Lactones, Part 28:[1] A New Approach for the Synthesis of α-Methylene Lactones from Alkenes

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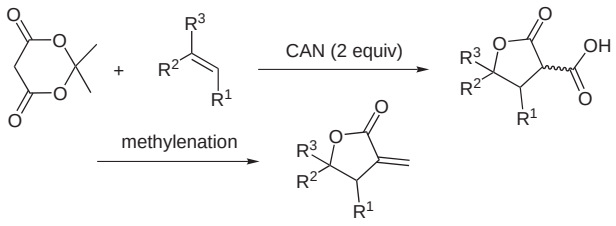
Received 23 January 2006

Abstract: A facile two-step procedure for synthesis of α-methylene lactones from alkenes and cycloalkenes is presented. Reactions carried out on some monoterpene alkenes afforded corresponding lactones in enantiomerically pure forms.

Key words: α-methylene lactone, CAN, Meldrum's acid

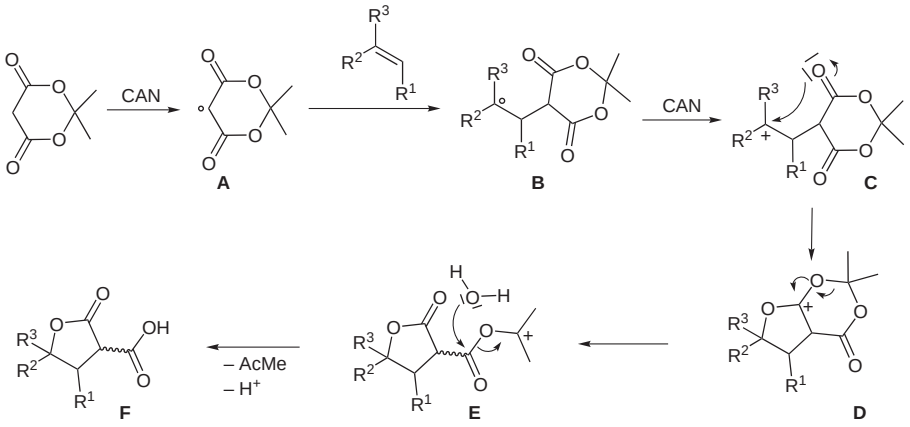
α-Methylene-γ-butyrolactones exhibit a broad range of biological activities. The intensive studies have been focused on their cytotoxic,[2] antitumoral,[3] antibacterial[4] and plant growth inhibitory activities.[5] They are also known as insect feeding deterrents.[6] In recent years it has been recognized that α-methylene group is essential for these activities.[7] Because of that it is not surprising that chemists elaborated many methods for the synthesis of α-methylene-γ-lactones.[8–10]

Our research interest in the synthesis of lactones and their α-methylene analogues was inspired by antifeedant activity of natural α-methylene sesquiterpenoid lactones.[11] We obtained many isoprenoid lactones,[12a–d] including some α-methylene-γ-lactones.[13] The two-step procedure via α-carboxylactones was applied for synthesis of α-methylene lactones. The carboxy group was introduced into the lactone ring by using of methoxymagnesium methyl carbonate (MMC). The decarboxylative methylenation was performed with solution of formaldehyde, *N*-methylaniline, acetic acid and sodium acetate, as was described earlier by Murta.[14] Here we present a simple two-step procedure for the synthesis of α-methylene-γ-lactones from alkenes. The first step, the addition of Meldrum's acid to alkenes or cycloalkenes mediated by cerium(IV) ammonium nitrate (CAN)[15] afforded corresponding α-carboxylactones (Scheme 1). They, without purification, were subjected to decarboxylative methylenation in the second step. In this way, following the simple procedure,[20] α-methylene lactones were obtained in 35–50% yields (Table 1). The structures of products were established on the basis of their ^{1}H NMR, IR and MS (EI) data.[21]



Scheme 1

The analysis of data presented in the Table 1 allows us to draw up several features of this reaction. In this analysis the following mechanism for the formation of α-carboxylactone **F** (Scheme 2) was considered.



Scheme 2

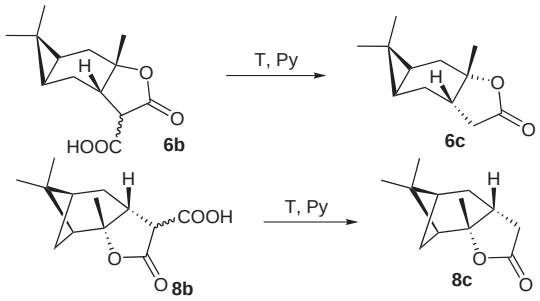
SYNLETT 2006, No. 10, pp 1523–1526
Advanced online publication: 12.06.2006
DOI: 10.1055/s-2006-941598; Art ID: G02506ST

The reaction begins with a formation of Meldrum's acid radical **A** and its addition to a double bond. The radical **B** in the reaction with CAN is converted into carbocation **C** which via the next carbocations **D** and **E** rearranges into α-carboxylactone **F** and acetone.

The process of addition of Meldrum's acid radical to a double bond is highly regioselective and chemoselective. The reaction of β-myrcene (**3**) and limonene (**5**) with one equivalent of Meldrum's acid afforded lactones **3a** and **5a**, respectively, as the only products. It is a result of both electronic and steric requirements of this process. In the case of β-myrcene (**3**), the higher stability of the radical formed after Meldrum's acid radical addition to alkene is the determining factor. In the case of limonene the regioselectivity can be explained taking into consideration the steric interactions in the process of addition of Meldrum's acid radical. Such analysis indicates that the approach and addition of this radical to a less-hindered double bond of isopropenyl group is preferred.

The lactone ring formation step in the reaction of cycloalkenes in which the ring's double bond is involved is highly diastereoselective. In the reactions of 1-methylcyclohexene (**4**), (+)-3-carene (**6**), and (+)-α-pinene (**8**) and (–)-α-pinene (**9**) the respective bi- or tricyclic lactones **4a**, **6a**, **8a**, **9a** with a *cis*-fused lactone ring were formed. Such junction of the lactone and cyclohexane rings is confirmed by spectral data of the corresponding products.

The spectral data of lactone **4a**, obtained by us, are the same as those of the *cis* lactone synthesized by Campaigne.[16] The *cis* junction of the lactone ring to cyclohexane in the pinane system and its *trans* orientation towards the *gem*-dimethyl group was indirectly confirmed by spectral data of saturated lactone **8c** obtained by thermal decarboxylation in pyridine of the crude carboxy lactone **8b** (Scheme 3). The physical ($[\alpha]_D^{20}$, n_D^{20}) and spectral data of lactone **8c** are the same as those determined for the lactone obtained earlier by Paruch et al.[12d]

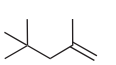
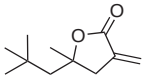
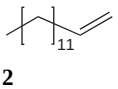
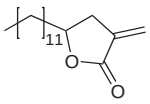
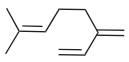
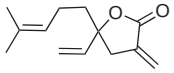
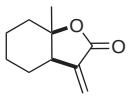
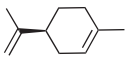
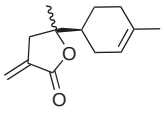
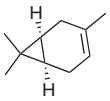
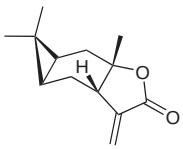
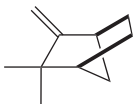
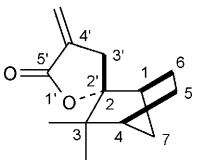
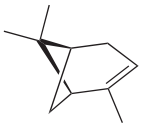
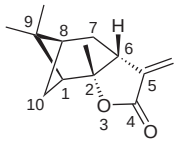
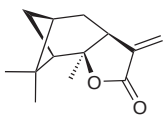


Scheme 3

The spectral data of lactone **6a** obtained from (+)-3-carene (**6**) suggest also the *cis*-junction of the lactone ring and its *trans*-orientation towards the cyclopropane ring. The *trans*-orientation of the lactone ring towards the *gem*-dimethylcyclopropane ring could be supposed from the small difference in chemical shifts ($\Delta\delta$ = 0.01 ppm) of *gem*-dimethyl groups. α-Methylene lactone (**6a**) obtained by us is a diastereoisomer of the lactone obtained earlier by Dulcère et al.[17] The configuration of α-methylene lactone **6a** was also indirectly proven by the structure of saturated lactone **6c**, the product of thermal decarboxylation of lactone **6b** (Scheme 3). The spectral data of this product were identical with data of the pure enantiomer of **6c** obtained by Lamarque.[18]

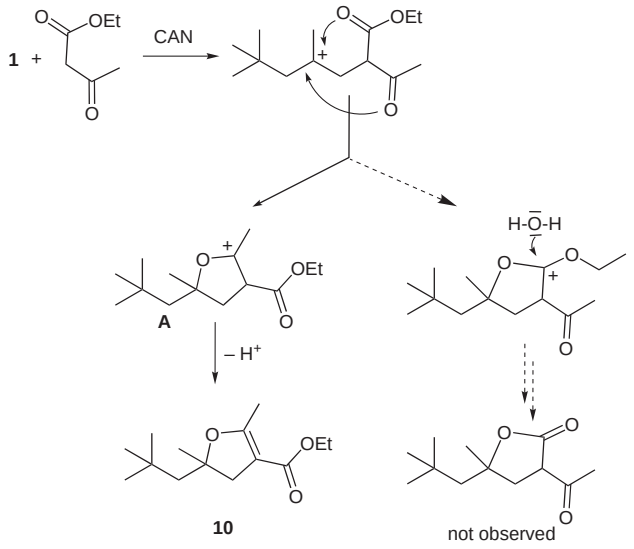
The formation of (+)-α-methylene lactone **8a** from (–)-α-pinene and (–)-α-methylenelactone **9a** from (+)-α-pinene indicates the stereoselectivity of the lactone ring-closing

Table 1 Yields of α-Methylene Lactones

Substrate	Product	Yield (%)
 **1**	 **1a**	40
 **2**	 **2a**	39
 **3**	 **3a**	36
 **4**	 **4a**	50
 **5**	 **5a**	38
 **6**	 **6a**	35
 **7**	 **7a**	40
 **8**	 **8a**	42
 **9**	 **9a**	42

process. High stereoselectivity of this process was also observed in the reaction of racemic camphene, where the racemic α-methylene lactone **7a** was obtained as a product. The structure of lactone **7a** was established on the basis of NMR spectral data, especially those obtained from ^{13}C–^{1}H COSY method. The *exo* orientation of lactone ring was indicated by relatively large difference ($\Delta\delta$ = 0.99 ppm) of chemical shifts of protons of CH_2-7 group and much smaller difference of chemical shifts of CH_2-6 protons ($\Delta\delta$ = 0.25 ppm). The large difference of chemical shifts of CH_2-7 protons indicates that one of them is much closer to the lactone moiety than the other three protons (CH_2-6 and one of CH_2-7).

We have also tried to replace Meldrum's acid by ethyl acetoacetate to synthesize from alkenes, proper α-acetyl lactones. They could be next transformed via α-hydroxyethyl derivative into α,β-unsaturated lactone with exocyclic double bond. Unfortunately instead of α-acetyl lactone ethyl 2-methyl-5-neopentyl-4,5-dihydrofuran-3-carboxylate (**10**) was obtained in 70% yield (Scheme 4). It is a result of a nucleophilic attack of the more reactive ketone carbonyl group and easy proton abstraction from the obtained carbocation **A**. Similar types of compounds were obtained in the reaction of alkenes with ethyl acetoacetate in the presence of manganese(III) acetate.[19]



Scheme 4

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(19) Heiba, E. A. I.; Dessau, R. M. *J. Org. Chem.* **1974**, *39*, 3456.
(20) **General Procedure.**
CAN (20 mmol) was slowly added to a cooled (ice bath) and vigorously stirred solution of alkene (10 mmol) and Meldrum's acid (or ethyl acetoacetate for compound **10**) (10 mmol) in 50 mL MeCN. The reaction was complete when the orange color of the mixture turned to pale-yellow (usually after 1 h). Then the solvent was evaporated (below 50 °C, because of possible decarboxylation reaction). Then, H_2O (100 mL) was added to the residue and the product was extracted with EtOAc (3 × 40 mL). Combined ethereal solutions were washed with brine. The purification of crude product via $NaHCO_3$–HCl procedure significantly decreased the yield of this reaction. So in the next step crude α-carboxylactone was stirred overnight with 3 mL of stock solution containing Et_2NH (3 mL), 30% formaldehyde (6 mL), NaOAc (0.2 g) and AcOH (8 mL). The reaction mixture was acidified with 10% HCl (50 mL) and extracted with Et_2O. Crude product was purified by column chromatography (eluent hexane–Et_2O, starting from 20:1 and next 2:1).The physical and spectral data of compounds obtained are presented below.
(21) **Analytical Data for Compounds Obtained.**
Compound **1a**: n_D^{20} 1.4605. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.19 (1 H, t, *J* = 2.8 Hz, $=CH_2$), 5.57 (1 H, t, *J* = 2.4 Hz, $=CH_2$), 2.72 (1 H, dt, *J* = 16.8, 2.8 Hz, CH_2 in lactone), 2.68 (1 H, dt, *J* = 16.8, 2.4 Hz, CH_2 in lactone), 1.71 and 1.65 [2 H, 2 d, *J* = 14.8 Hz ,$(CH_3)_3CCH_2$, AB system], 1.44 [3 H, s, $(CH_3)CO$], 1.00 [9 H, s, $(CH_3)_3CCH_2$]. IR (film): 1778 (s), 1675 (m), 1290 (m), 1108 (m) cm^{-1}. MS (EI): *m/z* (%) = 183 [M + H](7), 167 (1), 126 (4), 111 (100), 83 (18), 68 (5).
Compound **2a**: mp 86 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.21 (1 H, t, *J* = 2.9 Hz, $=CH_2$), 5.61 (1 H, t, *J* = 2.4 Hz, $=CH_2$), 4.50 [1 H, tt, *J* = 7.6, 5.6 Hz, >CH(O)], 3.01 (1 H, ddt, *J* = 17.0, 7.6, 2.5 Hz, CH_2 in lactone), 2.56 (1 H, ddt, *J* = 17.0, 5.9, 2.9 Hz, CH_2 in lactone), 1.52–1.76 [2 H, m, $CH_3(CH_2)_{10}CH_2$], 1.16–1.44 [20 H, m, $CH_3(CH_2)_{10}CH_2$], 0.86 [3 H, t, *J* = 6.9 Hz, $CH_3(CH_2)_{10}CH_2$]. IR (KBr): 1776 (s), 1676 (w), 1284 (m), 1124 (m), 944 (m) cm^{-1}. MS (EI):

m/z (%) = 267 (72) [M + H], 249 (13), 227 (13), 221 (25), 171 (23), 123 (34), 109 (52), 97 (100), 83 (31), 69 (69).
Compound **3a**: n_D^{20} 1.4885. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.22 (1 H, m, >C=C*H*$_2$), 5.85 (1 H, dd, *J* = 17.2, 11.0 Hz, CH_2=C*H*), 5.60 (1 H, m, =C*H*$_2$), 5.22 (1 H, d, *J* = 17.2 Hz, C*H*$_2$=CH), 5.17 (1 H, d, *J* = 11.0 Hz, C*H*$_2$=CH), 5.06 [1 H, t, *J* = 5.6 Hz, $(CH_3)_2$C=C*H*], 2.82 (2 H, s, CH_2 in lactone), 2.06 (2 H, m, =CHC*H*$_2$CH$_2$), 1.76 (2 H, t, *J* = 8.2 Hz, =CHCH$_2$C*H*$_2$), 1.67 [3 H, s, =C$(CH_3)_2$], 1.59 [3 H, s, =C$(CH_3)_2$]. IR (film,): 1766 (s), 1665 (w), 1276 (m), 1072 (w), 934 (w) cm^{-1}. MS (EI): *m/z* (%) = 207 [M + H] (59), 189 (54), 173 (8), 161 (100), 145 (35), 133 (18), 121 (80), 105 (29), 93 (48), 67 (4).
Compound **4a**: n_D^{20} 1.4962. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.20 (1 H, d, *J* = 3.0 Hz, =C*H*$_2$), 5.44 (1 H, d, *J* = 2.7 Hz, =C*H*$_2$), 2.73 (1 H, m, >C*H*CH$_2$), 1.71–1.25 [m, 8 H, $(CH_2)_4$ in cyclohexyl], 1.46 (3 H, s, CH_3). IR (film): 1776 (s), 1676 (m), 1168 (m), 936 (m) cm^{-1}. MS (EI): *m/z* = 167 (100) [M + H], 151 (14), 138 (10), 123 (61), 108 (9), 95 (18), 79 (8), 67 (10).
Compound **5a**: n_D^{20} 1.5085. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.20 (1 H, t, *J* = 2.8 Hz, =C*H*$_2$), 5.58 (1 H, m, =C*H*$_2$), 5.35 (1 H, m, >C=CH), 2.87 (dt, *J* = 17.1, 2.8 Hz, CH_2 in lactone, diastereomer A), 2.86 (dt, *J* = 17.0, 3.1 Hz, CH_2 in lactone, diastereomer B), 2.57 (1 H, dt, *J* = 17.0, 2.8 Hz, CH_2 in lactone, diastereomer B), 2.56 (1 H, dt, *J* = 17.1, 2.4 Hz, CH_2 in lactone, diastereomer A), 1.70–2.12 (7 H, m, CH_2 and >CH in cyclohexyl), 1.61 [3 H, s, =C(CH_3)], 1.35 and 1.34 [3 H, 2 s, >C(O)CH_3 for both diastereomers]. IR (film): 1768 (s), 1668 (w), 1296 (s), 1060 (m) cm^{-1}. MS (EI): *m/z* (%) = 207 (40) [M + H], 189 (9), 161 (15), 121 (100), 111 (37), 93 (27), 93 (27), 83 (19).
Compound **6a**: $[\alpha]_D^{20}$ –46 (*c* 1.85 $CHCl_3$); n_D^{20} 1.5321. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.25 (1 H, d, *J* = 2.7 Hz, =C*H*$_2$), 5.54 (1 H, d, *J* = 2.3 Hz, =C*H*$_2$), 2.69 (1 H, m, CH< in lactone), 2.07 (1 H, dd, *J* = 14.6, 6.8 Hz, >CHC*H*$_2$), 1.88 (1 H, dd, *J* = 14.6, 5.1 Hz, >CHC*H*$_2$), 1.30 [3 H, s, (CH_3)CO<], 1.10 (1 H, m, >CHC*H*$_2$CH<), 0.93 and 0.94 [6 H, two s, $(CH_3)_2$C<], 0.81 (1 H, m, >CHC*H*$_2$CH<), 0.44–0.56 (2 H, m, cyclopropyl). IR (film): 1768 (s), 1668 (w), 1296 (s), 1060 (m) cm^{-1}. MS (EI): *m/z* (%) = 206 (53) [M$^+$], 191 (23), 177 (13), 163 (53), 145 (25), 121 (22), 110 (98), 96 (73), 82 (100), 67 (30).

Compound **7a**: mp 73–74 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.13 (1 H, t, *J* = 2.8 Hz, =C*H*$_2$), 5.57 (1 H, t, *J* = 2.7 Hz, =C*H*$_2$), 2.91 (1 H, dt, *J* = 17.0, 2.7 Hz, CH_2 in lactone), 2.80 (1 H, dt, *J* = 17.0, 2.8 Hz, CH_2 in lactone), 2.15 (1 H, dd, *J* = 6.4, 1.1 Hz, H-1), 2.10 (1 H, dd, *J* = 10.4, 1.8 Hz, CH_2-7), 1.85 (1 H, d, *J* = 1.8 Hz, H-4), 1.58 (1 H, ddd, *J* = 12.4, 10.1, 3.2 Hz, CH_2-6), 1.52 (1 H, ddd *J* = 13.2, 6.5, 3.2 Hz, CH_2-5), 1.33 (1 H, ddd, *J* = 12.4, 6.5, 1.3 Hz, CH_2-6), 1.25 (1 H, ddd, *J* = 13.2, 10.1, 1.3 Hz CH_2-5), 1.21 (1 H, d, *J* = 10.4 Hz, CH_2-7), 0.99 [3 H, s, C$(CH_3)_2$], 0.95 [3 H, s, C$(CH_3)_2$]. ^{13}C NMR ($CDCl_3$): 169.9, 136.5, 120.5, 93.7, 49.2, 49.1, 44.0, 34.8, 32.1, 25.7, 24.4, 24.1, 22.2. The NMR assignments were aided by ^{13}C DEPT, ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectroscopy. IR (KBr): 1759 (s), 1667 (w), 1120 (w), 975 (w) cm^{-1}. MS (EI): *m/z* (%): 207 (40) [M + H], 191 (13), 133 (24), 138 (72), 123 (100), 121 (67), 108 (56), 95 (64), 79 (45), 67 (94).
Compound **8a**: $[\alpha]_D^{20}$ +35 (*c* 2.01 $CHCl_3$); mp 73–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.25 (1 H, d, *J* = 2.9 Hz, =C*H*$_2$), 5.61 (1 H, d, *J* = 2.5 Hz, =C*H*$_2$), 2.95 (1 H, dq, *J* = 10.8, 2.8 Hz, H-6), 2.54 (1 H, ddt, *J* = 13.5, 10.8, 2.2 Hz, CH_2-7), 2.22 (1 H, ddd, *J* = 12.0, 6.0, 2.2 Hz H-8), 2.21 (1 H, d, *J* = 5.4 Hz, H-1), 1.93 (1 H, dddd, *J* = 11.0, 6.0, 5.4, 2.2 Hz, CH_2-10), 1.76 (1 H, dt, *J* = 13.5, 3.3 Hz, CH_2-7), 1.47 (3 H, s, CH_3, C-2), 1.28 [3 H, s, $(CH_3)_2$C<], 1.02 (1 H, dd, *J* = 12.0, 11.0 Hz, CH_2-10), 0.90 [3 H, s, $(CH_3)_2$C<]. IR (KBr): 1758 (s), 1655 (m), 1288 (m), 1066 (m), 1016 (m) cm^{-1}. MS (EI): *m/z* (%) = 207 (100) [M + H], 191 (16), 136 (41), 151 (21), 135 (22), 121 (26), 107 (25), 91 (34), 79 (44).
Compound **9a**: $[\alpha]_D^{20}$ –30 (*c* 1.29 $CHCl_3$).
Compound **10**: yield 70%; n_D^{20} 1.4673. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.14 (2 H, q, *J* = 7.1 Hz, CH_3CH_2O-), 2.80 (1 H, dq, *J* = 11.3 Hz, J^5 = 1.5 Hz, CH_2), 2.57 (1 H, dq, *J* = 11.3, 1.5 Hz, CH_2), 2.14 [3 H, t, J^5 = 1.5 Hz, C(O)CH_3], 1.70 and 1.63 [2 H, two d, *J* = 14.6 Hz $(CH_3)_3CCH_2$, AB system], 1,37 [3 H, s, (CH_3)CO], 1.26 (3 H, t, *J* = 7.1 Hz, CH_3CH_2O), 0.99 [9 H, s, $(CH_3)_3CCH_2$]. ^{13}C NMR ($CDCl_3$): 166.7, 166.6, 101.0, 89.2, 59.3, 53.2, 43.5, 31.2, 28.2, 14.5. IR (film): 2960 (s), 1708 (s), 1660 (s), 1268 (m), 1224 (m), 1096 (m) cm^{-1}. MS (EI): *m/z* (%) = 241 (11) [M + H], 222 (21), 207 (20), 198 (42), 166 (43), 141 (100), 111 (56), 95 (70), 67 (43).