1,3-Dioxin-4-ones as Versatile Intermediates for Organic Synthesis

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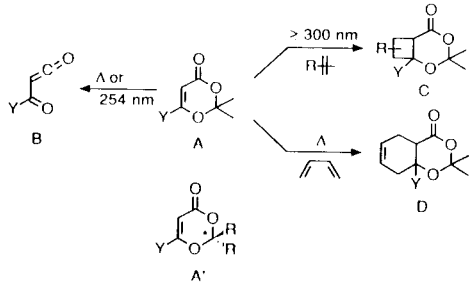
Creation of versatile synthons useful for a variety of compounds is one of the main targets in organic synthesis. Especially, if an introduction of a variety of substituents into their common skeleton can be accomplished readily and some novel transformations of them can be attained irrespective of the substituents, they can provide new and general routes to a variety of organic molecules. Involvement of a cyclic array in these compounds seems to be desirable, because if one can prepare them as chiral compounds by introduction of chiral auxiliary and elaborate new methods to introduce some substituents in them in a way which distinguishes the side of the ring system, they could be used as suitable intermediates for the synthesis of enantiomerically pure compounds.

For several years, we have investigated the synthesis of 1,3-dioxin-4-ones as one of possible candidates for such synthons and examined their reactions in detail. As a result, we have got enough data showing that these 1,3-dioxin-4-ones fit all of the above requirements.

Two important characteristics of these compounds are shown in Scheme 1 taking **A** as the typical example: 1) ready ring-opening of **A** to acylketene (**B**) either under thermal or photochemical condition and 2) the C-C double bond in the dioxinone moiety acts as the enol form of masked acylacetic acids (e.g. **A** → **C** or **D**), which are important building blocks in organic synthesis.

Scheme 1



The latter characteristic (2) provides an ability that **A'** serves as an enol form of chiral acylacetic acid which could be used for the synthesis of a variety of enantiomerically pure compounds, if suitable functions are introduced to the dioxinones (*c.f.* **A'**) in order not only to make them chiral but also to provide diastereofacial selectivity to the double bond in them.

To economize space, we report the above study in the following order: 1) synthesis of these dioxinones, 2) use of these dioxinones as the equivalent of acylketenes, and 3) creation of chiral spirocyclic dioxinones and their use in the synthesis of enantiomerically pure compounds. Since most of the works concerning items 1 and 2 have appeared in print already, the stress of this review is focussed on item 3.

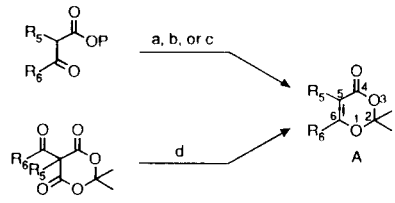
1. Synthesis of 1,3-Dioxin-4-ones.

Though two methods had already been published: synthesis of 6-methyl derivative from diketene [1] and that of 6-aryl derivatives from furandiones [2], we developed two general synthetic methods a and b which afforded all kinds of dioxinones.

Method a.

This method consists of treating β-ketoacids with an appropriate ketone (as a typical example, we use acetone unless otherwise noted) under acidic conditions [3].

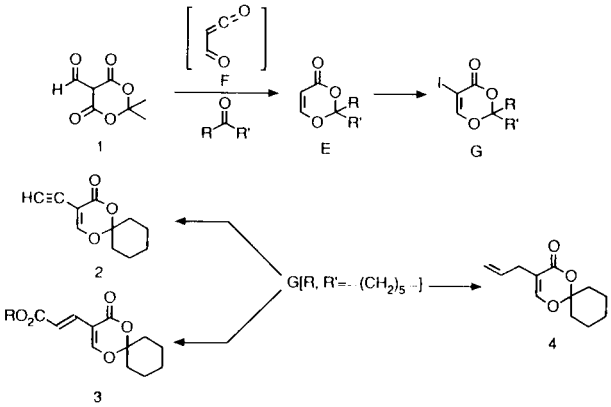
Scheme 2



a: P=H, conc. H_2SO_4, Ac_2O, acetone
b: P=H, conc. H_2SO_4, $AcOCMe{=}CH_2$
c: P=t-Bu, conc. H_2SO_4, Ac_2O, acetone
d: Δ / aprotic solvent

Instead of acetone, use of isopropenyl acetate gave better results in some cases. Also, the use of *t*-butyl esters instead of ketoacids also gave the same results [4]. By these methods, 6-substituted and 5,6-disubstituted dioxinones can be synthesized. It should be noted that acylated Meldrum's acids readily available by the Yonemitsu-Oikawa method [5] could also be

Scheme 3



used for the synthesis of 6-substituted dioxinones [6], though it gave poor results when applied to the synthesis of 5,6-disubstituted derivatives.

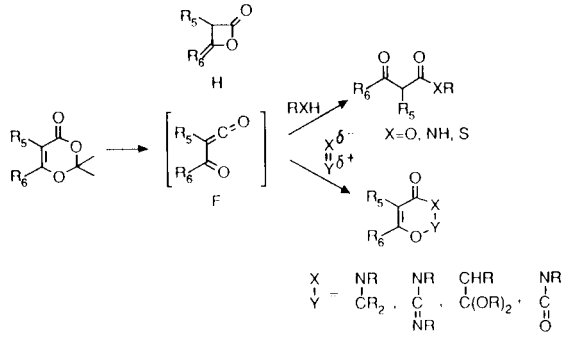
For the synthesis of 5,6-unsubstituted dioxinones (**E**), the following method (Method b) was elaborated. Thus, when formylated Meldrum's acid (**1**) was heated in toluene in the presence of acetone, the desired dioxinone (**E**) was obtained in high yield [7].

It was found that a variety of 2- or 2,2-disubstituted dioxinones can also be synthesized from **1** (or **E**: R,R' = Me) by heating in an aprotic solvent containing aldehydes or ketones [7]. These methods surely involve the thermal cycloreversion of **1** or **E** to the corresponding formylketene (**F**), which then cycloadded to the carbonyl compounds in 4 + 2 manner. The ready availability of 5,6-unsubstituted dioxinones opened a new route to 5-substituted derivatives [8]. Thus, halogenation (i: NBS or NIS/AcOH, ii: Et_3N) of **E** followed by palladium-catalyzed cross-coupling afforded the 5-substituted dioxinones (*e.g* **2** and **3**). The 5-iodo derivative (**G**), when photolyzed by ≥300 nm rays in the presence of allyltrimethylsilane, afforded the allyl dioxinone (**4**). These synthesis as well as some of their reactions are reviewed by one (M. S.) of the present authors [9,10].

2. General Survey of the Reactions of 1,3-Dioxin-4-ones.

So far, three types of reactions have been disclosed: 1) the dioxinones can function as equivalents of formyl- or acylketenes and hence, as mixed diketenes (**H**) whose synthetic method has not yet been established (Scheme 4) [11], 2) they also function as equivalents of formyl- or acylacetates in de Mayo reactions (**A** → **C** in Scheme 1), and 3) they also function as the dienophiles in Diels-Alder reaction, when suitable electron-withdrawing groups are introduced into their double bond (**A** → **D** in Scheme 1).

Scheme 4

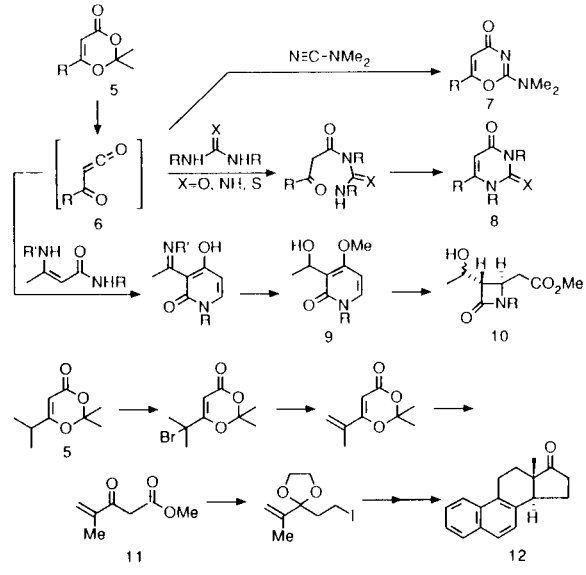


These functions of the dioxinones are further broadened in the following two points; 1) the reactions proceed likewise intramolecularly and 2) the use of chiral spirocyclic dioxinones in de Mayo as well as Diels-Alder reactions permits the ready access of enantiomerically pure compounds.

2-1. Reactions of the Dioxinones as Equivalents of Formyl- or Acyketenes.

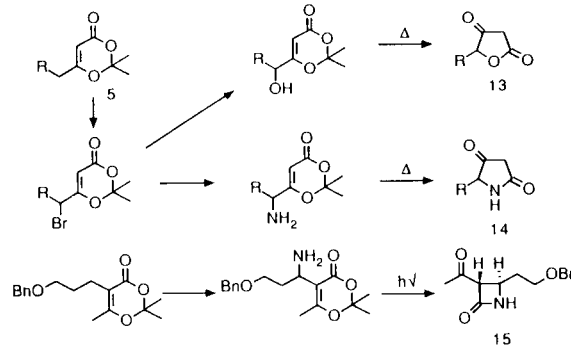
When 6-alkylated dioxinone (**5**) is heated in an appropriate solvent they cyclorevert to the corresponding ketenes (**6**). Though there exists marked temperature dependence, even 5,6-dialkylated dioxinones (the most stable ones among these dioxinones) ring-open in boiling mesitylene. Even, the same ring opening can be brought about by irradiation at 254 nm and hence, if the products are unstable at a high temperature, the reaction can also be carried out at room temperature. Acylketenes thus generated can be converted to six-membered heterocycles, *e.g.* oxazinones (**7**), uracils (**8**) and 2-pyridones (**9**), if suitable dipolarophiles or nucleophiles are present in the reaction medium [12]. The pyridones prepared in this manner were utilized as the direct precursors of carbapenams (**10**) [13]. The ketenes thus obtained can also be trapped by nucleophiles to give acylacetic acid derivatives. Formylacetates have been prepared for the first time in neutral form when 5,6-unsubstituted dioxinones are heated in toluene in the presence of a variety of alcohols [14]. Even the *t*-butyl formylester was prepared in this manner and the ester can be purified by distillation *in vacuo*. In the same manner, unsaturated β-ketoester (**11**), useful in the synthesis of steroids (*e.g.* **12**), has been synthesized from 6-isopropyldioxinone (**5**) *via* 6-isopropenyl derivative [15]. Several examples of intermolecular ketene trapping reactions are summarized in Scheme 5.

Scheme 5



Intramolecular ketene trappings are also possible as illustrated in the synthesis of tetronic acid (**13**: R = H) [16] and tetramic acid (**14**: R = H) [17] and their derivatives. Novel syn-

Scheme 6

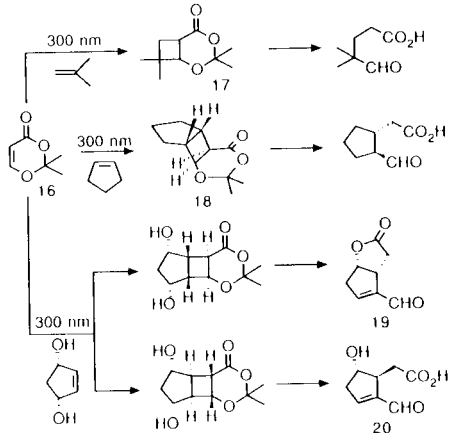


thetic method of β-lactam derivatives (*e.g.* **15**) has also been established by means of photochemical ring opening as the key step [17].

2-2. Use of the Dioxinones as the Equivalents of Acylacetates in de Mayo Reactions.

Baldwin *et al.* originally pointed out that the 6-methyldioxinone could act as the enol derivatives of acetoacetates (which are inactive by themselves in the reaction due to facile *cis-trans* photoisomerization) in de Mayo reaction [18]. (±)-Grandisol was thus synthesized in this manner [19]. Since we first prepared 5,6-unsubstituted dioxinones (*e.g.***16**), we utilized them as the equivalents of formylacetates. It should be noted that this dioxinone shows remarkable regio- and stereoselectivities in photoaddition reaction to alkenes. Thus with alkenes it gave head-to-tail adducts (**17**), and with cycloalkene it gave only the *cis-anti-cis* adduct (**18**) [20]. By using these characteristics, we have been able to synthesize Corey lactone analogue (**19**) by the shortest route [21]. The adducts (two isomers in *ca.* 1:1 ratio) formed by the photoaddition, when refluxed in water and extraction by dichloromethane, gave the lactone (**19**). Since the undesired product (**20**) remained in aqueous layer, the method provided an efficient and practical one-pot synthesis of **19**.

Scheme 7

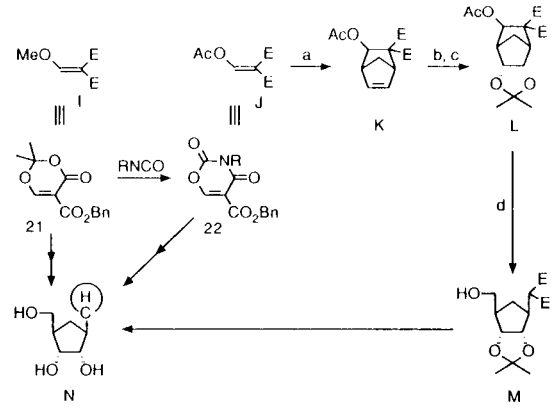


Winkler *et al.* synthesized taxane and histrionicotoxin derivatives by an application of the corresponding intramolecular photocycloaddition reaction [22,23].

2-3. Use of the Dioxinones as the Equivalents of 3-Oxygenated Acrylate Derivatives.

Though these unsubstituted and alkylated dioxinones can not react with cyclopentadiene or other dienes, their derivatives having an electron-withdrawing group at 5- and/or 6-position give the Diels-Alder adducts if suitable catalyst or high-pressure is used. Thus, for example, 5-carboxylates (**21**) [24] reacted with the diene at room temperature if diethylaluminum chloride was used as the catalyst [25]. The 6-formyl derivative is more active and hence gave the adduct, when these two components were merely kept standing in toluene. The corresponding oxazinones (**22**), which were readily prepared from the dioxinones and isocyanates, are more reactive than **21** (isoelectronic with **J**) and hence gave the corresponding adducts under a much milder condition [26]. The adducts obtained from either **21** and **22** could, by an application of reductive retrograde aldol reaction (RRA reaction: d in Scheme 8 [27]), gave the stereospecific route to carbocyclic *C*-nucleosides (**N**) [25,26].

Scheme 8



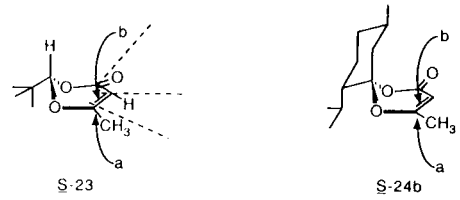
Essentially in the same manner, we already have established a stereospecific synthetic route of carbocyclic C-nucleosides (**J** → **K** → **L** → **M** → **N**) by using acetoxymethylenemalonates (**J**: isoelectronic with **22**) as the dienophile [27c].

3. Chiral Spirocyclic Dioxinones as the Synthons for Enantiomerically Pure Compounds.

In order to develop a new method for the synthesis of enantiomerically pure compounds (abbreviated hereafter as EPC), it is necessary to synthesize chiral dioxinones having highly diastereofacial selectivity (a- or b-side preference) in some types of reactions. Obviously, such reactions are those belonging to item 2 in which the dioxinones are used as equivalents of the enol form of formyl- or acylacetates (*e.g.* de Mayo, Diels-Alder, and other related reactions).

Two important developments (1 and 2) have been made recently which use chiral dioxinones as synthons of EPC. 1) Seebach *et al.* have synthesized 2-alkylated dioxinones (*e.g.* chiral 2-*t*-butyl derivative: **23**) and examined their behaviour in some reactions [28]. As a results, they found remarkable b-side preference for some thermal reactions (catalytic hydrogenation, Michael additions, and conjugated additions) and reasoned their selectivity by pyramidarization depicted in formula **23** (*vide infra*). 2) Demuth *et al.*, on the contrary, have found that chiral spirocyclic dioxinones (*e.g.* **24b**) exhibit remarkable a-side preference in the photoaddi-

Scheme 9



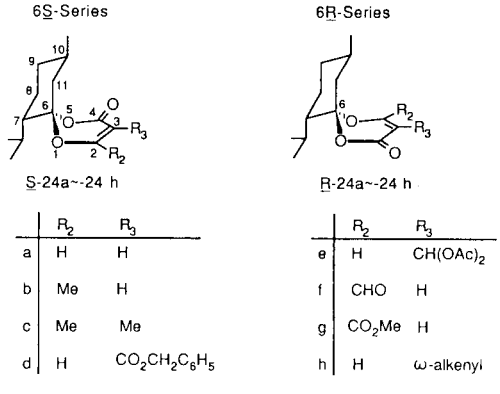
tion to alkenes and explained the selectivity by assuming that the alkenes approach from the more-exposed a-side based on the sofa-conformation as depicted in formula **24b** [29]. Both assumptions (pyramidarization and sofa-conformation) were verified by X-ray crystallographic analysis.

We have also been interested in using spirocyclic dioxinones as chiral synthons by the reasons stated below. Originally, we were interested in synthesizing Corey lactone analogue (**19** in Scheme 7) by using chiral dioxinones. For that, two preliminary experiments were performed. 1) Use of 2-monosubstituted dioxinones (*e.g.* 6-unsubstituted derivative of **23**) and 2) use of the spirocyclic dioxinones (2-unsubstituted derivatives of **24b**) in de Mayo reaction. The study along line 1, however, did not give fruitful results: the d.e. was only *ca.* 25% even the photolysis was carried out at *ca.* -70°C [30]. On the contrary, when the spirocyclic dioxinone was used instead, remarkably high d.e. was found even the irradiation was carried out at room temperature [31].

Based on these and Demuth's results [29], we have synthesized a series of spirocyclic dioxinones as chiral synthons. The synthesis was readily accomplished by the methods 1 and 2 as described in item 1, in which *l*- and *d*-menthones were used as the carbonyl compounds. In all cases, two diastereomers were formed, but their separation was readily attained by chromatography on silica gel. The 6*S*-isomers (*S*-**24a-h**) are always less polar than the corresponding 6*R*-isomers (*R*-**24a-h**). The absolute structure of each diastereoisomer has been determined unequivocally by X-ray crystallographic analysis [31,32].

Scheme 10

Chiral dioxinones derived from *l*-menthone



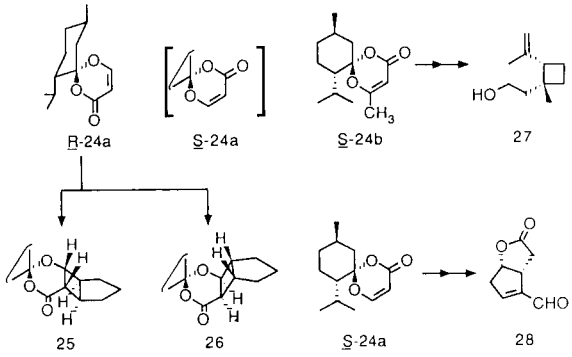
	R_2	R_3
a	H	H
b	Me	H
c	Me	Me
d	H	$CO_2CH_2C_6H_5$

	R_2	R_3
e	H	$CH(OAc)_2$
f	CHO	H
g	CO_2Me	H
h	H	ω-alkenyl

3-1. Use of Chiral Spirocyclic Dioxinones in Asymmetric de Mayo Reactions.

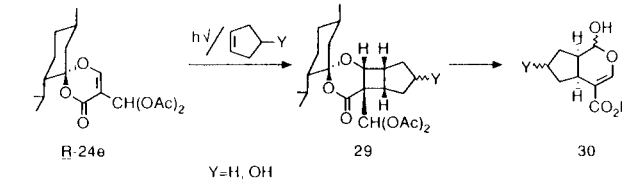
When *R*-**24a** was photolyzed in hexane in the presence of cyclopentene, two adducts (**25** and **26**) were obtained in a *ca.* 6:1 ratio. The major isomer (**25**) was determined as the adduct formed by the a-side addition of the alkene. The same a-side preference was also observed when *S*-**24a** was photoadded to the same alkene [31]. By using *cis*-2-cyclopentane-1,4-diol [33] as the alkene, practical one-pot synthesis of (+)-Corey lactone analogue (**28**) has thus been accomplished [32]. The a-side preference has originally been found by Demuth *et al.* who synthesized (+)-grandisol (**27**) by the de Mayo reaction of *S*-**24b** with 1-methylcyclobutene [29].

Scheme 11



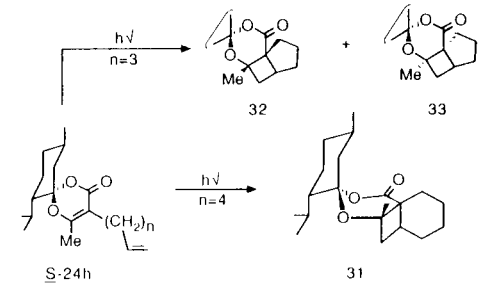
By using this remarkable a-side preference, we also have succeeded in the synthesis of iridiods [34]. Thus, by using *R*-**24e** as the enone, Buchi's intermediate (**30**) [35] was synthesized as EPC. It should be noted that in this photoaddition *cis-syn-cis* adduct (**29**) was formed exclusively, probably due to bulkiness of the diacetoxymethyl group.

Scheme 12



Since the use of optically active olefins is not necessary in this case, this method is much more economical than the previously reported de Mayo reactions for chiral iridoids, in which chiral alkenes had to be used in large amounts [36]. It should be noted that the dioxinones having ω-alkenyl chain at the 3-position (*S*-**24h**, n = 3 or 4) afforded the parallel adducts (**31-33**) exclusively [37]. The fact that while *S*-**24h** (n = 3) afforded two adducts (**32** and **33**) in ca. 1:1 ratio single adduct (**31**: the structure was verified by X-ray analysis) was obtained from *S*-**24h** (n = 4) indicates that the a-side preference is retained so long as the length of methylene chain is 4 or above [37]. This fact shows clearly that spirocyclic dioxinones can also be used as building blocks for chiral complex carbon skeleton compounds, as already exemplified in the racemic series by elegant synthesis of taxane and histrionicotoxin related compounds reported by Winkler's group [22,23].

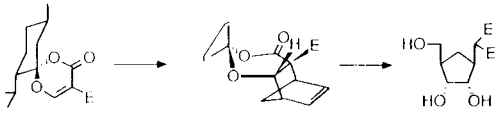
Scheme 13



3-2. Use of Chiral Spirocyclic Dioxinones as the Dienophile in Asymmetric Diels-Alder Reactions.

The same a-side preference has also been found in Diels-Alder reactions. Thus, though the 2,3-unsubstituted dioxinones or their alkylated derivatives did not react with cyclopentadiene, the introduction of an electron-withdrawing group at either 2- or 3-position gives them an ability to act as the dienophiles. Thus, for example, when *S*-**24d** was reacted with the diene, single adduct (**34**) was formed as the sole product [25]. Hence, the a-side preference in these spirocyclic dioxinones seems to be a common phenomenon for pericyclic reactions, irrespective of their electronic states (ground and excited states).

Scheme 14

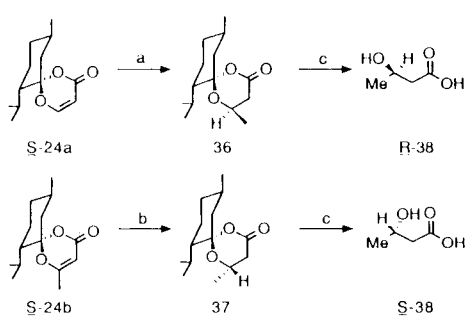


The adducts obtained as above have been transformed to carbocyclic *C*-nucleosides (**35**, *c.f.* Scheme 8). The related dioxinones (*S*-**24f** and *S*-**24g**) having an electron-withdrawing substituent at 2-position also afforded the adducts with cyclopentadiene [38]. These facts show that application of this method to asymmetric Diels-Alder reaction would provide a novel methodology for EPC synthesis.

3-3. Use of Spirocyclic Dioxinones in Other Reactions (Preference of the b-Side Addition).

Several reactions which proceeded with high b-side preference have been found in our study [31]. Thus, when *S*-**24a** was reacted with lithium dimethylcuprate, the methylated derivative (**36**) was obtained. The same b-side preference was also observed, when the 2-methyldioxinone (*S*-**24b**) was hydrogenated over platinum catalyst to give the dihydro derivative (**37**). Both dioxanones (**36** and **37**) when hydrolyzed by acidic water afforded chiral 3-hydroxybutanoic acid (*R*-**38** or *S*-**38**).

Scheme 15



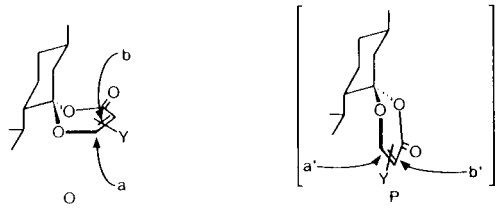
The fact that d.e.s. for both reactions were *ca.* 85% shows clearly that preference of the b-side is again quite high in these reactions. The same preference has also been reported by Seebach *et al.* in the corresponding reactions of chiral 2-*t*-butyldioxinone (**23**) [28].

3-4. Mechanisms for Preferential a- and/or b-Side Attack of the Chiral Spirocyclic Dioxinones.

It is obvious from the experimental data given in items 3-1 ~ 3-3 that the spirocyclic dioxinones (*S*- and *R*-**24**) show, in thermal reactions, two diastereofacial selectivities (either a- or b-side preference) depending upon the type of reactions. Thus, the b-side preference was observed in catalytic hydrogenation and methylation by lithium dimethylcuprate [31], while the Diels-Alder reactions proceeded by the a-side preference [25,38]. It should be noted that the preferred side for the attacking alkenes is again the a-side in the photo-[2 + 2]cycloaddition reactions [29,31,32,34,37].

Previously, we explained the a-side preference in the photo-reactions by assuming that the spirocyclic dioxinones exist in an equilibrium between two sofa conformers (**O** and **P**) and the major conformer (**O**: its conformation was verified by X-ray crystallographic analysis) takes the major role when the attacking reagents are relatively small so as to accept them from the more exposed a-side, while when the reagents are much more bulky they only attack the least hindered b'-side of the minor conformer (**P**) [31]. Demuth and his collaborators also explained the a-side preference of photoaddition of **24b** to alkenes by assuming that **O** is the sole conformer, whose a-side being more exposed than the b-side [29].

Scheme 16



Only 6S-isomers are shown

So long as we can assume that cyclopentadiene in Diels-Alder reaction is a small reagent, the same explanation can still be applied for the a-side preference. Seebach and his collaborators proposed recently a novel mechanism concerning the b-side preference found in some thermal reactions of chiral 2-*t*-butyldioxinone (*S*-**23**) and related compounds including our spirocyclic dioxinones [28]. By assuming that the stable conformer (*e.g.* *S*-**23**: Scheme 9) is the only species present, they have proposed a novel idea for higher selectivity of the diastereotopic face (b-side) which appears to be more hindered than the a-side by the presence of the axial hydrogen atom on the acetal center. In the proposal, the trigonal centers of *S*-**23** are pyramidarized in the same direction from which the reaction occurs [28]. Though we agree that the proposal could be extended to some reactions of our spirocyclic dioxinones (*e.g.* methylation by lithium dimethylcuprate and catalytic hydrogenation, both of which would occur through the b-side attack of conformer (**O**) with the same pyramidarization as **23**), the preponderance of the a-side attack in the Diels-Alder reaction of spirocyclic dioxinones (*S*-

and *R*-24) has revealed that there exists another mechanism.

By assuming single conformer (O) being the only species present in the reaction medium, it is tempting to propose further that the a-side attack is due solely to the preferential attack of the diene from the less-hindered side of O, and not to the pyramidarization. In other words, Seebach's proposal for the preferential b-side attack rests entirely on the conformation of the unperturbed substrates (see the pyramidarized sofa-conformations depicted by formula **23** in Scheme 9) and hence corresponds to the assumption that the transition states are much more closely related to the starting materials than the products. Our proposal for the a-side attack corresponds to the assumption that the transition states are much closer to the products than the substrates.

Knowing the preponderance of a-side attack of the spirocyclic dioxinones (*S*- and *R*-**24**) in photo[2 + 2]cycloaddition reactions, it seems clear that more thorough experiments are needed for complete clarification of the diastereofacial selectivity of these chiral dioxinones (**23** and O).

In conclusion, the results described in this review suggest that an improved understanding of the relationship between structure and function in the dioxinones is at hand and that it is becoming possible to rationally design new synthetic methods for a variety of compounds (both racemic as well as chiral).

Acknowledgements.

This review summarizes recent research done with a group of very able and enthusiastic coworkers, whose names appear in the references. We thank them for their efforts. We are also grateful to Drs. Noriyoshi Inukai and Toshio Furuya (Tsukuba Research Laboratories, Yamanouchi Pharmaceutical Co. Ltd) for the X-ray crystallographic analysis.

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References and Notes

[1] M. F. Carrol and A. R. Bader, *J. Am. Chem. Soc.*, **74**, 6305 (1952); *idem, ibid.*, **75**, 5400 (1953); E. V. Dehmlow and A. R. Shamout, *Liebigs Ann. Chem.*, 1753 (1982).

[2] G. Jager, *Chem. Ber.*, **105**, 137 (1972); S. Murai, K. Hasegawa and N. Sonoda, *Angew. Chem., Int. Ed. Engl.*, **14**, 636 (1975).

[3] M. Sato, H. Ogasawara, K. Oi and T. Kato, *Chem. Pharm. Bull.*, **31**, 1896 (1983).

[4] The use of *p*-methoxybenzyl instead of *t*-butyl as the protecting group was reported recently: K. E. Heneger and J. D. Winkler, *Tetrahedron Letters*, **28**, 1051 (1987).

[5] Y. Oikawa, K. Sugano and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).

[6] I. Iwasaki, S. Makisawa and K. Sato, Japanese Patent, 79,106,466; *Chem. Abstr.*, **92**, 58755r (1980).

[7] M. Sato, K. Sekiguchi, H. Ogasawara and C. Kaneko, *Synthesis*, 224 (1985).

[8] M. Sato, N. Yoneda and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 4577 (1986).

[9] M. Sato, *J. Synth. Org. Chem. Japan*, **46**, 596 (1988).

[10] M. Sato, *Yakugaku Zasshi*, **108**, 805 (1988).

[11] For a review on diketene: R. J. Clemens, *Chem. Rev.*, **86**, 241 (1986).

[12] M. Sato, N. Yoneda and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 621 (1986).

[13] N. Katagiri, M. Sato, N. Yoneda, S. Saikawa, T. Sakamoto, M. Muto and C. Kaneko, *J. Chem. Soc., Perkin Trans. I*, 1289 (1986).

[14] Originally, we used formyl Meldrum's acid as the equivalent of formylketene [a] but later found that the 5,6-unsubstituted dioxinones could also be used [8]. [a] M. Sato, N. Yoneda, N. Katagiri, H. Watanabe and C. Kaneko, *Synthesis*, 672 (1986).

[15] M. Sato, K. Kawakami, T. Suzuki, H. Morisawa, S. Nishimura and C. Kaneko, *Steroids*, **53**, 739 (1989). See also, M. Sato, T. Suzuki, H. Morisawa, S. Fujita, N. Inukai and C. Kaneko, *Chem. Pharm. Bull.*, **35**, 3647 (1987).

[16] M. Sato, J. Sakaki, K. Takayama, S. Kobayashi, M. Suzuki and C. Kaneko, *Chem. Pharm. Bull.*, in press.

[17] M. Sato, H. Ogasawara, K. Takayama and C. Kaneko, *Heterocycles*, **26**, 2611 (1987).

[18] For reviews: P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971); M. Demuth and G. Mikhail, *Synthesis*, 145 (1989).

[19] For a review: S. W. Baldwin, "Organic Photochemistry", Vol 5, A. Padwa, ed, Marcel Dekker Inc., New York, 1981, p 123.

[20] M. Sato, H. Ogasawara, K. Sekiguchi and C. Kaneko, *Heterocycles*, **22**, 2563 (1984).

[21] M. Sato, K. Sekiguchi and C. Kaneko, *Chem. Letters*, 1057 (1985).

[22] Synthesis of taxane skeletal compounds: J. Winkler and J. Hey, *J. Am. Chem. Soc.*, **108**, 6425 (1986); J. Winkler, J. Hey and S. Darling, *Tetrahedron Letters*, **27**, 5959 (1986).

[23] Synthesis of histrionicotoxins: J. D. Winkler, P. M. Hershberger and J. P. Springer, *Tetrahedron Letters*, **27**, 5177 (1986).

[24] M. Sato, N. Katagiri, K. Takayama, M. Hirose and C. Kaneko, *Chem. Pharm. Bull.*, **37**, 665 (1989).

[25] M. Sato, K. Takayama and C. Kaneko, *Chem. Pharm. Bull.*, **37**, 2615 (1989).

[26] N. Katagiri, M. Hirose, M. Sato and C. Kaneko, *Chem. Pharm. Bull.*, **37**, 933 (1989).

[27] RRA reaction (reductive retrograde aldol reaction) and its use in synthesis: [a] for a review: C. Kaneko, M. Sato and N. Katagiri, *J. Synth. Org. Chem. Japan*, **44**, 1058 (1986); [b] for β-lactams: C. Kaneko, N. Katagiri, M. Sato, M. Muto, T. Sakamoto, S. Saikawa, T. Naito and A. Saito, *J. Chem. Soc., Perkin Trans. I*, 1283 (1986); M. Sato, N. Katagiri, M. Muto, T. Haneda and C. Kaneko, *Tetrahedron Letters*, **27**, 6091 (1986); [c] for *C*-nucleoside and related compounds: N. Katagiri, H. Akatsuka, T. Haneda, C. Kaneko and A. Sera, *J. Org. Chem.*, **53**, 5463 (1988); N. Katagiri, H. Akatsuka, C. Kaneko and A. Sera, *Tetrahedron Letters*, **29**, 5397 (1988); review: N. Katagiri, *J. Synth. Org. Chem. Japan*, **47**, 707 (1989).

[28] D. Seebach, J. Zimmermann, U. Gysel, R. Ziegler and T.-K. Ha, *J. Am. Chem. Soc.*, **110**, 4763 (1988); D. Seebach and J. Zimmermann, *Helv. Chim. Acta*, **69**, 1147 (1986).

[29] M. Demuth, A. Palomer, H.-D. Sluma, A. K. Dey, C. Kruger and Y.-H. Tsay, *Angew Chem., Int. Ed. Engl.*, **25**, 1117 (1986).

[30] a-Side preference (d.e. 25%) was confirmed by NOE study of the major diastereomer obtained by the photoaddition to cyclopentene. D.e. was, however, almost 0% when the photolysis was carried out at room temperature: M. Sato, Y. Abe and C. Kaneko, unpublished results.

[31] M. Sato, K. Takayama, T. Furuya, N. Inukai and C. Kaneko, *Chem. Pharm. Bull.*, **35**, 3971 (1987).

[32] M. Sato, K. Takayama, Y. Abe, T. Furuya, N. Inukai and C. Kaneko, *Chem. Pharm. Bull.*, in press.

[33] C. Kaneko, A. Sugimoto and S. Tanaka, *Synthesis*, 876 (1974).

[34] M. Sato, K. Takayama, K. Sekiguchi, Y. Abe, T. Furuya, N. Inukai and C. Kaneko, *Chem. Letters*, in press.

[35] G. Buchi, J. A. Carlson, J. E. Powell, Jr., and L.-F. Tietze, *J. Am. Chem. Soc.*, **92**, 2165 (1970); *idem, ibid.*, **95**, 540 (1973).

[36] C. R. Hutchison, K. C. Mattes, M. Nakane, J. J. Partridge and M. R. Uskokovic, *Helv. Chim. Acta*, **61**, 1221 (1978).

[37] M. Sato, Y. Abe, C. Kaneko, T. Furuya and N. Inukai, *Heterocycles*, in press.

[38] M. Sato, C. Orii, J. Sakaki and C. Kaneko, *J. Chem. Soc., Chem. Commun.*, in press.