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Ring expansions using Baeyer-Villager oxidation: An efficient strategy for the construction of substituted AB-ring systems

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Abstract: An approach to the synthesis of regioselective cis fused substituted AB-ring systems is described. The key step involves a thermal cycloaddition to substituted cyclobutanones. The resulting cyclobutanones were subjected to regioselective Baeyer-Villager oxidation protocol.

Keywords: Bicyclic lactones; thermal; cyclcoaddition; cyclobutanone; Baeyer-Villager oxidation.

1. Introduction

The AB-ring system is present in many naturally occurring molecules.[1,2,3] Brasoside **1** and littoralisone **2** are two representative examples. The AB ring system are also extensively used as synthetic intermediates taking advantage of their inherent presence in many natural products. Thus the development of methodologies for the synthesis of highly substituted AB-ring systems could be very important. It is envisaged that AB-ring systems **3** and **4** may lead to access the natural products **1** and **2** (Scheme 1)

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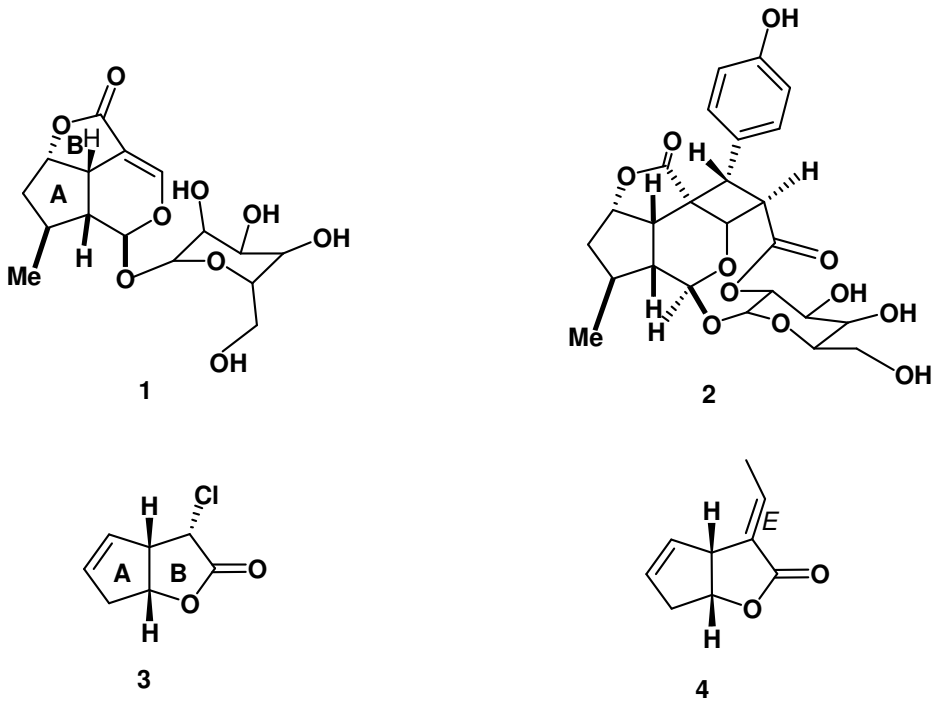
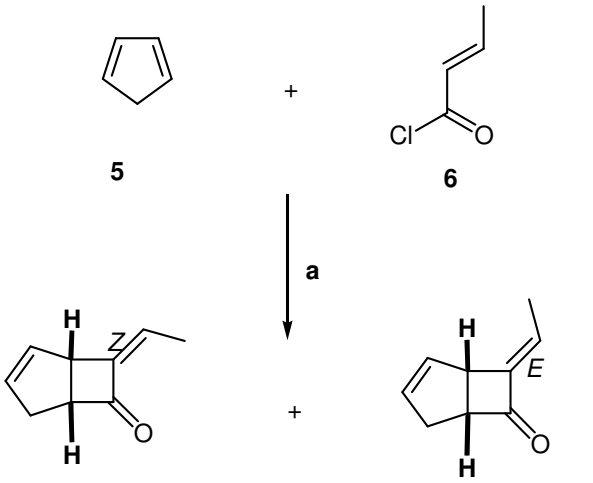


Scheme 1. Substituted AB ring Systems

2. Results and Discussion

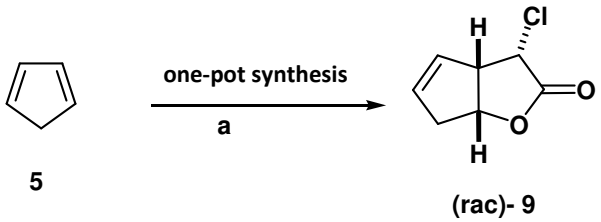
Ketene cycloaaditions is one of the few synthetic methodologies to access four membered rings.[4] It was decided to explore the [2+2] cycloaddition with vinyl ketene, which can be generated *in situ* from the reaction of crotonyl chloride **6** with triethylamine. Indeed, when the vinyl ketene generated from crotonyl chloride was reacted with cyclopentadiene **5**, the reaction successfully gave a mixture of *Z*-7-ethylidenebicyclo [3.2.0]-hept-2-en-6-one **7** and *E*-7-ethylidenebicyclo [3.2.0]-hept-2-en-6-one, **8** in 16% and 82% yields respectively (Scheme 2). Initially these adduct isomers could only be differentiated by ^{1}H NMR analysis. Attempts at separation were not successful initially since at temperatures above 70 ^{o}C on attempted Kugelrohr distillation or with long retention times on silica gel chromatography the isomers suffered apparent cycloreversion. The separation of these adducts was later achieved using flash chromatography on alumina as the stationary phase. The IR spectrum of compound **8** obtained from flash chromatography exhibited a carbonyl band at 1745 cm^{-1}, a stretching due to an exocyclic olefin at 1668 cm^{-1} and a stretching due to endocyclic olefin at 1605 cm^{-1}. The ^{1}H NMR spectrum confirmed the bridgehead protons at δ 3.72-3.79 ppm and a doublet centred at δ 1.87 ppm for the methane adjacent to the double bond. The IR of compound **7** amongst other things exhibited a carbonyl stretching at 1746 cm^{-1} and stretching due to the double bond at 1664 cm^{-1} and at 1600 cm^{-1}



(a) DCM, triethylamine, 0 ^{o}C

Scheme 2. Ketene Cycloaddition

With this background data, the ring expansion strategy began. Firstly, It was envisaged that the modification of the report by Greico[5] on dechlorination and ring enlargement of cyclobutanones could lead to the desired **9**. Thus, a mixture of cyclopentadiene **(5)** and dichloroacetyl chloride in DCM was treated with triethylamine at room temperature, and the resulting mixture was stirred for 12 h and then treated with aqueous acetic acid, followed by addition of H_2O_2 to afford an intermediate that was not purified but was reacted with a suspension of zinc powder in acetic acid over a period of 30 min at room temperature, by which time TLC analysis showed no presence of starting material. The ^{1}H NMR analysis confirmed that **9** had been formed as a single isomer. Examination of the ^{1}H NMR of lactone **9** revealed that the alkene protons were exhibited as multiplets at δ 5.95-5.92 ppm and at δ 5.82-5.79 ppm. The methine proton adjacent to the oxygen in the lactone showed a resonance centered at δ 5.14-5.12 ppm. The spectrum also displayed a one proton doublet at δ 4.80 ppm (*J* 8.7 Hz), corresponding to the proton adjacent to the ester (CHCl). The IR spectrum revealed a carbonyl absorption at 1783 cm^{-1} and an absorption at 1638 cm^{-1} for the endocyclic alkene. This data along with the presence of a single CH_2 resonance in the DEPT spectrum at 40.3 ppm confirmed that **9** had been formed (Scheme 3).



(a) Dichloroacetyl chloride, triethylamine, DCM, rt, 12 h; then AcOH, 27.5% H_2O_2 ; then zinc powder, 30 min, 65% .

Scheme 3. One-pot synthesis of Substitued AB Ring System

In addition, a single crystal selected of compound **9** provided excellent X-ray diffraction data from which the structure was confirmed (Figure 1).

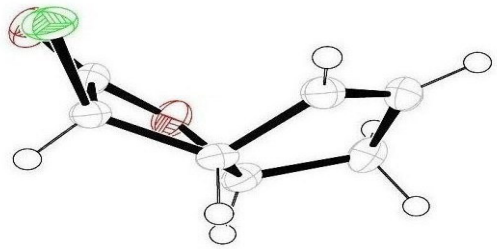
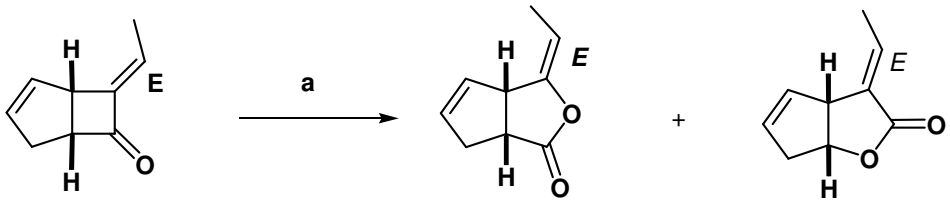


Figure 1. X-ray Structure of Compound 9

The successful preparation of the AB-ring system **(9)** appeared to set the stage for exploiting the ring expansion of **(8)**. In accordance with our prediction, the treatment of the ketene-adduct isomer **8** with a solution of hydrogen peroxide and glacial acetic acid gratifyingly produced **10** and **11** as two regioisomers in a ratio of 1:3. The adduct isomers were separated by distillation. In each case, the ^{1}H NMR spectra fully supported the proposed structures **10** and **11**. The ^{1}H NMR spectrum of **10** displayed a quartet at δ 5.25 ppm corresponding to the vinylic proton bonded to methyl group; a doublet at δ 4.12 ppm (*J* 5.1 Hz) for the methine proton adjacent to the double bonds; and a doublet of doublet of doublet at δ 3.32 ppm (*J* 5.1, 3.1 and 3.1 Hz) for methine adjacent to the carbonyl ester and a doublet at δ 1.72 ppm for the methyl group. The IR disclosed a stretching at 1789 cm^{-1} for the lactone carbonyl, and absorptions at 1645 cm^{-1} and 1616cm^{-1} for both the *exo* and endocyclic alkenes. The ^{1}H NMR of lactone **(11)** showed a methine proton at δ 4.04-4.02 ppm corresponding to that adjacent to the oxygen in the lactone, a one proton signal at δ 3.66 ppm corresponding to the methine adjacent to the double bond. Furthermore, the presence of the carbonyl absorption at 1734 cm^{-1} shown in the IR spectrum is that expected for an α-β-unsaturated lactone. The mass ion of 150 gave further evidence for the successful preparation of **(11)** (Scheme 4).

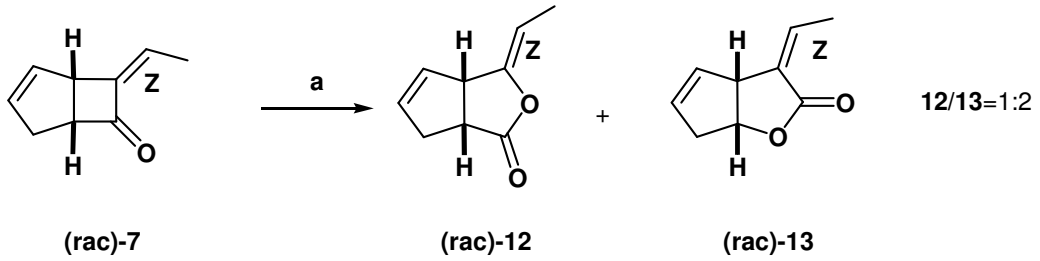


(rac)-8 **(rac)-10,** 24% **(rac)-11,** 74%

(a) acetic acid, 27.5% H_2O_2,

Scheme 4. Ring Expansion of Ketene-adduct *(rac)*-8

In a similar way, when compound **7** was subjected to oxidation, two spots were observed on the TLC. The ^{1}H NMR spectrum of the crude material supported the formation of **12** and **13** in a ratio of 1:2. Efforts to separate the regioisomers **12** and **13** met with difficulty **(Scheme 5)**. Among the techniques investigated in an attempt to effect the separation were, column chromatography (eluting with hexane : ethyl acetate using a gradient of 100% hexane to 100% ethyl acetate) and vacuum distillation in a Keugelrour (0.3 mmHg, 0-200 ^{o}C). In all these attempts, it was found the regioisomers resisted separation and only decomposition was observed. The final attempt to separate these isomers by a column chromatography on alumina (eluting with hexane : EtOAc) proved to be partially successful, and the pure isomer **12** was isolated. The IR spectrum of the purified **12** exhibited a carbonyl band at 1759 cm^{-1} in accord with that expected for a cycloadduct of structure **12**, a band at 1651 cm^{-1} and 1609 cm^{-1} corresponding to the double bond in **12**. The ^{1}H NMR spectrum of this product confirmed the presence of exocyclic alkene proton as a quartet at δ 4.66 ppm, a one proton doublet at δ 3.89 ppm (*J* 7.5 Hz) for the methine adjacent to the double bond, a one proton multiplet centred at δ 3.28-3.24 ppm for the methine adjacent to the carbonyl group of ester and a doublet at δ 1.62 ppm for the methyl carbon. This data led us to conclude that the Baeyer-Villager oxidation had furnished the cyclic ester **(12)** (Scheme 5).



(rac)-7 **(rac)-12** **(rac)-13**

(a) acetic acid, 27.5% H_2O_2, 18%

Scheme 5. Scheme 5- Ring Expansion of Ketene-adduct *(rac)*-7

The regiochemical outcome of the oxidized was confirmed by NOE measurements. By means of this technique, the stereochemistry of the product **10, 11** and **12** was resolved unambiguously; regioisomer **12** had *Z*-geometry. The stereochemistry at C-6, C-7 and C-8 of compound **10** is shown below (Figure 2). A significant enhancement in the C-8 methyl signals was observed when the C-6 methine hydrogen was irradiated. Enhancement was also observed with the C-6 methine hydrogen when the C-7 methine proton was irradiated. Based on these data the stereochemistry was assigned, leading to justification of the *cis*-stereochemistry at the C-6, C-7 ring junction as well as the *E*-geometry of the exocyclic alkene as shown in (Figure 2).

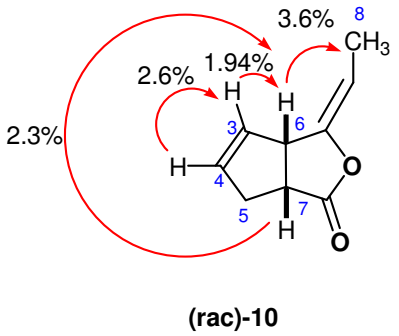


Figure 2. NOE Measurements of *(rac)*-10

3. Conclusion

This approach to AB-ring systems, which involves cycloadditions of cyclopentadiene through the agency of suitable ketenes, was pursued successfully. AB-ring frameworks of brasoside were constructed in excellent yields by the combination of this protocol and regioselective Baeyer Villager oxidation.

4. Experimental

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.[6] 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 ^{o}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.^{1}H 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 ^{1}H 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). Melting points were measured using a Reichert Kofler heated-stage microscope and are uncorrected.

(Z)-7-ethylidenebicyclo[3.2.0]-hept-2-en-6-one (7) and (E)-7-ethylidenebicyclo[3.2.0]-hept-2-en-6-one (8). To a vigorously stirred solution of freshly distilled cyclopentadiene, (22.4 g, 340 mmol) and of *trans*-crotonylchloride (8.84 g, 85 mmol) in anhydrous DCM (200 mL) at 0 ^{o}C was added a solution of triethylamine (9.09 g, 90 mmol) in DCM (200 mL) over a period of 1.5 h. Stirring was continued at rt for another 12 h, at the end of which time TLC analysis of the supernatant liquid showed five components. The reaction mixture was filtered and the filter cake was washed with DCM (200 mL). The solvent was removed *in vacuo*, yielding a brown liquid weighing (17.1 g). Careful chromatography on alumina eluting with hexane : ethyl acetate furnished *Z*-7-ethylidenebicyclo [3.2.0]-hept-2-en-6-one (7) as a colourless oil (3.6 g, 31%); υ_{max} (thin film/cm^{-1}), 3061, 2946, 2860, 1746, 1664, 1600, 1444, 1170, 1047, 896, 776, 743, 696; δ_H (250 MHz, $CDCl_3$) 5.86-5.82 (2H, m, CH=CH), 5.68 (dq, 1H, ^{3}J 7.0 Hz, ^{4}J 1.5 Hz, CH_3CH=C,), 3.82-3.79 (2H, m, CH-CH, bridgehead), 2.67-2.65 (2H, m, CH_2), 2.06 (3H, d, *J* 7.0 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$); 200.6, 136.1, 134.9, 133.3, 130.3, 49.1, 46.3, 34.7, 20.6; further elution afforded *E*-7-ethylidenebicyclo [3.2.0]-hept-2-en-6-one (8) (7.8 g, 68%); υ_{max} (thin film/cm^{-1}), 3030, 2931, 2860, 1745, 1668, 1605, 1442, 1171, 1075, 793, 735, 690; δ_H (250 MHz, $CDCl_3$) 6.46- 6.23 (1H, m, CH_3CH=C), 5.84-5.64 (2H, m, CH=CH), 3.79-3.72 (2H, m, CH-CH, bridgehead), 2.66-2.61 (m, 2H, CH_2), 1.87 (d, 3H, *J* 7.0 Hz, *J* 1.0 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 200.7, 139.5, 136.5, 136.1, 129.6, 48.5, 43.7, 34.3, 19.8; $^{m}/_{z}$ (C.I) 134 (MH^+, 100%), $C_9H_{11}O$, requires 134.0732, found ,134.0736.

3-chloro-tetrahydrocyclopenta[b]furan-2-one (9). To a vigorously stirred solution of freshly distilled cyclopentadiene **(5)** (3.4 g, 51.5 mmol, 1.00 equiv) and of dichloroacetyl chloride (3.8 g, 25.8 mmol, 0.50 equiv) in dry DCM (25 mL) was added of dry triethylamine(2.7 g, 26.7 mmol, 0.50 equiv) in DCM (25 mL) over a period of 1 h. After stirring for 13 h under an N_2 atmosphere, 90% aqueous acetic acid (50 mL) cooled to 0 ^{o}C was added 27.5% H_2O_2 (13.6 g, 110 mmol, 8.00 equiv) in 90% aqueous acetic acid (50 mL). The reaction was allowed to warm-up to room temperature for 24 h, by which time TLC analysis showed a new product been formed. The product was extracted with ether (4 x 15 mL), washed with 10% aqueous sodium sulfite (4 x 7 mL) and saturated sodium carbonate (4 x 10 mL). The ether layer was dried over $MgSO_4$ and the solvents were removed *in vacuo.* To the resulting residue was added in portions a suspension of zinc powder (1.0 g) in acetic acid (1.4 mL) over a period of 15 min and the mixture was further stirred for 15 min at room temperature. The resulting mixture was stirred for further 30 min, by which time, TLC analysis showed no presence of starting material. Brine (30 mL) was added and the product was extracted with ether (4 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The solidified product was recrystallized from diisopropyl ether to give **(9)** as colourless crystals. The mother liquor was concentrated *in vacuo* and the residue was subjected to column chromatography using benzene as the eluant to give additional **(9)**, (3.1 g, 76%), melting point (68-70 ^{o}C); υ_{max} (KBR/cm^{-1}), 2255, 1783, 1638, 1403.1, 1174, 908.8; δ_H (400 MHz, $CDCl_3$) 5.95-5.92 (1H, m, CH=CH), 5.82-5.79 (1H, m, CH=CH), 5.14-5.12 (1H, m, (HC-O(CO)) 4.80 (1H, d, *J* 8.7 Hz, CHCl), 3.87-3.82 (1H, m, CH), 2.82-2.79 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$), 171.5, 131.7, 126.9, 80.9, 54.7, 51.3, 40.3; $^{m}/_{z}$ (C.I) 159 (MH^+, 100%), $C_7H_8ClO_2$, requires 158.0135, found , 158.0131.

E-3-ethylidenetetrahydrocyclopenta[c]furan-1-one (10) and E-3-ethylidenetetrahydrocyclopenta[b]-furan-2-one (11). To a stirred solution of E-7-ethylidenebicyclo [3.2.0]-hept-2-en-6-one **(8)** (200 mg, 1.47 mmol, 1.00 equiv) in 90% aqueous acetic acid (10 mL) cooled to 0 ^{o}C was added 27.5% H_2O_2 (405 mg, 3.27 mmol) in (10 mL) of 90% aqueous AcOH. The reaction was allowed to warm-up to room temperature for 24 hr, after which time, TLC showed the presence of a new product. The product was extracted with ether (4 x 7 mL), washed with 10% aqueous sodium sulfite (2 x 5 mL) and saturated sodium carbonate (4 x 5 mL). The ether layer was dried over $MgSO_4$ and the solvents were removed *in vacuo*. Distillation in a Kugelrohr (90-110 ^{o}C oven temp, 0.3 mmHg) afforded (10) as a colourless oil (53 mg 24%); υ_{max} (thin film/cm^{-1}), 2926, 1789, 1645, 1616; δ_H (400 MHz, $CDCl_3$) 5.86-5.82 (1H, m, CH=CH), 5.68-5.65 (1H, m, CH=CH), 5.25 (1H, q, *J* 5.6 Hz, CH=CH_3), 4.12 (1H, d, *J* 5.1 Hz, CH-CHC=O), 3.32 (1H, ddd, *J* 5.1 Hz, *J* 3.1 Hz, *J* 3.1 Hz, CHC=O), 2.84-2.79 (2H, m,

$CH_2CH=CH$), 1.72 (3H, d, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 178.3, 151.3, 131.5, 128.8, 99.0, 47.6, 42.5, 36.4, 10.8; further distillation afforded (11) (164 mg, 74%); υ_{max} (thin film/cm^{-1}), 2962, 1734, 1634, 1614, 1382; δ_H (400 MHz, $CDCl_3$) 6.16 (1H, bq, *J*, 4.9, $CHCH_3$), 5.87-5.82 (1H, m, CH=CH), 5.81-5.76 (1H, m, CH=CH), 4.04-4.02 (1H, m, CHO), 3.66-3.58 (1H, m, CHCH=CH), 2.80 (1H, dd, *J* 15.1 Hz, *J* 2.4 Hz, CH_2CHO), 2.57-2.52 (1H, m, CH_2CHO), 1.81 (3H, d, *J* 1.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 170.0, 139.2, 136.6, 131.4, 129.0, 79.6, 37.7, 34.8, 13.1; $^m/_z$ (C.I) 150 (M^+, 100%), 130, (6.2%), 118, (5.9%) $C_9H_{11}O_2$, requires 150.0681, found, 150.0678.

Z-3-Ethylidenetetrahydrocyclopenta[c]furan-1-one (12). To a stirred solution of *Z*-bicyclo [3.2.0] hept-2-ene-6-one **(7),** (300 mg, 2.20 mmol in 90% aq. AcOH (10 mL) cooled to 0 ^oC was added 27.5% H_2O_2 (609 mg, 4.9 mmol) in (10 mL) of 90% aq. AcOH. The reaction was allowed to warm-up to room temperature for 24 h, after which time TLC analysis revealed the formation of new product. The product was extracted with ether (4 x 15 mL), washed with 10% aqueous sodium sulfite (2 x 7 mL) and saturated sodium carbonate (2 x 7 mL). The ether layer was dried over $MgSO_4$ and the solvents were removed *in vacuo* to afford the title compound as a mixture of two components. Column chromatography on alumina eluting with hexane : ethyl acetate (2:1) afforded **(12)** (59 mg, 18%); υ_{max} (thin film/cm^{-1}), 2924, 1729, 1651, 1609; δ_H (250 MHz, $CDCl_3$) 5.60-5.59 (1H, m, CH=CH), 5.51-5.5.49 (1H, m, CH=CH), 4.66 (q, 1H, *J* 5.9 Hz, $CH=CH_3$), 3.89 (1H, d, *J* 7.5 Hz, CHCHC=O) 3.28-3.24 (1H, m CHCO), 2.77-2.69 (2H, m, $CH_2CH=CH$), 1.62 (3H, d , *J* 1.1 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.6, 141.3, 131.1, 126.6, 104.1, 42.6, 39.7, 34.0, 9.8; $^m/_z$ (C.I) 150 (M^+, 100%), 130, (6.2%), 118, (5.9%) $C_9H_{11}O_2$, requires 150.0681, found, 150.0678.

Acknowledgments

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