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Photochemical Cycloaddition as a Gateway to Bicyclic Lactones: Toward Tricyclic Iridoid-Inspired Scaffolds

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Abstract

A photochemical [2+2] cycloaddition between cyclopentene-1-one and 1,1-dimethoxyethylene was effectively utilized to synthesize a key bicyclic intermediate in the preparation of tricyclic iridoid-inspired scaffolds. The regioselective outcome of the cycloadduct was confirmed through ^{1}H NMR and subsequent chemical reactivity studies, indicating that the methoxy groups do not occupy positions β to the carbonyl. Following this, hydrolysis of the cycloadduct yielded a diketone in an excellent yield of 85%, which was subsequently subjected to Baeyer-Villiger oxidation, resulting in a fused γ-lactone with a yield of 64%. Structural elucidation of the intermediates and the final product was conducted using NMR, IR, and mass spectrometry techniques. This photochemical synthetic pathway offers a concise approach to bioinspired tricyclic architectures that may hold significance in natural product chemistry and the design of neuroactive compounds.

Keywords

Photochemical Cycloaddition, Bicyclic Lactones, Tricyclic İridoid Scaffold, Baeyer-Villiger Oxidation, Regiochemistry, 1,1-Dimethoxyethylene, Cyclopentenone, Natural Product Synthesis, Spectroscopic Characterization

1. Introduction

This study is part of an ongoing effort to develop synthetic access to bicyclic lactones (AB-ring system) and later tricyclic iridoid lactones, structures that are inherently present in many bioactive secondary metabolites. Among the most notable sources of such compounds is *Verbena littoralis*, a medicinal plant traditionally used across South America to treat diarrhea, typhoid, and tonsillitis. More recently, extracts of *V. littoralis* have been reported to potentiate nerve growth factor (NGF)-induced neurite outgrowth in PC12D cells, suggesting that its iridoid lactone constituents may serve as promising lead structures for neurodegenerative disease research [1] [2].

The key bioactive component littoralisone, a highly oxygenated iridoid lactone, embodies a complex tricyclic lactone scaffold. Such motifs are frequently found in natural products with neurotrophic, anti-inflammatory, and cytoprotective properties [3]. Motivated by their pharmacological potential, our group has previously reported multiple routes for the stereoselective synthesis of bicyclic lactones, including an annelation protocol involving 2-chlorocyclopentanone and diesters [4], and a Lewis acid-mediated ene-reaction strategy utilizing silver triflate as a promoter [5].

In this work, we expand our synthetic toolbox by applying a photochemical [2+2] cycloaddition strategy, specifically the reaction of cyclopentene-1-one with ketene, to access highly functionalized bicyclic lactone cores. This approach offers several synthetic advantages, including mild reaction conditions, minimal byproducts, and high stereocontrol. Photochemical [2+2] cycloadditions of enones and ketenes are well-established for generating strained and reactive bicyclic intermediates, suitable for further derivatization into natural product-inspired scaffolds [6] [7].

As shown in **Figure 1**, this method provides an efficient entry into the target lactone framework while simultaneously enabling ketone functionalization. This feature is particularly important for elaboration toward tricyclic iridoid analogs, positioning this approach as a versatile and practical alternative for accessing neuroactive lactone architectures.

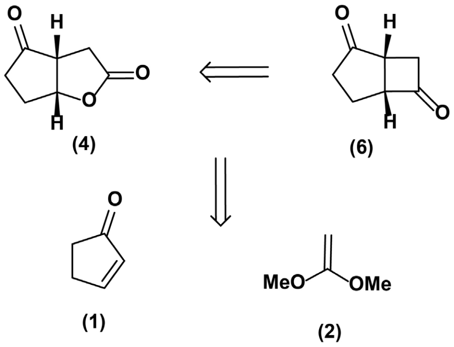
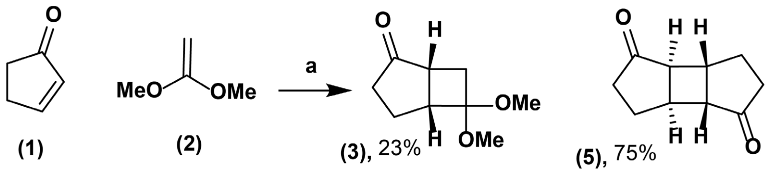


Figure 1. Retro-synthetically guided photochemical [2+2] cycloaddition of cyclopent-2-en-1-one ketene.

The photochemical [2+2] cycloaddition of cyclopent-2-en-1-one with 1,1-dimethoxyethylene, a ketene acetal, was carried out under UV irradiation to produce the corresponding bicyclic cyclobutane adduct. The use of 1,1-dimethoxyethylene serves as a stabilized enol-ether analogue of ketene, offering safer handling while maintaining the reactivity required for photocycloaddition. This approach provides a convenient route to bicyclic lactone intermediates that serve as precursors to iridoid-inspired tricyclic scaffolds. A quick retrosynthetic analysis reveals that replacement of cyclopentadiene with cyclopentene-1-one **(1)** should lead us to AB-ring system **(4)** lacking a side chain. It was hoped the ketone could provide easier functionalization and further elaboration of the bicyclic framework. This strategy in the end finally rewarded us with some success.

2. Results and Discussion

The protocol is depicted in **Figure 1**. 1,1-Dimethoxyethene **(2)** was redistilled twice prior to its photochemical reaction; the ensuing photochemical [2+2] cycloaddition proceeded without any problem and the reaction was quantitative with two products being formed. The cycloadduct **(3)**, thus formed, had a ^{1}H NMR spectrum that displayed methylene protons (dd, *J* 8.8 Hz, centred at 2.49 ppm), two resonances for the methoxy groups (s, 3.18 ppm and 3.16 ppm), and bridgehead protons at 2.68 - 2.49 ppm. The molecular ion peak (MH^+ 171) together with the presence of nine carbons as shown in the ^{13}C NMR bears testimony to a successful [2+2] cycloaddition. The carbonyl stretches at 1735 cm^{-1} together with ^{13}C NMR chemical shifts 221.9 (C=O), 101.3 ($C(OMe)_2$), also provide additional evidence for the formation of **(3).** However, a side product was also isolated. This product **(5)** was characterized by the appearance of a band at 1748 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum showed a two proton multiplet at 3.82-3.65 ppm and a two proton multiplet at 3.39 - 3.15 ppm corresponding to the four methine protons. The molecular ion peak at (MH^+ 164) further showed the undesired adduct to be **(5)** The photochemical [2+2] cycloaddition between cyclopent-2-en-1-one and 1,1-dimethoxyethylene afforded two products: the desired cycloadduct **(3)** in 23% yield and the cyclopentenone photodimer **(5)** as the major product (75%). This outcome suggests that under the present reaction conditions, self-dimerization of cyclopentenone competes strongly with the intended cross-cycloaddition. Such behavior is consistent with literature reports of enone photochemistry, where high substrate concentration or extended irradiation often favors dimer formation. Optimization of reaction parameters, such as lowering the concentration of cyclopentenone, modifying solvent polarity, or using a selective wavelength filter could potentially suppress homodimerization and enhance the formation of the target cycloadduct **(3)**. The side product **(5)** was identified as the known photodimer of cyclopent-2-en-1-one**,** formed through [2 + 2] self-cycloaddition of the enone under UV irradiation. This side reaction competes effectively with the intended cycloaddition, accounting for the high proportion of dimer observed relative to the desired adduct **(3)** (**Figure 2**).

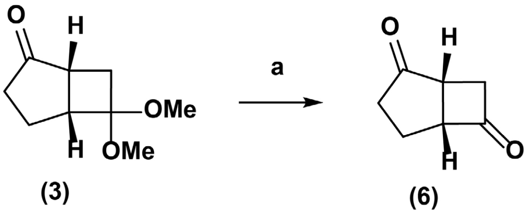


(a) pentane, Rayonet photoreactor

Figure 2. Photochemical [2+2] cycloaddition of cyclopent-2-en-1-one with 1,1-dimethoxyethylene and competing enone photodimerization.

2.1. Regiochemistry of Cycloadduct (3) and Synthesis of Diketone (6)

Corey [8] raised possible problems pertaining to the regiochemistry of cycloadditions involving 1,1-dimethoxyethylene with cycloalkanones. As much as we hoped that the cycloaddition of the cyclopentene-1-one would afford the desired cycloadduct **(3)** there was some uncertainty about the regiochemical outcome of the reaction. However, when the cycloaddition was accomplished ^{1}H NMR studies of the desired product **(3)** revealed that cycloaddition had indeed occurred. Evidence that confirmed the orientation to be of structure **(3)** came from the fact that when the photoadduct was treated with sodium ethoxide in ethanol, we noted a lack of replacement of methoxy by ethoxy, which suggests that the methoxy groups are not β to the carbonyl. The conversion of the cycloadduct **(3)** into the diketone **(6)** was readily achieved by treatment with concentrated hydrochloric acid. The diketone was obtained in high yield (85%). The data obtained for **(6)** were consistent with those published in the literature (**Figure 3**).



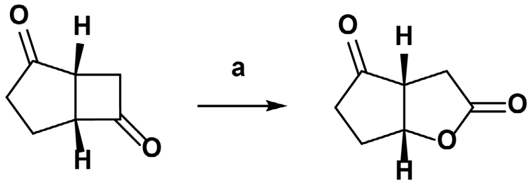
(a) H_2O, THF, conc. HCl, 85%

Figure 3. Regiochemical assignment of cycloadduct (3) and its conversion to diketone (6).

2.2. Ring Expansion of Diketone (6)

The lactone **(4)** was derived from the diketone **(6)** in essentially quantitative yield via Baeyer-Villager oxidation, (acetic acid and H_2O_2) to afford a potentially useful product **(4)**. The ^{1}H NMR spectrum of the lactone was diagnostic, with a single methine proton appearing as a broad triplet at 5.24 ppm (*J* 5.0 Hz), a methine proton as double double doublet at 2.96 ppm (*J* 5.0 and 2.5 Hz), the diastereotopic CH_2 protons adjacent to the ester appeared as a doublet, centred at 2.85 ppm (*J* 10 and 2.5 Hz) and a doublet at 2.78 ppm. The carbonyl stretching at 1751

cm^{-1} and 1737 cm^{-1} are those expected for the γ-lactone **(4)** (Figure 4). "synthetic sequence, from photochemical [2 + 2] cycloaddition to Baeyer-Villiger oxidation—provides a concise route to a bicyclic γ-lactone (4) that serves as a key intermediate for constructing tricyclic iridoid-inspired scaffolds. Future work will focus on intramolecular annelation and selective functionalization of this lactone to access fully elaborated tricyclic frameworks reminiscent of neuroactive natural products".



(6) **(4)**

(a) acetic acid, 27.5% H_2O_2, 64%

Figure 4. Baeyer-Villiger ring expansion of diketone (6) to bicyclic γ-lactone (4).

3. Experimental Techniques

Commercial reagents were obtained from Aldrich and Lancaster chemical suppliers and were used directly as supplied or purified prior to use following the guidelines of Perrin and Amarego [9]. Dichloromethane and acetonitrile were refluxed over and distilled from CaH_2 prior to use. Diethyl ether and ethanol were obtained dry from Aldrich. THF was dried by distillation from the sodium benzophenone ketyl radical under nitrogen. Light petroleum is the fraction of petroleum ether boiling in the range 30-40˚C, and it was fractionally distilled through a 36 cm Vigreux column before use.

Non-aqueous reagents were transferred under argon *via* syringe. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Thin-layer chromatography (TLC) was performed on Merck aluminium-backed plates coated with 0.2 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV fluorescence quenching at 254 nm, or by staining with a $KMnO_4$ solution.

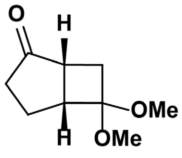
^1H and ^{13}C NMR spectra were recorded on a Bruker DPX250 (250 MHz for protons) and a Brüker AMX400 (400 MHz for protons). Data for ^1H NMR are reported as follows: chemical shift (δ-ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (ppm) down field from TMS.

IR spectra were recorded on a Perkin Elmer Paragon 1000 or a Perkin Elmer 881 spectrometer as a thin film between sodium chloride plates or as a KBr disk. All absorptions are reported in terms of frequency of absorption (cm^{-1}).

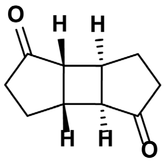
Mass spectrometric data were recorded on VG Autospec, under conditions of chemical ionisation (C.I) using ammonia as the ionising source. Peaks are quoted in the form (*m*/*z*) (relative intensity).

6,6-dimethoxybicyclo[3.2.0]heptan-2-one (6) [10]

***anti*-tricyclo[5.3.0 ^{2,6}]decan-3,8-dione (5)**



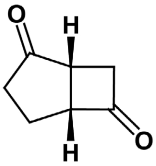
(3)



(5)

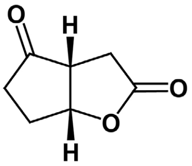
Solution of redistilled cyclopentanone (4.00 g, 48.8 mmol, 1.00 equiv) in pentane (70 mL) was added 1,1-dimethoxy-ethylene (4.30 g, 48.8 mmol, 1.00 equiv) under nitrogen was cooled in a dry ice bath and irradiated using high pressure mercury arc, quartz well, and corex filter in a Rayonet$^{®}$ photoreactor (366 nm) for 3 h. TLC analysis indicated no starting material was present. The solvent was removed *in vacuo,* and the residue was subjected to column chromatography on silica, eluting with hex: ethyl acetate (2:1) to afford **(273)** as a colourless oil (6.1 g, 75%); υ_{max} (thin film/cm^{-1}), 2928, 1718, 1636, 1158; δ_H (250 MHz, $CDCl_3$) 3.82 - 3.65 (2H, m, O=CC**H**=C**H**C=O), 3.39 - 3.15 (2H, m, O=CC**H**=C**H**C=O), 2-86-2.70 (4H, m, C**H$_2$**C=O, C**H$_2$**C=O), 2.52 - 1.99 (4H, m, C**H$_2$**C=O, C**H$_2$**C=O); δ_C (62.5 MHz, $CDCl_3$) 220.1, 49.9, 37.7, 36.5, 28.5; *m*/*z* (C.I) 164 (M$^+$, 100%), 162, (56%), 161, (8%) $C_{10}H_{13}O_2$, requires 164.0837, found, 164.0834; further elution gave **(272)** (1.9 g, 23%), m.p. 29-30˚C; υ_{max} (thin film/cm^{-1}), 2970, 2836, 1735, 1142, 1043; δ_H (250 MHz, $CDCl_3$) 3.18 (1H, s, COC**H$_3$**), 3.16 (1H, s, COCH$_3$), 2.68 - 2.49 (2H, m, **CH**=**CH** bridgehead), 2.49 (1H, dd, *J* 8.8 Hz, *J* 3.0 Hz, C**H$_2$**COMe$_2$), 2.33 - 2.15 (3H, m, C**H$_2$**COMe$_2$, C**H$_2$**CH$_2$, CH$_2$C**H$_2$**), 2.02 - 1.93 (2H, m, C**H$_2$**CH$_2$, CH$_2$C**H$_2$**); δ_C (62.5 MHz, $CDCl_3$) 221.9, 101.3, 48.8, 48.7, 45.5, 37.9, 37.1, 35.8, 20.9; *m*/*z* (C.I) 171 (MH$^+$, 79%), 169 (48%), 167 (9%), 163 (5%), 161 (11%), $C_9H_{16}O_3$, requires 171.1022 found, 171.1016.

Bicyclo[3.2.0]heptane-2,6-dione (6) [10]



To a stirred solution of 6,6-dimethoxybicyclo[3.2.0]heptan-2-one **(272)** (70 mg, 0.41 mmol, 1.00 equiv) in water (5 mL) and THF (1 mL) was added two drops of concentrated hydrochloric acid. The reaction was stirred at room temperature for 10 h until TLC analysis showed no presence of starting material. The product was concentrated *in vacuo* to remove the THF and most of the water. The residue was extracted with ethyl acetate (4 × 10 mL), washed with brine (4 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a near colourless oil. The oil was further purified by column chromatography on silica using hexane: ethyl acetate (1:1) to afford the title compound **(268)** as a colourless oil (43 mg, 85%); υ_{max} (thin film/cm^{-1}), 3164, 2360, 1783, 1738, 1145; δ_H (250 MHz, $CDCl_3$) 3.95 - 3.51 (2H, m, C**H**C=O, $\mathbf{CH_2}$C=O), 3.06 - 2.98 (2H, m, C**H**CH_2C=O, $\mathbf{CH_2}$C=O), 2.58 - 2.15 (4H, m, $\mathbf{CH_2}CH_2$, $CH_2\mathbf{CH_2}$C=O); δ_C (62.5 MHz, $CDCl_3$) 224.4, 221.6, 61.9, 52.4, 36.2, 36.1, 22.3; *m*/*z* (C.I) 124 (M^+, 21%), 123, (67%), 100, (99%), 86 (54%), 84 (82%), $C_7H_9O_2$, requires 124.0524, found, 124.0519.

Tetrahydro-cyclopenta[*b*]furan-2,4-dione (4)



To a stirred solution of bicyclo [3.2.0] hept-2-ene-6-one **(268)** (50.0 mg, 0.40 mmol, 1.00 equiv) in 90% aqueous acetic acid (5 mL) cooled to 0˚C was added 27.5% H_2O_2 (110 mg, 3.23 mmol, 8.00 equiv) in 90% aqueous acetic acid (5 mL). The reaction was allowed to warm-up to room temperature for 24 hr, by which time TLC analysis revealed a new product had been formed. The product was extracted with ether (4 × 10 mL), washed with 10% aqueous sodium sulfite (2 × 5 mL) and saturated sodium carbonate (4 × 5 mL). The ether layer was dried over $MgSO_4$ and the solvents were removed *in vacuo*. Column chromatography on silica, eluting with hexane: ethyl acetate gave the product as a colourless oil (36 mg, 64%); υ_{max} (thin film/cm^{-1}), 2929, 2851, 1751, 1737, 1644, 1088; δ_H (250 MHz, $CDCl_3$) 5.24 (1H, t, *J* 5.0 Hz, **CH**O), 2.96 (1H, dddd, *J* 5.0 Hz, *J* 2.5 Hz, **CH**=CH_2C=O), 2.85 (1H, d, *J* 10 Hz, *J* 2.5 Hz, $\mathbf{CH_2}$C=O), 2.78 (1H, d, *J* 15.0 Hz, $\mathbf{CH_2}$C=O), 2.57 - 2.43 (3H, m, $\mathbf{CH_2}$CHO, $\mathbf{CH_2}$C=O), 2.32 - 2.22 (1H, m, $\mathbf{CH_2}$CHO); δ_C (62.5 MHz, $CDCl_3$) 209, 176.6, 82.6, 77.6, 48.0, 35.0, 32.8, 27.3; *m*/*z* (C.I) 141 (MH^+, 90%), 130 (61%), 132 (100%), 112 (21%), 99 (11%) $C_7H_{10}O_3$ requires 141.0809, found, 141.0549.

Authors' Contributions

Dr. Bello Makama conducted all experimental work, analyzed the results, and drafted the manuscript. **Prof. Laurence M. Harwood** supervised the project and contributed to the characterization of all compounds via NMR, IR, and mass spectrometry, as well as providing critical revisions to the manuscript. While Samia Elashry contributed significantly to the writing of the manuscript.

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Conflicts of Interest

The authors declare that there are no competing interests.

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