steric hindrance around the ester groups.

In our mind, the present method is a new approach to this class of compounds. Because of the high crystallinity of the products, the diastereomerically pure adducts are readily available in synthetically useful quantities. We think that the present method is a viable alternative to the reported routes.[14]



Scheme 2.

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