

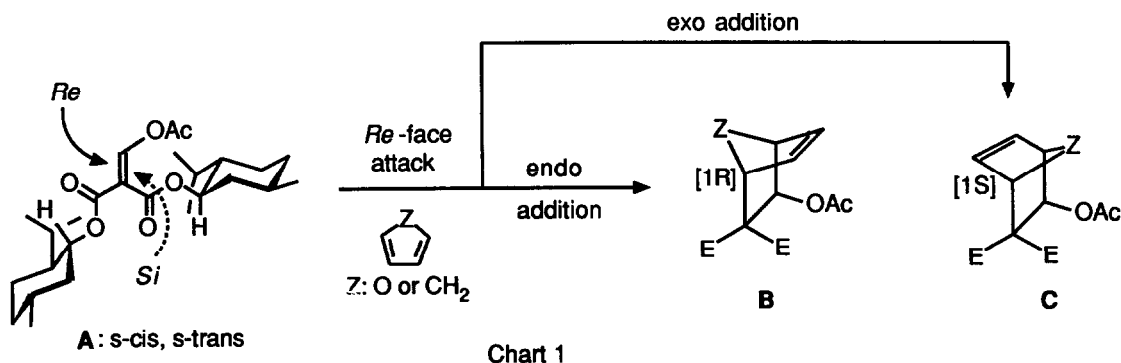
1,3-DIPOLAR CYCLOADDITION OF DI-1-MENTHYL BENZYLIDENEMALONATE TO (Z)-N, α -DIPHENYLNITRONE: EXPLANATION FOR DIASTEREOSELECTIVITY^{1,2}

Nobuya Katagiri,^{*a} Nobuhisa Watanabe,^a Jun-ichi Sakaki,^a
Takatoshi Kawai,^b and Chikara Kaneko^{*a}

^a Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980,
Japan; ^b Tsukuba Research Laboratories, Eisai Co., Ltd., Tokodai
5-Chome, Toyosato, Tsukuba, Ibaraki 300-26, Japan

Abstract: 1,3-Dipolar cycloaddition of di-1-menthyl benzylidenemalonate to (Z)-N, α -diphenylnitrone proceeds by Si-face preference to give the endo-adduct as the major product among all four possible adducts. An explanation for this diastereofacial selectivity (Si-face preference) is proposed based on X-ray crystallographic analysis of the malonate as well as effects of high-pressure to the ratio of the adducts.

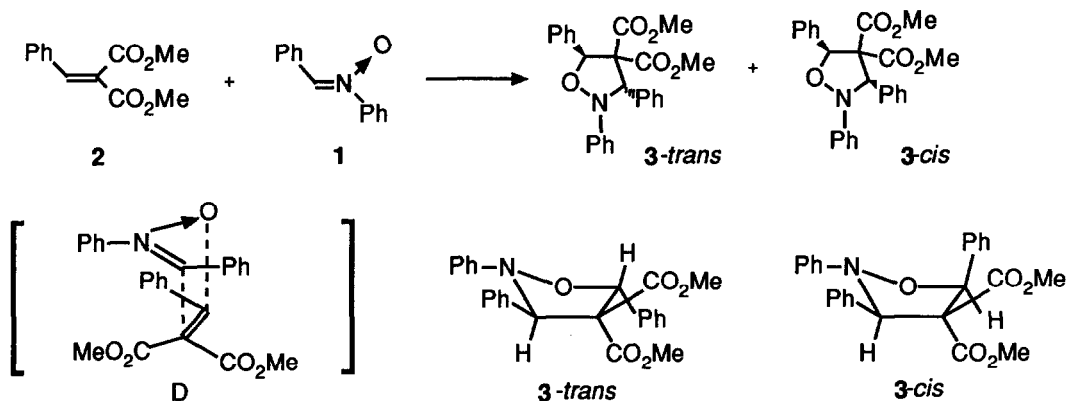
Previously, we have found that, though dimethyl acetoxymethylenemalonate did not react with furan by mere heating under an ordinary atmosphere (1 atm.), the endo- and exo-adducts are obtained if the reaction is carried out under high pressure.³ The absolute structures of the major two diastereoisomers (B and C) obtained by using the di-1-menthyl ester (A), are different each other for the endo- (B) and exo-adducts⁴ (C) and the former has [1R]- and the latter [1S]-configurations.⁵ The same result was also obtained when cyclopentadiene was used instead of furan.⁶ We have proposed the mechanism accounting for the diastereoselectivities by assuming the dienophile to take a s-cis, s-trans conformation (A). In this conformation, the dienes should approach preferentially to the Re-face which is more exposed than the Si-face to give the actually obtained two major diastereomers (B and C) in predominance.



In order to obtain more thorough understanding for this kind of asymmetric induction, we have examined the 1,3-dipolar cycloaddition of di-1-menthyl

benzylidenemalonate (4) to (Z)-N, α -diphenylnitrone⁷ (1) and, here, report the result.

At first, we examined the 1,3-dipolar cycloaddition of achiral dimethyl benzylidenemalonate⁸ (2) to the nitrone (1). As a result, it was found that, though the reaction proceeded in dichloromethane at room temperature under 1 atm.,⁹ the reaction was much accelerated under high pressure. The acceleration was also accomplished by mere heating (toluene, 110 °C) at 1 atm.



The fact that, in all cases, the trans-3,5-diphenylisoxazolidine (3-trans) was obtained as the major product (trans/cis ratio =ca. 10) shows clearly that the reactions proceed mostly via the endo-transition state¹⁰ (D). The structures of two products were determined unambiguously by ¹H-NMR spectrum in which the proton signals of H-3 and H-5 were observed in each product as singlets and, further, in the major adduct (3-trans) the chemical shifts of methyl signals were both in a higher field (δ 3.08 and 3.11) due to the current effect of the benzene ring, while in the minor adduct (3-cis) these appeared in significantly different regions (δ 3.10 and 3.82). No regioisomer was detected in the reaction product, even if 500 MHz NMR spectroscopy was used for the product analysis.

Next, the same reaction using di-1-menthyl benzylidenemalonate¹¹ [4: mp 106-107 °C (methanol), $[\alpha]_D^{23}$ -39 °C ($c=2.44$, CHCl_3)] was investigated. When the reaction was carried out at 10 kbar at 50 °C,¹² the adducts (5) were obtained in 52% yield as a mixture of four diastereoisomers. By 500 MHz NMR analysis of the product, the ratio of the four isomers was determined as 76:15:6:3 in which the former two were again the trans-adducts. Though the same four adducts were formed at 1 atm. by carrying out the reaction in refluxing toluene, both the yield (10%) and the selectivity of the reaction (54:26:10:10) became much poor.

The absolute structure of the major product was determined as [3S,5S]-5-trans in the following way. Thus, the trans-adducts (the major two adducts) which could be separated from the other two cis-adducts (the minor two adducts)

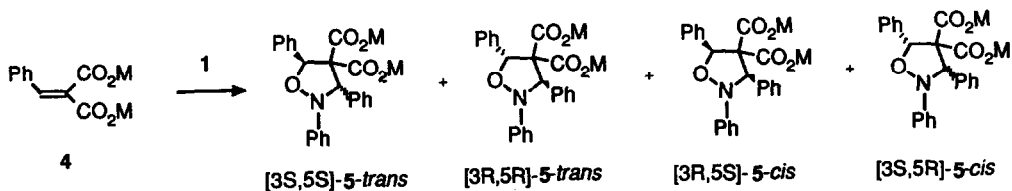


Chart 3: M=l-menthyl

by silica gel column chromatography were reduced with lithium aluminum hydride to give the diol (6-trans), which by recrystallization to give the single enantiomer [chiral 6-trans mp 145-147 °C (hexane-benzene), $[\alpha]_D^{24} +50$ °C (c=0.45, CHCl_3)]. Catalytic hydrogenation of the diester (chiral 7) obtained by treating with (1R)-(-)-camphanic acid chloride (2.5 mol equiv.) and pyridine gave the ring-opened aminoalcohol (chiral 8), which on acetylation (acetic anhydride/pyridine) led to the corresponding monoacetate [chiral 9: mp 172-174 °C (toluene), $[\alpha]_D^{27} -28.0^\circ$ (c=0.2, CHCl_3)]. X-Ray crystallographic analysis of 9 shown in Fig. 2 determined its structure unambiguously.¹³

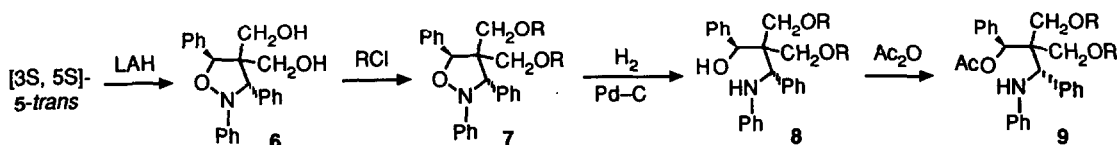
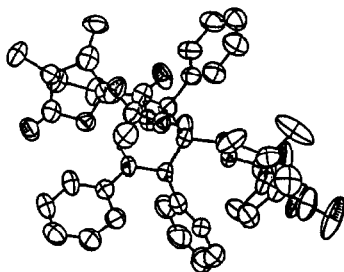
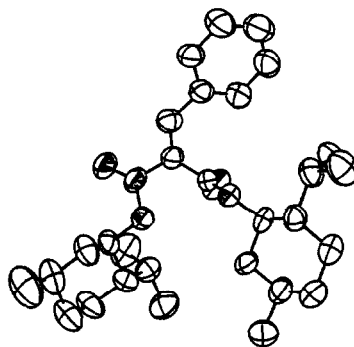


Chart 4: RCl=(1R)-(-)-camphanic acid chloride

Fig. 1. ORTEP View of 9¹³Fig. 2. ORTEP View of 4¹³

ORTEP view of the dipolarophile (4) shown in Fig 2 has revealed two important characteristics in its conformation. 1) One ester carbonyl (E to the phenyl group) is nearly in an a-plane while the other (Z to the phenyl group) is in a b-plane which is almost perpendicular to the a-plane (cf. E in Chart 5), and 2) both sp^2 -carbon atoms in C=C bond are pyramidarized to the direction to Si-face (cf. Fig. 3).

By assuming that this conformation is still preserved in solution, it seems to be an attractive proposal that preponderance of the Si-face attack is caused by the pyramidarization¹⁴ and this pyramidarization is increased by the pres-

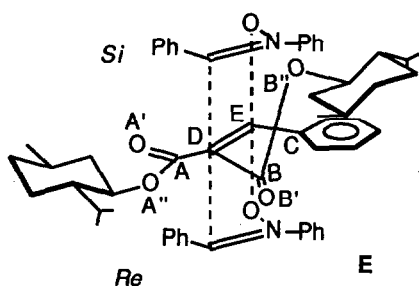


Chart 5. a-plane: A, A', A'', B, D, E, C (phenyl ring);
b-plane: D, B, B', B''.

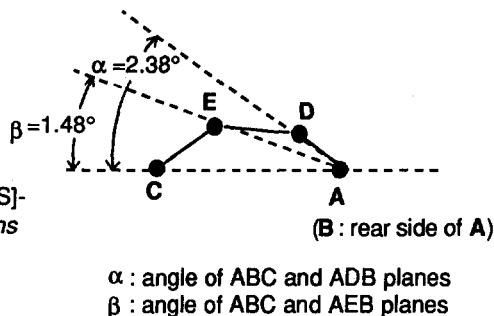


Fig. 3. Deviation of the Trigonal Centers in the 1- and 2-Positions of 4 (Left-side view of E)

sure. Though the validity of the proposal should await further study, it is likely that the previously reported high-pressure mediated Diels-Alder reaction of A with furan⁵ or cyclopentadiene⁶ both proceeded in high Re-face preference could also be explained nicely, if one assumes the same pyramidarization in this dienophile (cf. E in which the phenyl group is replaced with an acetoxy group).

References and Notes

- Part 18 of "Synthesis of nucleosides and their related compounds". Part 17: N. Katagiri, S. Ise, N. Watanabe, and C. Kaneko, Chem. Pharm. Bull., in press.
- This also forms Part 50 of "Cycloadditions in syntheses". Part 49: M. Sato, K. Kano, N. Kitazawa, H. Hisamichi, and C. Kaneko, Heterocycles, in press.
- A. Sera, M. Ohara, T. Kubo, K. Itoh, H. Yamada, Y. Mikita, C. Kaneko, and N. Katagiri, J. Org. Chem., **53**, 5460 (1988).
- Endo- and exo are defined relative to the acetoxy group of the dienophile.
- N. Katagiri, H. Akatsuka, C. Kaneko, and A. Sera, Tetrahedron Lett., **29**, 5397 (1988).
- The same diastereofacial selectivity has also been observed in high-pressure mediated Diels-Alder reaction of this dienophile to cyclopentadiene. N. Katagiri, N. Watanabe, and C. Kaneko, Chem. Pharm. Bull., **38**, 69 (1990).
- O. H. Wheeler and P. H. Gore, J. Am. Chem. Soc., **78**, 3363 (1956).
- C. H. F. Allen and F. W. Spangler, Organic Syntheses, Coll. Vol. 3, 377.
- Joucla et al. reported previously that only the trans isoxazoline (3-trans) was obtained when the reaction was carried out in benzene at room temperature (1 atm.): Joucla, J. Hamelin, and R. Carrie, Bull. Soc. Chim. Fr., **29**, 3115 (1973).
- Endo and exo are defined relative to the N-O function of the nitronium (1) and phenyl group of the malonate (2).
- Compound 4 was prepared by piperidine-catalyzed condensation of di-1-menthyl malonate with benzaldehyde.
- If this reaction was carried out at 80 °C the yield of the adducts decreased to 40%, probably due to decomposition and/or dimerization of the nitronium. On the contrary, if the reaction was carried out at room temperature, no adduct was formed at all.
- X-Ray analysis: All intensity measurements were carried out with an ENRAF NONIUS CAD4 diffractometer with a graphite monochromator (CuK α radiation, $\lambda=1.54184$ Å). All calculations were performed on a VAX11/750 computer using SDP/VAX. The final R's were 0.082 for 4 and 0.079 for 9, respectively. Details will be reported in a full paper.
- Recently, a novel idea concerning to conformation-face selectivity in terms of pyramidarization has been proposed: D. Seebach, J. Zimmermann, U. Gysel, R. Ziegler, and T. -K. Ha, J. Am. Chem. Soc., **110**, 4763 (1988) and references cited therein.

(Received in Japan 28 May 1990)