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CYCLOADDITIONS IN SYNTHESES. PART 41.[1] CHIRAL SPIROCYCLIC 5-ARYLMETHYLENE-1,3-DIOXANE-4,6-DIONES AS NOVEL SYNTHONS FOR ENANTIOMERICALLY PURE 2-ARYLCYCLOPROPANE-1,1-DICARBOXYLATES[2]

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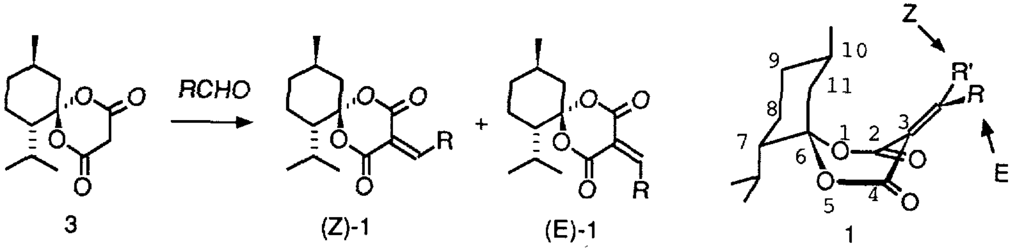
Abstract: *E- and Z-isomers of spirocyclic 5-arylmethylene-1,3-dioxane-4,6-dione, useful synthons for enantiomerically pure cyclopropane-1,1-dicarboxylates, have been synthesized from l-menthone. Their diastereofacial selectivity is explained by a boat conformation in their dioxanedione ring.*

The development of new methods as well as the creation of new synthons for organic stereocontrol are important concerns of current synthetic organic research. In this respect, we have been interested to synthesize some chiral vinyl Meldrum's acids 1 and examine their diastereofacial selectivity at the exocyclic double bond. One of the inherent uncertainty in this plan lies in controlling the stereochemical (geometrical) disposition of the substituents (R, R') at the terminal (prochiral) carbon of the vinyl group.[3] This problem has, however, been solved in two cases by crystallization-induced asymmetric transformations (second-order asymmetric transformations).[4,5]

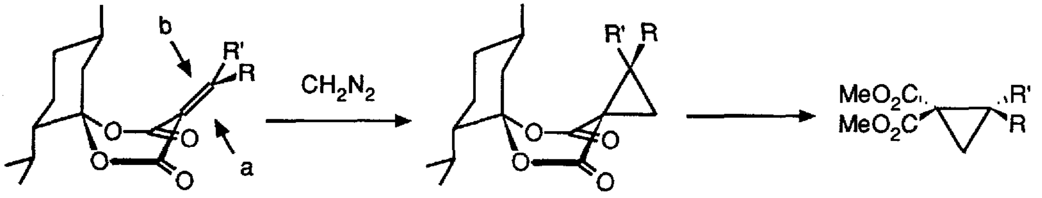
l-Menthone 2 was condensed with malonic acid in the presence of acetic anhydride and p-toluenesulfonic acid to give the chiral Meldrum's acid 3[6] [mp 114-115 °C, $[\alpha]_D$ -24.1° ($CHCl_3$)]. Base-catalyzed condensation of 3 with a variety of arylaldehydes in the presence of molecular sieve 4A then afforded



Scheme 1

the desired arylidenes 1 as mixtures of both E- and Z-isomers (ca. 1:1) quantitatively.

Though separation of the isomers by silica gel column chromatography had failed, 1a and 1b were found to crystallize as single isomers [(Z)-1a: mp 147-149 °C and (E)-1b: mp 132-134 °C] on slow recrystallization from ether apparently accompanying E/Z-isomerization during the process. The methylenemalonate unit in 1 obviously facilitates such cis-trans isomerization. The stereochemistries of both isomers were rigorously confirmed by X-ray analysis as Z- for 1a and E-forms for 1b, respectively (vide infra).[7] Though the equilibration is prohibited to occur when these compounds are kept standing in ethyl acetate at -78 °C, it is attained within 1 h at room temperature.



(Z)-1a (S)-4a (S)-5a

(E)-1b (R)-4a,b (R)-5b

a, R= H, R'= $C_6H_4NO_2$(p) b, R= C_6H_4Cl(p), R'= H

Scheme 2. The stereostructures of 1 and 4 correspond to those confirmed by X-ray crystallographic analyses (see Figs. 1 and 2).

When (Z)-1a was treated with diazomethane in a mixture of ethyl acetate and ether at -78 °C, only the single diastereomer (S)-4a (mp 210-212 °C, $[\alpha]_D$ -174.3 °($CHCl_3$)) was obtained in 70% yield.[8] Since the same cyclopropanation reaction if carried out using the pre-equilibrated mixture (vide supra) gave two diastereomers (S)- and (R)-4a [mp 208-209 °C, $[\alpha]_D$ +217.0° ($CHCl_3$)] in ca. 1:1 ratio, it is evident that the cyclopropanation of (Z)-1a proceeded under complete diastereofacial selection. The same selection was also found in the cyclopropanation of (E)-1b giving (R)-4b [mp 178-180 °C, $[\alpha]_D$ +205.6°($CHCl_3$)] as the sole product. The structure of (S)-4a determined unequivocally by X-ray analysis shows clearly that diazomethane attacked 1 from the a-side (the diastereotopic face same to the isopropyl group) with complete selection.

The selective addition of diazomethane to the a-side of 1 is apparently determined conformationally as evidenced by X-ray crystallographic analysis showing that the dioxane ring adopts a boat conformation whose a-side is far more exposed than the other side (b-side).[9,11] It seems noteworthy that (S)-

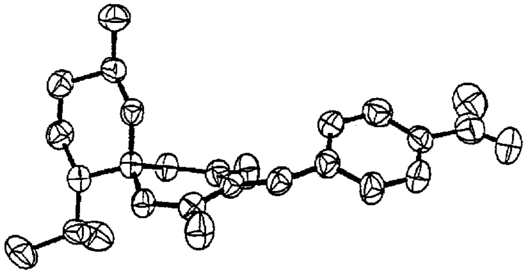


Fig. 1. ORTEP view of (Z)-1a.[9]

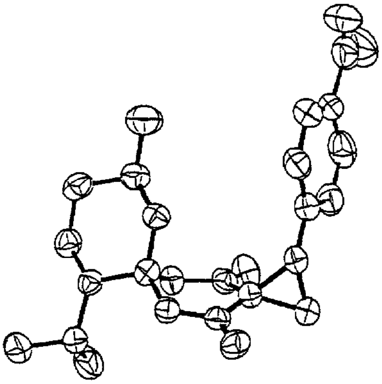


Fig. 2. ORTEP view of (S)-4a.[10]

4a still adopts boat conformation (see Fig. 2).

The result obtained by the present study offers two valuable informations for synthetic organic chemistry. The first one is that it provides an efficient synthetic method of enantiomerically pure, functionalized, and electrophilic cyclopropanes which are synthetically useful intermediates of other chiral molecules.[12,13] Thus, (S)-**4**a and (R)-**4**b were smoothly hydrolyzed under mild conditions (KOH, MeOH, room temperature) to give the corresponding acids. By methylation with diazomethane, the dicarboxylates (S)-**5** (mp 70-71 °C, $[\alpha]_D$ -96.5°) and (R)-**6** (oil, $[\alpha]_D$ +117.0°) were obtained both as enantiomerically pure compounds.[14,15] The second one is that both (Z)-1a and (E)-1b have a boat conformation in a crystalline state and this fact indicates strongly that 1 and related spirocyclic dioxanone derivatives would serve as valuable synthons for a variety of enantiomerically pure compounds.

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2. This paper also forms Part 19 of the series "Synthesis 1,3-dioxin-4-ones and their use in synthesis." Part 18: J. Sakaki, S. Kobayashi, M. Sato, C. Kaneko, Chem. Pharm. Bull., in press.
3. Since C3, C6, C7, and C11 of 1 lie in a plane, we designate the E- and Z-isomers according to this plane. See, formula 1 shown in Scheme 1.
4. Several examples on second-order asymmetric transformations are reported, J. Jacques, A. Collet, S. H. Wilen, "Enantiomers, Racemates, and Resolutions," Wiley, New York, 1981. See also, S. H. Wilen, A. Collet, J. Jacques, Tetrahedron, 1977, 33, 2725.

5. To the best of our knowledge, use of this phenomenon for the synthesis of chiral synthons has been reported only in one case, M. Ihara, M. Takahashi, N. Taniguchi, K. Fukumoto, T. Kametani, J. Chem. Soc., Chem. Commun., 1987, 721.
6. All new isolated compounds reported herein exhibited satisfactory ^{1}H NMR, IR, and HRMS or combustion analytical data.
7. The olefinic protons in the E-isomers appear at the higher field than those of the Z-isomers in ^{1}H NMR spectra in C_6D_6:δ 8.07 for (E)-1a, 8.13 for (Z)-1a, 8.20 for (E)-1b, and 8.24 for (Z)-1b.
8. The reaction of the 5-methylene derivatives of Meldrum's acid with diazoalkanes has been studied in a great detail. In all cases, cyclopropane derivatives are obtained directly even under quite mild conditions, see: F. Wessely, A. Eitel, Monatsh., 1964, 95, 1577. G. Swoboda-Adametz, A. Eitel, J. Swoboda, F. Wessely, Monatsch., 1964, 95, 1355. F. P. Schmook, O. E. Polansky, Monatsch., 1969, 100, 1631. H. Kisch, F. Mark, O. E. Polansky, Monatsch., 1971, 102, 448.
9. Crystals from ether had space group symmetry $P2_1$ and cell constants of a = 12.677(7)Å, b = 7.155(1)Å, c = 12.494(6)Å, and β=117.57(5)° for Z = 2, and a calculated density of 1.281 g/cm^3. The final R was 0.038. Details of the X-ray crystallographical analysis of (Z)-1a will be reported in a full paper.
10. Crystals from ether had space group symmetry $P2_12_12_1$ and cell constants of a = 8.028(1)Å, b = 35.838(3)Å, c = 6.5798(8)Å for Z = 4, and a calculated density of 1.310 g/cm^3. The final R was 0.043. Details will be reported in a full paper.
11. The problem of the conformation of the 1,3-dioxane-4,6-dione system has been approached by ^{1}H NMR and dipole-moment methods. Although there is no overall agreement, the consensus of opinion favours a boat structure for most derivatives. See, H. McNab, Chem. Soc. Rev., 1978, 7, 345.
12. Cyclopropane derivatives activated by two electron-withdrawing substituents such as COOR, COR, and CN at geminal position were found to be useful intermediates in organic synthesis: S. J. Danishefsky, Acc. Chem. Res., 1979, 12, 66.
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14. Specific rotation values of a series of 2-phenylcyclopropanecarboxylic acids having COOR, $CONH_2$, or CN at 1-position have been reported and it is known without exception that (2S)-isomers possess the minus sign, while (2R)-isomers the plus sign: A. B. Chmurny, D. J. Cram, J. Am. Chem. Soc. 1973, 95, 4237.
15. The optical purities of **4** thus obtained were assigned as 100%, since by repeated recrystallization neither mp's nor specific rotation values did not change.

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