American Journal of Organic Chemistry 2012, 2(6): 127-131
DOI: 10.5923/j.ajoc.20120206.01

Stereoselective Synthesis of Bicyclic Lactones Via Annelation Protocol

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Abstract A successful two-step annelation protocol of diesters and methyl bromoacetate with 2- chlorocyclopentanone derivatives was efficiently pursued, which gave suitably substituted bicyclic lactones in high overall yields and with complete streoselectivity mediated by K-Selectride and Wilkinsons catalyst, is reported. As part of a program aimed at rapid synthesis of bicyclic lactones which inherently occurs in many active natural products, this paper has shown a novel and rare methods for the synthesis of these important compounds based on alkylation of cyclopentanone derivatives and further demonstrate efficient reduction protocol of these compounds to the bicyclci lactones

Keywords Annelation, Diesters, Methyl Bromo Acetate, Bicyclic Lactones

1. Introduction

Bicyclic lactones systems are among Nature's preferred building blocks for the construction of tricyclic lactones of varied biological activities. In particular, the γ-butyrolactone moiety is a recurrent feature of many naturally occurring substances examples are brasoside and littoralissone.[1,2] The synthetic approaches to this bicyclic lactones have been imaginative and numerous,[3-8] there is a continued demand for efficient methods for the assembling of these key compounds which give especially high levels of stereoselectivity. In this report, it is reported some of our preliminary results in the establishment of an effective methodology for the construction of these important compounds. It was envisaged that reduction of substituted cyclopentanone derivatives using methods of alkylation described by Fumihinko[9] would give the ester (276). Stereocontrolled reduction with Selectride® reagents and subsequent lactonization would furnish the cis-fused bicyclic ring system (278). It therefore remained to investigate the annelation of a diketone with methyl bromoacetate and later explore the cyclization protocol. The success of this synthetic methodology would require the viability of the condensation between the cyclopentanone derivatives with the diester and methyl bromoacetate. The most important step would now be the selective Selectride® mediated reduction of the ketone in compounds (276) and (283) to give the *syn*-alcohols which could readily ring closed into the desired bicyclic structures.

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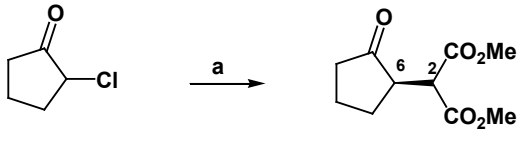
Published online at http://journal.sapub.org/ajoc

2. Results & Discussion

2.1. Exploration of Direct Formation of Dimethy 2-(2-Oxocyclopentyl) Malonate

Following a report by Fumihinko[9] that 2-chlorocyclopentanone (275) can be converted into dimethyl 2-(2-oxocyclopentyl) malonate (276) we obtained the corresponding diester (276) in 53% yield. The 1H NMR spectrum fully supported the proposed structure (276), displaying a doublet centred at δ 3.84 ppm (J 5.8 Hz) corresponding to a methine proton bonded to the diester, a pair of three proton singlets at δ 3.78 ppm and at δ 3.73 ppm for methyl esters and a one proton resonance at δ 2.97-2.88 ppm for the methine adjacent to the ketone. The presence of the ester groups and the ketone was manifested in the IR spectrum, with characteristic absorptions at, 1738 cm^{-1} and 1749 cm-1 respectively. The mass spectrum fully supported this with a molecular ion of m/z 214 Scheme 1.1.



(275) (276)

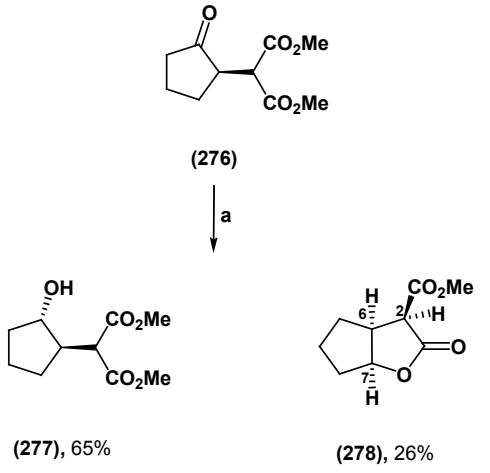
Scheme 1.1. **(a)** dimethyl malonate, DMF/THF (1:1), NaH, 53%

The reduction of the ketone in (276) by treatment with 1.2 equiv of sodium borohydride at 0℃ furnished a mixture of two products which were chromatographically separable.

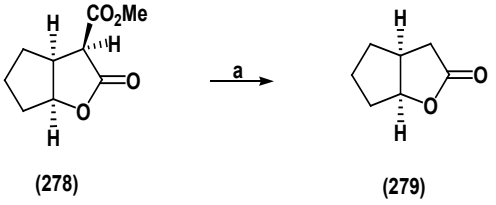
The major compound turned out to be (277) with the ketone group having been reduced, and having a distinct broad absorption in the IR spectrum at 3504 cm^{-1} corresponding to the hydroxyl group. The 1H NMR spectrum showed a one proton resonance at δ 3.96-3.91 ppm due the methine proton adjacent to the hydroxyl bearing carbon and two three proton singlets at δ 3.68 ppm and δ 3.67 ppm for the two methoxy groups. The C-2 proton appeared at δ 3.32 ppm with a coupling constant of 7.8 Hz, which lent support to the cis configuration of this predominant product at C-6 and C-2. The minor product (278) turned out to be the desired lactone, obtained in a totaly yield of 26%. The IR spectrum displayed a characteristic band at 1742 cm^{-1}, that strongly supported the presence of a γ-lactone and absorption at 1733 cm^{-1} for the acyclic ester. The 1H NMR spectrum had a triplet at δ 5.06 ppm due to the C-7 methine proton with a coupling constant of (5.3 Hz) and a singlet at δ 3.73 ppm associated with the methoxy ester protons. The *cis* configuration between the C-2 and C-6 was fully confirmed due to a doublet at δ 3.68 ppm indicative of the proton adjacent to the ester with a characteristic *cis* coupling of (3.3 Hz). The molecular ion of m/z 184 for the compound was also in accord with structure (278) Scheme 1.2.

In our attempt to improve the selectivity *syn*-alcohol which readily cyclizes to (278), sterically bulky reagents were considered as suitable reagents. It was decided to examine the reduction L and K-Selectrides®.[10-12] It was envisaged that reduction with these reagents, which are very bulky and have low coordinating ability, could follow the model of Felkin and Anh.[13] This plan finally rewarded us with success because as it was hoped, the Selectride reagents produced syn-alcohol selectivity under all conditions studied, the steroselectivity was found to increased with decreasing temperature to produce the diastereoisomers (277) and (278). The highest selectivity was achieved with K-Selectride® at -78°C (100% syn-selectivity) and L-Selectride® (99:1 syn-selectivity) Table 1.1.

When **(278)** was subjected to further purification on column chromatography eluting with hexane : ethyl acetate, a number of spots began to show in the TLC analysis, indicating decomposition of the lactone. Two products could be separated and identified from the complex mixture. The major product was the desired lactone, **(278)**, but the decarboxylated compound (**279)** was also produced. The decarboxylated product **(279)** exhibited an absorption in the IR spectrum at 1769 cm^{-1} which is expected of the γ-lactone **(279)**. The ^{1}H NMR spectrum included a one proton triplet at δ 5.02 ppm (*J* 5.0 Hz) accounting for methine adjacent to the oxygen in the γ-lactone , and a combination of a multiplet and a doublet at δ 2.97-2.80 ppm and at δ 2.79 ppm accounting for the diastereotopic CH_2 adjacent to the lactone carbonyl group. The absence of the exocyclic methyl ester protons was evident. These data, combined with a molecular ion of m/z 126, led us to conclude that the decarboxylation had occurred to produce the lactone **(279)** Scheme 1.3.



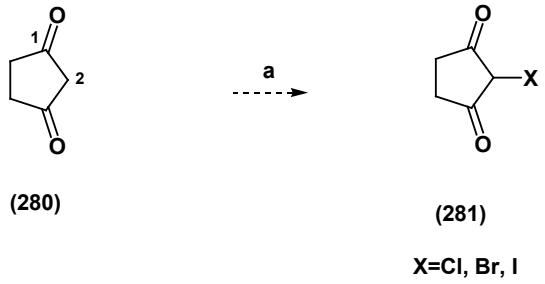
Scheme 1.2. (a) ethanol, $NaBH_4$, 0℃, 30 min



Scheme 1.3. (a) silica gel, hex : ethyl acetate (1:3), 32%

Table 1.1. Stereoselectivity of reduction of (278)

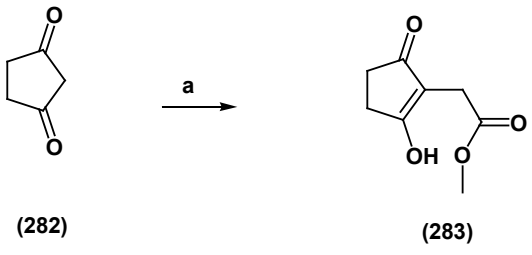
Reagents	Temp. (°C)	syn -(**278**): anti (**277**)
$NaBH_4$	RT	44:56
	0 °C	35: 65
	-78 °C	29:71
K-Selectride®	RT	79:21
	0 °C	98:8
	-78 °C	100:0
L-Selectride®	RT	73: 27
	0 °C	91: 9
	-78 °C	99: 1



Scheme 1.4. (a) NBS, NCS, KIO_3, THF

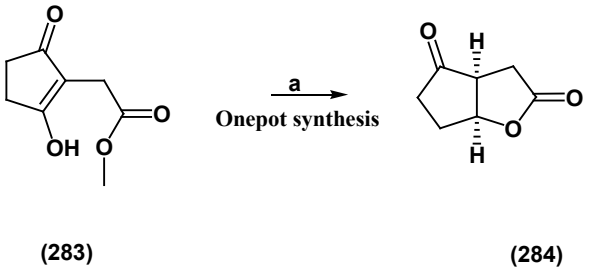
Attempts to introduce functionality at C-2 of compound (280) by direct halogenation with either NBS or NCS were to no avail, and unchanged starting material was recovered, in some cases the reaction yielded compounds which could not be characterised. Attempted direct iodination of compound (280) by treatment with KIO_3 was likewise unsuccessful Scheme 1.4.

The approach at this juncture was to capitalise on the propensity of methyl bromacetate to react cyclopentene-1,3-dione (282). Fortunately, ester (283) could be derived from cyclopentene-1,3-dione (282) in excellent yield. A modification of Fumihinko's conditions (CH_3CN, THF and methyl boromoacetate) with cyclopententene-1,3-dione (282), afforded ester (283) in an isolable yield of 78%. The 1H NMR spectrum of the ester (283) was diagonistic, with the methylene protons adjacent to the ester appearing as a singlet at δ 4.61 ppm, the three methyl ester protons appearing as a singlet at δ 3.38 ppm and a two proton triplet centred at δ 2.72 ppm. For methylene bonded to the ketone and the methylene adjacent to the enol hydroxyl, two protons were shown as a triplet centred at δ 2.49 ppm. Furthermore, the presence of the enol hydroxyl was manifested by a characteristic absorption at 3389 cm^{-1} in the IR spectrum. When the ester (283) was subjected to the conditions developed for cyclisation, namely, acidifying the mixture to pH 2 and stirring at room temperature, TLC analysis indicated a new product had been formed, However, after aqueous work up, ^{1}H NMR analysis showed no reaction has taken place and only starting material had been recovered Scheme 1.5.



Scheme 1.5. (a) MBA, Et_3N, CH_3CN, pH 2, 78%

Efforts to saturate the ring using PtO_2 or Pd-C, however, only met with failure. One may suppose, based on the structure of (283), that the steric hindrance in the vicinity of the olefinic bond is responsible for the lack of success with the hydrogenation protocol. However attempt to reduce the ketone in (283) using Wilkinson catalyst in catecholborane proved to be successful [14], followed by attempts to cyclize the product using the conditions developed for cyclization, namely, acidifying the mixture to pH 2 and stirring at room temperature, produced the bicyclic lactone (284) Scheme 1.6



Scheme 1.6. (a) Wilkinsons Catalyst, Catecholborane, aq. HCl, pH 2, 73%

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.15 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^{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 KMnO4 solution. 1H and 13C 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 13C 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).

3.1. Experimental Procedures

Dimethyl 2-(2-oxocyclopentyl)malonate (276)

To a stirred solution of NaH (209 mg, 5.49 mmol, 1.30 equiv) in THF-DMF (10 mL, 1:1) at 0^{o}C was added dimethyl

malonate (724 mg, 5.49 mmol, 1.3 equiv) and the solution was stirred for 30 min at room temperature. 2-chlorocyclopentanone (275) (500 mg, 4.22 mmol, 1.00 equiv) was added to the solution and then further stirred at room temperature for 8 h, by which time TLC analysis, revealed the formation of a new product. Saturated aqueous NH4Cl solution (10 mL) was added to the mixture and the organic layer was extracted with ether (4 x 15 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (4 x10 mL), brine (4 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using a gradient of solvents, hexane: ethylacetate from (5:1-100% ethylacetate) to afford the title compound as a colourless oil (192 mg, 53%); υmax (thin film/cm^{-1}), 2961, 1749, 1738; δH (250 MHz, CDCl3) 3.84 (1H, d, J 5.8 Hz, CH(CO2CH3)2), 3.78 (3H, s, CH3), 3.73 (3H, s, CH3), 2.97-2.88 (1H, m, CHC=O), 2.56-1.99 (4H, m, CH2CH, CH2C=O), 2.00-1.81 (2H, m, CH2CH2C=O); δC (62.5 MHz, CDCl3), 216.2, 169.1, 168.6, 53.9, 51.6, 51.2, 41.2, 38.2, 23.8 20.8; m/z (C.I) 215 (MH^+, 100%), 214 (4%), 183 (11%), 155 (7%), 123 (3%), C10H15O5, requires 215.092, found , 215.0913

Dimethyl -2,2-hydroxycyclopentyl)malonate (277)

Methyl-2-oxo-hexahydro-2H-cyclopenta[b]furan-3-carboxylate (278)

To a stirred solution of dimethyl 2-(2-oxocyclopentyl)malonate (276) (80 mg, 0.37 mmol, and 1.00 equiv) in ethanol (7 mL) in an Erlenmeyer flask was added $NaBH_4$ at room temperature (16.8 mg, 0.44 mmol, 1.20 equiv) in small portions over a period of 15 min The reaction mixture was stirred for further 30 minutes and then poured into water (5 mL). (5%) dilute hydrochloric acid (4 drops) was added and the organic layer was extracted with ether (2 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo. Column chromatography on silica, eluting with hexane : ether (3:1) afforded (277) as a colourless oil (66 mg, 65%); υmax (thin film/cm-1), 3504, 2955, 2255, 1731; δH (250 MHz, CDCl3) 3.96-3.91 (1H, m, CHOH), 3.68 (3H, s, CH3), 3.67 (3H, s, CH3), 3.32 (1H, d, J 7.8 Hz, CH(CO2Me)2), 2.33-2.28 (1H, m, CH), 1.88-1.83 (2H, m, CH2), 1.63-1.53 (3H, m, CH2), 1.28-1.25 (1H, m, CH2); δC (62.5 MHz, CDCl3) 169.2, 168.6, 76.2, 55.9, 51.5, 51.0, 46.8, 33.4, 28.3, 21.3; m/z (C.I) 216 (MH+, 9%), 159 (10%), 150 (4%), C10H17O5, requires 216.0998, found, 216.0935; further elution yielded (278) (18 mg, 26%); υmax (thin film/cm-1), 2957, 1742, 1733, ; δH (250 MHz, CDCl3) 5.06 (1H t, J 5.3 Hz, CHO), 3.73 (3H, s, CO2CH3), 3.68 (1H, d, J 3.3, CHC=O), 3.14-3.10 (1H, m, CHCHC=O), 1.98-1.56 (6H, m, CH2); δC (62.5 MHz, CDCl3) 176.9, 168.5, 86.5, 54.8, 53.7, 43.5, 33.5, 32.9, 23.9; m/z (C.I) 185 (MH+, 45%), 141 (51%), 134 (43%), 124(67), 101 (77%) 84 (54%) C9H13O4, requires 185.0814, found, 185.0806

Hexahydrocyclopenta[b]furan-2-one (279)

Methyl-2-oxo-hexahydro-2H-cyclopenta[b]furan-3-carboxylate (278) (50 mg, 0.27 mmol, 1.00 equiv) was subjected to column chromatography on silica eluting Hex : ethyl acetate (1:3) to afford the title compound (279) as a colourless oil (11 mg, 32%); υmax (thin film/cm^{-1}), 2962, 2879, 1769, 1205, 982; δH (250 MHz, CDCl3) 5.02 (1H t, J 5.0 Hz, CHO), 2.97-2.80 (1H, m, CH2COO), 2.79 (1H, d, J 10 Hz, CH2COO), 2.28-2.15 (1H, m, CHCHO), 2.09-2.02 (1H, m, CH2), 1.97-1.80 (5H, m, CH2); δC (62.5 MHz, CDCl3) 177.2, 86.6, 37.8, 36.0, 33.5, 29.9, 23.4; m/z (C.I) 125 (MH-, 56%), 124 (58%), 109 (8%), 124 (58), 109 (8%) 107 (9%) C7H11O2, requires 125.0603, found, 125.062

Methyl 2-(2-hydroxy-5-oxocyclopent-1-enyl)acetate (283)

To a stirred solution of 1,3-cyclopentanedione (279) (5 g, 0.05 mmol, 1.00 equiv) in acetonitrile (80 mL) at 0°C was added triethylamine (7.6 g, 0.07 mmol, 1.30 equiv), and the solution was stirred for 10 min at room temperature. Methyl bromoacetate (9.9 g, 0.07 mmol, 1.30 equiv) was then added and stirring was continued over night by which time TLC revealed a new spot. Saturated aqueous NH4Cl solution (15 mL) was added to the mixture and the organic layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (2 x15 mL), brine (2 x 15 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using a solvent gradient hexane : ethyl acetate from (4:1) to afford the title compound as a white powder (6.6 g, 78%); m.p. (148-151 °C); υmax (KBR/cm-1), 3389, 2927, 1726, 1656, 1574; δH (250 MHz, CDCl3) 4.61 (2H, s, CH2CO2CH3), 3.38 (3H, s, COOCH3), 2.72 (2H, t, J 2.5 Hz, CH2C=O), 2.49 (2H, t, J 2.5 Hz, CH2COH) ; δC (62.5 MHz, CDCl3) 205.8, 189.4, 167.5, 106.7, 67.9, 53.1, 34.8, 28.6; m/z (C.I) 171 (MH+, 100%), 170 (10%), 142 (14%), 131 (5%), 81 (2%) C8H11O4, requires 171.0657, found, 171.0657

Tetrahydro-cyclopenta[b]furan-2,4-dione (284)

To a stirred solution of Wilkinsons catalyst ($RhPPh_3Cl$) (236.00 mg, 0.589 mmol, 0.5 equiv) in anhydrous THF (7 mL) under N2 cooled to -20 oC was added to methyl 2-(2-hydroxy-5-oxocyclopent-1-enyl)acetate (283) (200.0 mg, 1.18 mmol, 1.00 equiv), followed by the addition of catecholborane (424.45 mg, 3.54 mmol, 3.0 equiv). The reaction was allowed to stir for 24 hr, by which time TLC analysis revealed a new product been formed. The reaction was quenched by the addition phosphate buffer pH 7.00, (4 mL). The product was extracted with ether (4 x 10 mL), washed with 10% aqueous sodium sulfite (2 x 5 mL) and saturated sodium carbonate (4 x 5mL). The ether layer was followed by the addition of dilute hydrochloric acid (5%) at 0 °C until the pH 2 was reached, by which time, TLC analysis showed a new product has been formed. The aqueous layer was extracted with ether (4 x 10 mL), the extract dried over $MgSO_4$ and concentrated in vacuo. Column chromatography on silica, eluting with hexane : ethyl acetate gave the product as a colourless oil (122 mg, 73%); υmax (thin film/cm^{-1}), 2929, 2851, 1751, 1737, 1644, 1088; δH (250 MHz, CDCl3) 5.24 (1H, t, J 5.0 Hz, CHO), 2.96 (1H, dddd, J 5.0 Hz, J 2.5 Hz, CH=CH2C=O), 2.85 (1H, d, J 10 Hz, J 2.5 Hz, CH2C=O), 2.78 (1H, d, J 15.0 Hz, CH2C=O), 2.57-2.43 (3H, m, CH2CHO, CH2C=O), 2.32-2.22 (1H, m, CH2CHO); δC (62.5 MHz, CDCl3) 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%) C7H10O3 requires 141.0809, found, 141.0549.

4. Conclusions

In this paper we have shown an expeditious approach to the synthesis of bicylcic lactone using stereocontrol bulky reagents such as K selectride and L-Selectride. These two reagents proved successful in deriving the readily desired syn-alcohol selectivities which cyclises to furnish the desired lactones in average good yields. We have also shown the versatility of Wilkinson's catalyst in a one-pot synthesis of lactones

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