SYNTHESIS OF 1,3-DIOXIN-4-ONES AND THEIR USE IN SYNTHESIS. 21.[1] INTRAMOLECULAR PHOTO[2+2]CYCLOADDITION REACTIONS OF CHIRAL SPIROCYCLIC DIOXINONES HAVING ω-ALKENYL GROUPS AT 3-POSITION[2]

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Abstract——Chiral spirocyclic dioxinones having an ω-alkenyl group at 3-position were synthesized and their intramolecular photo[2+2]cycloaddition reactions were examined. The results not only provide enantioslective synthetic route to 2S-acetonylcyclohexanecarboxylic acids but also clarify the reason why these dioxinones exhibit remarkable diastereofacial selectivities in both intra- and intermolecular photo[2+2]-cycloaddition reactions.

The [2+2]cycloaddition of enones and enone-like chromophores to olefins is by far the most widely employed photochemical reaction in organic synthesis.[3] Most obviously it constitutes a major route to products containing the cyclobutane moiety. Enol derivatives or even tautomers of β-dicarbonyls act as the enone component in the de Mayo variant,[4] in which the photoadducts undergo retro-aldol cleavage of the cyclobutane and hence the method is applicable to the synthesis of complex molecules. The use of achiral dioxinones, **A**[5] and **B**[6,7], as the alternatives for acetoacetates and formylacetates (**A'** and **B'**: both of which are incapable of photoaddition to olefins), has further broadened the scope of the de Mayo reaction.

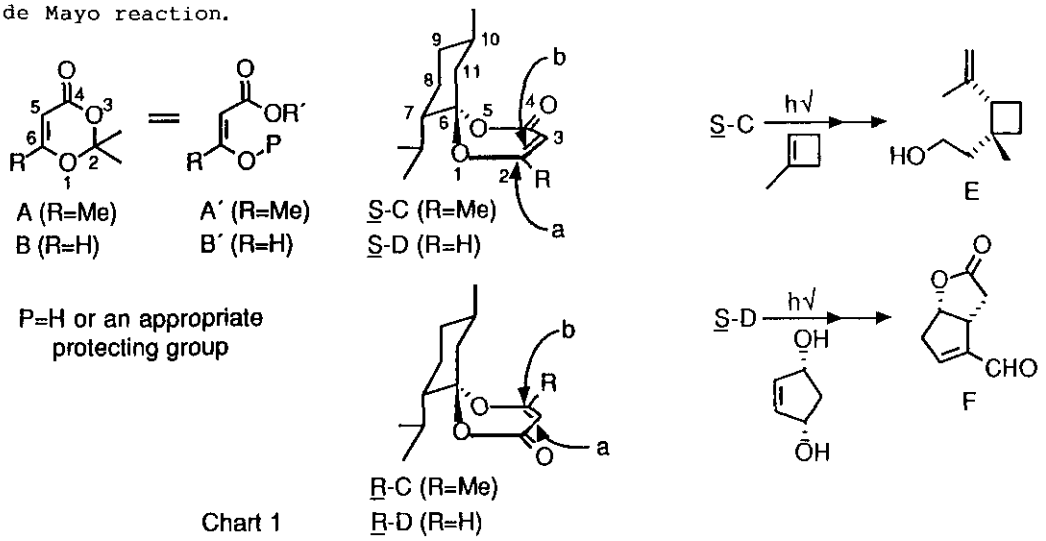

Chart 1

Recently, two lines of development have further been brought about in the de Mayo reaction using the dioxinones. These are 1) the intramolecular variant,[8,9] in which the problems inherent to the regio- and/or stereoselectivities are substantially reduced owing to geometrical constraints imposed on the reaction sites and 2) the use of the rigid spirocyclic dioxinones (**C**[10] and **D**[11]) as the chiral enones, which permits by the preferential a-side addition, the ready access of diastereoisomeric, and ultimately enantiomeric products. In the work along line 2, (+)-grandisol (**E**) and (+)-Corey lactone analogue (**F**) were synthesized from S-**C**[10] (R=Me) and S-**D**[1] (R=H), respectively.

In this paper, we wish to report the photoaddition of chiral dioxinones having ω-alkenyl group at 3-position (**5**) in order to attain not only the enantioselective synthesis of cycloalkanecarboxylic acids having 2-acetonyl group with specified absolute configuration at 2-position, but also a reasonable explanation why the dioxinones (**C** and **D**) show preferential a-side addition in the corresponding intermolecular photocycloadditions.

The substrates (both achiral and chiral) for the intramolecular dioxinone photocycloaddition were prepared as outlined in Chart 2.[12,13] Alkylation of tert-butyl acetoacetate with corresponding ω-alkenyl bromides under basic conditions [i: NaH/DMF, ii: Br-$(CH_2)_n$-$CH=CH_2$, 60 °C] followed by dioxinone formation (cyclohexanone, acetic anhydride, sulfuric acid, 0 °C) gave the achiral dioxinones (**2a-2c**) in ca. 40% overall yields (the yields of the second step were ca. 70%), respectively. Treatment of 2-alkenylated esters (**1**) with l-menthone under the same conditions as above furnished the chiral alkenylated dioxinones (S- and

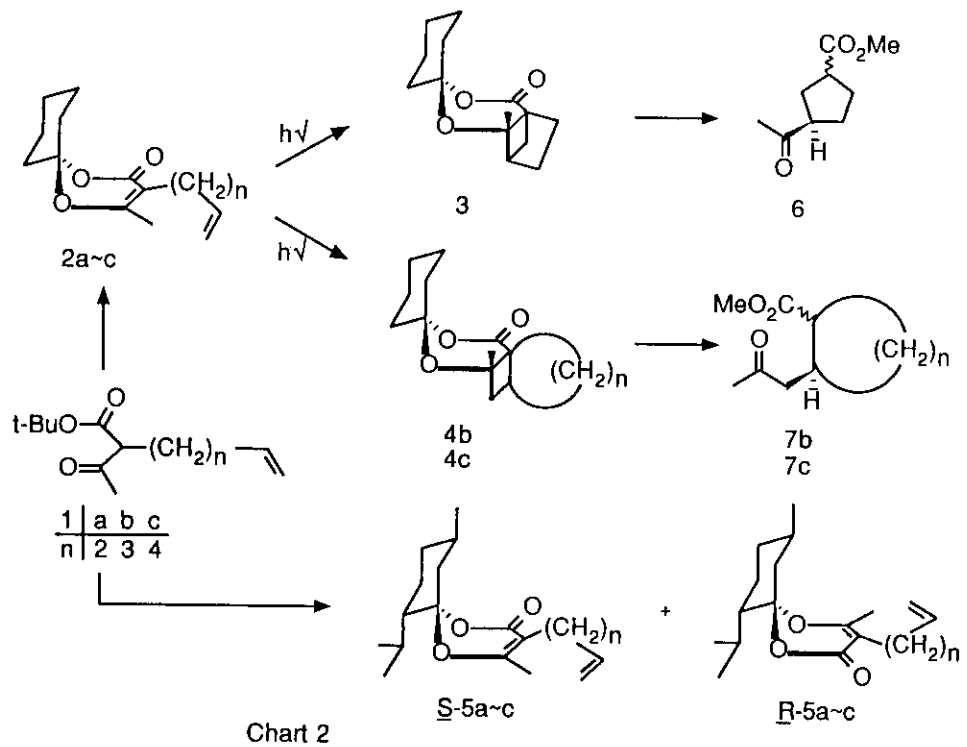

Chart 2

R-5a-5c) in ca. 40% yields as a mixture of diastereisomers. The diastereoisomers were separated by Rober column to give the less (S-series) and more polar isomers (R-series), respectively.[14] The determination of absolute structure of each diastereoisomer can readily be achieved by nmr spectroscopy.[14] In addition, the structure of **5c** was verified by X-ray crystallographic analysis (vide infra). It should be noted that in the chiral series the total yields of the dioxinones were decreased appreciably (ca. 40%) and 6S isomers were obtained in much larger amounts than 6R isomers (ca. 2:1 for **5a** and 7:1 for **5b** and **5c**).

While irradiation of **2a** (10% acetone/acetonitrile, 300 nm Rayonet photochemical reactor) gave the cross adduct (**3**: mp 45 °C, 66%), compounds **2b** and **2c** under identical conditions, afforded the corresponding parallel adducts (**4b**: mp 84 °C, 87% and **4c**: mp 73 °C, 56%). The structures of the photoproducts were determined not only from nmr spectra but also by their transformations [1) H_2O-heat and 2) CH_2N_2/ether] to the ring-opened keto esters (**6**, **7b**, and **7c**) whose structures were determined unequivocally by nmr spectra. The keto esters obtained were a mixture of both cis- and trans-isomers, as the latters always being the major isomers. Obviously, the regioselectivity observed in the above reactions is the one as expected from the so-called rule of five.[15]

Next, we examined the intramolecular cycloaddition reactions by using the 6S-isomers [S-**5a-5c**: the major isomers obtained in the above synthesis] as the chiral dioxinones. Though photolysis of S-**5a** proceeded only slowly and after prolonged irradiation resulted in a complex mixture, the same photolysis if applied to S-**5c** afforded a single adduct (**8**: mp 108 °C) in 90% yield in a comparable rate as in the corresponding achiral compound (**2c**). The stereochemistry of **8** was determined as formed by a-side addition from X-ray crystallographic analysis.[16] The adduct **8**, on hydrolysis with 10% HCl followed by methylation with diazomethane, afforded the 2-acetonylcarboxylate (**11**) as a mixture of trans- and cis-isomers both having 2S-configuration.[17]

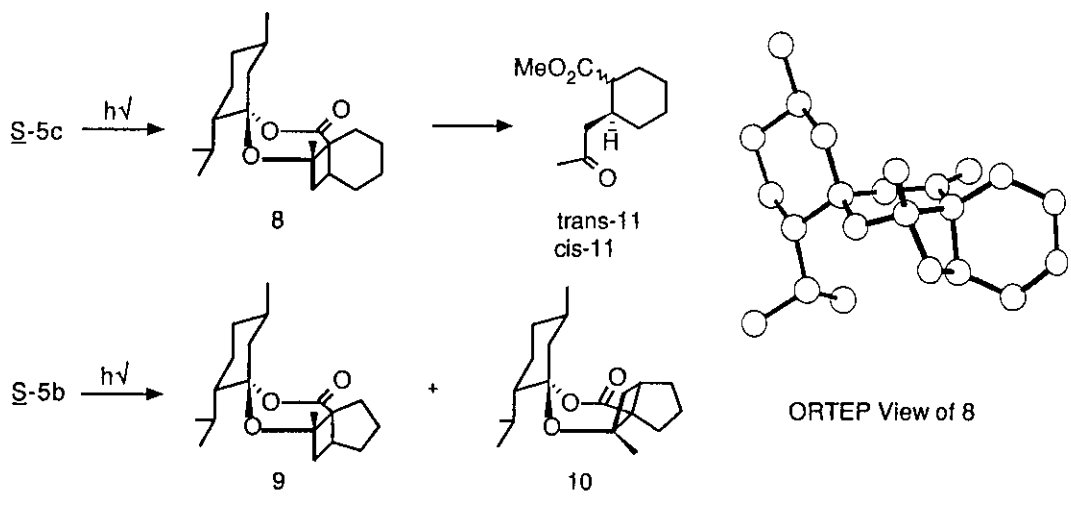

Chart 3

The same photolysis of S-**5b**, though proceeded in much faster rate than that of S-**5c**, resulted in the formation of the two adducts (**9** and **10**: ca. 1:1) in a total yield of 70%.

Two important informations were obtained in the present study: 1) since S-**5c** shows high preference for a-side addition, the methodology previously established in achiral series for highly stereoselective construction of complex carbocyclic systems[9] can evidently be extended in the chiral series if one uses chiral spirocyclic dioxinones as the enones, so long as the methylene chain is 4, and 2) the fact that preferential a-side addition is observed in S-**5c** just like as in the case of the intermolecular additions strongly supports the mechanism proposed previously by Demuth[10] and our groups[11]: i.e. the addition occurs from the more exposed a-side (we believe that these dioxinones exist as the sofa-conformation even in the excited state, just like as in the ground state[10,11]; cf. Chart 1)[18,19] The lack of selectivity in S-**5b** probably reflects the fact that shortness of the methylene chain brought about extra geometrical constraints imposed on the reaction sites which mainly determines the preferential site by kinetic control irrespective to the conformation of the dioxinone. The high rate of photoaddition of S-**5b** over that of S-**5c** supports the above view. Further studies in the photochemistry of chiral **5** and their related compounds [the corresponding 2-(ω-alkenyl) derivatives] are currently under way and will be reported in due course.

REFERENCES AND NOTES

1. Part 20: M. Sato, K. Takayama, T. Furuya, N. Inukai, and C. Kaneko, Chem. Pharm. Bull., in press.
2. This paper also forms part 45 of the series "Cycloadditions in Syntheses". part 44: N. Katagiri, M. Nomura, and C. Kaneko, Heterocycles, in press.
3. M. Demuth and G. Mikhail, Synthesis, **1989**, 145; C. Kaneko and T. Naito, Heterocycles, 1982, **19**, 2183; T. Naito and C. Kaneko, Yuki Gosei Kagaku Kyokai Shi, 1984, **42**, 51; S. W. Baldwin, "Org. Photochem.", ed. A. Padwa, Vol. 5, 123 (1981), Marcel Dekker Inc., New York.
4. P. De Mayo, Acc. Chem. Res., 1971, **4**, 41.
5. S. W. Baldwin and J. M. Wilkinson, J. Am. Chem. Soc., 1980, **102**, 3634.
6. The 5,6-unsubstituted dioxinones when photoadded to cyclopentene gave almost exclusively the cis-anti-cis adducts, irrespective of the kind of substituents at 2-position. M. Sato, H. Ogasawara, K. Sekiguchi, and C. Kaneko, Heterocycles, 1984, **22**, 2563. See also, M. Sato, K. Sekiguchi, H. Ogasawara, and C. Kaneko, Synthesis, **1985**, 224.
7. Previously, a practical one-pot synthesis of the Corey lactone analogue, racemic cis-6-formyl-2-oxabicyclo[3.3.0]oct-6-en-3-one was accomplished in our laboratory by using 2,2-dimethyl-1,3-dioxin-4-one as the enone. M. Sato, K. Sekiguchi, and C. Kaneko, Chemistry Lett., **1985**, 1057.
8. For the intramolecular variant, see: W. Oppolzer, Acc. Chem. Res., 1982, **15**, 135 ; M. T. Crimmins, Chem. Rev., 1988, **88**, 1453.
9. Highly stereoselective synthesis of taxane- and histrionicotoxin-type compounds has been accomplished from 6-(ω-alkenylated) dioxinones using intra-

molecular photoaddition as the key step: J. D. Winkler, P. M. Herschberger, and J. P. Springer, Tetrahedron Lett., 1986, **27**, 5177; J. D. Winkler and J. Hey, J. Am. Chem. Soc., 1986, **108**, 6425; J. D. Winkler, J. Hey, and S. Darling, Tetrahedron Lett., 1986, **27**, 5959.

10. M. Demuth, A. Palomer, H.-D. Sluma, A. K. Dey, C. Kruger, and Y.-H. Tsay, Angew. Chem. Int. Ed. Engl., 1986, **25**, 1117.
11. M. Sato, K. Takayama, T. Furuya, N. Inukai, and C. Kaneko, Chem. Pharm. Bull., 1987, **35**, 3971.
12. The general synthetic method of the dioxinones from tert-butyl esters of β-keto acids has been established already in our laboratory, in which the corresponding β-keto acids can also be used: M. Sato, H. Ogasawara, K. Oi, and T. Kato, Chem. Pharm. Bull., 1981, **31**, 1896.
13. All new compounds were characterized by full spectroscopic (nmr, ir, ms) data. Yields refer to spectroscopically and chromatographically homogeneous (≥95%) materials. Optical purities of chiral materials were further supported by definite specific rotations and, if diastereomeric, by 500 MHz nmr spectroscopy.
14. So far, we have prepared many chiral spirocyclic dioxinones, determined their absolute configuration of several isomers by X-ray crystallographic analysis,[10,11] and examined their properties. As a result, two characteristics which distinguish the two isomers have been found: 1) in nmr spectra, the signals of C_{11}-H_{axial} and the methine proton in the isopropyl group of the 6S-isomers appear in a higher field than those of the 6R-isomers and 2) on chromatography by silica gel, the 6S-isomers are, without exception, less polar than the 6R-isomers.
15. R. Srinivasan and K. H. Carlough, J. Am. Chem. Soc., 1967, **89**, 4932; M. Ohsaku, J. Chem. Soc., Perkin Trans. II, **1987**, 1027.
16. Full details of the X-ray structure data will be published in the full paper.
17. The isomers were readily separated by usual chromatography. The major isomer [yield, 65%; $[\alpha]_D$ +23°(c=1.0, $CHCl_3$)] should be assumed as trans.
18. Concerning to the diastereofacial selectivities observed in the related chiral dioxinones (e.g. 2-tert-butyl-6-methyl-1,3-dioxin-4-one), Seebach and his collaborators proposed a novel idea based on the pyramidalization of the reaction sites. In our opinion, their explanation is not applicable to photo[2+2]cycloadditions: See D. Seebach, J. Zimmermann, V. Gysel, R. Ziegler, and T.-K. Ha, J. Am. Chem. Soc., 1988, **110**, 4763.
19. It seems worthy to note that chiral spirocyclic dioxinone 3-carboxylates [i.e. S-D having methoxycarbonyl group at 3-position] exhibit almost complete a-side preference in Diels-Alder reaction with cyclopentadiene. Based on this fact, we have accomplished highly enantioselective synthesis of carbocyclic C-nucleosides. M. Sato, K. Takayama, and C. Kaneko, Chem. Pharm. Bull., in press.

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