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Diels–Alder reaction of α-tropolone and electron-deficient dienophiles prompted by Et_3N or silica gel: a new synthetic method of highly functionalized homobarrelenone derivatives

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ABSTRACT

A Diels–Alder reaction of α-tropolone and electron-deficient dienophiles prompted by Et_3N or silica gel was performed. Reaction with the highly reactive dienophile, *N*-methylmaleimide, proceeded smoothly in the presence of Et_3N or silica gel to yield adducts as a mixture of *endo* and *exo* isomers. Both catalysts accelerated *endo*/*exo* isomerization of the product, and detailed examination of the reaction using hinokitiol and *N*-methylmaleimide revealed that isomerization proceeds via an intramolecular path without retro Diels–Alder reaction. Successful cycloaddition reactions were established with six other dienophiles: acrylonitrile, methyl acrylate, ethyl vinyl ketone, dimethyl fumalate, dimethyl malate, and dimethyl acetylenedicarboxylate, and the corresponding adducts were obtained in good to moderate yields.

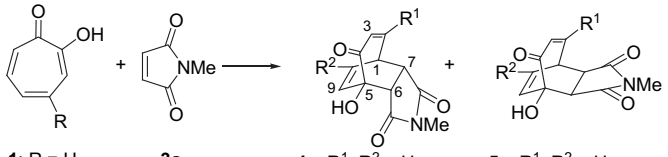
1. Introduction

Tropone and α-tropolone (**1**) are non-benzenoid aromatic compounds whose properties and reactivities are well documented.[1] In particular, Diels–Alder (DA) and other types of cycloaddition reactions of non-benzenoid aromatic compounds including tropones and tropolones were of great interest in early molecular orbital studies, and have been studied since the 1950s.[2] However, synthetic applications of DA reactions of tropones and tropolones have been limited[3] because of the lower reactivity of these dienes, which can be explained by their aromatic character and electron-deficient nature. In fact, most DA reactions involve reactive strained and/or electron-rich dienophiles, and few examples of reactions are involving electron-deficient dienophiles. In addition, most DA reactions are performed under thermal[4] or high-pressure conditions.[5] No efficient catalytic DA reaction that provides cycloadducts in good yield has been established yet.

In our long-term studies of base-catalyzed DA reactions, we have developed efficient base-catalyzed DA reactions of 3-hydroxy-2-pyrone[6] and *N*-protected 3-hydroxy-2-pyridones[7] with various electron-deficient dienophiles. The resulting products are attractive building blocks for polyfunctionalized cyclohexane derivatives, and so these reactions have been used to synthesize biologically active compounds.[8] In these reactions, the base catalysts are considered to be diene activators, which provide anionic diene species with high 'HOMO' energies.[6a,7] This is in contrast to most catalytic DA reactions are activated by Lewis acids with dienophiles of low LUMO energies. Thus far, only a few base-catalyzed DA reactions have been reported.[9] To the best of our knowledge, only the following dienes are suitable for base-catalyzed DA reactions: anthrone,[10] 5-hydroxy-2-pyrone (2*H*-pyrane-2,5-dione),[11] and the previously mentioned 3-hydroxy-2-pyrone and *N*-protected 3-hydroxy-2-pyridones.

Another attractive catalyst for DA reactions is silica gel, which is known to be a useful heterogeneous Brønsted acid catalyst.[12] Although there are fewer examples of heterogeneous than of homogeneous acid catalysts, some silica-gel-catalyzed DA reactions have been reported.[13]

In this article, we describe DA reactions using α-tropolones (**1** and **2**) and electron-deficient dienophiles (**3a**, **3d**–**h**, and **10**) prompted by Et_3N or silica gel. All reactions proceeded under mild conditions and afforded corresponding cycloadducts in quantitative to moderate yields.



1: R = H
2: R = *i*-Pr

3a

4a: R^1, R^2 = H
6a: R^1 = H, R^2 = *i*-Pr
8a: R^1 = *i*-Pr, R^2 = H

5a: R^1, R^2 = H
7a: R^1 = *i*-Pr, R^2 = H
9a: R^1 = H, R^2 = *i*-Pr

(1)

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2. Results and discussions

2.1. Cycloaddition of tropolones and *N*-methylmaleimide

Results of the reactions of **1** and reactive electron-deficient dienophile *N*-methylmaleimide (**3a**) are shown in Table 1 (Eq. 1). Compound **1** is a less reactive diene, and without the use of any catalyst, it yielded no product (entry 1). With the addition of 1 equiv of Et_3N, the colorless reaction mixture changed immediately to yellow, indicating the formation of anionic species of **1**,[14] and reaction proceeded very smoothly to give the desired products **4a** and **5a** in almost quantitative yield within 12 h (entry 2). Catalytic amount of Et_3N (0.1 equiv) was also effective (entry 3). Although the reaction rate was slightly lower, reaction completed after 48 h and afforded the product in nearly quantitative yield. No significant solvent effect was observed in either the polar protic solvent (entry 4) or nonpolar aromatic solvent (entry 5), and products were obtained quantitatively within 24 h.

Table 1
DA reaction of **1** and **3a**

Entry	Catalyst (eq)	Condition	**4**/**5**	Yield (%)[a]
1	None	CH_2Cl_2, rt, 24 h	—	0[b]
2	Et_3N (1.0)	CH_2Cl_2, rt, 12 h	1/2.2	quant.
3	Et_3N (0.1)	CH_2Cl_2, rt, 24 h	1/2.4	74[c]
4	Et_3N (1.0)	MeOH, rt, 24 h	1/2.5	quant.
5	Et_3N (1.0)	Toluene, rt, 12 h	1/2.2	quant.
6	Pyridine	Pyridine, rt, 24 h	—	0[b]
7	NaOMe (1.0)	MeOH, rt, 24 h	—	0[d]
8	NaOMe (0.1)	MeOH, rt, 24 h	—	0[e]
9	Silica gel	CH_2Cl_2, rt, 48 h	1/1.1	quant.
10	TsOH (0.1)	CH_2Cl_2, rt, 48 h	—	0[b]
11	AcOH	AcOH, rt, 48 h	—	0[b]

[a] Isolated yield.
[b] Starting materials were almost recovered.
[c] After 48 h, the yield increased to quantitative.
[d] A complex mixture was obtained.
[e] A complex mixture and small amount (<5%) of by-product shown in Ref. 14 were obtained.

The weak base pyridine was ineffective as a catalyst, and afforded no product even with pyridine as a solvent (entry 6). Because the color of the reaction mixture did not change, pyridine was judged to be a weak base that could not form sufficient tropolone anion to accelerate reaction. The strong base NaOMe also did not give the desired products (entries 7 and 8) because of product decomposition by the base.[15]

In addition to Et_3N, silica gel was an effective catalyst for this reaction. Reaction of **1** and **3a** in a slurry of silica-gel proceeded, although at a slower rate than the Et_3N-prompted reaction, and gave the products in quantitative yield (entry 9). Interestingly, the reactions carried out in the presence of acids gave no product (entry 10 and 11), which suggested that adsorption of the reactants onto the surface of silica gel might be important for the rate acceleration.[13a,13c]

Both Et_3N- and silica-gel-induced *endo*/*exo* isomerization of the products. A $CDCl_3$ solution of pure **5a**, unchanged after 72 h at room temperature, was transformed into a mixture of **4a**/**5a** (1/1.1) by the addition of 1 equiv of Et_3N at room temperature for 48 h. Similarly, by passage through a silica-gel column for 1 h, compound **5a** was converted into a mixture of **4a**/**5a** (1/2.2).

Silica-gel-induced isomerization explains the apparent *exo* selectivity observed for the Et_3N-prompted reactions (entries 2–5). For Et_3N-prompted reactions, silica-gel column chromatography was required to remove Et_3N prior to ^1H NMR measurement, and thus the relatively polar *endo* isomer **4a**, which remains in the column longer than the less polar *exo* isomer **5a**, partially isomerizes to the *exo* form. In contrast, for silica-gel-prompted reactions, only simple filtration was required to isolate the products, and the reactions gave a mixture of **4a**/**5a** (1/1.1), in agreement with the results of equilibrium (vide infra).

2.2. Pathway of *endo*/*exo* isomerization

Detailed examination of the reaction of **1** and **3a**, and of **2** and **3a**, revealed an intramolecular *endo*/*exo* isomerization pathway (Eq. 2). Table 2 summarizes the results of Et_3N- and silica-gel-prompted reactions carried out in $CDCl_3$. Yields and *endo*/*exo* ratios were calculated based on integration values of ^1H NMR spectra for the reaction mixtures. Reaction of **1** and **3a** initially produced *endo* adduct **4a** as a major isomer in the ratio 2.6/1 (entry 1), which gradually changed to 1/1.1 (entries 2–5) with prolonged reaction time.

Table 2
DA reaction of **1** and **3a**, and **2** and **3a**, in $CDCl_3$

Entry	Diene	Condition[a]	Time (h)	**4a**/**5ab**[b]	Yield[b] (%)
1	**1**	A	1	2.6/1	57
2	**1**	A	4	2.0/1	84
3	**1**	A	12	1.1/1	>99
4	**1**	A	24	1/1.1	>99
5	**1**	A	120	1/1.1	>99
6	**1**	B	12	3.9/1	79
7	**1**	B	48	1/1.2	>99
				6a/**7a**/**8a**/**9a**[b]	
8	**2**	A	6	2.3/1/6.7/2.8	94
9	**2**	A	24	1.6/1/4.6/3.0	>99
10	**2**	A	63	1.5/1/4.3/3.0	>99
11	**2**	A	120	1.4/1/4.1/3.0	>99
12	**2**	B	12	2.8/1/9.6/2.8	89
13	**2**	B	48	1.6/1/3.2/5.4	>99

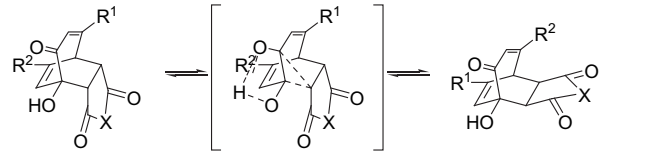
[a] Condition A: To a 0.1 M $CDCl_3$ solution of diene were added 1.0 equiv of Et_3N and 1.1 equiv of **3a** at rt. Condition B: To a 0.1 M $CDCl_3$ solution of diene (1.0 mL) were added 500 mg of silica gel and 1.1 equiv of **3a** at rt.
[b] Yields and isomer ratios were determined by ^1H NMR.

Reaction of **2** and **3a** also proceeded smoothly and gave two *endo*/*exo* pairs of regioisomers, **6a**/**7a** and **8a**/**9a** (entries 8–11), although the rates were slower than for reaction of **1**. Isomer ratio **6a**/**7a** changed from 2.3/1 to 1.4/1, and **8a**/**9a** changed from 2.4/1 to 1.4/1, with reaction time, which suggests that the initial *endo* products **6a** and **8a** isomerized into *exo* products **7a** and **9a**. Interestingly, isomer ratio **6a**+**7a**/**8a**+**9a** remained almost unchanged (ca. 1/2.9). In addition, pure *endo* products **6a** and **8a** isomerized exclusively to **6a**+**7a** and **8a**+**9a**, respectively, in the presence of 1 equiv of Et_3N in $CDCl_3$ solution. These results indicate that Et_3N-induced isomerization proceeds via intramolecular fashion, as shown in Eq. 2, and no retro-DA pathway is included. If the retro-DA pathway was included in this process, pure **6a** (or **8a**) should be transformed into all four possible isomers, and the ratio of **6a**+**7a**/**8a**+**9a** would be changed during the longer reaction time.

The results of the silica-gel-prompted reaction were almost the same as for the Et_3N-prompted reaction. Reaction of **1** and **3a** first gave **4a** as a major isomer, but after 48 h the major product had changed to **5a** in the ratio 1/1.2 (entries 6 and 7). Reaction of **2** and **3a** gave isomer ratio **6a**+**7a**/**8a**+**9a** that remained almost unchanged (ca. 1/3.3), although ratio **6a**/**7a** changed from 2.8/1 to 1.6/1 and ratio **8a**/**9a** changed from 3.5/1 to 1.7/1 (entries 12 and 13). Again, these results indicate that silica-gel induces the intramolecular isomerization.

Endo/*exo* isomerization has already been reported for thermal cycloaddition of **1** and maleic anhydride (**3b**)[16] and high-pressure cycloaddition of **1** and *N*-phenylmaleimide (**3c**),[17] and a reaction of deuterated **1** and **3b** disclosed that the isomerization proceeded via intramolecular pathway. Mechanism of the isomerization has been explained by acyloin rearrangement of adducts having

α-hydroxycarbonyl moiety, as illustrated in Eq. 2. Since all the results summarized in Table 2 are well described by Eq. 2, compounds **4a**–**9a** can be considered as interesting substrates for acyloin rearrangement under extremely mild condition.[18]



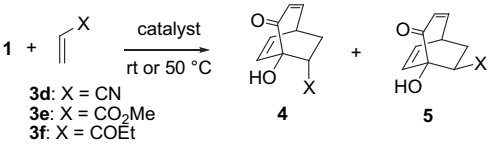
4a: R^1, R^2 = H, X = NMe
4b: R^1, R^2 = H, X = O
4c: R^1, R^2 = H, X = NPh
6a: R^1 = H, R^2 = i-Pr, X = NMe
8a: R^1 = i-Pr, R^2 = H, X = NMe

5a: R^1, R^2 = H, X = NMe
5b: R^1, R^2 = H, X = O
5c: R^1, R^2 = H, X = NPh
7a: R^1 = H, R^2 = i-Pr, X = NMe
9a: R^1 = i-Pr, R^2 = H, X = NMe

(2)

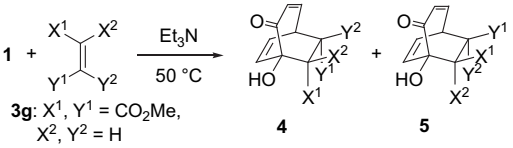
2.3. Cycloaddition of 1 and other dienophiles

The Et_3N- or silica-gel-prompted reaction of **1** was also effective for other electron-deficient dienophiles (Eqs. 3–5, Table 3). Reaction with acrylonitrile (**3d**) gave adducts **4d** and **5d** in the presence of Et_3N under mild heating, and no regioisomer was obtained (entry 1). The yield improved at higher temperature (80 °C), and then decreased at much higher temperature (110 °C) because of product decomposition (entries 2 and 3). The best result was obtained with reaction using acrylonitrile as solvent (entry 4); reaction proceeded smoothly at room temperature and afforded the products in good yields.



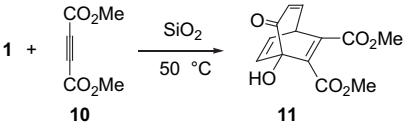
3d: X = CN
3e: X = CO_2Me
3f: X = COEt

4 **5** (3)



3g: X^1, Y^1 = CO_2Me, X^2, Y^2 = H
3h: X^1, Y^2 = CO_2Me X^2, Y^1 = H

4 **5** (4)



10 **11** (5)

The neat condition was also effective for the liquid dienophiles methyl acrylate (**3e**) and dimethyl maleate (**3g**), which gave products at 50 °C (entries 5 and 9). For the solid dienophile dimethyl fumalate (**3h**), a small amount of dichloromethane was added to give a thick paste of the mixture, and reaction proceeded smoothly to give the desired products (entry 10).

Base-sensitive dienophiles such as ethyl vinyl ketone (**3f**) and dimethyl acetylenedicarboxylate (**10**) were not suitable for the base-prompted reaction. For reaction using **3f**, formation of a small amount of desired product was observed by ^{1}H NMR analysis but purification was hampered by the presence of thick brown by-products (entry 7). Compound **10**, which was reactive with Et_3N, gave only a complex polymeric dark brown mixture (entry 11).

Silica-gel catalyst, which was less effective than Et_3N (entry 6), was nonetheless useful for reaction of **3f** or **10** (entries 8 and 12). Although yields were moderate, the corresponding products formed without any polymeric by-products and were easily isolated by silica-gel column chromatography as pure forms.

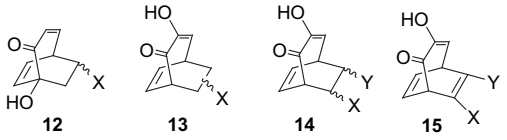
Table 3
DA reaction of **1** with various dienophiles

Entry	Dienophile	Condition[a]	**4**/**5**	Yield[b] (%)
1	**3c**	$CHCl_3$,[c] Et3N,[d] 60 °C	1/3.3	60
2	**3c**	Toluene,[c] Et_3N,[d] 80 °C	1/3.4	86
3	**3c**	Toluene,[c] Et_3N,[d] 110 °C	1/3.1	27[e]
4	**3c**	Neat, Et_3N,[d] rt.	1/4.3	88
5	**3d**	Neat, Et_3N,[d] 50 °C	1/3.9	85
6	**3d**	Neat, SiO_2, 50 °C	1/2.0	40
7	**3e**	Neat, Et_3N,[d] 50 °C	—	Trace
8	**3e**	Neat, SiO_2, 50 °C	1/2.2	41
9	**3f**	Neat, Et_3N,[d] 50 °C	1/5.1	29[f]
10	**3g**	$CHCl_3$,[g] Et_3N,[d] 50 °C	1/1.1[h]	61
11	**10**	Neat, Et_3N,[d] 50 °C	—	0
12	**10**	Neat, SiO_2, 50 °C	11	50

[a] Reaction was performed with **1** and 3 equiv of dienophile in a sealed tube for 72 h.
[b] Isolated yield.
[c] Concentration of **1** was 1.0 M.
[d] Amount of catalyst: Et_3N, 1 equiv for **1**; SiO_2, 1.0 g for 1 mmol of **1**.
[e] A complex mixture was obtained along with the products.
[f] A small amount (ca. 3%, based on the integral values of ^{1}H NMR) of **4h** and **5h** was contaminated.
[g] A small amount of solvent was used to give a thick paste of the reaction mixture.
[h] The isomer structure was not assigned.

2.4. Stereochemistry, stereoselectivities and plausible reaction mechanism

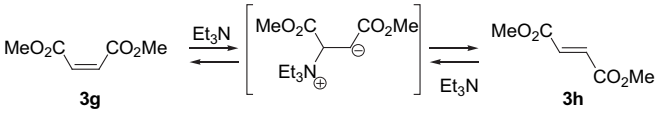
Structures and stereochemistries of the products obtained by the Et_3N- or silica-gel-prompted reaction were determined by ^{1}H NMR analysis with comparing to their related compounds.[4,16,19] In all reactions, no regioisomeric product such as shown in Figure 1 was obtained, which agrees well with previous observations of thermal DA reactions.[4]



12 **13** **14** **15**

Figure 1. Regioisomers that were not obtained.

Stereospecificity of the cycloaddition, which is a key feature of concerted DA reaction, was not fully confirmed for the Et_3N-prompted reactions. As shown in Table 3, reaction of **1** and dimethyl fumalate (**3h**) gave only *anti*-substituted products as an *endo*/*exo* mixture (entry 10). However, reaction of dimethyl malate (**3g**) gave a small amount (ca. 3%) of *anti* products (**4h** and **5h**) along with the major *syn* isomers (**4g** and **5g**, entry 9). *Anti*-product formation was probably due to Et_3N-induced isomerization of **3g** into sterically stable *trans* isomer **3h** (Eq. 6). In fact, ^{1}H NMR experiments revealed isomerization of **3g** into **3h** in the presence of Et_3N at room temperature for 24 h.



3g **3h** (6)

For a base-catalyzed [4+2] cycloaddition reaction, it is difficult to establish that reaction proceeds by a concerted DA or stepwise Michael–Aldol reaction mechanism. For reactions using 3-hydroxy-2-pyrone,[6a] 3-hydroxy-2-pyridone[7] or anthrone[10a,b] as dienes, concerted base-catalyzed DA reaction mechanisms have been suggested because of their complete stereospecificities. Although the stereospecificity of the Et_3N-catalyzed reaction of **1** is not perfect, the concerted reaction mechanism seems a good candidate because of perfect regioselectivity that agrees with previous DA reactions[4,19] and *endo* selectivity of the initial stage of reaction.

In conclusion, we found that α-tropolone (**1**) and hinokitiol (**2**) reacted with various electron-deficient dienophiles (**3a**, **3d**–**f**, and **10**) in the presence of Et_3N or silica gel to give the corresponding cycloadducts in quantitative to moderate yields. Since the highly functionalized bicyclo[3.2.2]nonatriene and -diene products, known as homobarrelenones and their derivatives, are attractive building blocks for organic synthesis,[3a,3g,20] various applications can be developed using these reactions.

3. Experimental

3.1. General

Melting points were measured by Yanagimoto micro melting point apparatus and were uncorrected. R_f values were measured by Merck TLC Aluminium Sheets 1.05554.0009 (20×50 mm). IR spectra were determined with JASCO FT/IR 5300 spectrometer. The NMR spectra were recorded by JEOL GSX400 spectrometer. FAB mass spectra were obtained from JEOL JMX-SX/SX 102A spectrometer. All reagents were commercially available and used without further purification. Silica gel 60, purchased form Merck, 0.063–0.200 mm, was used for column chromatography and catalysis.

3.2. Cycloaddition reaction of tropolone (1) and *N*-methylmaleimide (3a)

*3.2.1. Et_3N-prompted reaction of **1** and **3a** (Table 1, entry 2).* To a solution of **1** (61 mg, 0.50 mmol) and **3a** (67 mg, 0.60 mmol) in solvent (5 mL) was added Et_3N (70 μL, 0.50 mmol) at room temperature. After stirring for 12 h, the reaction mixture was concentrated by rotary evaporator, and the resulting crude products were purified by silica-gel column to give the products **4a** and **5a** as a mixture (white powder, 115 mg, quantitative). The *endo*/*exo* ratio was determined as 1/2.2 by ^1H NMR analysis of the mixture. Further purification was carried out by repeated silica-gel column chromatography and recrystallization from Hex:AcOEt 1:1 mixture to give pure **4a** and **5a** as white powder.

3.2.1.1. ***4a***. White powder, Mp 129–131 °C; R_f=0.52 (AcOEt); IR (KBr) 3443, 2961, 1779, 1696, 1439, 1381, 1292, 1116, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.33 (1H, dd, *J*=11.0, 8.8 Hz, H-2), 6.40 (1H, dd, *J*=9.2, 7.3 Hz, H-8), 6.09 (1H, dd, *J*=11.0, 0.7 Hz, H-3), 5.99 (1H, d, *J*=9.2 Hz, H-9), 4.94 (1H, s, –OH), 4.00 (1H, m, H-1), 3.34 (1H, dd, *J*=8.4, 2.2 Hz, H-7), 3.06 (1H, d, *J*=8.4 Hz, H-6), 3.01 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$) δ=192.8, 176.0, 173.4, 152.9, 134.0, 133.1, 127.0, 81.5, 46.5, 46.0, 37.2, 25.4; Anal. Calcd for $C_{12}H_{11}NO_4$: C 61.40, H 4.87, N 5.84. Found: C 61.80, H 4.75, N 6.01.

3.2.1.2. ***5a***. White powder, Mp 144–146 °C; R_f=0.41 (AcOEt); IR (KBr) 3441, 2924, 1779, 1711, 1453, 1379, 1289, 1115, 962, 860, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.04 (1H, dd, *J*=11.4, 8.4 Hz, H-2), 6.54 (1H, dd, *J*=8.8, 7.3 Hz, H-8), 6.07 (1H, dd, *J*=8.8, 0.7 Hz, H-9), 6.02 (1H, dd, *J*=11.4, 0.7 Hz, H-3), 4.85 (1H, s, –OH), 4.01 (1H, m, H-1), 3.49 (1H, d, *J*=9.9 Hz, H-6), 3.34 (1H, dd, *J*=9.9, 5.1 Hz, H-7), 2.92 (3H, s, NCH_3); ^{13}C NMR ($CDCl_3$) δ=191.9, 175.9, 175.1, 151.1, 136.2, 134.0, 128.4, 82.9, 49.7, 44.5, 37.4, 24.8, Anal. Calcd for $C_{12}H_{11}NO_4$: C 61.40, H 4.87, N 5.84. Found: C 61.75, H 4.77, N 5.95.

*3.2.2. Silica-gel-prompted reaction of **1** and **3a** (Table 1, entry 9).* To a mixture of **1** (122 mg, 1.0 mmol), **2a** (134 mg, 1.2 mmol), and silica gel (1.0 g) was added CH_2Cl_2 (5 mL) at room temperature. The resulting slurry was stirred for 24 h, and the mixture was filtered through a glass filter. After concentration of the resulting filtrate, almost pure products **4a** and **5a** were obtained (white powder, 233 mg, quant.) and the ratio was determined as 1/1.1 by ^1H NMR analysis without any further purification.

For chemical properties and spectra data of **4a** and **5a**, see above.

3.3. DA reaction of α-tropolone (1) and *N*-methylmaleimide (3a), and hinokitiol (2) and *N*-methylmaleimide (3a) in $CDCl_3$

*3.3.1. Et_3N-prompted DA reaction of **1** and **3a** in $CDCl_3$ (Table 2, entries 1–5).* A solution of **1** (12.2 mg, 0.10 mmol), **3a** (13 mg, 0.12 mmol) and Et_3N (14 μL, 0.10 mmol) in $CDCl_3$ (1.0 mL) was put in an NMR sample tube and left at room temperature. The yields and the *endo*/*exo* ratios listed in Table 2 were calculated from the integral values of the corresponding signals.

*3.3.2. Et_3N-prompted DA reaction of **2** and **3a** in $CDCl_3$ (Table 2, entries 8–11).* As same with the above described procedure, reaction of **2** and **3a** was carried out in NMR tube, and the yields and the *endo*/*exo* ratios listed in Table 2 were calculated from the integral values of the corresponding signals. After the NMR measurement, the resulting reaction mixture was purified by silica-gel column chromatography and preparative TLC to give four adducts (**6a**–**9a**) in pure form.

3.3.2.1. ***6a***. White powder, Mp 109–110 °C; R_f=0.22 (Hex:AcOEt=4:6); IR (KBr) 3432, 2961, 1777, 1703, 1439, 1385, 1289, 1238, 1121, 810, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.34 (1H, dd, *J*=11.0, 8.8 Hz, H-2), 6.07 (1H, d, *J*=11.0 Hz, H-3), 5.52 (1H, s, H-9), 4.92 (1H, s, –OH), 3.80 (1H, br d, *J*=7.3 Hz, H-1), 3.31 (1H, dd, *J*=8.4, 2.2 Hz, H-7), 3.05 (1H, d, *J*=8.4 Hz, H-6), 2.99 (3H, s, NCH_3), 2.27 (1H, sep, *J*=6.6 Hz, –C*H*$(CH_3)_2$), 0.97 (3H, d, *J*=6.6 Hz, –CH(C*H*$_3)_2$), 0.96 (3H, d, *J*=6.6 Hz, –CH(C*H*$_3)_2$); ^{13}C NMR ($CDCl_3$) δ=193.3, 175.9, 173.6, 153.5, 152.8, 127.5, 123.4, 81.4, 46.6, 45.9, 40.3, 33.8, 25.3, 20.5, 19.8; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C 65.65, H 5.97, N 5.25.

3.3.2.2. ***7a***. White powder, Mp 143–145 °C; R_f=0.42 (Hex:AcOEt=4:6); IR (KBr) 3466, 2963, 1777, 1705, 1431, 1377, 1289, 1240, 1094, 976, 822, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.03 (1H, dd, *J*=11.4, 8.4 Hz, H-2), 6.01 (1H, d, *J*=11.4 Hz, H-3), 5.59 (1H, s, H-9), 4.82 (1H, s, –OH), 3.84 (1H, dd, *J*=8.4, 5.1 Hz, H-1), 3.45 (1H, d, *J*=9.5 Hz, H-6), 3.24 (1H, dd, *J*=9.5, 5.1 Hz, H-7), 2.91 (3H, s, NCH_3), 2.40 (1H, sep, *J*=7.0 Hz, –C*H*$(CH_3)_2$), 1.06 (3H, d, *J*=7.0 Hz, –CH(C*H*$_3)_2$), 1.04 (3H, d, *J*=7.0 Hz, –CH(C*H*$_3)_2$); ^{13}C NMR ($CDCl_3$) δ=192.3, 176.2, 175.3, 154.3, 150.7, 128.8, 125.6, 82.7, 50.0, 44.8, 40.7, 33.5, 24.8, 20.3, 19.8; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C 65.55, H 5.85, N 5.14.

3.3.2.3. ***8a***. White powder, Mp 153.5–155.5 °C; R_f=0.28 (Hex:AcOEt=4:6); IR (KBr) 3416, 2962, 1779, 1698, 1661, 1441, 1389, 1290, 1121, 883, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.30 (1H, dd, *J*=8.8, 7.3 Hz, H-8), 6.00 (1H, d, *J*=8.8 Hz, H-9), 5.87 (1H, s, H-3), 5.02 (1H, s, –OH), 3.88 (1H, br d, *J*=7.3 Hz, H-1), 3.19 (1H, dd, *J*=8.4, 2.2 Hz, H-7), 3.04 (1H, d, *J*=8.4 Hz, H-6), 3.01 (3H, s, NCH_3), 2.64 (1H, sep, *J*=6.6 Hz, –C*H*$(CH_3)_2$), 1.21 (3H, d, *J*=6.6 Hz, –CH(C*H*$_3)_2$), 1.20 (3H, d, *J*=6.6 Hz, –CH(C*H*$_3)_2$); ^{13}C NMR ($CDCl_3$) δ=193.2, 176.3, 174.4, 173.5, 134.7, 132.3, 120.0, 80.8, 47.2, 46.4, 40.9, 37.7, 25.4, 20.1, 19.9; Anal. Calcd

for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C 65.68, H 5.98, N 4.89.

3.3.2.4. ***9a***. White powder, Mp 143.5–145 °C; R_f=0.32 (Hex:AcOEt=4:6); IR (KBr) 3474, 2963, 1773, 1703, 1653, 1433, 1377, 1277, 1121, 893, 799 cm^{-1}; ^1H NMR ($CDCl_3$) δ=6.47 (1H, dd, J=8.8, 7.3 Hz, H-8), 6.08 (1H, d, J=8.8 Hz, H-9), 5.81 (1H, s, H-3), 4.91 (1H, s, –OH), 3.88 (1H, br t, J=6.6 Hz, H-1), 3.46 (1H, d, J=9.5 Hz, H-6), 3.35 (1H, dd, J=9.5, 5.9 Hz, H-7), 2.89 (3H, s, NCH_3), 2.49 (1H, sep, J=6.6 Hz, –C*H*$(CH_3)_2$), 1.12 (3H, d, J=6.6 Hz, –CH(C*H*$_3)_2$), 1.00 (3H, d, J=6.6 Hz, –CH(C*H*$_3)_2$); ^{13}C NMR ($CDCl_3$) δ=192.2, 175.7, 175.0, 174.0, 136.9, 133.3, 120.3, 82.1, 50.0, 44.3, 43.0, 38.2, 24.7, 20.7, 19.6; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C 65.58, H 6.00, N 4.97.

*3.3.3. SiO_2-prompted DA reaction of **1** and **3a** in $CDCl_3$ (Table 2, entries 6 and 7).* A mixture of **1** (12.2 mg, 0.10 mmol), **3a** (13 mg, 0.12 mmol) and silica gel (100 mg) in $CDCl_3$ (1.0 mL) was stirred at room temperature. After the reaction time listed at Table 2, the mixture was filtered through a glass filter, and the filtrate was measured by ^1H NMR to calculate the yields and the *endo*/*exo* ratios of products listed in Table 2.

*3.3.4. SiO_2-prompted DA reaction of **2** and **3a** in $CDCl_3$ (Table 2, entries 12 and 13).* As same with the above described procedure, reaction of **2** and **3a** was carried out in NMR tube, and the yields and the *endo*/*exo* ratios listed in Table 2 were calculated from the integral values of the corresponding signals.

3.4. DA reaction of α-tropolone (1) and various dienophiles (3d–3h, 10)

*3.4.1. Et_3N-prompted DA reaction of **1** and **3d**, **3e**, or **3g** (Table 3, entries 4, 5).* Compound **1** (61 mg, 0.50 mmol), dienophile (1.5 mmol) and Et_3N (70 μL, 0.50 mmol) were mixed in a glass ample tube, which was sealed by a gas burner. After leaving the tube for 72 h at 50 °C, it was broken and washed with AcOEt to take the reaction mixture out. The solution of crude mixture was concentrated by rotary evaporator and purified by silica gel column chromatography to give the products. The yields and the *endo*/*exo* ratios are listed in Table 3.

3.4.1.1. ***4d*** *and* ***5d*** *(as a mixture).* Colorless oil; R_f=0.43 (Hex:AcOEt=4:6); IR (film) 3432, 2926, 2361, 2340, 2240, 1667, 1454, 1383, 1356, 1248, 1125, 847, 720 cm^{-1}; ^1H NMR for **4d** ($CDCl_3$) δ=7.31 (1H, dd, J=11.0, 8.2 Hz, H-2), 6.62 (1H, dd, J=8.4, 7.7 Hz, H-8), 6.07 (1H, d, J=8.4 Hz, H-9), 6.04 (1H, d, J=11.0 Hz, H-3), 4.98 (1H, s, –OH), 3.56 (1H, m, H-1), 3.06 (1H, dd, J=10.6, 5.1 Hz, H-6), 2.40 (1H, ddd, J=13.0, 10.6, 1.5 Hz, H-7), 2.18 (1H, ddd, J=13.0, 10.6, 5.1 Hz, H-7); ^1H NMR for **5d** ($CDCl_3$) δ=7.33 (1H, dd, J=11.0, 8.8 Hz, H-2), 6.53 (1H, dd, J=8.8, 7.3 Hz, H-8), 6.15 (1H, d, J=11.0, H-3), 5.99 (1H, dd, J=8.8, 0.7 Hz, H-9), 5.11 (1H, s, –OH), 3.56 (1H, m, H-1), 3.23 (1H, dd, J=11.0, 4.0 Hz, H-6), 2.30 (1H, ddd, J=13.2, 11.0, 4.8 Hz, H-7), 2.20 (1H, ddd, J=13.2, 4.0, 1.8 Hz, H-7); ^{13}C NMR for **4d** ($CDCl_3$) δ=193.1, 155.8, 136.1, 132.8, 126.0, 119.6, 80.5, 35.6, 34.3, 30.8; ^{13}C NMR for **5d** ($CDCl_3$) δ=192.5, 155.1, 136.0, 133.7, 126.8, 119.9, 82.5, 35.8, 34.3, 29.7; HRFABMS m/z=$[M+H]^+$ calcd for $C_{10}H_{10}NO_2$ 176.0712, found: 176.0700.

3.4.1.2. ***4e*** *and* ***5e*** *(as a mixture).* Colorless oil; R_f=0.52 (Hex:AcOEt=4:6); IR (film) 3439, 2953, 2361, 1736, 1669, 1435, 1352, 1217, 1196, 1163, 1121, 1034, 831, 727 cm^{-1}; ^1H NMR for **4e** ($CDCl_3$) δ=7.21 (1H, dd, J=11.4, 8.8 Hz, H-2), 6.56 (1H, dd, J=8.8, 7.3 Hz, H-8), 6.00 (1H, d, J=11.4 Hz, H-3), 5.93 (1H, d, J=8.8 Hz, H-9), 4.75 (1H, s, –OH), 3.75 (3H, s, –OMe), 3.51 (1H, m, H-1), 2.95 (1H, dd, J=9.5, 7.3 Hz, H-6), 2.18 (1H, m, overlapped with **5e**, H-7), 2.02 (1H, m, overlapped with **5e**, H-7); ^1H NMR for **5e** ($CDCl_3$) δ=7.21(1H, dd, J=11.0, 8.8 Hz, H-2), 6.47 (1H, dd, J=8.4, 7.3 Hz, H-8), 6.09 (1H, d, J=11.0 Hz, H-3), 5.97 (1H, d, J=8.4 Hz, H-9), 4.90 (1H, s, –OH), 3.65 (3H, s, –OMe), 3.45 (1H, br dd, J=7.7, 6.4 Hz, H-1), 3.19 (1H, dd, J=11.7, 4.8 Hz, H-6), 2.24 (1H, m, overlapped with **4e**, H-7), 2.06 (1H, m, overlapped with **4e**, H-7); ^{13}C NMR for **4e** ($CDCl_3$) δ=194.5, 173.2, 155.6, 135.5, 132.0, 126.0, 81.5, 52.1, 46.8, 36.7, 30.2; ^{13}C NMR for **5e** ($CDCl_3$) δ=194.6, 173.8, 154.4, 135.6, 135.4, 127.6, 83.2, 52.2, 49.1, 36.2, 29.8; HRFABMS m/z=$[M+H]^+$ calcd for $C_{11}H_{13}O_4$, 209.0814, found 209.0812.

3.4.1.3. ***4g***. Colorless oil; R_f=0.49 (Hex:AcOEt=4:6); IR (film, as a mixture of **4g** and **5g**) 3422, 2955, 1732, 1662, 1437, 1362, 1323, 1219, 1090, 855, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.32 (1H, dd, J=11.0, 8.8 Hz, H-2), 6.50 (1H, dd, J=8.8, 7.7 Hz, H-8), 6.15 (1H, d, J=11.0 Hz, H-3), 6.00 (1H, dd, J=8.8, 0.7 Hz, H-9), 4.94 (1H, s, –OH), 3.73 (1H, br dd, J=7.7, 4.0 Hz, H-1), 3.65 (3H, s, –CO_2CH_3), 3.63 (3H, s, –CO_2CH_3), 3.60 (1H, d, J=12.1 Hz, H-6), 3.39 (1H, dd, J=12.1, 4.0 Hz, H-7); ^{13}C NMR for **4g** ($CDCl_3$) δ=194.1, 172.6, 170.6, 154.5, 134.1, 132.6, 126.9, 81.9, 52.3, 52.2, 50.9, 46.3, 37.8; HRFABMS (as a mixture of **4g** and **5g**) m/z=$[M+H]^+$ calcd for calcd for $C_{13}H_{15}O_6$, 267.0869, found 267.0869.

3.4.1.4. ***5g***. Colorless oil; R_f=0.42 (Hex:AcOEt=4:6); ^1H NMR ($CDCl_3$) δ=7.27 (1H, dd, J=11.0, 8.8 Hz, H-2), 6.67 (1H, br t, J=8.8 Hz, H-8), 6.06 (1H, d, J=11.0 Hz, H-3), 6.00, (1H, d, J=8.8 Hz, H-9), 4.81 (1H, s, –OH), 3.87 (1H, br t, J=8.4 Hz, H-1), 3.69 (3H, s, –CO_2CH_3), 3.63 (3H, s, –CO_2CH_3), 3.40 (1H, dd, J=11.4, 0.7 Hz, H-7), 3.29 (1H, d, J=11.4 Hz, H-6); ^{13}C NMR for **4g** ($CDCl_3$) δ=194.6, 171.5, 171.4, 152.4, 136.1, 135.3, 127.1, 83.2, 52.5, 52.3, 52.2, 47.5, 38.4.

*3.4.2. Et_3N-prompted DA reaction of **1** and **3h** (Table 3, entry 10).* Compound **1** (61 mg, 0.50 mmol), powdered **3h** (216 mg, 1.5 mmol), Et_3N (70 μL, 0.50 mmol) and few drops of CH_2Cl_2 were mixed in a glass ample tube, which was sealed by a gas burner. After leaving the tube for 72 h at 50 °C, it was broken and washed with AcOEt to take the reaction mixture out. The solution of crude mixture was concentrated by rotary evaporator and purified by silica gel column chromatography to give a mixture of **4h** and **5h** as colorless oil (81 mg, 61%). The NMR signals of these products were not be assigned to each structure.

3.4.2.1. ***4h*** *and* ***5h*** *(as a mixture).* Colorless oil; R_f=0.57 (Hex:AcOEt=4:6); IR (film) 3441, 2957, 1732, 1672, 1437, 1372, 1206, 1013, 831, 733 cm^{-1}; ^1H NMR (as a mixture, signals were not assigned for compound **4h** or **5h**, $CDCl_3$) δ=7.20 (2H, dd, J=11.4, 8.4 Hz, overlapped, H-2), 6.57 (1H, br t, J=8.0 Hz, H-8), 6.43 (1H, br t, J=8.0 Hz, H-8), 6.10 (1H, d, J=11.4 Hz, H-3), 6.03 (2H, br d, J=9.0 Hz, overlapped, H-3 and H-9), 5.93 (1H, d, J=8.0 Hz, H-9), 4.82 (1H, s, –OH), 4.69 (1H, s, –OH), 3.93–3.83 (2H, m, overlapped, H-1), 3.79 (3H, s, –OMe), 3.75 (3H, s, –OMe), 3.72 (3H, s, –OMe), 3.69 (3H, s, –OMe), 3.69 (1H, d, overlapped with –OMe signal, H-6), 3.35 (2H, m, overlapped, H-7), 3.23 (1H, d, J=7.7 Hz, H-6); ^{13}C NMR (as a mixture, signals were not assigned for compound **4h** or **5h**, $CDCl_3$) δ=193.9, 193.8, 172.6, 172.2, 172.3, 172.0, 153.4, 152.0, 135.8, 134.7, 133.7, 133.0, 128.3, 126.3, 82.8, 81.3, 52.9, 52.6, 52.5, 52.0, 49.8, 48.3, 46.8, 38.8, 38.6; HREIMS m/z=$[M]^+$ calcd for $C_{13}H_{14}O_6$, 266.0790, found 266.0796.

*3.4.3. Et3N-prompted DA reaction of **1** and **3f** or **10** (Table 3, entries 8 and 12).* Compound **1** (122 mg, 1.0 mmol), dienophile (3.0 mmol) and silica gel (500 mg) were put in a glass ample tube, which was sealed by a gas burner. The tube was shaken well, and left for 72 h at 50 °C. The reaction mixture was brought out by breaking the tube, and washed with AcOEt for three times to extract the products. After filtration and concentration, the resulting crude products

were purified by silica gel column chromatography. In case of the reaction using **3f**, the *endo*/*exo* ratio of the products was determined by ^{1}H NMR analysis of the mixture.

3.4.3.1. ***4f*** *and* ***5f*** *(as a mixture).* Colorless oil; R_f=0.41 (Hex:AcOEt=4:6); IR (film) 3425, 2940, 1715, 1665, 1356, 1250, 1121, 843, 709 cm^{-1}; ^{1}H NMR for **4f** ($CDCl_3$) δ=7.25 (1H, dd, J=11.0, 8.7 Hz, H-2), 6.57 (1H, dd, J=8.7, 7.3 Hz, H-8), 6.00 (1H, d, J=11.0 Hz, H-3), 5.89 (1H, d, J=8.7 Hz, H-9), 4.77 (1H, s, –OH), 3.52 (1H, m, H-1), 3.09 (1H, dd, J=9.6, 6.9 Hz, H-6), 2.62–2.40 (2H, m, –COCH_2CH$_3$), 2.04 (1H, ddd, J=12.8, 9.6, 2.3 Hz, H-7), 1.96 (1H, ddd, J=12.8, 6.9, 4.1 Hz, H-7), 1.05 (3H, t, J=7.3 Hz, –COCH$_2$CH_3); ^{1}H NMR for **5f** ($CDCl_3$) δ=7.19 (1H, dd, J=11.0, 8.7 Hz, H-2), 6.44 (1H, dd, J=8.7, 7.3 Hz, H-8), 6.11 (1H, d, J=11.0 Hz, H-3), 5.97 (1H, d, J=8.7 Hz, H-9), 4.91 (1H, s, –OH), 3.47–3.41 (1H, m, H-1), 3.41 (1H, dd, J=11.4, 5.0 Hz, H-6), 2.62–2.49 (2H, m, –COCH_2CH$_3$), 2.16 (1H, ddd, J=12.8, 11.9, 5.4 Hz, H-7), 1.94 (1H, br dd, J=12.8, 5.1 Hz, H-7) 1.01 (3H, t, J=7.3 Hz, –COCH$_2$CH_3); ^{13}C NMR for **4f** ($CDCl_3$) δ=210.4, 194.8, 156.0, 135.7, 132.0, 125.8, 82.0, 51.1, 38.0, 37.0, 29.7, 7.5; ^{13}C NMR for **5f** ($CDCl_3$) δ=211.6, 195.0, 154.3, 136.3, 135.1, 127.8, 83.7, 55.3, 38.0, 36.2, 29.3, 7.3; HRFABMS m/z=[M+H]$^+$ calcd for $C_{12}H_{15}O_3$, 207.1021, found 207.1026.

3.4.3.2. ***11****.* Colorless oil; R_f=0.56 (Hex:AcOEt=4:6); IR (film) 3444, 2955, 1722, 1683, 1657, 1437, 1325, 1271, 1195, 1111, 831, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.30 (1H, dd, J=11.0, 8.2 Hz, H-2), 6.78 (1H, dd, J=7.8, 6.9 Hz, H-8), 6.32 (1H, dd, J=7.8, 1.4 Hz, H-9), 5.59 (1H, d, J=11.0 Hz, H-3), 5.01 (1H, br s, –OH), 4.62 (br dd, J=8.2, 6.9 Hz, H-1), 3.83 (3H, s, –CO_2CH_3), 3.79 (3H, s, –CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ=186.0, 165.4, 163.4, 153.6, 149.3, 136.1, 134.8, 134.3, 122.4, 85.2, 52.9, 52.6, 41.0; HRFABMS m/z=[M+H]$^+$ calcd for $C_{13}H_{13}O_6$, 265.0712, found: 265.0710.

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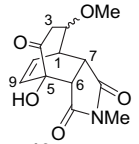
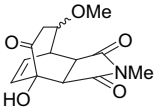
14. The pK_a value of hydroxyl group in a-tropolone was estimated as 6.7 in Ref. 1a.
15. Small amounts of by-products were isolated from the NaOMe catalyzed reaction of **1** and **3a**, and their structures were suggested as **16** and **17** by ^{1}H NMR analysis. ^{1}H NMR for **16** or **17** ($CDCl_3$) δ=7.01 (1H, dd, J=11.4, 8.7 Hz, H-8), 6.30 (1H, d, J=11.4 Hz, H-9), 4.56 (1H, s, –OH), 3.68–3.57 (3H, m, H-1, H-2, H-7), 3.38 (3H, s, –OCH_3), 3.34 (1H, d, J=9.2 Hz, H-6), 2.89 (3H, s, –NCH_3), 2.10 (1H, dd, J=15.1, 8.7 Hz, H-3), 1.98 (1H, dd, J=15.1, 3.2 Hz, H-3); ^{1}H NMR for **17** or **16** ($CDCl_3$) δ=6.94 (1H, dd, J=11.4, 9.6 Hz, H-8), 6.45 (1H, d, J=11.4 Hz, H-9), 4.69 (1H, s, –OH), 3.91–3.84 (2H, m, H-1, H-2), 3.35 (3H, s, –OCH_3), 3.20 (2H, m, H-6, H-7), 2.90 (3H, s, –NCH_3), 2.45 (1H, dd, J=15.1, 9.2 Hz, H-3), 1.71 (1H, dd, J=15.1, 4.1 Hz, H-3);



16



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