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CHIRAL SPIROCYCLIC 1,3-OXAZINE-4,6-DIONES AS NOVEL SYNTHONS FOR ENANTIOMERICALLY PURE COMPOUNDS[1]

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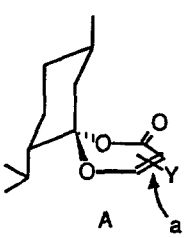
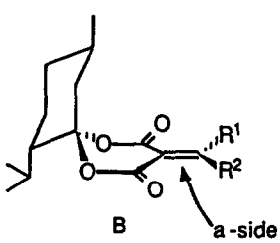
Abstract: Chiral spirocyclic 1,3-oxazine-4,6-diones have been synthesized from l-menthone. Base-catalysed alkylation of the 5-monosubstituted derivatives provides an efficient synthetic method of enantiomerically pure malonamic acids.

The development of new methods as well as the creation of new synthons for organic stereocontrol are important concerns of synthetic organic research. Among them, the diastereoselective addition reactions to chiral α,β-unsaturated carbonyl derivatives (Michael addition,[2] Diels-Alder reaction utilizing them as dienophile or heterodiene,[3] and de Mayo reaction[4] are the typical examples) has attracted much attention. Previously, we have shown that chiral spirocyclic dioxinones[5] **A** as well as (E or Z)-5-arylmethylene-1,3-dioxane-4,6-diones[6] **B** exhibit remarkable diastereofacial selectivity at the C-C double bond (preferential attack at the a-side: convex side) in a variety of pericyclic reactions and reasoned the preference by the sofa-conformation of the dioxane ring. In this connection, we have been interested in synthesizing the title compounds **4** whose methylene carbon acts by itself as the stereogenic center due to nonequivalent carbonyl groups attached to it and examining their diastereofacial selectivity in base-catalyzed alkylation reactions. In this paper, we describe these results.



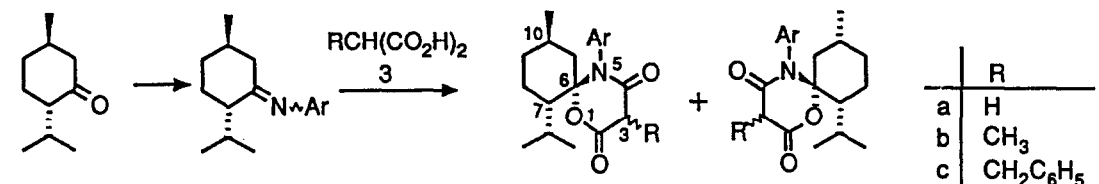
Y = an appropriate substituent



Z : $R^1 \neq H$, $R^2 = H$
E : $R^1 = H$, $R^2 \neq H$

Refluxing benzene solution of l-menthone **1** and p-anisidine in the presence of a small amount of p-toluenesulphonic acid (1 d with Dean-Stark trap) afforded the corresponding imine **2**.[7] The imine **2** thus obtained was, without

purification, condensed with malonic acid 3a in acetic anhydride (0 °C, 4 d) to give the oxazinedione **4a** as a mixture of two diastereomers. Recrystallization (CH_2Cl_2-hexane) of the more polar isomer, which crystallized from the reaction mixture, gave a single diastereomer (R)-**4a**[8] (mp 107-108 °C). Silica gel chromatography of the product left in the mother liquor afforded the less polar product (S)-**4a** (mp 153-155 °C).

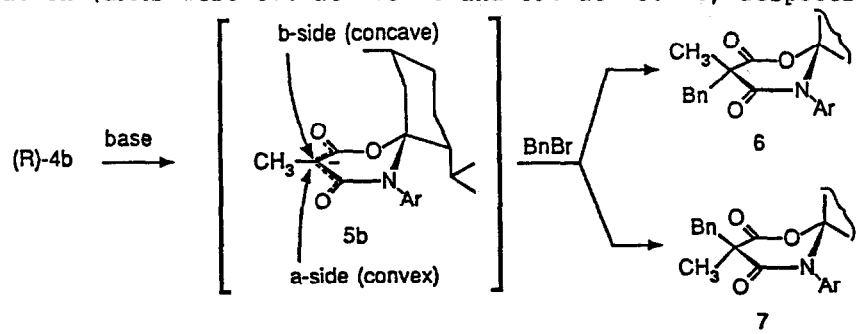


1 2

Ar : p-methoxyphenyl

The same procedure (procedure a) using methylmalonic acid **3b** afforded the corresponding spirocyclic oxazinediones (R)-**4b** (mp 125-127 °C) and (S)-**4b** (mp 163-164 °C).[9] Though the preparation of the corresponding benzyl derivative **4c** by the above method afforded the desired products in poor yields due to their instability, the relatively stable diastereomer (the less polar product) (S)-**4c**[9] (mp 135-137 °C) could be synthesized from (S)-**4a** by condensation with benzaldehyde in the usual manner (piperidine/benzene) followed by hydrogenation with palladium charcoal (procedure b). The stereochemistry of both types of products [(R)- and (S)-**4**] were rigorously confirmed by X-ray analysis (*vide infra*) as (6S,7S,10R) for the less polar products and as (6R,7R,10R) for the more polar ones.[10]

When (R)-**4b** was treated with benzyl bromide in DMF after metalation with sodium hydride, two isomers **6** (major product, mp 184-185 °C, $[\alpha]_D$ -90.5°)[11] and **7** (minor product, mp 147-149 °C, $[\alpha]_D$ +104.9°)[11] were obtained in 85-90% total yield. Two isomers were separated by silica gel column chromatography. The ratio of two isomers (**6** and **7**) depended upon the temperature of the alkylation (d.e.s were 81% at -15 °C and 89% at -50 °C, respectively).



The stereostructure of the major product **6** was established by X-ray analysis as 3S,6R,7R,10R with the sofa-conformation of the oxazinedione ring (Figure 1). It is obvious that the alkylation reagent (benzyl bromide) attacked the anion (R)-**5b** from the a-side.

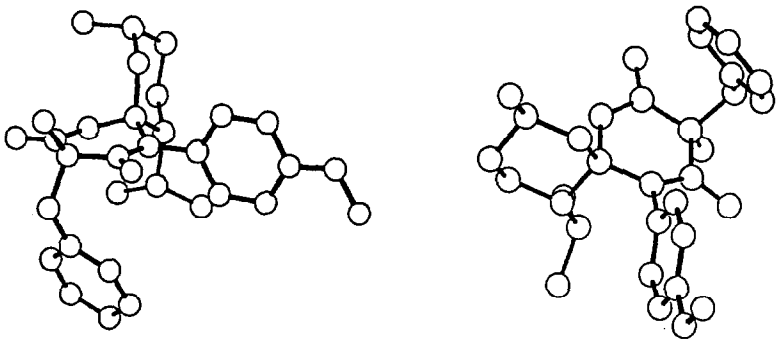
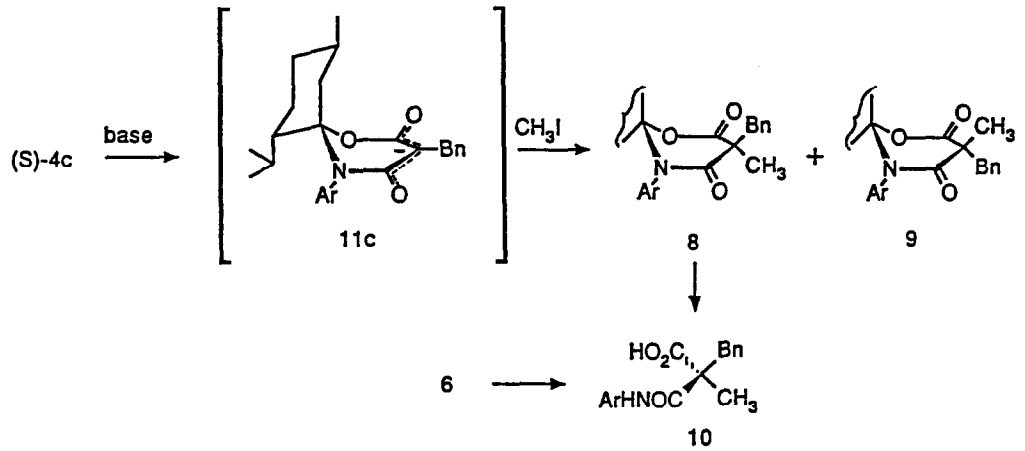


Figure 1. Molecular structures of **6**[12] and **8**[13,14]

When (S)-**4c** was methylated (CH_3I) in the same manner, the a-side alkylation product **8** (mp 141-142 °C, $[\alpha]_D$ -103°)[11] was obtained as the major product. The d.e. of the product was 76% even at 20 °C. X-Ray analysis of the major product **8** revealed again that the alkylation occurred from the a-side (Figure 1). In accordance with the above data, the base-catalyzed hydrolysis of either **6** or **8**



gave the same chiral malonamic acid (S)-**10** (mp 113-114 °C, $[\alpha]_D$ -53°).[11]

It is reasonable to assume that the carbanions **5b** and **11c** take the sofa-conformation. Two facts support this view: 1) X-ray analysis of **6** shows clearly the sofa-conformation[15] and 2) the same sofa-conformation has also been verified for spirocyclic dioxinones **A**,[16] which are isoelectronic with the carbanions **5** and **11**. If this assumption is correct, it is obvious that the reagents attack the carbanions preferentially from the more exposed a-side (convex face). Since the 6-benzylideneoxazepane-5,7-diones (either E- or Z-forms), which were introduced by Mukaiyama,[17] have been known as valuable synthons (as chiral Michael acceptors,[17-19] heterodienes,[3b,19], and dipolarophiles[20]) for a variety of enantiomerically pure compounds, our efforts are now paid for methylenation of **4** to obtain E- and Z-configuration at the terminal carbon and for examining these compounds as the new and more attractive alternatives.[21]

References and Notes

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7 By HPLC of the imine, at least two isomers were detected.

8 All new substances exhibited satisfactory spectroscopic (NMR, IR, UV) and combustion or high resolution mass spectral analytical data.

9 In general, (R)-4 or (S)-4 obtained was a mixture of epimers at the 3-position and its ratio differed markedly by the procedure (a or b) employed. Recrystalization of each type of the products [(R)- or (S)-4], however, gave always the single epimers, respectively.

10 We designate the more polar and less polar isomers as (R)- and (S)-4, because the absolute configuration at the 6-position can readily differentiate these chiral spirocycles in two types.

11 Specific rotations were measured in chloroform at 24°C (c,1~2).

12 Crystal data for 6: space group $P2_12_12_1$, a=9.015(2) Å, b= 30.107(4) Å, c=8.979(2) Å, Z=4, R=0.034 for 1963 reflections with $F_o > 3\sigma(F_o)$.

13 Crystal data for 8: space group $P2_12_12_1$, a=14.024(2) Å, b= 19.031(3) Å, c=9.469(9) Å, Z=4, R=0.044 for 1718 reflections with $F_o > 3\sigma(F_o)$.

14 Further details have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

15 The almost flat conformation of the oxazinedione ring in the molecular structure of 8 is attributable to the steric repulsion between benzyl and C_{11}-methylene groups.

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21 One serious drawback of these oxazepanediones is an inevitable use of ephedrine. This chiral auxiliary is the direct synthetic precursor of methamphetamine (notorious for tolerance and physical dependence). Hence, its use is severely restricted in most countries.

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