This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Lactone-fused cyclohexadiene as versatile platform for diversified synthesis of 5,6,5-tricyclic scaffolds

M. Shibuya, T. Sudoh, T. Kawamura and Y. Yamamoto

A lactone-fused cyclohexadiene, which can be readily prepared by the ruthenium(III)-catalyzed [2 + 2 + 2] cyclization of an enediyne, functioned as a versatile platform for the stereoselective synthesis of differently functionalized 5,6,5-tricyclic scaffolds.

The 5,6,5-tricyclic lactone scaffold has been found in natural products such as anticancer agent pleurotin,1 diterpene glycoside farnesiaside,2 and seco-prezizaane-type sesquiterpenes.3 In particular, the last family consists of diversely oxygenated congeners, some of which display neurotrophic activity, such as jiadifenin, jiadifenolide, and jiadienoxolane A (Figure 1).4 Owing to these attractive properties, considerable efforts have been devoted to the syntheses of these highly intriguing molecules.5 Notably, some of the intermediates with structures simpler than the parent natural products exhibit more potent neurotrophic activities.6,7 This fact suggests that the diversified synthesis of relevant small molecules ultimately leads to the formation of a novel neurotropic modulator. Herein, we report our study along this line on the facile access to differently functionalized 5,6,5-tricyclic lactone scaffolds using a lactone-fused cyclohexadiene as a versatile platform. Generally, the basic 5,6,5-tricyclic lactone framework is constructed in a stepwise manner.8 However, we envisaged that the transition-metal-catalyzed [2 + 2 + 2] cyclization of enediyne 1 possessing a propiolate moiety provides straightforward access to the desired lactone-fused cyclohexadiene platform 2, which can be further transformed into diverse scaffolds (Scheme 1). To the best of our knowledge, the transition-metal-catalyzed [2 + 2 + 2] cyclization approach to 5,6,5-tricyclic lactone systems relevant to the abovementioned natural products has not been reported thus far.9

To realize this strategically new approach to polycyclic lactone natural products, it would be highly beneficial to investigate the reactivity profile of lactone-fused cyclohexadiene 2. Herein, we disclose the results of our study along this line on the synthesis of tricyclic lactone-fused cyclohexadienes and their reactivity and selectivity toward diverse transformations.

To this aim, we investigated the synthesis of model compounds 2 with a tetrahydrofuran ring (X = O) because ether-tethered enediyne 1 (X = O) is readily prepared. In the presence of 5 mol% Cp*RuCl(cod) (Cp* = η^5-pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene), 1 (X = O, R = H) underwent cyclization even at room temperature in 1,2-dichloroethane. However, a complex mixture of products was formed due to extensive isomerizations of the cyclohexadiene moiety, resulting in detection of a trace amount of 2. Thus, methallyl analog 1a was subjected to the same reaction conditions to afford the desired cycloadduct 2a as a sole product in 82% yield (Scheme 1).8

Previously, it was found that [Cp*RuCl2], which is the precursor of Cp*RuCl(cod), effectively catalysed the cycloaddition of 1,6-diynes with 3,4-dihydrofuran.8a Therefore, the cyclization of 1a was...
performed with 1.5 mol% (3 mol% Ru) [Cp*RuCl₂]₂ at room temperature for 1.5 h, affording 2a in 85% yield. Using this procedure, the cyclization of 1a could be carried out in 1.9 g scale, affording 2a in 88% yield.

Having obtained the desired platform 2a, its transformation was investigated, with particular focus on the introduction of oxygen functionalities (Scheme 2). Thus, 2a was treated with dimethyldioxirane (DMDO) in THF at ~30 °C to selectively afford epoxide 3 in 51% yield. The osmium-catalyzed dihydroxylation of 2a in aqueous THF at room temperature also afforded cis diol 4 in 88% yield. Furthermore, the copper-catalyzed conjugate borylation of 2a was conducted according to the report by Yun and coworkers. After the oxidation of the crude product with NaBO₃, hydroxybutenolide 5 was obtained in 67% yield as a result of concomitant alkene transposition. All these reactions proceeded regioselectively at the electron-deficient alkene in such a way that the epoxy and hydroxyl groups were introduced cis to the angular methyl substituent, as evidenced by X-ray crystallographic analyses.

These reactions took place from the convex face of 2a due to the axially oriented protons hampering the approach from the concave face (Figure 2). Moreover, the tetrasubstituted olefin moiety is rather unreactive because of steric congestion due to the angular methyl substituent, although electrophilic epoxidation and dihydroxylation are expected to occur more electron-rich olefin rather than electron-deficient olefin.

Next, the Diels–Alder (DA) reaction with singlet oxygen was examined, as shown in Scheme 3. In the presence of 1 mol % rose bengal, 2a was irradiated in ethanol at room temperature under O₂, affording endoperoxide 6 as a single stereoisomer in 65% yield. Upon treatment with thiourea in methanol, the crude 6 was also directly converted to diol 7 in 83% overall yield. Previously, Jones and Snyder have reported the DA reaction of a related 5,6,5-tricyclic cyclohexadiene with singlet oxygen. In their study, the corresponding endoperoxide was obtained as a 13:1 diastereomeric mixture in 37% yield with 70% conversion. From the above observations, 2a has distinctly high reactivity and stereoselectivity, although its 1,3-diene moiety is electronically deactivated by the lactone carbonyl group (vide infra). The DA reaction of 2a with tert-butyl nitrosoformate, which was generated in situ by the oxidation of N-Boc hydroxylamine, also proceeded under mild conditions to selectively afford 8 in 80% yield as the sole product. The N–O bond cleavage of 8 using Mo(CO)₆ in refluxing aqueous acetonitrile under irradiation also afforded cis amino alcohol 9 in 73% yield. The stereochemistry of these hetero-DA reactions was unambiguously confirmed by the X-ray crystallographic analysis of 6 and 8, revealing that the DA reaction occurs from the face opposite to the angular methyl substituent.

As abovementioned, 2a exhibited superior DA reactivity to the relevant tricyclic diene, which was previously used by the Snyder group, although 2a must be deactivated by the electron-withdrawing carbonyl group. The facial selectivity opposite to those of other reactions presented in Scheme 2 is also intriguing. However, there has been no report on the detailed study disclosing the facial selectivity and structure-activity relationship of tricyclic cyclohexadienes. To investigate the DA reactivity in more detail, various 5,6,5-tricyclic compounds were prepared using the ruthenium-catalyzed cyclization and their DA reactivity toward N-phenyltriazolinedione (10a) and N-phenylmaleimide (10b) was compared (Figure 3). When 2a was treated with 10a in toluene at room temperature for 0.5 h, endo-cycloadduct 11a was obtained in 95% yield. The stereochemistry of 11aa was unambiguously confirmed by X-ray crystallography. In contrast, the reaction with the less reactive dienophile 10b required an elevated temperature: refluxing a solution of 2a and 10b in toluene for 6 h afforded 11ab in 83% yield.
Cyclohexadienes 12a and 12b, which have no lactone carbonyl group, were prepared in high yields by treating the corresponding enediynes with the ruthenium catalyst (1.5 mol%) at room temperature. The cycloaddition of 12a with 10a and 10b proceeded at room temperature for 0.5 h or in refluxing toluene for 6 h, affording the corresponding cycloadducts 13aa and 13ab in 92% and 76% yields, respectively. In striking contrast, the DA reaction of ester-substituted analog 12b with 10a took 1 h for completion, although 13ba was obtained in a comparably high yield of 95%. Moreover, the reaction with less reactive dienophile 10b was incomplete even after refluxing for 6 h, affording 13bb in 7% yield along with the recovery of 12b (78%). These results imply that 2a is significantly superior to 12b as the DA substrate, although both cyclohexadienes are deactivated by the conjugated carbonyl groups.

To gain further insights into the selectivity and reactivity of the 5,6,5-tricyclic compounds for the DA reaction, DFT calculations were performed using the PCM (toluene) M06-2X/6-31+G(d,p)//M06-2X/6-31G(d) method (see ESI for details). First, the activation energies of the four transition states (TSs) for the DA reactions of 2a with maleimide (10c) as a model dienophile were estimated (Figure 4). As a result, the TSs for cycloaddition from the face opposite to the angular methyl substituent (TS1 and TS2) were located 6.8 and 9.2 kcal/mol lower than the corresponding syn TSs (TS3 and TS4), respectively. The most favorable anti-endo TS (TS1) was located 6.4 kcal/mol lower than the anti-exo TS (TS2). On the other hand, the syn-endo product was 1.8 kcal/mol more stable than the anti-endo product, indicating that the latter is a kinetic product. These results qualitatively agree with the experimentally observed product selectivity, with the exclusive formation of anti-endo products.

Next, the free energies of activation and reaction (ΔG° and ΔG°‡) for the DA reactions of 2b and 2c as well as other model lactones 2a and 2c were compared in terms of the anti-endo cycloaddition with 10c (Table 1, for structures of 2b and 2c, see Figure 1). The HOMO energies of 2b and 2a (−8.1 and −8.3 eV, respectively) were higher than those of other cyclohexadienes (−8.8 to −8.6 eV). The smallest ΔG° (24.4 kcal/mol) was estimated for 12a. On the other hand, ΔG°‡ calculated for lactone-fused cyclohexadienes 2a and 2c, which have the lowest HOMO energies of −8.8 eV, were around 25 kcal/mol, values of which are only slightly higher than that for 12a. The highest ΔG° of 29.7 kcal/mol was calculated for lactone 2b, which has a phenyl group similar to the relevant cyclohexadiene of Jones and Snyder. Moreover, a similarly high ΔG° value of 28.9 kcal/mol was estimated for ester-substituted cyclohexadiene 12b, although its HOMO energy (−8.6 eV) was 0.2 eV higher than those of 2a and 2c. Therefore, the DA reactivity trend cannot be explained only by the HOMO energy levels of these compounds. In addition, there was no correlation between ΔG°‡ and ΔG°.
Distortion analysis was applied to the DA reactions of the 5,6,5-tricycles to understand the structure-reactivity relationship. Houk's group has successfully introduced this method to estimate the degree of distortion in the TSs, which significantly contributes to the activation energy in the DA reactions involving strained cycloalkenes.\textsuperscript{10} According to their study, each transition structure was separated into cyclohexadiene and dienophile fragments, and single-point energy calculations were performed for each fragment to obtain the distortion energies $\Delta E_{\text{dist,all}}^{\alpha}$ and $\Delta E_{\text{dist,2e}}^{\alpha}$, respectively. The total distortion energy $\Delta E_{\text{dist,all}}^{\alpha}$ is the sum of $\Delta E_{\text{dist,all}}^{\alpha}$ and $\Delta E_{\text{dist,2e}}^{\alpha}$. The distortion energies of the diene fragment ($\Delta E_{\text{dist,all}}^{\alpha}$) ranged from 21.0 to 26.5 kcal/mol, while those of dienophile ($\Delta E_{\text{dist,2e}}^{\alpha}$) ranged from 7.3 to 9.4 kcal/mol (Table S5 in ESI). From these values, the former significantly affects the reactivity trend.

Among 5,6,5-tricycles, 12a without a conjugated carbonyl group exhibited the smallest $\Delta E_{\text{act}}^{\alpha}$ (4.5 kcal/mol), while other lactone-fused cyclohexadienes 2a–c exhibited larger $\Delta E_{\text{act}}^{\alpha}$ values (5.7–10.3 kcal/mol). However, the $\Delta E_{\text{dist,all}}^{\alpha}$ of 2a and 2c (28.5 and 28.7 kcal/mol, respectively) was smaller than that of 12a (31.4 kcal/mol). Thus, the negative effect of a larger $\Delta E_{\text{act}}^{\alpha}$ value is partially lessened by a smaller $\Delta E_{\text{dist,all}}^{\alpha}$ value in the reactions of 2a and 2c. In good accordance with this analysis, $\Delta G$ for 2a and 2c were only slightly (0.5±0.8 kcal/mol) higher than that for 12a. In contrast, the $\Delta E_{\text{dist,all}}^{\alpha}$ of 12b was the highest of all (35.5 kcal/mol), although its $\Delta E_{\text{act}}^{\alpha}$ of 6.4 kcal/mol was comparable to those of 2a and 2c. Consequently, 12b was expected to be a less efficient substrate as its $\Delta G^{\ddagger}$ (28.9 kcal/mol) was the second highest among others. This result is reasonable because the ester substituent of 12b not only decreases the HOMO energy but also increases the distortion energy. Similarly, the phenyl substituent $\beta$ to the carbonyl group in 2b increased $\Delta E_{\text{dist,all}}^{\alpha}$ by 5.8 kcal/mol compared with that of 2a, and this high $\Delta E_{\text{dist,all}}^{\alpha}$ surpasses the favorable HOMO energy. Accordingly, $\Delta G^{\ddagger}$ increased from 24.9 kcal/mol for 2a to 29.7 kcal/mol for 2b.

To confirm the theoretically expected reactivity trend, cyclohexadienes 2b–d were newly prepared in good yields by the Ru(III)-catalyzed cycloaddition and subjected to the DA reaction with triazolinodione 10a (Table 1). The standard cyclization method was applied to the synthesis of 2c, while 2b and 2d were obtained in high yields by performing cycloadditions with increased amounts of the catalyst at elevated temperatures (5 mol%, 80 °C or 10 mol%, 60 °C, respectively). The DA reactions of these cyclohexadienes with 10a were performed in acetone at room temperature for 30 min to afford the corresponding cycloadducts 11ba, 11ca, and 11da in high yields. To estimate the relative reactivity of the cyclohexadienes, a series of competition experiments were then performed. A 1:1:1 mixture of 2a, 12a, and 10a was stirred in toluene at 0 °C for 1 h. The $^1$H NMR analysis of the crude reaction mixture indicated that the ratio of the remaining substrates was 2a:12a:10a = 67:33 and that of products was 11ba:11ca:11da = 24:76. Therefore, the rate of DA reaction was approximately 3 times faster for 12a than for 2a. The difference in activation barriers inferred from this experiment was ca. 0.5 kcal/mol, which is similar to the calculated value by the DFT method (0.3 kcal/mol, Scheme 4).

The competition reaction of 2a and 2c showed that the latter has slightly higher reactivity as the ratios of the remaining substrates and the DA adducts were 2a:2c = 56:44 and 11ba:11ca = 42:58, respectively. In contrast, the competition reactions of 2a with 2b or 12b exclusively afforded 11ba. Moreover, the competition reaction of 2a and 2d was similarly performed in acetone at 0 °C for 1 h. As a result, 2d was found to be superior to 2a as the ratio of the remaining substrates was 2a:2d = 67:33 and that of products was 11aa:11da = 30:70. Finally, the competition reaction of 2d and 12a revealed that the latter is still more reactive as the ratios of the remaining substrates and the DA adducts were 2d:12a = 71:39 and 11da:13aa = 34:66, respectively. From these results, the order of the reactivity was estimated as 12a > 2d > 2c ≥ 2a ≫ 2b,12b. This reactivity trend is qualitatively consistent with that expected by computational results.

Conclusions

Table 1 Calculated parameters for Diels–Alder reactions of 2a–d and 12a,b with 10a.\textsuperscript{4}

<table>
<thead>
<tr>
<th></th>
<th>HOMO</th>
<th>$\Delta G^{\ddagger}$</th>
<th>$\Delta G_{\text{act}}^{\alpha}$</th>
<th>$\Delta E_{\text{dist,all}}^{\alpha}$</th>
<th>$\Delta E_{\text{dist,2e}}^{\alpha}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-8.8</td>
<td>24.9</td>
<td>-22.4</td>
<td>5.7</td>
<td>21.2</td>
</tr>
<tr>
<td>2b</td>
<td>-8.1</td>
<td>29.7</td>
<td>-16.1</td>
<td>10.3</td>
<td>24.9</td>
</tr>
<tr>
<td>2c</td>
<td>-8.8</td>
<td>25.2</td>
<td>-21.1</td>
<td>6.3</td>
<td>21.0</td>
</tr>
<tr>
<td>2d</td>
<td>-8.7</td>
<td>23.5</td>
<td>-23.0</td>
<td>5.5</td>
<td>19.4</td>
</tr>
<tr>
<td>12a</td>
<td>-8.3</td>
<td>24.4</td>
<td>-20.6</td>
<td>4.5</td>
<td>23.3</td>
</tr>
<tr>
<td>12b</td>
<td>-8.6</td>
<td>28.9</td>
<td>-15.2</td>
<td>6.4</td>
<td>26.5</td>
</tr>
</tbody>
</table>

*HOMO and other energies are given in eV and kcal/mol, respectively.

\textsuperscript{4}The competition reaction of 2a and 2c showed that the latter has slightly higher reactivity as the ratios of the remaining substrates and the DA adducts were 2a:2c = 56:44 and 11ba:11ca = 42:58, respectively. In contrast, the competition reactions of 2a with 2b or 12b exclusively afforded 11ba. Moreover, the competition reaction of 2a and 2d was similarly performed in acetone at 0 °C for 1 h. As a result, 2d was found to be superior to 2a as the ratio of the remaining substrates was 2a:2d = 67:33 and that of products was 11aa:11da = 30:70. Finally, the competition reaction of 2d and 12a revealed that the latter is still more reactive as the ratios of the remaining substrates and the DA adducts were 2d:12a = 71:39 and 11da:13aa = 34:66, respectively. From these results, the order of the reactivity was estimated as 12a > 2d > 2c ≥ 2a ≫ 2b,12b. This reactivity trend is qualitatively consistent with that expected by computational results.
In conclusion, we synthesized lactone-fused cyclohexadiene 2a in a gram scale by the Ru(III)-catalyzed [2 + 2 + 2] cyclization of enediyne 1a containing propiolate and methallyl moieties. The versatility of 2a as a synthetic platform was demonstrated by its regio- and stereoselective transformations to various 5,6,6-tricyclic lactone scaffolds with oxygen functional groups. Moreover, the exceptional selectivity and reactivity of 2a were also revealed by a combination of computational and experimental investigations on the Diels–Alder reactions of a series of cyclohexadienes.

Acknowledgements

This work was partially supported by Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” and Platform for Drug Discovery, Informatics, and Structural Life Sciences from the Ministry of education, Culture, Sports and Technology, Japan.

Notes and references


