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Synthesis and Diels-Alder reactions of novel styrylcyclohexenol dienes: a general pathway for the synthesis of tricyclic lactone and octahydronaphthalene systems

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Synthesis and Diels-Alder reactions of novel styrylcyclohexenol dienes: a general pathway for the synthesis of tricyclic lactone and octahydronaphthalene systems

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ABSTRACT

A series of novel (*E*)-5,5-dimethyl-3-styrylcyclohex-2-en-1-ol dienes were synthesized by reduction of the respective ketones and their Diels-Alder reactivity explored with *N*-phenylmaleimide and methyl acrylate. Consequently, two groups of novel products were synthesized in high yields. In reactions with *N*-phenylmaleimide, the initially formed cycloadducts undergo an additional *in situ* lactonization to give tricyclic lactone systems, due to spontaneous attack of the allylic hydroxyl on the neighboring carbonyl group of the dienophile residue. All reactions proceeded stereoselectively to give solely the *endo* products.

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The Diels-Alder (DA) reaction,¹ which generates six-membered rings with up to four stereogenic centers in a single step with predictable regio- and stereoselectivity,² has arguably become the most important synthetic transformation in organic chemistry. As a consequence, the DA cycloaddition has had a significant impact on organic chemistry as the key step in the synthesis of numerous natural products,³ pharmaceuticals,⁴ industrial materials,⁵ and libraries of important compounds.⁶ The development of several variants including hetero-,⁷ intramolecular,⁸ transannular,⁹ catalytic asymmetric,¹⁰ temporary tethered,¹¹ and self-assembled¹² DA cycloadditions have also considerably broadened the scope of the process.

Tricyclic lactone moieties with three consecutive stereogenic centers (**A**, Fig. 1) are a group of polycyclic fused lactones found in the structures of natural products and biologically active compounds.¹³ In many reports for the total synthesis of target molecules having such lactones in their structures, a DA cycloaddition serves as the key reaction step. Myrocin C, isolated from a soil fungus and possessing antibacterial, antifungal, and antitumor properties, was synthesized in racemic form¹⁴ using an intermolecular DA reaction. In another approach toward the synthetic study of tetracyclic myrocin analogues, the lactone fused-tricyclic ring was synthesized *via* an intramolecular DA reaction of a propionate containing triene.¹⁵ These lactones are also key intermediates in the synthesis of other multicyclic natural products such as forskolin.¹⁶ In the synthesis of ochromycinone, the DA reaction between maleic anhydride and a vinylcyclohexenol diene led to the successful synthesis of a

racemic tricyclic lactone synthon.¹⁷ Other closely related studies include the stereoselective hydroxy-controlled DA reaction of a diene with various dienophiles¹⁸ and an investigation towards the total synthesis of tetrangomycin.¹⁹

In the framework of our investigations on aldol condensation reactions,²⁰ we have reported the synthesis of several styrylcyclohex-2-enone dienes **1** through the aldol condensation of isophorone with aldehydes.²¹ The dienes **1** were then studied

Figure 1. Important natural products containing or related to the tricyclic lactone moiety.

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Scheme 1 Synthesis and DA reactions of dienols **2**

in the DA cycloaddition with various dienophiles.²² As part of these studies, we have continued to explore this chemistry using the hydroxyl equivalents of these dienes (Scheme 1). Thus, we herein report the results of this investigation towards the synthesis of novel tricyclic lactones **4** and octahydronaphthalenes **5** as a consequence of the reactions of **2** with *N*-phenylmaleimide (NPM) and methyl acrylate (MAC), respectively.

The NaBH₄ reduction of **1** in an aqueous/ethanolic solvent at room temperature gave dienols **2a–j** bearing various substituents with different electronic natures (Table 1). All reactions proceeded efficiently and the products were obtained as solids which were purified *via* recrystallization from petroleum ether.

Subsequently, the phenyl substituted diene **2a** was used for optimization of the cycloaddition reaction with NPM (Table 2). A mixture of the two reactants at room temperature in toluene gave no product after 48 h and the starting materials were recovered (Entry 1). When the reaction mixture was heated at reflux, **4a** was obtained in 92% yield after 8 h (Entry 2). Alternatively, cycloaddition in MeCN gave 75% of **4a** after the same time interval (Entry 3), while in CH₂Cl₂ (Entry 4) only a low yield of **4a** was obtained.

Table 1. Synthesis of dienols **2a–j** from ketones **1**

Entry	Ar	Product ^a	Yield (%) ^b
1	C ₆ H ₅	2a	90
2	4-MeC ₆ H ₄	2b	90
3	3-MeC ₆ H ₄	2c	87
4	2,4-(MeO) ₂ C ₆ H ₃	2d	88
5	4-MeOC ₆ H ₄	2e	87
6	2,4,5-(MeO) ₃ C ₆ H ₂	2f	84
7	4-ClC ₆ H ₄	2g	84
8	2-naphthyl	2h	82
9	2-thienyl	2i	84
10	2,4-Me ₂ C ₆ H ₃	2j	85

^a Reagents and conditions: **1** (4.0 mmol), NaBH₄ (6.0 mmol), H₂O/EtOH (1:5, 12 mL), rt, 2 d.

^b Isolated yields.

Table 2. Optimization of the conditions for the synthesis of **4a**

Entry	Conditions ^a	Time (h)	Yield (%) ^b
1	PhMe/rt	48	0
2	PhMe/reflux	8	92
3	CH ₃ CN/reflux	8	75
4	CH ₂ Cl ₂ /reflux	8	10
5	MgBr ₂ ·OEt ₂ /PhMe/rt	0.5	0 ^c
6	MgBr ₂ ·OEt ₂ /NEt ₃ /PhMe/rt	8	85
7	MgBr ₂ ·OEt ₂ /NEt ₃ /PhMe/50 °C	1.5	92
8	MgBr ₂ ·OEt ₂ /NEt ₃ /PhMe/reflux	0.5	93
9	MgBr ₂ ·OEt ₂ ^d /NEt ₃ /PhMe/reflux	1.5	90
10	MgBr ₂ ·OEt ₂ ^d /NEt ₃ /PhMe/rt	8	55
11	MgBr ₂ ·OEt ₂ ^e /NEt ₃ /PhMe/reflux	8	90
12	MgBr ₂ ·OEt ₂ /NEt ₃ /CH ₂ Cl ₂ /rt	8	70
13	MgBr ₂ ·OEt ₂ ^d /NEt ₃ /CH ₂ Cl ₂ /rt	24	40
14	SnCl ₄ ^d /CH ₂ Cl ₂ /rt	24	0 ^c
15	TiCl ₄ ^d /CH ₂ Cl ₂ /rt	24	0 ^c
16	LiClO ₄ ^d /CH ₂ Cl ₂ /rt	24	0 ^c
17	AlCl ₃ ^d /CH ₂ Cl ₂ /rt	24	0 ^c

^a Reagents and conditions: **2a** (1.0 mmol), NPM (1.1 mmol), NEt₃ (2.0 mmol), catalyst (1.0 mmol), solvent (4 mL).

^b Isolated yields.

^c Diene decomposition.

^d 0.50 mmol of catalyst.

^e 0.25 mmol of catalyst.

Several Lewis acids were used to increase the reaction rate. With MgBr₂·OEt₂, rapid decomposition of the starting dienol was observed (Entry 5). The decomposition of dienes possessing allylic hydroxy groups in the presence of Lewis acids has precedence²³ and can be attributed to the facile formation of allylic carbocations and thus undesired polymerization. Therefore, triethylamine (NEt₃) was added to the reaction mixture.²⁴ As a result, the reaction improved considerably giving 85% of the cycloadduct after 8 h (Entry 6). The reaction was further improved and gave **4a** (92–93%) in shorter times using higher temperatures (Entries 7, 8). Use of substoichiometric amounts of the Lewis acid prolonged the time and lowered the reaction efficiency (Entries 9–11). Similarly, alteration of the solvent or the Lewis acid (Entries 12–17) did not further improve the conditions.

The optimum conditions (Table 2, Entries 6 and 9) were then used to evaluate the generality of the cycloaddition process by reacting different dienes **2** with NPM (Table 3). Besides the phenyl substituted diene (Entries 1, 2), the reactions of electron donating (Entries 3–12), electron withdrawing (Entries 13, 14), 2-naphthyl (Entries 15, 16), and heterocyclic (Entries 17, 18) substituted dienes proceeded equally well and gave high yields of the respective products within 6–10 h at room temperature (or 1–2 h at reflux). Under both room temperature and reflux conditions, only a single *endo* adduct was obtained out of four possible products illustrating the high stereoselectivity of the process. In

all cases the formation of the lactones was observed as the final product and **3** was not isolated from the mixtures.

The structure of the adducts was assigned based on spectral data. In the IR spectra, the NH, lactone, and amide C=O bands were diagnostic, while the ^1H NMR spectroscopy showed the presence of a vinylic proton and five single C-H protons corresponding to the five consecutive adjacent stereogenic carbons. Additionally, in the ^{13}C NMR spectrum, two signals at ~ 178 and ~ 170 ppm corresponded to the lactone and amide carbonyls, respectively. In order to confirm the stereochemistry of the products, single crystal X-ray was used to analyze compound **4a**.²⁵ As depicted in Figure 2, **4a** possesses an *endo* structure, where the lactone is formed at the expense of the imide ring.

Figure 2. Single crystal X-ray structure of compound **4a**, (thermal ellipsoids set at the 40% probability level). Selected bond lengths [Å] and angles [°]: C1-O2 1.211(3), C1-O1 1.343(4), C12-N1 1.341(4), O2-C1-O1 121.0(3), O3-C12-N1 123.1(4).

To further explore the scope of the process, we next studied the diene cycloaddition with the singly activated dienophile MAC. Dienol **2a** was again chosen as the model reaction (Table 4). At room temperature no product was obtained after 22 h in toluene (Entry 1). However, the reaction mixture in toluene at reflux gave 30% of **5a** after 72 h (Entry 2). The outcome worsened when $\text{MgBr}_2\cdot\text{OEt}_2$ was added to catalyse the reaction (Entry 3), and decomposition of the reactants was observed. Addition of NEt_3 to the reaction mixture improved the outcome (Entries 4, 5), but the enhancement was more significant when excess $\text{MgBr}_2\cdot\text{OEt}_2$ was used. As a result, the optimum conditions were obtained when the reaction was conducted in the presence of $\text{MgBr}_2\cdot\text{OEt}_2/\text{NEt}_3$ giving 76% of cycloadduct **5a** (Entry 6).

Table 3. DA reactions of **2** with NPM to produce **4**

Entry	Ar	Product	Time (h)	Yield (%) ^a
1	C ₆ H ₅	4a	8 ^b	85
2	C ₆ H ₅	4a	1.5 ^c	90
3	4-MeC ₆ H ₄	4b	8 ^b	90
4	4-MeC ₆ H ₄	4b	1.5 ^c	88
5	3-MeC ₆ H ₄	4c	8 ^b	89
6	3-MeC ₆ H ₄	4c	1.5 ^c	89
7	2,4-(MeO) ₂ C ₆ H ₃	4d	6 ^b	93

8	2,4-(MeO) ₂ C ₆ H ₃	4d	1 ^c	90
9	4-MeOC ₆ H ₄	4e	8 ^b	90
10	4-MeOC ₆ H ₄	4e	1.5 ^c	90
11	2,4,5-(MeO) ₃ C ₆ H ₂	4f	6 ^b	93
12	2,4,5-(MeO) ₃ C ₆ H ₂	4f	1 ^c	89
13	4-ClC ₆ H ₄	4g	10 ^b	86
14	4-ClC ₆ H ₄	4g	2 ^c	87
15	2-naphthyl	4h	8 ^b	92
16	2-naphthyl	4h	1.5 ^c	90
17	2-thienyl	4i	8 ^b	92
18	2-thienyl	4i	1.5 ^c	91

^a Isolated yields.

^b Reagents and conditions: **2** (1.0 mmol), NPM (1.1 mmol), NEt_3 (2.0 mmol), $\text{MgBr}_2\cdot\text{OEt}_2$ (1.0 mmol), PhMe (4 mL), rt.

^c Reagents and conditions: **2** (1.0 mmol), NPM (1.1 mmol), NEt_3 (2.0 mmol), $\text{MgBr}_2\cdot\text{OEt}_2$ (0.5 mmol), PhMe (4 mL), reflux.

Under the optimized conditions, electron rich and electron deficient dienes reacted with MAC equally well to produce the respective adducts within 18–24 h (Table 5, Entries 1–6). Similarly, the 2-thienyl substituted diene underwent cycloaddition with MAC to give 76% of **5i** (Entry 7). In all cases, the reactions led stereoselectively to the formation of a single *endo*-isomer out of eight possible diastereomers. Similarly, the structures of products **5** was determined based on their spectral properties. Additionally, single crystal X-ray experiments clearly supported the formation of the *endo* adducts (Fig. 3).²⁵

Table 4. Optimization of the reaction conditions for the synthesis of **5a**

Entry	Conditions ^a	Temp. (°C)	Time (h)	Yield (%) ^b
1	-	rt	22	0
2	-	reflux	72	30
3	$\text{MgBr}_2\cdot\text{OEt}_2$	rt	0.5	0 ^c
4	$\text{MgBr}_2\cdot\text{OEt}_2$, NEt_3 ^d	rt	22	5
5	$\text{MgBr}_2\cdot\text{OEt}_2$, NEt_3 ^d	reflux	22	20
6	$\text{MgBr}_2\cdot\text{OEt}_2$, NEt_3	reflux	22	76

^a Reagents and conditions: **2a** (1.0 mmol), MAC (2.0 mmol), NEt_3 (4.0 mmol), $\text{MgBr}_2\cdot\text{OEt}_2$ (2.0 mmol), PhMe (4 mL).

^b GC yields.

^c Diene decomposition.

^d NEt_3 (1.0 mmol), $\text{MgBr}_2\cdot\text{OEt}_2$ (1.0 mmol).

Table 5. DA reactions of **2** with MAC to produce **5**

Reaction scheme for Table 5: A substituted cyclohexadiene (2) with a hydroxyl group and an allyl group (Ar) reacts with MAC (2 equiv.) and $\text{MgBr}_2 \cdot \text{OEt}_2$ / NEt_3 to form a bicyclic product (5) with a hydroxyl group, a methyl ester group (CO_2Me), and an allyl group (Ar). The product is labeled (±) 5.

Entry	Diene	Ar	Product	Time (h)	Yield (%) ^{a,b}
1	2a	C_6H_5	5a	21	76

2	2b	4-MeC ₆ H ₄	5b	19	78
3	2j	2,4-Me ₂ C ₆ H ₃	5j	19	80
4	2e	4-MeOC ₆ H ₄	5e	19	80
5	2f	2,4,5-(MeO) ₃ C ₆ H ₂	5f	18	82
6	2g	4-ClC ₆ H ₄	5g	24	72
7	2i	2-thienyl	5i	21	76

^a Isolated yields.

^b Reagents and conditions: **2** (1.0 mmol), MAC (2.0 mmol), NEt₃ (4.0 mmol), MgBr₂·OEt₂ (2.0 mmol), PhMe (4 mL), reflux.

Figure 3. Single crystal X-ray structure of compound **5f**, (thermal ellipsoids set at the 40% probability level). Selected bond lengths [Å] and angles [°]: O1-C1 1.325(3), O2-C1 1.208(3), O6-C16 1.417(3), O4-C8 1.373(3), C5-O3-C6 118.4(2), C1-O1-C23 115.7(3).

Based on these results, it appeared that no transient intramolecular participation by the OH group would intervene to direct the selectivity of the process, at least for the reaction between MAC and **2**. The dominant “*endo* OH” transition state which was previously reported by Ward and co-workers^{12b} and Barriault and co-workers¹⁸ for the reactions of MAC with dienols, is interrupted by the strong regioselectivity of the process which prefers the “*endo* Ar” transition state due to the directing effects of the substituents on **2**. However, the OH intervention might be responsible to some extent for the reaction with NPM during the cycloaddition or in the final lactonization step (Fig. 4).

Figure 4. Plausible transition states.

Conclusion

In summary, we have succeeded in the synthesis of a new series of tricyclic lactone and octahydronaphthalene derivatives *via* the reactions of dienols with NPM and MAC, respectively. The reactions exclusively take place giving *endo* adducts in high yields. Attempts to develop an intramolecular version of the process and to obtain the opposite regioadducts from the same reactants are in progress.

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25. CCDC-1481911 and CCDC-1481912 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.