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l-MENTHYL (2*S*)-2-PHENYL-3-(*p*-ANISYL)-(5Z)-BENZYLIDENE-4,6-DIOXO-1,3-OXAZINE-2-CARBOXYLATE: A NEW CHIRAL HETERODIENE AND MICHAEL ACCEPTOR

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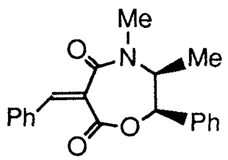
The title homochiral oxazinedione has been synthesized from *l*-menthyl phenylglyoxylate in three steps and found to exhibit high diastereofacial selectivity (≥99%) when used as heterodiene and Michael acceptor.

KEYWORDS asymmetric reaction; (Z)-5-benzylidene-1,3-oxazine-4,6-dione; heterodiene; Michael acceptor; (Z)-6-benzylidene-1,4-oxazepane-5,7-dione

Previously, Mukaiyama *et al.* synthesized the 6-benzylideneoxazepane-5,7-dione (**1**) from malonate and ephedrine and used it for a highly efficient synthesis of enantiomerically pure 3-substituted carboxylic acids.1) So far, these oxazepanediones have been used successfully in a variety of asymmetric reactions as chiral Michael acceptors,1,3,4) heterodienes,2,5) and dipolarophiles.6) One serious drawback of these oxazepanediones is an inevitable use of ephedrine. Since the latter is the direct synthetic precursor of methamphetamine (notorious for causing tolerance and physical dependence), its use is severely restricted in many countries. The recent successful use of homochiral (Z)-5-benzylidene-1,3-oxazine-4,6-diones having either cyclic or acyclic stereogenic center at the 2-position (**2**7) and **3**8)) as chiral heterodienes indicates that they could serve as alternatives for the oxazepanediones. However, these oxazinediones (**2** and **3**) not only needed chromatographic separation in their preparation, but also exhibit unsatisfactory de for their reactions (e.g. *ca.* 70% for hetero-Diels-Alder reaction using **3**), and none of them has been used as a Michael acceptor.



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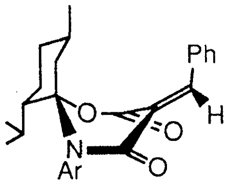

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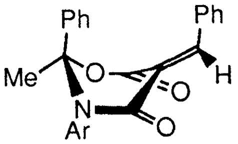

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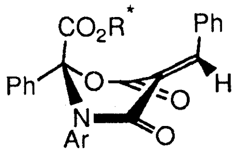

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Knowing that diastereofacial selectivity has arisen by boat conformation in their hetero ring system, we have planned the synthesis of title compounds (**4**) because, if such compounds can be synthesized, separation into each diastereomer could be expected to be carried out by mere fractional crystallization due to the diastereomeric nature of both isomers. In addition, the stereoelectronic nature of two substituents at the 2 position would be expected not only to be enough to fix the heterocyclic system in a specified boat conformation, but also to enhance the diastereofacial selectivity.

Reaction of *l*-menthyl phenylglyoxylate (**5**) wth *p*-anisidine ($AnNH_2$) gave the imine (**6**). When **6** was reacted with malonic acid, a 1:1 mixture of two diastereomers [(2*R*)- and (2*S*)-**7**] was obtained. Two isomers could be separated into the less soluble isomer [(2*S*)-**7**: mp 141-142 °C, $[\alpha]_D^{22}$ -27.4° (c 1.00, $CHCl_3$)] and the more soluble isomer [(2*R*)-**7**: mp 137-138 °C, $[\alpha]_D^{24}$ -54.6° (c 1.25, $CHCl_3$)] by mere fractional recrystallization from ether-hexane. Condensation of the former with benzaldehyde led to the formation of the corresponding (Z)-benzylidene derivative [(2*S*)-**4**: mp 171-174 °C, $[\alpha]_D^{24}$ +102.5° (c 1.10, $CHCl_3$)]. Though a mixture of (*E*)- and (*Z*)-isomers was formed in the reaction, its

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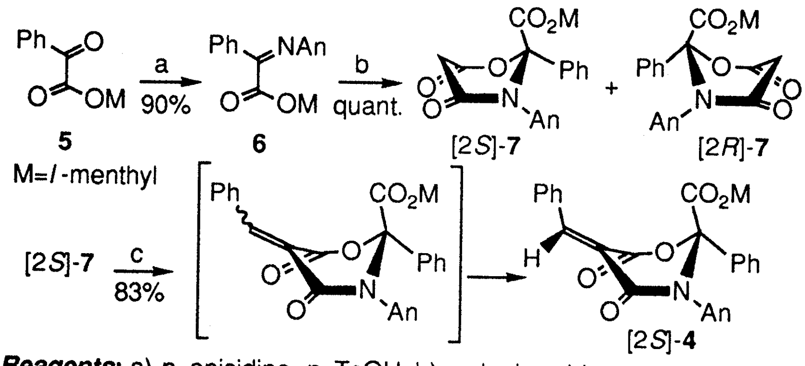


Reagents: a) *p*-anisidine, *p*-TsOH; b) malonic acid, Ac_2O; c) PhCHO, piperidine, AcOH, MS 4A .

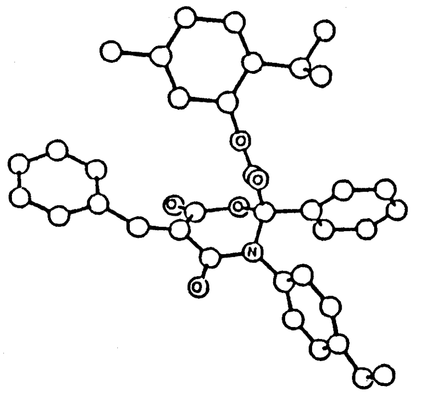
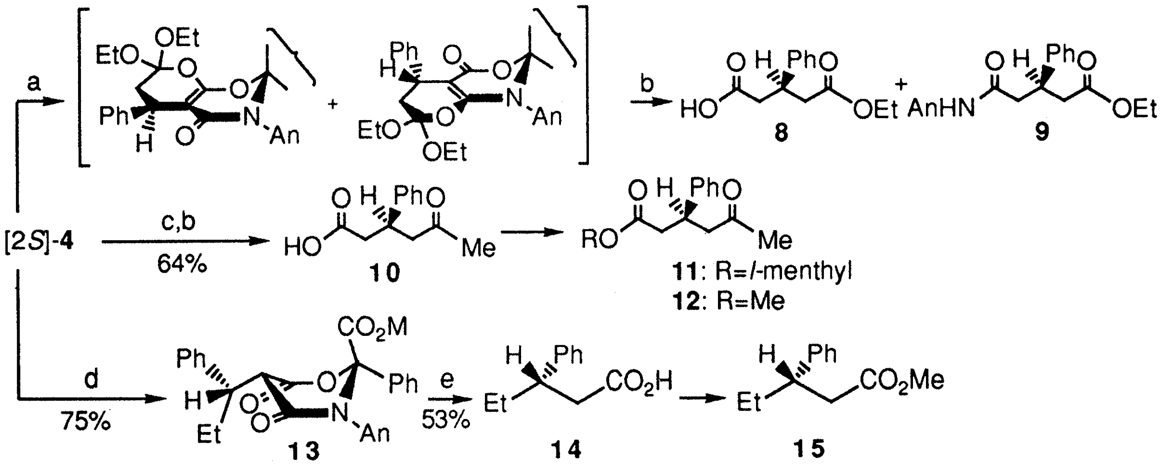


Fig. 1. Molecular Structure of (2*S*)-**4**

recrystallization from hexane-ether was accompanied by *E*/*Z* -isomerization and afforded the (Z)-**4** in nearly quantitative yield. It should be noted that, while this kind of recrystallization-induced isomerization has ample precedents,[9)] the induction always occurs to give the (Z)-isomers in the related oxazienediones[7)] irrespective of the kind of chiral auxiliaries and the aryl group. X-ray crystallographic analysis of (2*S*)-**4** has revealed that *l*-menthyloxycarbonyl group takes the quasi-axial orientation in pseudo-boat conformation of the oxazinedione ring.[10)] Inspection of X-ray data of **4** has also revealed that a downward flexion of the lactone C=O to the plane of Ph-C=C is much larger than that of the amide C=O. Hence, the formation of (Z)-isomer may be explained by steric ground.[11)]

Two reactions (hetero Diels-Alder reaction and conjugate addition) using (2*S*)-**4** as the substrate have shown that the reactive side of this oxazinedione is the bottom of the boat conformation (the same side of phenyl group). Thus, Diels-Alder reaction with ketene diethylacetal afforded, after hydrolysis of the crude adducts, **8** [$[\alpha]_D^{25}$ +10.5° (c 1.10, benzene)] and **9** [$[\alpha]_D^{22}$ +32.6° (c 1.00, benzene)] in 84% and 4% yields, respectively. The same reaction using 2-methoxypropene gave, after hydrolysis, **10**. This compound was converted to *l*-menthyl ester (**11**) and methyl ester (**12**) in the usual manner. Ee of **10** was determined as $\geq$ 99% by 500 MHz ^1H NMR spectrum of **11**. The absolute structures of the products were determined by their comparison with authentic samples (**8**,[7)] **9**,[7)] and **12**[12)]), respectively. In both reactions, starting materials (**5** and **6**) were recovered in almost quantitative combined yield.

Next, the conjugate addition of ethylmagnesium bromide in the presence of CuI was carried out. Here again, the single product (**13**) was obtained. Hydrolysis of **13** with aq. sulphuric acid/acetic acid



Reagents: a) ketene diethylacetal, CH_2Cl_2, -40 °C; b) 1,4-dioxane, H_2O, reflux; c) 2-methoxypropene, CH_2Cl_2, -16 °C; d) EtMgBr, CuI, THF, -78 °C; e) 3M aqueous H_2SO_4, AcOH, reflux.

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afforded the carboxylic acid [**14**: $[\alpha]_D^{25}$ +47.5° (c 1.25, benzene)].[13] The fact that the ee of the corresponding methyl ester [**15**: $[\alpha]_D^{25}$ +37.6° (c 1.05, benzene)] was 99% as determined by HPLC with CHIRALCEL OD, further, confirmed that the addition has proceeded in a completely stereoselective manner. Use of methyl-, vinyl-, and allylmagnesium bromides also gave the respective single adducts.[14]

In summary, the following can be said: 1) The title oxazinediones (**4**) could serve as the alternative to **1** as heterodiene and Michael acceptors and show remarkably high diastereofacial selectivities ($\geq$98%); 2) the diastereofacial selectivity can be predicted simply from the boat conformation they have and the reagents are expected to attack from the more exposed side (the same side of pseudo-equatorial substituent at the 2-position of 1,3-oxazine-4,6-dione ring). Other merit for the use of **4** as the intermediates for the synthesis of enantiomerically pure compounds is that *l*-menthyloxycarbonyl group as the chiral auxiliary at the 2-position in the oxazinedione ring permits, added to ready preparation of chiral species, the ready recovery of the auxiliary after the reaction.

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10) Crystal data for (2*S*)-**4** are as follows: Orthorhombic, $P2_12_12_1$, a = 13.245(2) Å, b = 28.814(4) Å, c = 8.2132(8) Å, Z = 4, Mr = 567.68, V = 3134.5(7) Å^3, and D(calc) = 1.203 g/cm^3. X-ray diffraction data were collected at room temperature on a 0.4 x 0.3 x 0.2 mm crystal for 4272 independent refractions. The structure was solved by direct methods using SHELXS86, and all non-hydrogen atoms were located from E maps and refined anisotropically by block-diagonal least-squares caluculations. The final value for R and Rw were 0.064 and 0.077, respectively.
11) Essentially in the same manner, Tietze explained the stability of the (Z)-isomer over the (*E*)-isomer in the 6-benzylideneoxazepane-5,7-dione (**1**). See ref. 5.
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14) Diastereoselectivity of each reaction was determined as $\geq$98% by inspection of 500 MHz ^{1}H-NMR of the products. None of the stereoisomers was detected in any of the cases.

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