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ASYMMETRIC DIELS-ALDER REACTION. A FACILE ROUTE TO CHIRAL ALKYL HYDROGEN CYCLOHEXENE-1,2-DICARBOXYLATE

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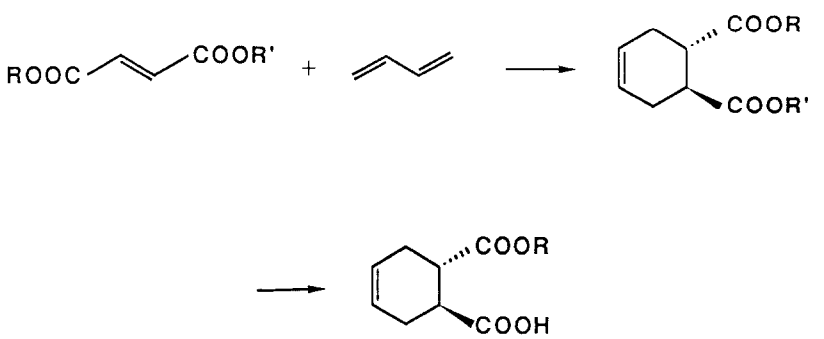
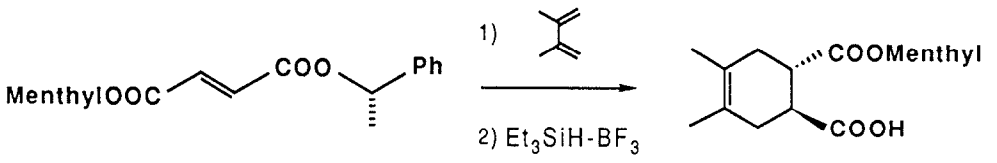
Summary: An efficient route to optically active alkyl hydrogen cyclohexene-1,2-dicarboxylate derivatives by means of asymmetric Diels-Alder reaction of rationally modified chiral fumarates is described.

In a recent paper, we have described the asymmetric Diels-Alder reaction of dimenthyl fumarate which could afford various dialkyl cyclohexene-1,2-dicarboxylate skeletones with over 95% optical purity.[1] The unprecedented high asymmetric induction observed in the above reaction has well been rationalized by the concept of cooperative blocking effect.[2] Now we wish to report the extension of this methodology to the synthesis of chiral alkyl hydrogen cyclohexene-1,2-dicarboxylate frameworks, useful for the construction of the functionalized chiral cyclic molecules.

The attractive solution to this problem was provided simply by employing the unsymmetrically modified chiral fumarates, in which one ester group can be transformed selectively leaving the other one intact.

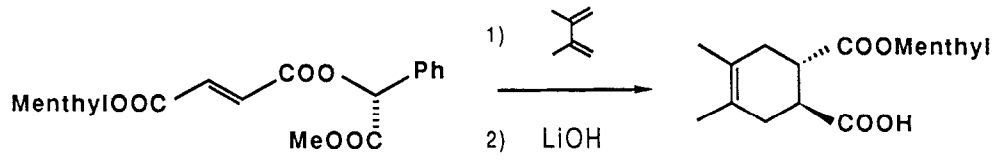


The readily available (-)-menthyl (-)-phenethyl fumarate **1**[3] was treated with 2 equiv. of diethylaluminum chloride at -20 °C in toluene followed by 2,3-dimethyl-1,3-butadiene to afford Diels-Alder adduct in 70% yield and 82% de.[4,5] The adduct, on exposure with Et_3SiH-BF_3·OEt_2 in CH_2Cl_2 at 0 °C, underwent reductive cleavage of phenethyl moiety to give menthyl hydrogen 4,5-dimethyl-4-cyclohexene-1,2-dicarboxylate **2** having the same optical purity with the adduct in 92% yield.



1 **2**

For further improvement in the optical yield of the adduct, fumarate **3**[6] was then examined. Thus, the fumarate was subjected to the reaction with 2,3-dimethyl-1,3-butadiene in the presence of 3 equiv. of diethylaluminum chloride[7] in toluene at -40 °C to give adduct in 82% yield and over 99% de.[8,9] The adduct thus obtained was efficiently transformed to the desired monoester monoacid **2** by selective hydrolysis of mandelyl ester moiety with LiOH (4 equiv., THF-H_2O 5:4, r.t., 44h) without racemization.



3 **2**

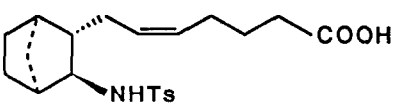
The observed rigorous stereoselectivity in the present system can adequately prove that the concept of cooperative blocking effect is working effectively even for the unsymmetrically modified fumarates.

The potential of the present methodology for the synthesis of chiral cyclic molecules is demonstrated by the short synthesis of newly designed thromboxane receptor antagonist **4**.[10]

Diels-Alder reaction of the fumarate **3** with cyclopentadiene in toluene in the presence of 3 equiv. of diethyl aluminum chloride (-78 °C, 1h)[11] followed by selective hydrolysis with LiOH gave ester-acid **5** in 93% yield. Treatment of **5** with ethyl chloroformate and triethylamine in dry acetone (-20 °C, 1h) followed by sodium azide (1.5 equiv., dissolved in H_2O) produced acyl azide which was converted to benzyl carbamate **6** by

Curtius rearrangement-esterification sequence.[12] Hydrogenolysis of carbamate **6** (Pd/C, 1 atm H_2, cat. HCl, MeOH) followed by tosylation produced saturated tosylamide **7** in 94% yield. The remaining α-side chain was successively introduced by the following sequence. Reduction of the ester **7** with LAH in ether at 0 °C (96%) followed by Swern oxidation gave aldehyde **8** in 93% yield. Treatment of the aldehyde **8** with the ylide **9** derived from 6-triphenylphosphonio-4-hexenoate ion in DMSO afforded conjugate diene **10** in 71% yield.[13] Finally, the diene moiety was selectively reduced to desirable cis-monoene by 1,4-hydrogenation ($PhCO_2Me{\cdot}Cr(CO)_3$, acetone, 70 °C, 70 atm H_2),[14] affording desired thromboxane receptor antagonist **4** in 49% yield.[15] This compound was tested for its ability to inhibit platelet aggregation and was observed to be significantly potent.

Further biological results together with synthetic details will be reported in full elsewhere.



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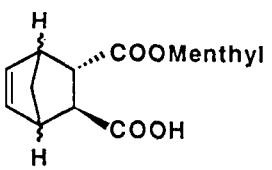

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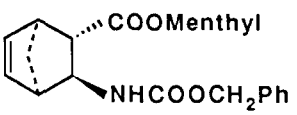

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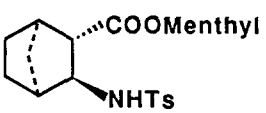

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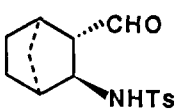

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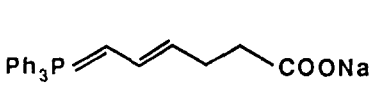

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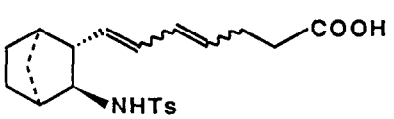

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References and Notes

1. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.*, **1986**, *27*, 4507.
2. Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.*, **1984**, *106*, 3806 and references therein. See also: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1.
3. (-)-Menthyl (-)-phenethyl fumarate was prepared by the following sequence: (1) mono-esterification of maleic anhydride with menthol; (2) acid catalyzed isomerization of the maleic acid mono-ester to fumarate; (3) esterification of the menthyl hydrogen fumarate with phenethyl alcohol by DCC method.
4. The diastereomeric ratio was determined by HPLC analysis of MTPA ester derived from the adduct after reduction-esterification sequence. The absolute configuration of the adduct was assigned to (S,S) by comparison of the HPLC behaviour of MTPA ester with authentic sample. See reference 1.
5. The corresponding mono-chiral species, i. e., menthyl methyl fumarate and methyl phenethyl fumarate, revealed lower selectivity (69% and 17% de respectively) under the same reaction condition.
6. Fumarate **3** was prepared by the same procedure as that for menthyl phenethyl fumarate by using (-)-methyl mandelate instead of phenethyl alcohol.
7. The use of less amount of catalyst resulted in a lower selectivity.
8. (S,S)-Adduct was obtained. The diastereomeric ratio was determined by HPLC analysis of the adduct.
9. The corresponding mono-chiral fumarate (derived from methyl mandelate) afforded the adduct in 77% de at -20 °C.
10. For example, see: Mais, D.; Knapp, D.; Halushka, P.; Ballard, K.; Hamanaka, N. *Tetrahedron Lett.*, **1984**, *25*, 4207.
11. A mixture of exo- and endo-menthyl isomers should be obtained. No assignment was made to these four isomers, but HPLC analysis of the corresponding MTPA esters derived from the mixture proved the high diastereoselectivity of the reaction (over 99%). See reference 12.
12. Two isomers, exo-menthyl and endo-menthyl, were detected on TLC analysis and were separated by column chromatography. The major isomer (47% from **5**) was assigned to desirable exo-menthyl compound by comparison with authentic specimen prepared independently. The minor one (15% from **5**) was confirmed by the comparison with authentic to be end-menthyl structure.
13. A mixture of olefinic isomers was obtained.
14. For example: Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.*, **1984**, *49*, 4096.
15. Antagonist **4** was also prepared from **8** by the double-Wittig method which will be reported elsewhere.

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