

FACE SELECTIVITY IN DIELS-ALDER REACTION OF 4-SUBSTITUTED SEMICYCLIC DIENES WITH DIENOPHILES†

Shigeru Nagashima, Yumiko Takaoka, Kumiko Kawakami, Motoo Shiro,[†] and Ken Kanematsu*

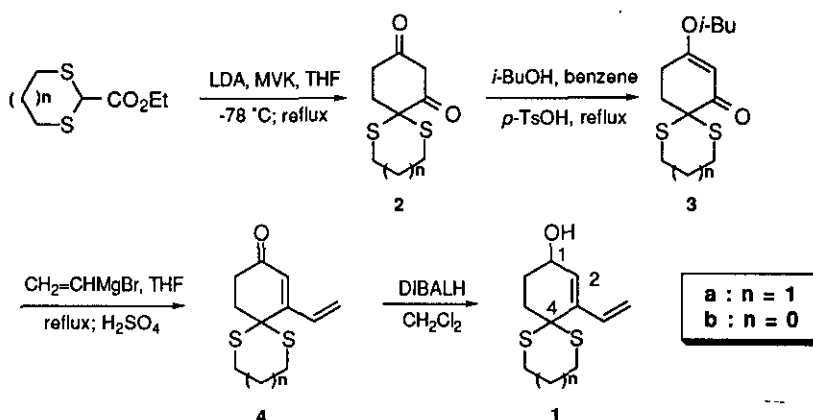
Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Higashi-ku, Fukuoka 812, Japan, and [†]Rigaku Corporation, Matsubara-cho, Akishima, Tokyo 196, Japan

Abstract - Face selectivity in Diels-Alder reactions of the semicyclic dienes (**1a**) and (**1b**) with maleic anhydride (MA) and *N*-phenylmaleimide (NPM) was examined. Cycloaddition reaction of **1** with MA occurred preferentially from the diene face *anti* to the allylic hydroxy group, on the other hand, the cycloaddition with NPM occurred preferentially from the *syn* to the hydroxy group.

The Diels-Alder reaction is one of the most useful synthetic reactions in organic chemistry because of its ability to generate two carbon-carbon σ bonds and up to four contiguous stereogenic centers in a single synthetic operation.¹ Allylic substitution of a diene has a pronounced effect on diastereofacial selection, and the recent interest in the face selectivity of the Diels-Alder reaction has focused on semicyclic dienes.² In a continuation of our systematic studies of the intramolecular Diels-Alder reaction of the semicyclic dienes,³ we report herein our results of the face selectivity on intermolecular Diels-Alder reactions of 4-substituted semicyclic dienes (**1a** and **1b**).

The corresponding semicyclic dienes (**1a**) and (**1b**) were prepared from ethyl 1,3-dithiane-2-carboxylate or ethyl 1,3-dithiolane-2-carboxylate as follows: (1) Michael addition to methyl vinyl ketone (MVK) and *in situ* aldol condensation; (2) treatment of the 1,3-diketone (**2**) with *i*-BuOH in the presence of a catalytic amount of *p*-TsOH; (3) treatment of the isobutyl enol ether (**3**) with vinylmagnesium bromide, then with aqueous H₂SO₄; (4) reduction of the dienone (**4**) with DIBALH (Scheme I).

† This paper is dedicated to Professor Rolf Huisgen, on the occasion of his 75th birthday.



Scheme 1

A series of Diels-Alder reaction was carried out by using dienophiles maleic anhydride (MA) and *N*-phenylmaleimide (NPM), as detailed in **Table I**.

Entries 1 and 2 record the reaction of the diene (**1a**) with MA (**Chart I**). Thus, the initial adducts (**5a**) and (**6a**) were spontaneously converted into the tricyclic lactones (**7a**) and (**8a**), probably due to the acidic nature of MA. The major product (**8a**) shows the proton Ha at δ 4.02, as a triple doublet ($J = 11.2, 4.0$ Hz), indicating a *trans* coupling between Ha and Hb, on the other hand, the same proton in the minor product (**7a**) appears as a broad singlet at δ 4.67, indicating a very small coupling constant between Ha and Hb (*cis*). In these cases, a modest *anti* selectivity was observed (*vide infra*).

Table I. Results of Diels-Alder Reactions^a

entry	diene	dienophile	solvent	products <i>syn</i> : <i>anti</i> ^b	isolated yield (%)
1	1a	MA	CH ₂ Cl ₂	1 : 1.4	72
2	1a	MA	benzene	1 : 1.6	66
3	1a	NPM	CH ₂ Cl ₂	1.8 : 1	66
4	1a	NPM	benzene	1.9 : 1	68
5	1b	MA	CH ₂ Cl ₂	1 : 1.4	34(71 ^c)
6	1b	NPM	CH ₂ Cl ₂	1.2 : 1	57

^a The reactions were carried out at ambient temperature for 12 h. ^b The ratios were determined from distinct peaks in the 270 MHz ¹H nmr of the reaction mixture. ^c Yield based on recovery of the starting diene.

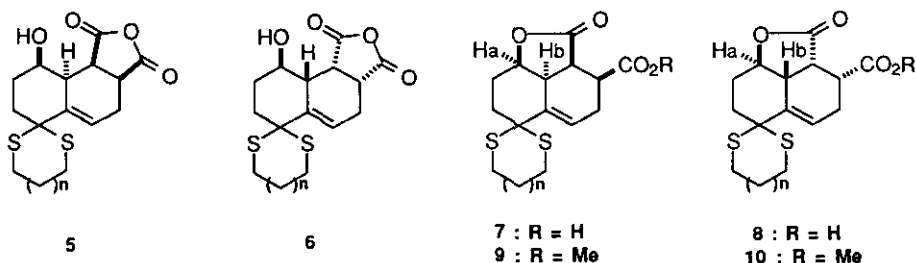


Chart I

Entries 3 and 4 record the reaction of the diene (**1a**) with NPM (Chart II). In these cases, the major product was the adduct (**11a**), which could be easily converted into the tricyclic lactone (**13a**) by acid catalysis, but the minor adduct (**12a**) did not cyclize on treatment with acid. Thus, the crude reaction mixture was treated with a catalytic amount of *p*-TsOH at ambient temperature for complete lactonization of the adduct (**11a**), and the two products (**12a**) and (**13a**) were separated by column chromatography. This cyclization strongly suggested that the major adduct (**11a**) was formed by the attack of NPM on the face of the diene (**1a**) that is *syn* to the hydroxy group. In contrast to the reaction with MA, the diene (**1a**) reacted with NPM with a modest *syn* selectivity.

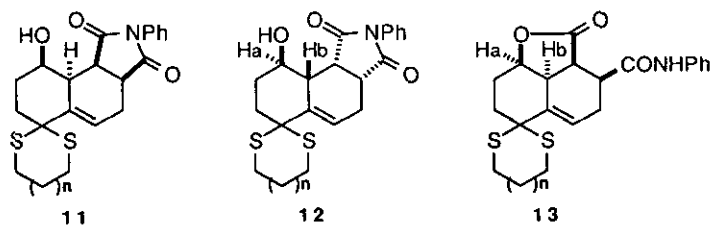


Chart II

Entry 5 records the reaction of the diene (**1b**) with MA. The major product (**8b**) shows the proton Ha at δ 3.89, as a triple doublet ($J = 11.6, 3.3$ Hz), on the other hand, the same proton in the minor product (**7b**) appears as a broad singlet at δ 4.74 (in DMSO- d_6). In this case, the crude mixture of tricyclic lactonic acids was treated with ethereal diazomethane to give the mixture of methyl esters (**9b**) and (**10b**), and a careful recrystallization from CH_2Cl_2 gave the pure methyl ester as a crystalline solid. The compound was identified as the tricyclic lactone (**10b**) (*anti-endo*) on the basis of the ^1H nmr evidence and X-ray crystallography (Figure I).⁴ Entry 6 records the reaction of the diene (**1b**) with NPM, the ratio of *syn* / *anti* was similar to the cases of entries 3 and 4.

In summary, all Diels-Alder reactions of semicyclic dienes (**1a**) and (**1b**) with MA and NPM produced only *endo* adducts; cycloaddition of the diene (**1**) with MA occurred with a modest *anti* preference, but cycloaddition

of the diene (**1**) with NPM occurred with a modest *syn* preference. Thus, the reactions lead to stereoselective syntheses of substituted octalins and masked aminocyclohexanols. The resulting cycloadducts contain several reactive sites for subsequent chemistry and should find useful application in natural products synthesis.

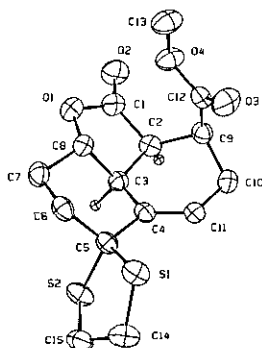


Figure 1. ORTEP diagram of **10b**

REFERENCES AND NOTES

1. G. Desimoni, G. Tacconi, A. Barco, and G. P. Pollini, 'Natural Products Synthesis Through Pericyclic Reactions,' ACS Monograph 180, American Chemical Society, Washington, DC, 1983, pp. 119-254; L. A. Paquette, In 'Asymmetric Synthesis,' Vol. 3, ed. by J. D. Morrison, Academic Press, Inc., New York, 1984, pp. 455-501; W. Carruthers, 'Cycloaddition Reactions in Organic Synthesis,' Pergamon Press, Oxford, 1990.
2. M. J. Fisher, W. H. Hehre, S. D. Kahn, and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 4625; S. C. Datta, R. W. Franck, R. Tripathy, G. J. Quigley, L. Huang, S. Chen, and A. Sihaed, *ibid.*, 1990, **112**, 8472; F. Fringuelli and A. Taticchi, 'Dienes in the Diels-Alder Reaction,' John Wiley & Sons, Inc., New York, 1990, pp. 149-170.
3. We have already reported the intramolecular cycloaddition of allenyl thioether and allenyl sulfonyl derivatives of semicyclic dienes, see: S.-K. Yeo, M. Shiro, and K. Kanematsu, *J. Org. Chem.*, 1994, **59**, 1621; Surprisingly, we have found that the propargyl ether derivatives of the 4-substituted semicyclic dienes (**1**) cyclized spontaneously to give adducts. The results of which will be reported in due course.
4. Crystal data for **10b**: (C₁₅H₁₈O₄S₂): MW = 326.42; colorless prisms, dimensions 0.500 x 0.200 x 0.150 mm; monoclinic, space group P2₁/n (#14); *a* = 8.668(1) Å, *b* = 16.483(1) Å, *c* = 11.352(1) Å, *V* = 1514.4(3) Å³, *Z* = 4, *d*_{calc} = 1.432 g/cm³, μ(CuKα) = 32.48 cm⁻¹, *F*(000) = 688. A total of 2521 reflections (2θ_{max} = 120.1°, ω-2θ scans) were recorded on a Rigaku AFC7R diffractometer at *T* = 293 K. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1890 observed reflections (*I* > 3.00σ(*I*)) and 200 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of: *R* = 0.046, *R*_w = 0.076.

Received, 9th May, 1994