(6*S*, 7*S*, 10*R*)- and (6*R*, 7*S*, 10*R*)-7-Isopropyl-10-methyl-4-oxo-1,5-dioxaspiro[5.5]undec-2-enes having an Electron-withdrawing Substituent at the 2-Position: Synthesis and Use in Asymmetric Diels–Alder Reactions

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Chiral spirocyclic dioxinones (*S*)-(**6**) and (*S*)-(**7**) have been synthesized from (−)-menthone and used in Diels–Alder reactions with cyclopentadiene; remarkable diastereofacial selectivity (isopropyl side) and *endo* preference observed in these reactions have offered a new methodology for asymmetric Diels–Alder reactions.

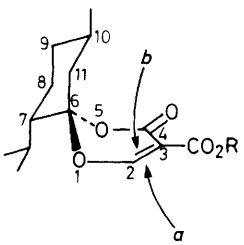
Recently, we have found that spirocyclic dioxinones (**A**) and (**B**) having an alkoxycarbonyl group at the 3-position react with cyclopentadiene, both with complete *a*-side and *exo* preference, to give a single adduct (**C**) or (**D**), respectively,[1] the former of which is an important intermediate for the synthesis of carbocyclic *C*-nucleosides.[2] It has also been verified that an electron-withdrawing group on the dioxinone ring is essential as the dienophile, since 2,3-unsubstituted or alkylated dioxinones are inactive towards the diene under any condition. We have explained the *a*-side preference of (**A**) by the sofa conformation (verified by *X*-ray crystallographic analysis) whose *a*-side is more exposed than the *b*-side.[1] The same preference was also observed in photo[2+2]cycloaddition of the related dioxinones to alkenes, by Demuth[3] and by ourselves,[4] who explained this preference by assuming that these dioxinones still retained the sofa conformation in their triplet excited states.[5,6]

As an extension of the asymmetric Diels–Alder reaction using the spirocyclic dioxinones as dienophiles, we have been interested in the synthesis of the corresponding dioxinones having an electron-withdrawing group at the 2-position and in their reactions with cyclopentadiene (reactivity, *endo* or *exo* preference, and diastereofacial selectivity). This paper reports these results.

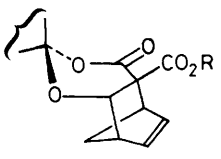
The chiral dioxinones (*S*)-(**2**) and (*R*)-(**2**) were synthesized readily from 4-bromoacetoacetic acid (**1**).[7] Thus, reaction of (**1**) with (−)-menthone in the presence of acetic anhydride under acidic conditions gave the 2-bromomethyl derivative (**2**) as a mixture of diastereoisomers. Two isomers could be separated by column chromatography (silica gel) to give the less polar {(*S*)-(**2**): m.p. 36—38 °C, $[\alpha]_D$ −60.2° (*c* 1.10)}† and the more polar {(*R*)-(**2**): m.p. 61—63 °C, $[\alpha]_D$ +16.0° (*c* 1.11)} dioxinones in 58 and 23% yields.

The absolute configuration of each product was determined unequivocally by hydrogenolysis over Pd–carbon to the 2-methyl derivatives (*S*)-(**3**) {m.p. 26—27 °C, $[\alpha]_D$ −30.3° (*c* 1.00)} and (*R*)-(**3**) {m.p. 56.5—58 °C, $[\alpha]_D$ −31.5° (*c* 1.20)}, whose structures had been determined already by *X*-ray crystallographic analysis.[3] The bromine of (*S*)-(**2**) (the major isomer) was replaced with an acetoxy group followed by hydrolysis to give the 2-hydroxymethyl derivative (*S*)-(**5**) {m.p. 57—58 °C, $[\alpha]_D$ −43.1° (*c* 0.98)}. While pyridinium chlorochromate (PCC) oxidation of (*S*)-(**5**) afforded the 2-formyl derivative (*S*)-(**6**) {m.p. 54—55 °C, $[\alpha]_D$ −171.8° (*c* 0.95)}, chromium oxide oxidation of (*S*)-(**5**) followed by methylation with diazomethane gave the 2-methoxycarbonyl derivative (*S*)-(**7**) {m.p. 32—34 °C, $[\alpha]_D$ −72.0° (*c* 1.03)}. In the same manner, the corresponding derivatives (*R*)-(**6**) {m.p. 45—52 °C (decomp.), $[\alpha]_D$ +65.1° (*c* 1.14)} and (*R*)-(**7**) {m.p. 69—71 °C, $[\alpha]_D$ +7.0° (*c* 1.00)} were prepared from (*R*)-(**2**). Since the compounds belonging to the (6*S*)-series are available in larger amounts than those of the (6*R*)-series, the following reactions were carried out using *S*-(**6**) and *S*-(**7**) as the dienophiles.

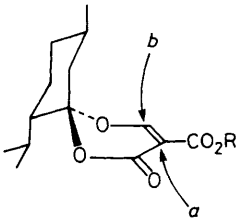
When (*S*)-(**6**) was treated (benzene, room temp., 3 days) with a 50 molar excess of cyclopentadiene, the adduct (**8**) was obtained in 66% yield as a mixture of two isomers (*ca.* 14 : 1 by ^{1}H n.m.r. spectroscopy). Though mere recrystallization of the crude adduct gave the major isomer *endo*-(**8**) {m.p. 97—98 °C,



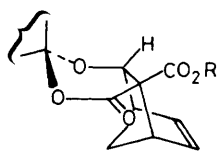
(**A**)



(**C**)



(**B**)

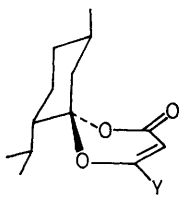


(**D**)

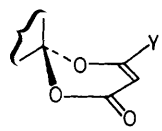
† Specific rotations were determined in $CHCl_3$ at room temperature.

$BrCH_2COCH_2CO_2H$

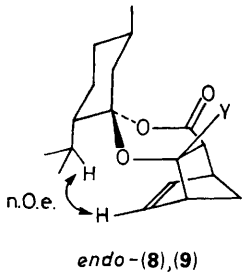
(**1**)



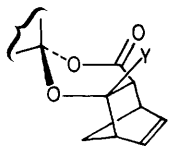
(*S*)-(**2**)-(**7**)



(*R*)-(**2**)-(**7**)



endo-(**8**),(**9**)



exo-(**8**),(**9**)

(**2**) Y = CH_2Br (**5**) Y = CH_2OH
(**3**) Y = Me (**6**), (**8**) Y = CHO
(**4**) Y = CH_2OCOMe (**7**), (**9**) Y = CO_2Me

$[\alpha]_D$ −22.7° (*c* 0.97)}, the minor isomer could not be obtained as a pure compound because of the almost identical properties of these two adducts on chromatography. By significant nuclear Overhauser enhancement (n.O.e.) (5%) between the tertiary proton of the isopropyl group and one of the alkenic protons, the structure of the major adduct was determined as *endo*-(**8**), formed by *a*-side addition of the diene to (*S*)-(**6**) with *endo* preference.‡

Though the corresponding ester (*S*)-(**7**) did not react under ordinary conditions, it reacted with cyclopentadiene at high pressure. Thus, under 11 kbar (CH_2Cl_2, room temp., 4 days), the *endo* adduct {*endo*-(**9**): m.p. 106—107 °C, $[\alpha]_D$ −21.7° (*c* 1.28)} was obtained in 64% yield as the sole product. The absolute structure of the product was determined by its synthesis from *endo*-(**8**). Thus, *endo*-(**8**) derived from (*S*)-(**6**), when oxidized by chromium oxide followed by methylation with diazomethane, afforded *endo*-(**9**).

The present work not only shows that the diastereofacial selectivity observed in the previous paper[1] [*a*-side preference of (**A**) and (**B**)] is a common phenomenon in the cycloaddition of these spirocyclic dioxinones irrespective of the nature and position of substituents, but also provides a novel enantioselective synthetic method for bicyclo[2.2.1]hept-2-enes. Since these are important intermediates in organic synthesis, their enantioselective synthesis has been examined intensively.[8]

Received, 15th June 1989; Com. 9/02530H

‡ The structure of *endo*-(**8**) was determined unequivocally by *X*-ray analysis. The details will be published in the full paper.

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