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Base-Catalyzed Diels−Alder Reactions of 2*H*-Pyran-2,5-diones: A Mild Approach to Basiliolide B

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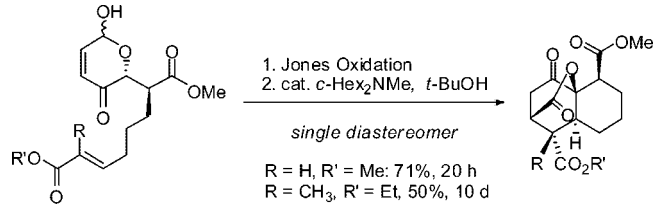
ABSTRACT



A new class of base-catalyzed Diels−Alder reactions of 2*H*-pyran-2,5-diones has been developed using catalytic amount of dicyclohexylmethylamine in *tert*-butyl alcohol. This method has been successfully employed for construction of the tricyclic core of basiliolide B at room temperature with good yields and exclusive *endo* selectivity.

Since its isolation from *Thapsia garganica* L. in 1978,[1] thapsigargin has been developed into an indispensable tool for studying calcium homeostasis.[2] Thapsigargin is a known selective, potent, and irreversible inhibitor toward sacroendoplasmic reticulum Ca^{2+}-ATPase (SERCA)[3] and is able to induce apoptosis through endoplasmic reticulum (ER) stress.[4] In efforts to search for thapsigargin analogues from plants of the *Thapsia* genus, two new series of structurally related natural products, basiliolides and transtaganolides, were recently identified.[5] The basiliolides and thapsigargin were both isolated from *T. garganica* L. and exhibited similar levels of inhibitory potency toward SERCA despite their structure diversity. More interestingly, unlike thapsigargin, the basiliolides were found to be noncytotoxic, suggesting a reversible binding mechanism toward SERCA. Since the basiliolides are noncytotoxic and are able to mobilize Ca^{2+} by targeting the ER, this class of natural products may have found potential application for the treatment of neurodegenerative diseases.[6]

The basiliolides feature an unprecedented 7-methoxy-4,5-dihydro-3*H*-oxepin-2-one ring and three six-membered rings fused into a tetracyclic framework. The continuous stereogenic centers around the six-membered rings make Diels−Alder (DA) reactions of substituted 2-pyrones an excellent choice for establishing the 10-oxatricyclo[6.2.2.$0^{1,6}$]dodecan-9-one

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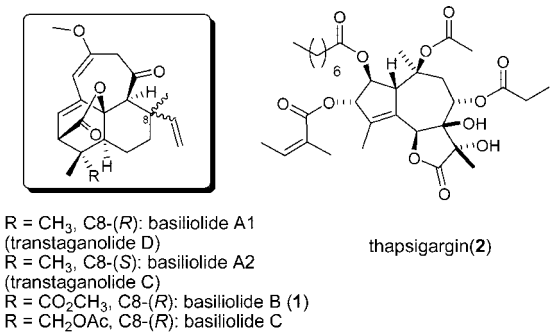
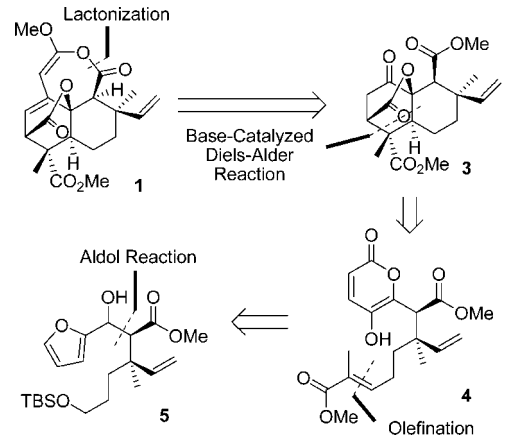


Figure 1. Bioactive natural products isolated from plants of the *Thapsia* genus.

core of the basiliolides. Recently, Stoltz's and Dudley's group have independently reported the construction of the tricyclic core of basiliolide B (**1**) via intramolecular DA reactions of halogenated 2-pyrones.[7] However, this type of DA reactions required high reaction temperature. Our synthetic strategy for establishing the tricyclic core of basiliolide B involved an intramolecular base-catalyzed DA reaction of 5-hydroxy-2-pyrone (Scheme 1), which was anticipated to proceed under room-temperature conditions. The 5-hydroxy-2-pyrone moiety of **4** could be obtained via base- or acid-induced equilibration of 2*H*-pyran-2,5-diones, which could be readily prepared from 2-furfuryl alcohol **5** using the Achmatowiz reaction followed by Jones oxidation. Synthesis of 2-furfuryl alcohol **5** could be obtained via an aldol reaction approach.

Surprisingly, although 2*H*-pyran-2,5-diones have been widely synthesized and utilized in natural product synthesis,[8] base-catalyzed equilibration of 2*H*-pyran-2,5-diones to 5-hydroxy-2-pyrones[9] followed by DA reactions in a one-pot condition have not been reported. Inspired by work on DA reactions of 3-hydroxy-2-pyrones from the groups of Nakatani and Deng[10] and the DA reactions of halogenated 2-pyrones from the groups of Posner, Afarinkia, and Cho,[11] 5-hydroxy-2-pyrones are expected to be active pyrones for DA reactions under basic conditions. Therefore, we have decided to develop a new class of base-catalyzed DA

Scheme 1. Retrosynthetic Analysis of Basiliolide B (**1**)



reactions of 2*H*-pyran-2,5-diones and explore its utilities in establishing the tricyclic core of the basiliolides.

In the course of a methodology study, 2*H*-pyran-2,5-dione **7** was prepared and used for determining the optimal base/solvent system for the DA reactions. As shown in Scheme 2, Achmatowiz reaction[12] of **6** using NBS in aqueous THF followed by Jones oxidation provided 2*H*-pyran-2,5-dione **7** in good yields. With the reaction precursor in hand, DA reaction between **7** and methyl acrylate was studied using Nakatani's conditions.[10a−c] The DA reaction proceeded rapidly (2 h) with 1 equiv of triethylamine in chloroform (Table 1, entry 1).[13] This condition gave 22% of the DA product with *endo* selectivity of 4:1. The formation of the DA product can be rationalized by equilibration of 2*H*-pyran-2,5-dione **7** to 5-hydroxy-2-pyrone **8** in the presence of triethylamine, and subsequent DA reaction between **8** and methyl acrylate afforded the DA product (**9**). Since 2*H*-pyran-2,5-dione **7** was found to be quite unstable with triethylamine

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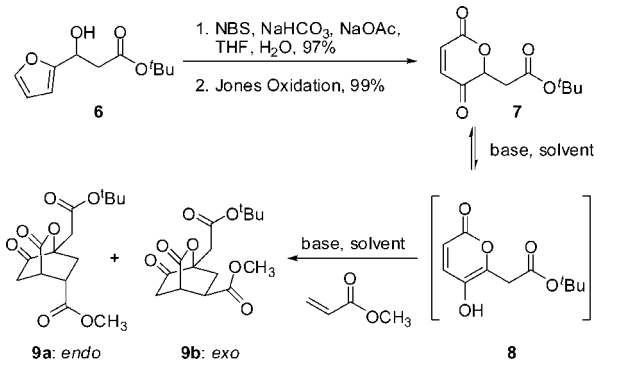
(13) General procedures for the base-catalyzed DA reactions: To a stirred solution of **7** (0.1 mmol) and methyl acrylate (0.5 mmol) in the selected solvent (1.5 mL) was added the appropriate amount of the base (0.01 mmol) at room temperature. The resulting mixture was stirred at room temperature and monitored by TLC until all the starting material was consumed. Silica gel (ca. 0.3 g) was added to the reaction mixture. After removal of the volatiles, the residue was purified by silica gel flash column chromatography. Alternative workup procedure: the reaction mixture was treated with 5% aqueous HCl solution and extracted with diethyl ether (3×). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silcia gel column chromatography. These two workup procedures gave the same results.

in chloroform, employing catalytic amount of triethylamine may improve the yields. Surprisingly, catalytic amounts of triethylamine led to only trace amount of **9** (entry 2). After screening various solvents including THF, CH_3CN, acetone, ethyl acetate, diethyl ether, and various alcohols, we found that 0.2 equiv of triethylamine in alcohol solvents provided optimal conditions for the DA reactions. As shown in Table 1, the yield of **9** was improved to 70% using isopropyl alcohol as the solvent, but poor *endo* selectivity (2.5:1) resulted (entry 3). Switching the solvent to *tert*-butyl alcohol improved the *endo* selectivity to 5.3:1 but the yield was down to 55% (entry 4). Employing different bases in *tert*-butyl alcohol showed only minor influences on the yields (58−67%) and *endo* selectivity (5.0:1 to 5.5:1) of the DA reactions (entry 5−9). Bulky base dicyclohexylmethylamine gave the highest *endo* selectivity with 62% yield of the DA products (entry 8).

Scheme 2. Base-Catalyzed DA Reactions of 2*H*-Pyran-2,5-diones



The base loading effects were investigated by using the dicyclohexylmethylamine/*tert*-butyl alcohol system, and the results are summarized in Table 2. High base loading generally resulted in high reaction rate and low *endo* selectivity. Although the DA reaction was complete in 1 day using 1 equiv of base, low yield and low *endo* selectivity resulted (entry 1). The highest *endo* selectivity was achieved using 0.02 equiv of dicyclohexylmethylamine, but the reaction required 10 days with only 18% yield of the DA products isolated (entry 6). The optimal condition was observed using 0.1 equiv of dicyclohexylmethylamine, which gave 58% yield of the DA products with *endo* selectivity equaling 8.5:1. Increasing the reaction temperature to 50 °C under the same conditions led to a shorter reaction time (2 days), but a lower yield (50%) and lower *endo* selectivity (endo/exo = 3.6: 1) resulted. The *exo* product (**9b**) was characterized unambiguously by analyzing the COSY and NOESY data.[14] However, the stereochemistry of the *endo* product (**9a**) cannot be determined using NMR experiments due to signal overlaps. Attempts to recrystallize **9a** using various solvent systems failed. Thus, **9a** was converted to

Table 1. Base-Catalyzed DA Reaction of 2*H*-Pyran-2,5-dione **7**[a]

entry	base[b]/solvent	time	yield[c] (%)	*endo*/*exo*[d]
1	Et_3N[e]/$CHCl_3$	2 h	22	4.0:1
2	Et_3N/$CHCl_3$	7 d	trace	
3	Et_3N/*i*-PrOH	7 d	70	2.5:1
4	Et_3N/*t*-BuOH	7 d	55	5.3:1
5	Et_2NH/*t*-BuOH	7 d	67	5.1:1
6	HMDS/*t*-BuOH	7 d	58	5.2:1
7	DIPEA/*t*-BuOH	7 d	61	5.1:1
8	*c*-Hex_2NMe/*t*-BuOH	7 d	62	5.5:1
9	*t*-BuOK/*t*-BuOH	5 d	61	5.0:1

[a] The general procedures were followed.[13] [b] 0.2 equiv of base was used. [c] Isolated yields after silica gel flash column chromatography. [d] The *endo*/*exo* ratios were estimated by comparing the signals at δ_{endo} 3.21 ppm and δ_{exo} 3.01 ppm in ^1H. [e] 1.0 equiv of base was used.

10 using triethylamine in methanol. The crystals of **10** obtained by recrystallization from *n*-hexane/dichloromethane were found to be suitable for X-ray crystallography.[15] As shown in Figure 2, the two methyl ester moieties of **10** were found to be *anti*, which is consistent with the stereochemistry of the expected *endo* product (**9a**).

Table 2. Effect of the Base Loading in DA Reactions[a]

entry	equiv	time	yield[b] (%)	*endo*/*exo*[c]
1	1.0	1 d	40	2.5:1
2	0.5	3 d	45	4.4:1
3	0.2	7 d	62	5.5:1
4	0.1	7 d	58	8.5:1
5	0.05	7 d	46	20:1
6	0.02	10 d	18	30:1

[a] The general procedures were followed (base = dicyclohexylmethylamine, solvent = *tert*-butyl alcohol).[13] [b] Isolated yields after silica gel flash column chromatography, [c] The *endo*/*exo* ratios were estimated by comparing the signals at δ_{endo} 3.21 ppm and δ_{exo} 3.01 ppm in ^1H.

With the base-catalyzed DA reaction developed, its utilities for construction of the tricyclic core of basiliolide B were investigated. As shown in the model study (Scheme 3), aldol reaction between **11** and 2-furfuryl aldehyde afforded 90% yield of **12**, which is a roughly 1:1 syn/anti diastereomeric mixture. These two diastereomers were separated by flash column chromatography, and were both converted to **13** via desilylation, oxidation, and HWE olefination. Achmatowiz reaction[12] of **13** followed by Jones oxidation afforded 2*H*-pyran-2,5-dione **15**. Upon treatment of catalytic amount of dicyclohexylmethylamine in *tert*-butyl alcohol, both **15a** and **15b** underwent DA reaction rapidly at room temperature (20 h) and afforded the same *endo* isomer (**17**) as the only product in very good yields (70−71%). The high selectivity of the base-catalyzed DA reaction could be rationalized by the chairlike conformation of intermediate **16**.

(14) The NOESY spectrum of **9b** is available in the Supporting Information.

(15) The crystallographic data for **10** is available in the Supporting Information.

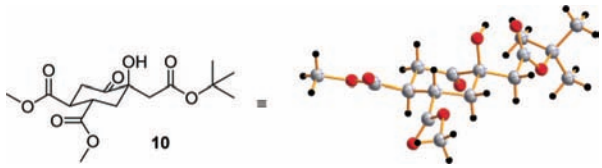
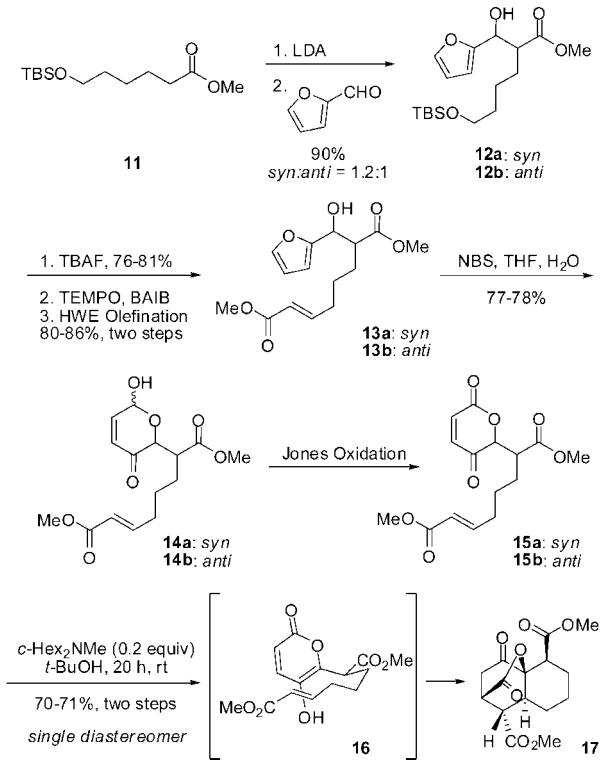


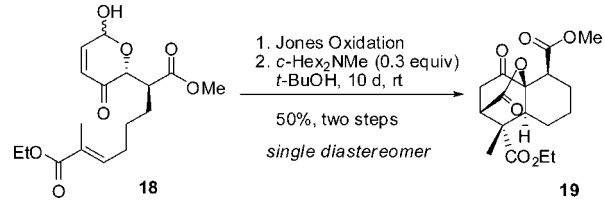
Figure 2. X-ray crystallography of **10**.

The base-catalyzed DA reaction of 2*H*-pyran-2,5-dione with a trisubstitutied acrylate was also investigated. As shown in Scheme 4, Jones oxidation of **18** gave the 2*H*-pyran-2,5-dione, which was submitted to a catalytic amount of dicyclohexylmethylamine in *tert*-butyl alcohol. Although the DA reaction required a long reaction time (10 days) at room temperature, this condition afforded the *endo* product (**19**) in good yields (50% for two steps). The DA product (**19**) was also found to be a single diastereomer. The structures of **17** and **19** were characterized unambiguously using NMR experiments.[16]

Scheme 3. Model Study of the Base-Catalyzed DA Reaction Approach to the Tricyclic Core of **1**



Scheme 4. Base-Catalyzed DA Reaction Approach to the Tricyclic Core of **1**



In summary, a new class of base-catalyzed DA reactions of 2*H*-pyran-2,5-diones has been developed. Various base/solvent systems have been studied. The triethylamine/isopropyl alcohol system provided the DA products with yields up to 70%, and the dicyclohexylmethylamine/*tert*-butyl alcohol system afforded the DA products with the highest *endo* selectivity. This method has been successfully demonstrated to be a mild and efficient reaction to establish the tricyclic core of basiliolide B with good yields and exclusively *endo* selectivity. We are currently exploring the scope of the base-catalyzed DA reaction and are developing an efficient synthetic entry to the basiliolides base on the DA reaction approach.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The NOESY spectra of **17** and **19** are available in the Supporting Information.