HIGHLY ASYMMETRIC INDUCTION IN THE DIELS-ALDER REACTION OF 3-ALKOXYCARBONYL-SUBSTITUTED CHROMONE

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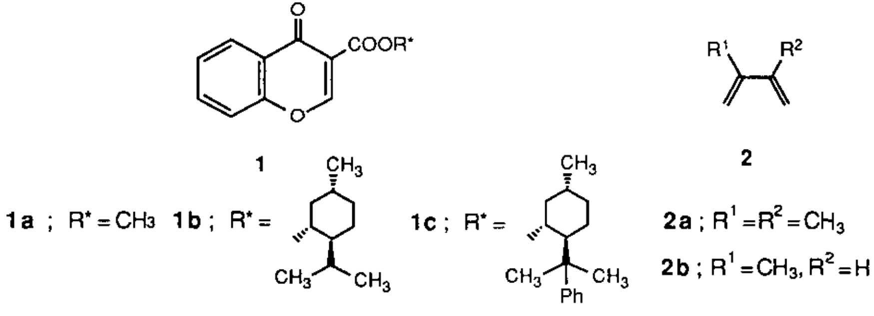
Abstract - The asymmetric Diels-Alder reactions of 3-alkoxycarbonyl-substituted chromones (**1c**) with 2,3-dimethyl- and 2-methyl-1,3-butadienes in the presence of $ZnCl_2$ at ambient temperature afforded the adducts (**3c** and **4b**) with high diastereofacial selectivity (>98%) in high yield.

Recently, asymmetric induction during [4 + 2] cycloaddition in pyrone derivatives has received much attention.[1] In this communication, we describe diastereofacial selectivity in the Diels-Alder reaction of 3-alkoxycarbonyl-substituted chromones (**1**) with conjugated dienes (**2a,b**). 3-Alkoxycarbonylchromones (**1b** and **1c**) were prepared by esterification (DCC-DMAP method) of 3-carboxychromone with the corresponding alcohol.[2]



1 **2**

1a ; $R^* = CH_3$ **1b** ; $R^* =$ **1c** ; $R^* =$

2a ; $R^1 = R^2 = CH_3$
2b ; $R^1 = CH_3$, $R^2 = H$

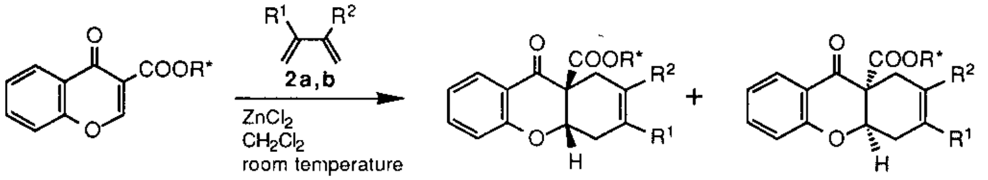
Reaction of **1a-c** with 1,3-butadiene derivatives (**2a,b**) in the presence of $ZnCl_2$ in CH_2Cl_2 at ambient temperature afforded [4+2] adducts (**3a-c** and **4a,b**) (Scheme 1).[3,4] In the ^1H nmr spectrum of diastereoisomeric mixtures of the adduct (**3b**), there were observed a pair of triplets [δ 5.05 (J = 2.5 Hz) and 5.06 (J = 4.9 Hz)] indicating angular protons and a pair of double triplets [δ 4.61 (J = 11.0, 4.4 Hz) and 4.71 (J = 10.8, 4.4 Hz)] indicating carbinyl protons with each *ca.* 3:2 intensity. However, a high diastereoisomeric excess (>98%) was achieved in the reaction of **1c** with **2a**; only one triplet [δ 4.23 (J = 1.0 Hz)] and one double triplet [δ 4.81 (J = 10.8, 4.0 Hz)] due to the groups described above were observed in the ^{1}H nmr spectrum of the adduct (**3c**, mp 129-130 °C). Reaction of **1c** with 2-methyl-1,3-butadiene (**2b**) gave the adduct (**4b**) with high regio- and stereoselectivity in 81% yield.[4] These results are shown in Table 1. Regiochemistry of **4b** was determined from the peaks between the angular proton (δ 4.17) and the neighboring methylene protons (δ 2.26 and 2.31) as well as another cross peaks between the vinyl proton (R^2 = H: δ 5.48) and the other methylene proton (δ 2.64) near the carbonyl groups in the COSY 2D-nmr spectrum.

Table 1. Asymmetric Induction of 3-Alkoxycarbonylchromone

entry	dienophile	diene			product			mp	yield[a]	d.e.[b]
			R^1	R^2		R^1	R^2	°C	%	%
1	**1a**	**2a**	Me	Me	**3a**	Me	Me	oil	49	0
2	**1a**	**2b**	Me	H	**4a**	Me	H	oil	14	0
3	**1b**	**2a**	Me	Me	**3b**	Me	Me	oil	61	22
4	**1c**	**2a**	Me	Me	**3c**	Me	Me	129-130	83	>98
5	**1c**	**2b**	Me	H	**4b**	Me	H	129-131	81	>98

[a] Yields refer to product after isolation and tlc chromatographic purification.
[b] Diastereomeric excess was determined by ^{1}H nmr ($CDCl_3$).

Scheme 1



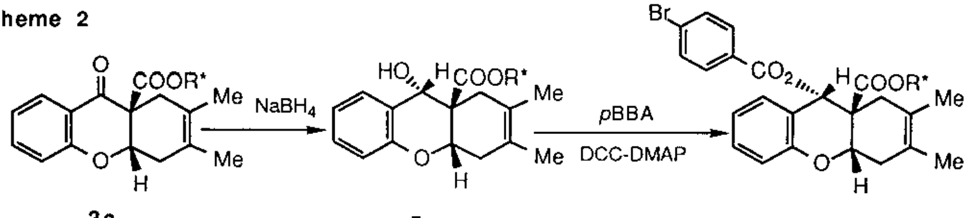
1a-c

3a-c-*S* (R^1 = R^2 = Me)
4a,b-*S* (R^1 = Me, R^2 = H)

3a-c-*R* (R^1 = R^2 = Me)
4a,b-*R* (R^1 = Me, R^2 = H)

Reduction of **3c** with $NaBH_4$ afforded hydroxy ester (**5**) (123-124 °C) stereoselectively in 72% yield. Stereochemistry of the hydroxy group was determined from NOE experiment in ^{1}H nmr spectrum. The NOED spectrum of **5** showed an enhancement (9 3%) in the magnitude of the signal at δ 4.57 of angular proton, when the signal at δ 3.86 of α-proton of the hydroxy group was irradiated. Esterification of **5** with *p*-bromobenzoic acid (*p*BBA) by DCC-DMAP method gave **6** in 49% yield (Scheme 2).[4]

Scheme 2



3c **5** **6**

Stereostructure of **6** was determined by X-ray crystallography.[5] The ORTEP representation of the molecular structure is shown in Figure 1. Three chiral centers of chromanone ring in **6** were confirmed to have all *S*-configuration as correlated to the chiral phenylmenthyl moiety. Therefore, the absolute stereochemistry of the newly formed ring-junction in **3c** was determined to be 2*S*,3*S*-configuration.

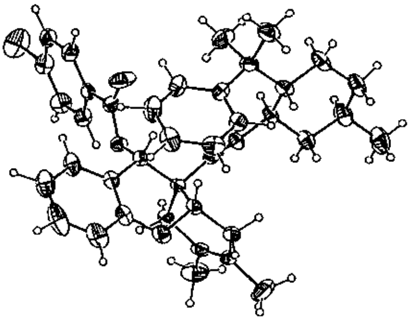
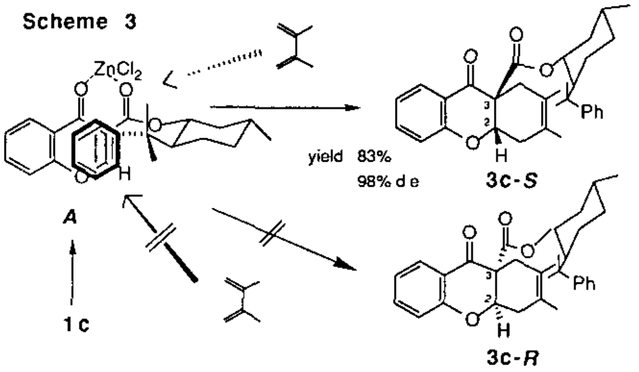


Figure 1. ORTEP drawing of **6**

Scheme 3



Such a high diastereoselective cycloaddition reaction to give 2*S*,3*S* product (**3c**-*S*) is understandable in terms of the favorable conformation of the chiral auxiliary. The carbonyl oxygens of the dienophile should be chelated to ZnCl$_2$, in which rotational freedom of the ester group must be restricted. Since the conformation (*A*) would lead to the observed selective diastereomer (**3c**-*S*), it seems reasonable that the π–π interaction between the phenyl ring of the chiral auxiliary and the electron-deficient C$_2$-C$_3$ double bond of the chromone ring in **1c** stabilizes the product-determining step (Scheme 3). Within this complex, the front face of the dienophilic double bond is blocked by the phenyl group with the result that diene approaches from the rear side of ***A***. This π–π interaction can be expected also in the ground state from ^{1}H nmr chemical shift of hydrogen at C$_2$ of **1c**. In fact, the ^{1}H nmr spectrum of **1c** in the presence of ZnCl$_2$ in CDCl$_3$ solution shows a singlet at δ 7.29, the upfield shift relative to its counterpart (δ 9.17) of **1b** is a direct consequence of the presence of the hydrogen at C$_2$ in the aromatic shielding region of the phenylmenthyl group. It is noteworthy here that the above facial selectivity for the 2-*Si* and 3-*Re* face of **1** and that for the 3-*Si* and 4-*Re* face of 3-alkoxycarbonylcoumarin in the similar Diels-Alder reaction is consistent with the expectation from molecular models.[1a]

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2. a) Preparation of **1a**: P. J. Cremins, S. T Saengchantara, and T. W. Wallace, *Tetrahedron*, 1987, **43**, 3075. b) Typical procedure for the esterification: To a solution of 3-carboxychromone (723 mg, 3.81 mmol) and (-)-8-phenylmenthol (919 mg, 3.96 mmol) in 20 ml of dry CH$_2$Cl$_2$ was added dicyclohexylcarbodimide (DCC) (1.238 g, 6.00 mmol) and 4-dimethylaminopyridine (DMAP) (53.1 mg, 0.435 mmol) at room temperature. The mixture was stirred at room temperature for 1 day. After ordinary work-up, the product was separated by column chromatography (SiO$_2$; *n*-hexane/EtOAc: 5 : 1). Recrystallization from *n*-hexane-ether gave **1c** (mp 145-147 °C), 627 mg (41%). b) The chiral auxiliary was prepared from (+)-pulegone; E. J. Corey and H. A. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908; O. Ort, *Org. Synth.*, 1987, **65**, 208

3. Typical procedure for the Diels-Alder reaction: To a suspension of **1c** (80 mg, 0.20 mmol) and ZnCl$_2$ (40 mg, 0.29 mmol) in 2 ml of CH$_2$Cl$_2$ was added 0.1 ml (0.88 mmol) of 2,3-dimethyl-1,3-butadiene (**2a**) at room temperature. The brown solution was monitored by tlc. The diene was added to the mixture periodically until the ester was no longer detectable (total 30 mmol). After ordinary work-up, tlc separation on silica gel (*n*-hexane/EtOAc; 5:2) gave **3c** in 83% yield.

4. All new compounds gave correct elemental analyses and reasonable spectra. **1c**; ^{1}H nmr (CDCl$_3$) δ 0.90-2.25 (m, 8H), 0.90 (d, *J*=4.0 Hz, 3H), 1.19 (s, 3H), 1.33 (s, 3H), 5.07 (dt, *J*=12.0, 4.0 Hz, 1H), 7.11-7.69 (m, 8H), 7.30 (s, 1H), 8.25 (d, *J*=1.6 Hz, 1H). **3c**; ^{1}H nmr (CDCl$_3$) δ 0.79-2.01 (m, 8H), 0.85 (d, *J*=6.4 Hz, 3H), 1.16 (s, 3H), 1.24 (s, 3H), 1.59 (s, 3H), 1.64 (s, 3H), 2.17-2.53 (m, 4H), 4.23 (t, *J*=1.0 Hz, 1H), 4.81 (dt, *J*=10.8, 4.0 Hz, 1H), 6.87 (t, *J*=7.3 Hz, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 6.98-7.06 (m, 3H), 7.19 (d, *J*=7.3 Hz, 2H), 7.49 (dt, *J*=8.3, 2.0 Hz, 1H), 7.92 (dd, *J*=8.3, 2.0 Hz, 1H). **4b**; ^{1}H nmr (CDCl$_3$) δ 0.79-2.04 (m, 8H), 0.85 (d, *J*=3.2 Hz, 3H), 1.15, (s, 3H), 1.25 (s, 3H), 1.59 (s, 3H), 2.16-2.77 (m, 4H), 4.17 (s, 1H), 4.80 (dt, *J*=10.2, 3.9 Hz, 1H), 5.48 (s, 1H), 6.85 (t, *J*=7.8 Hz, 1H), 6.93 (d, *J*=8.3 Hz, 1H), 6.99 (t, *J*=7.8 Hz, 2H), 7.05 (t, *J*=8.3 Hz, 1H), 7.19 (d, *J*=7.8 Hz, 2H), 7.50 (dt, *J*=8.3, 1.4 Hz, 1H), 7.91 (dd, *J*=8.3, 1.4 Hz, 1H). **6**; ^{1}H nmr (CDCl$_3$) δ 0.71 (d, *J*=6.4 Hz, 3H), 1.17 (s, 3H), 1.33 (s, 3H), 1.57 (s, 3H), 1.61 (s, 3H), 0.58-2.58 (m, 12H), 3.69 (s, 1H), 4.71 (dt, *J*=10.7, 3.9 Hz), 6.48 (s,1H), 6.82 (d, *J*=8.3 Hz, 1H), 6.87-6.93 (m, 2H), 7.05 (d, *J*=8.3 Hz, 1H), 7.12 (t, *J*=7.8 Hz, 2H), 7.19 (t, *J*=7.8 Hz, 1H), 7.34 (d, *J*=7.8 Hz, 2H), 7.62 (d, *J*=8.3 Hz, 2H), 7.67 (d, *J*=8.3 Hz, 2H).

5. X-ray Data: Compound (**6**) (169-171 °C) crystallized from CH$_3$CN/ether in the orthorhombic, space group P2$_1$2$_1$2$_1$ with a=14.139(3) Å, b=18.557(4) Å, c=13.231(3) Å, and V=3472(1) Å^3. For Z=4 and F$_w$=671.70, the calculated density is 1.29 g/cm^3. The data was collected at 25 °C using Mac Science MXC3. A total of 4056 reflections was collected. The linear absorption coefficient for MoKα is 11.72 cm^{-1}. The final cycle of full-matrix least-squares refinement was based on 3987 reflections (F>3.00 σ(F)) and converged to a final discrepancy factor of R=7.1% (R$_w$=5.4%). Detailed X-ray structural analysis of **6** will be published elsewhere.

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