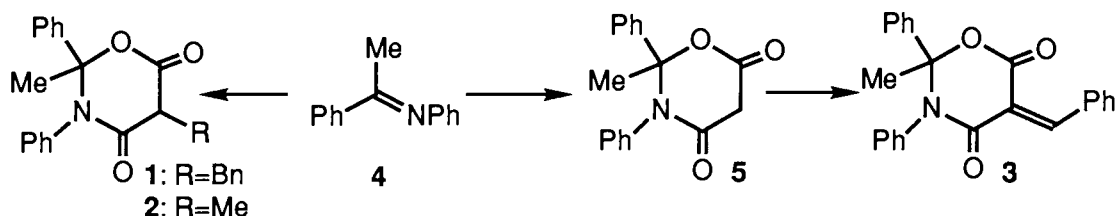


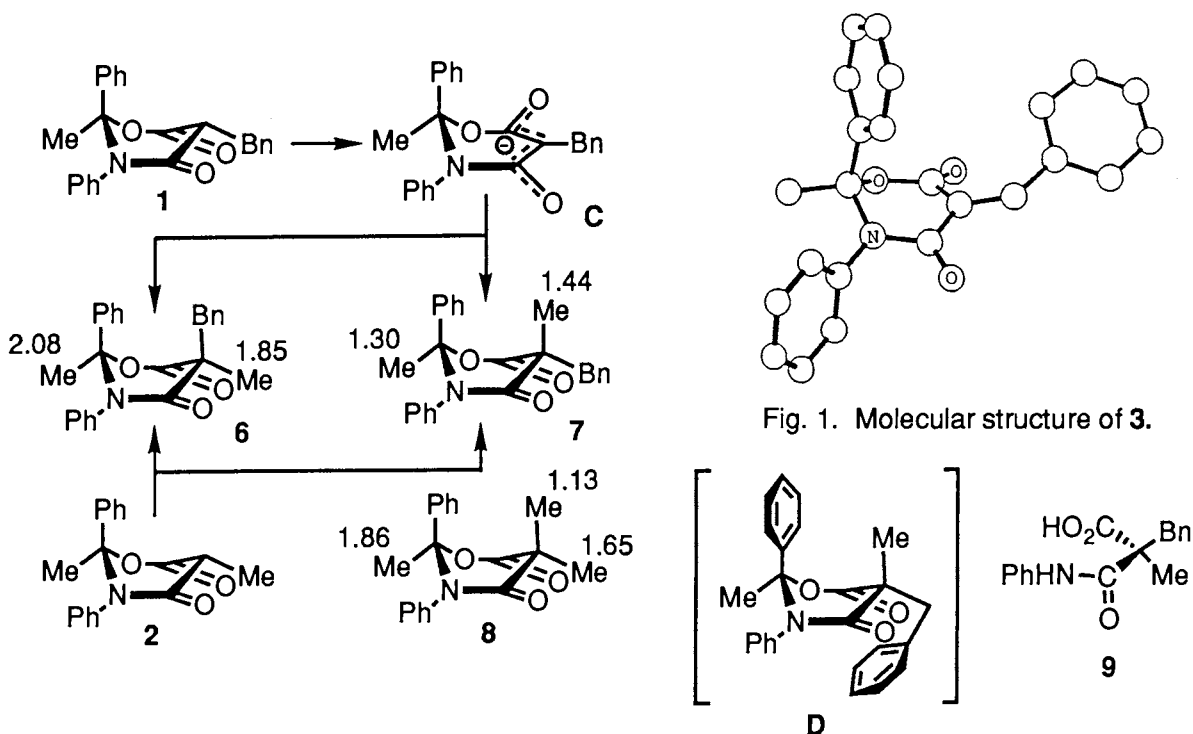
Refluxing benzene solution of acetophenone and aniline in the presence of a small amount of *p*-toluenesulphonic acid (1 d with Dean-Stark trap) afforded the corresponding imine (**4**). The imine (**4**) was, without purification, condensed with malonic acid in acetic anhydride (0 °C, 3 d) to give the oxazinedione (**5**: mp 112-114 °C). The optical resolution of **5** was accomplished by high-pressure liquid chromatography (HPLC) over ChiraSpher to give (*S*)- and (*R*)-**5**.^{4,5} Hereafter, we will

distinguish the compounds into racemic and optically active by using (*R*) and (*S*) for the latter. Knoevenagel condensation³⁾ of **5** with benzaldehyde (piperidine/AcOH) gave the expected benzylidene derivative as a *ca.* 1:1 mixture of *E*- and *Z*-isomers. Slow recrystallization from CH₂Cl₂-AcOEt afforded the *Z*-isomer⁶⁾ (**3**: mp 162-163 °C) in 98% yield. Catalytic hydrogenation of **3** over Pd/C gave the corresponding dihydro derivative (**1**: mp 129-131 °C) in a quantitative yield. Compound **1** as well as 5-methyl derivative (**2**: mp 177-179 °C) were also synthesized directly from the imine (**4**) by condensation with benzyl- and methylmalonic acids, respectively.



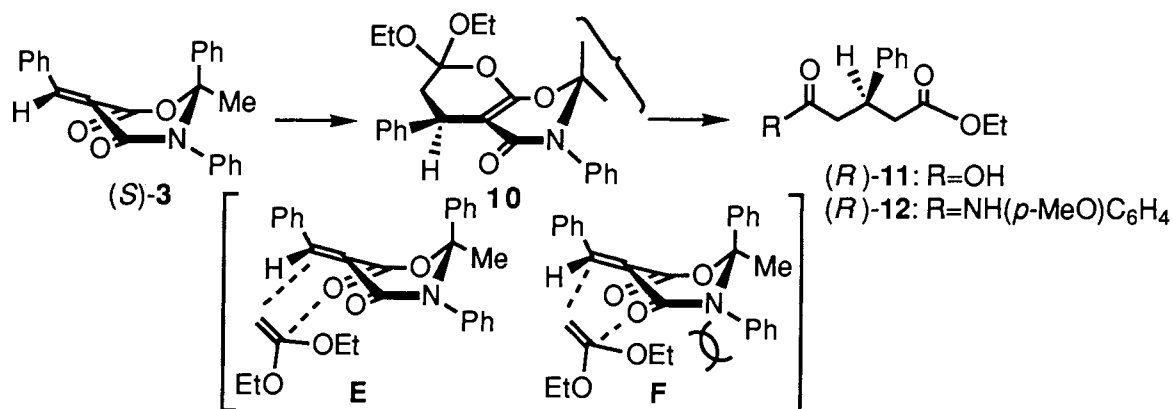
Scheme 1.

When **1** was treated with methyl iodide in DMF after metalation with sodium hydride, two isomers [major product (**6**: mp 189-190 °C) and minor product (**7**: mp 138-139 °C)] were obtained in nearly quantitative yield. Two isomers were separated by silica gel column chromatography. The ratio of two isomers (**6** and **7**) depended upon the temperature of the methylation reactions (d.e.s were 59% at 15 °C and 70% at -50 °C, respectively).

Scheme 2. Numerals attached to each methyl group correspond to the chemical shifts (δ).

The X-ray structure revealed that the oxazinedione ring in compound **3** adopted a pseudoboat conformation with axial 2-phenyl group (Fig. 1).⁷⁾ By assuming that the same conformation is still preserved in the anion (C), the alkylation was expected to take place from the side of methyl group due to steric reason. In accordance with this expectation, the stereostructure of the major product was deduced as **6**. Thus, by knowing the chemical shifts of three methyl groups in the trimethyl derivative (**8**: mp 124-126 °C) as δ 1.13, 1.65, 1.86,⁸⁾ the structures of major and minor products were assigned as **6** and **7** by the following reason. The chemical shifts of two methyl groups of **6** appeared both at a relatively low field (δ 1.85 and 2.08), whereas those of **7** appeared both in a relatively higher field (δ 1.30 and 1.44). This means that, like **3**, the oxazinedione ring in the methylated products (**6** and **7**) displays a pseudoboat conformation (*cf.* **D**: the probable conformation of **7**) in solution and, hence, each methyl group of **7** is deshielded by the nearby phenyl rings. The d.e. of the alkylation increased when **2** was benzylated under the same conditions to give **7** as the major and **6** as the minor products (d.e.s were 67% at 20 °C and 83% at -50 °C). This result also fits well to the above explanation, since the more bulky the reagents the more differentiation of the two sides would be expected. Base-catalyzed hydrolysis of the major methylated product [(2*R*)-**6**: mp 117-118 °C, $[\alpha]_D^{23}$ +51.2°] obtained from (2*R*)-**1** [mp 118-119 °C, $[\alpha]_D^{20}$ +93.7°]⁹⁾ in the same manner as in racemic series afforded the malonamic acid [(*S*)-**9**: $[\alpha]_D^{22}$ -83.2°]. The same sign as well as comparable magnitude of its specific rotation with those ($[\alpha]_D$ -53°) of the known malonamic acid [(*S*)-**9**: *p*-MeOPh instead of Ph]¹⁾ indicate the correctness of our assignment to homochiral oxazinediones [(*R*)- and (*S*)-**5**].⁴⁾

The same methyl side preference was also observed when optically active **3** was used as a heterodiene in Diels-Alder reaction with ketene diethylacetal. Thus, (*S*)-**3** [mp 172-176 °C (dec), $[\alpha]_D^{25}$ +251° (benzene)] was reacted with the acetal and the adduct (**10**) obtained was refluxed in aq. dioxane. From the base soluble fraction, the acid [(*R*)-**11**: $[\alpha]_D^{24}$ +2.35°] was obtained in 25% yield.¹⁰⁾ This compound was converted to the amide [(*R*)-**12**: $[\alpha]_D^{23}$ +13.4°], whose e.e. was determined as 71% by HPLC over Chiralcel OJ. The absolute structure of the amide [(*R*)-**12**] was determined by the



Scheme 3.

comparison of its specific rotation with that ($[\alpha]_D^{23}$ -20.7°) of (*S*)-**12**.³⁾ This verified again that the addition of the dienophile had occurred from the side of methyl group of (*S*)-**3**. As discussed in previous paper³⁾ dealing with the same reactions of **B**, the adduct (**10**) formed *via* transition state (**E**) is the precursor for (*R*)-**11**. The other adduct formed *via* **F** should not be formed in a significant amount due to steric reasons.¹⁰⁾ Two important informations have been brought about from the present study: (1) like **A** and **B** having a spirocyclic auxiliary at 2-position, their acyclic analogs (**1-3**) still exhibit diastereofacial selectivity and, hence, their homochiral analogs can serve as the building blocks for EPC and (2) the origin of diastereofacial selectivity is due to a pseudoboat (or sofa) conformation of the oxazinedione ring with an axial phenyl group at the 2-position.

If one can find out some other chiral functional groups capable to take axial conformation which not only act as the alternative for the phenyl group (as bulky groups) but also facilitate the optical resolution of the oxazinediones, the more efficient building blocks will be elaborated. Our efforts are now paid in creation of such compounds.

References

- 1) M. Sato, H. Hisamichi, N. Kitazawa, C. Kaneko, T. Furuya, N. Suzaki, and N. Inukai, *Tetrahedron Lett.*, **31**, 3605 (1990).
- 2) M. Sato, N. Kitazawa, and C. Kaneko, *Heterocycles*, in the press.
- 3) M. Sato, N. Kitazawa, S. Nagashima, C. Kaneko, N. Inukai, and T. Furuya, *Tetrahedron*, **47**, 7271 (1991).
- 4) Solvent: hexane-ethanol 9:1. The isomer eluted first: (*S*)-**5**: mp 122-123 °C ($[\alpha]_D^{26}$ -151° (*c* 1.23). The isomer eluted next: (*R*)-**5**: $[\alpha]_D^{24}$ +150° (*c* 1.07).
- 5) Unless otherwise noted, specific rotations were measured in CHCl₃ (*c* 1-2).
- 6) All of 6-benzylidene-1,3-oxazepane-5,7-diones (and spirocyclic 5-benzylidene-1,3-oxazine-4,6-diones³⁾) so far reported have (*Z*)-configuration. The reason for this phenomenon was proposed by Tietze. L. F. Tietze, *J. Heterocycl. Chem.*, **27**, 47 (1990).
- 7) X-Ray analysis of **3** was performed by Dr. Toshio Furuya and coworkers of Tsukuba Research Laboratory, Yamanouchi Pharmaceutical Co. Ltd. The detailed result will be reported separately.
- 8) The chemical shift of each methyl signal of **8** was definitely assigned by the analysis of NMR spectra of the methylated products (*cf.* **7** and **6**) of **2** using CD₃I.
- 9) (*R*)-**1** was prepared from (*R*)-**5** according to the method used in the corresponding racemic compounds (*cf.* **5**→**3**→**1** in Scheme 1).
- 10) Low yield of **11** was due to the formation of (HO₂C)₂CHCHPhCH₂CO₂Et (*ca.* 30% and PhNHCOCHCHPhCH₂CO₂Et (*ca.* 4%). The former afforded **11** by refluxing in xylene.

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