

USE OF 1,3-DIOXIN-4-ONES AND THEIR RELATED COMPOUNDS IN SYN-  
THESIS. 27<sup>1</sup>. NOVEL ASYMMETRIC HETERO-DIELS-ALDER REACTION  
USING CHIRAL SPIRO 5-METHYLENE-1,3-DIOXANE-4,6-DIONES HAVING  
1-MENTHONE AT THE 2-POSITION<sup>2</sup>

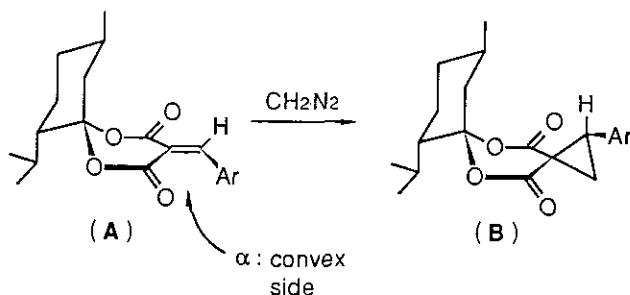
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**Abstract** Diastereofacially selective hetero-Diels-Alder reaction of spiro (E or Z)-5-arylidene-1,3-dioxane-4,6-diones and 2-methoxypropene was studied. The dihydropyrans thus obtained were converted to optically active  $\beta$ -arylated  $\delta$ -oxo-hexanoic acids. The diastereofacial selectivity of the hetero-Diels-Alder reactions is explained by the sofa-conformation of the heterodienes which accepts the dienophile at the convex  $\alpha$ -side preferentially.

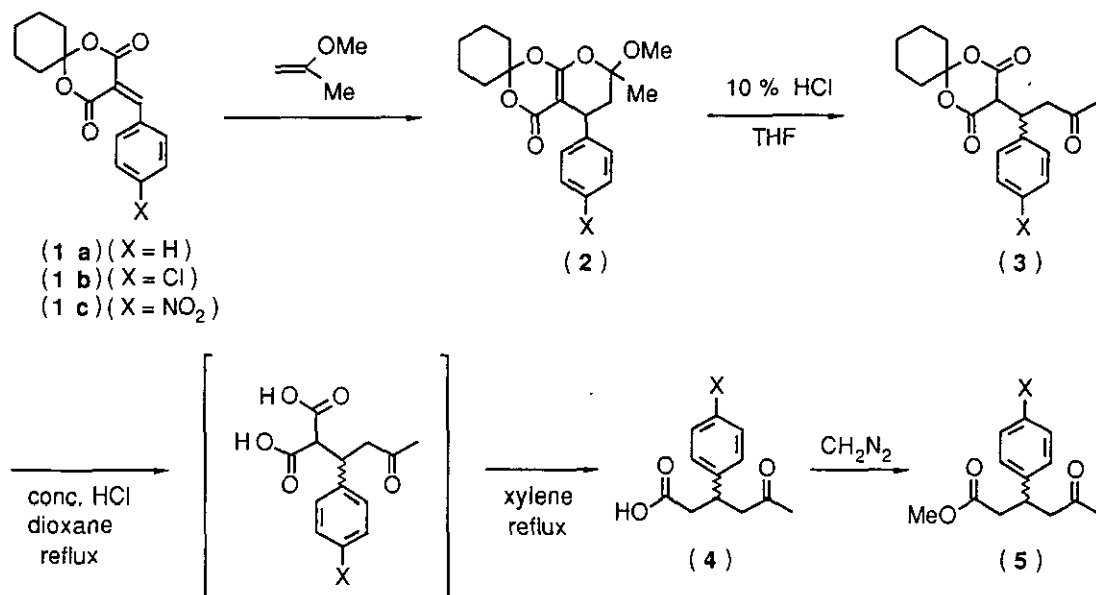
Previously, we have shown that chiral spiro (E or Z)-5-arylmethylene-1,3-dioxane-4,6-diones (**A**) when treated with diazomethane give cyclopropanes as an almost single diastereomer (**B**) and reasoned this remarkable diastereofacial selectivity (preferential attack at the isopropyl group-side) by the sofa-conformation of the dioxane ring whose  $\alpha$  face is more exposed.<sup>3</sup>

Hoping that this diastereofacial selectivity can be still preserved in Diels-Alder reaction, we have been interested in the use of (**A**) as the heterodienes so as to broaden the scope of their use in asymmetric synthesis. In this paper, we describe the successful results.



Scheme 1

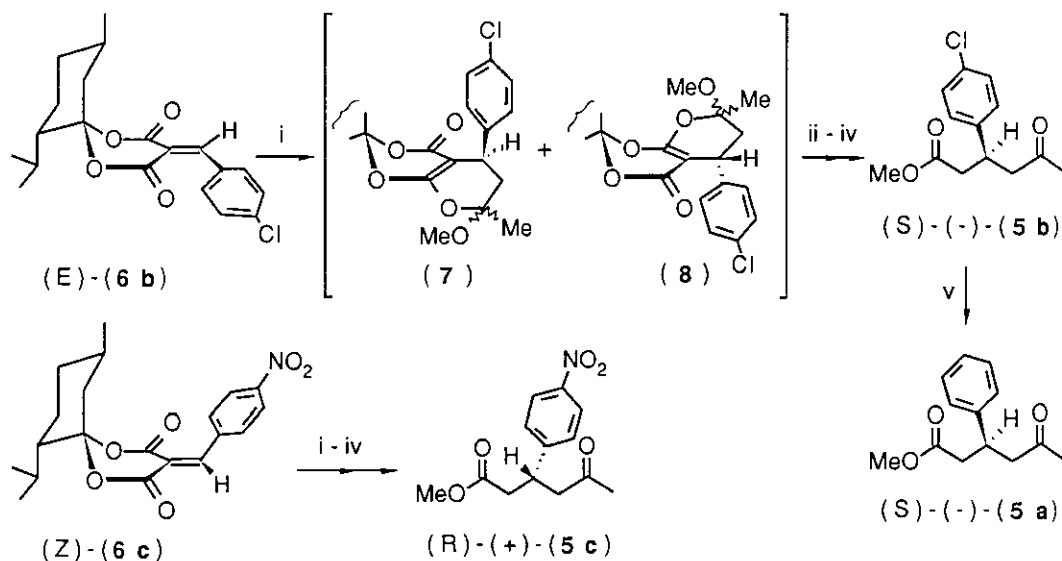
It is already known that methylene Meldrum's acid can act as heterodiene in the intramolecular hetero-Diels-Alder reactions.<sup>4,5</sup> As a model study for the intermolecular reactions, three spiro 5-arylidene-1,3-dioxane-4,6-diones<sup>6</sup> (1a-1c) were synthesized and subjected to react with 2-methoxypropene. All reactions proceeded within 20 min at 0 °C. Though the reaction proceeded quantitatively with complete regioselectivity to give (2), the mixtures of endo- and exo-adducts were formed. Hydrolysis of (2) (mixture of the endo- and exo-adducts) gave the ring-opened products (3). Refluxing of (3) in a mixture of concentrated hydrochloric acid and dioxane followed by decarboxylation (reflux in xylene) afforded the monocarboxylic acids (4), which were converted to the methyl esters (5) by diazomethane. In all cases, overall yields of (5) from (1) were above 80%.



Scheme 2

The above model study has revealed three characteristics (1-3), all of which fit the requirements of the use of (A) in asymmetric Diels-Alder reactions. 1) The heterodiene (A), like (1), is expected to be reactive enough to give the adduct even below room temperature [as reported,<sup>3</sup> the isomerization between the *E*- and *Z*-isomer of (A) in an aprotic nonpolar solvent is quite fast resulting equilibrated mixture within 1 h in dark at room temperature (25 °C)]. 2) Conversion of (1) to (5) can be carried out in a high overall yield (above 80%) without any purification of the intermediate species (2-4). Diastereofacial selectivity (convex-side preference) in the addition step can be evaluated by the enantiomeric excess (ee) of the final product [e.g. (5)]. And neither the endo/exo ratio nor the regioselectivity with respect to the two carbonyl groups in the heterodiene (A) does affect the ee of the final product.

Based on the above facts, chiral dioxanediones<sup>3</sup> [(*E*)-(6b) and (*Z*)-(6c)] were reacted with the vinyl ether in ethyl acetate at -30 °C (2 h).<sup>7</sup> The methyl ester (5b) obtained from (*E*)-(6b) in 82% overall yield crystallized in the crude state<sup>8</sup> with its  $[\alpha]_D^{24}$  being -19.70° (benzene). Repeated recrystallizations (three times) of the crude ester gave the ester<sup>†</sup> [mp 57-58 °C,  $[\alpha]_D^{24}$  -21.22° (c=2.01, benzene)] as an enantiomerically pure compound. Catalytic hydrogenation of the latter over palladium/charcoal afforded the dechlorinated ester<sup>†</sup> [(5a): mp 47-48 °C,  $[\alpha]_D^{24}$  -22.40° (c=2.00, benzene)]. The sign (-) and magnitude (22.40°), when compared with those of the authentic (*R*)-(+)-(5a),<sup>9</sup> show that the ester is (*S*)-(-)-(5a). Hence, the cycloaddition proceeded again from the convex  $\alpha$ -side with diastereo excess of 93%. The ester (5c)<sup>†</sup> derived from (*Z*)-(6c) in the same manner (overall yield 80%)<sup>8</sup> showed a positive specific rotation value [oil,  $[\alpha]_D^{24}$  +14.40° (c=2.20, benzene)]



Scheme 3. Reagents and conditions: i, 2-methoxypropene (3 mol. equiv.)/AcOEt, -30 °C, 2 h; ii, concentrated HCl-dioxane (3:8 v/v), reflux, 1 h; iii, xylene, reflux, 1.5 h; iv, diazomethane/ether, 0 °C; v, H<sub>2</sub>/Pd-C in MeCO<sub>2</sub>Na (1.2 equiv.)-methanol

and its ee was estimated as 80% by <sup>1</sup>H-nmr spectroscopy with the aid of a chiral shift reagent.<sup>10</sup> Though the absolute configuration of (5c) was not confirmed yet, it is reasonable to assume that the addition proceeds again with the convex-side preference giving the (*R*)-ester. A positive sign of the specific rotation well supports this view.

In conclusion, it has become evident that not only the intermolecular hetero-Diels-Alder reactions described here is very useful for asymmetric synthesis but also use of the spiro chiral auxiliary<sup>11</sup> offers an effective methodology for the preparation of enantiomerically pure compounds.

# REFERENCES AND NOTES

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  2. This paper also forms Part 49 of the series "cycloadditions in syntheses". Part 48: N. Katagiri, S. Ise, N. Watanabe, and C. Kaneko, Chem. Pharm. Bull., in press.
  3. M. Sato, H. Hisamichi, C. Kaneko, N. Suzuki, T. Furuya, and N. Inukai, Tetrahedron Lett., 1989, **30**, 5281.
  4. (a) L. F. Tietze and G. V. Kiedrowski, Tetrahedron Lett., 1981, **22**, 219; (b) S. Takano, S. Satoh, and K. Ogasawara, Heterocycles, 1985, **23**, 41.
  5. For a review on the tandem-Knoevenagel-hetero-Diels-Alder reaction: L. F. Tietze, J. Heterocycl. Chem., 1990, **27**, 47.
  6. These spirocyclic arylidenedioxanediones (1a-1c) were synthesized by Knoevenagel condensation of the spirocyclic Meldrum's acid with the corresponding aldehydes using piperidine and acetic acid as the catalysts.
  7. Periodical monitoring of the addition step by hplc revealed that no E-Z isomerization of (6) occurs under the reaction conditions and only four adducts corresponded to (7b) and (8b) are formed as the detectable products (two major and two minor adducts).
  8. All the optically active compounds were isolated by silica gel column chromatography in order to keep the ee.
  9. D. Enders and K. Papadopoulos, Tetrahedron Lett., 1983, **24**, 4967.
  10. The ee was determined by 60 MHz <sup>1</sup>H-nmr spectra in CDCl<sub>3</sub> using tris[3-(heptafluoropropylhydroxymethylene)- $\alpha$ -camphorato]europium(III).
  11. Recent reviews for the use of spirocyclic dioxinones and related compounds in asymmetric synthesis: (a) M. Sato, J. Synth. Org. Chem. Jpn., 1988, **46**, 596; (b) M. Demuth and G. Mikhail, Synthesis, 1989, 145; (c) C. Kaneko, M. Sato, J. Sakaki, and Y. Abe, J. Heterocycl. Chem., 1990, **27**, 25.
- + (5a) ir(CHCl<sub>3</sub>), 1734, 1718 cm<sup>-1</sup>; nmr(CDCl<sub>3</sub>),  $\delta$  2.05(3H, s, acetyl), 2.47-2.98 (4H, m, CH<sub>2</sub> x 2), 3.58(3H, s, OMe), 3.51-3.95(1H, m), 7.24(5H, s, ArH).  
 (5b) ir(CHCl<sub>3</sub>), 1734, 1721 cm<sup>-1</sup>; nmr(CDCl<sub>3</sub>),  $\delta$  2.00(3H, s, acetyl), 2.40-2.84(4H, m, 2 x CH<sub>2</sub>), 3.51(3H, s, OMe), 3.60(1H, m, C<sub>3</sub>-H), 7.14(4H, s).  
 (5c) ir(CHCl<sub>3</sub>), 1738, 1722 cm<sup>-1</sup>; nmr(CDCl<sub>3</sub>),  $\delta$  2.10(3H, s, acetyl), 2.62-2.96 (4H, m, CH<sub>2</sub> x 2), 3.60(3H, s, OMe), 3.84(1H, m), 7.43 and 8.17(each 2H, d, J 8.9 Hz, ArH).

Received, 7th May, 1990