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Synthesis of Bicyclic γ-Lactones Promoted by $Mn(OAc)_3$: Regio- and Diastereoselectivities

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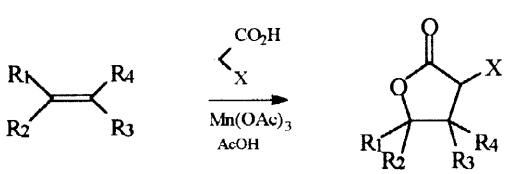
Abstract: *The regio- and diastereoselectivities of $Mn(OAc)_3$-induced addition of monomethyl malonate on some cycloalkenes and cycloalkadienes are studied. The latter is greatly improved when starting from cycloalkadienes.*

INTRODUCTION

γ-Lactones constitute an important class of compounds which is largely represented in the field of natural products.[1-3] They are also useful synthons for further elaboration.[4-10]

The simplest approach for their synthesis is formally the addition of acetic acid[11-14] or acetic acid derivatives[15-20] onto alkenes, which can be realized in the presence of $Mn(OAc)_3$. With di- or trisubstituted cycloalkenes, two or three new stereocentres are formed when acetic acid or acetic acid derivatives are involved in the reaction. Many studies have been carried out in this field,[21-25] particularly by Snider regarding intramolecular reactions.[24] The intermolecular approach has been studied by Fristad with acetic acid derivatives such as cyanoacetic, chloroacetic, 3-chloropropionic, monomethyl malonic[15] and malonic[16] acids (Scheme 1). Corey[17] and Trogolo[18,19] reported the addition of cyanoacetic acid and monoethyl or monomethyl malonate onto olefins but without determining the relative configuration of the products.

Scheme 1



X= H, Cl, CH_2Cl, CN, CO_2H, CO_2Me

In fact, few data concerning the regio- and stereoselectivities of the reaction were described with monomethyl malonate and even fewer with acetic acid. Accordingly, in this paper, we report our results about the regio- and stereoselectivities of the $Mn(OAc)_3$-mediated addition of monomethyl malonate (X= CO_2Me) on various cycloalkenes and cycloalkadienes.

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RESULTS AND DISCUSSION

As pointed out by Melikyan,[21] the experimental conditions described in the literature vary to a great extent: it is thus very difficult to compare the previous results between them.[15,17,18] A preliminary study conducted in our laboratory had shown that the best results were obtained when 1 eq. of the olefin was oxidized by 2.2 eq. of $Mn(OAc)_3$ and 2.5 eq. of potassium monomethyl malonate in AcOH at 70°C under an inert atmosphere (Scheme 2).

Scheme 2

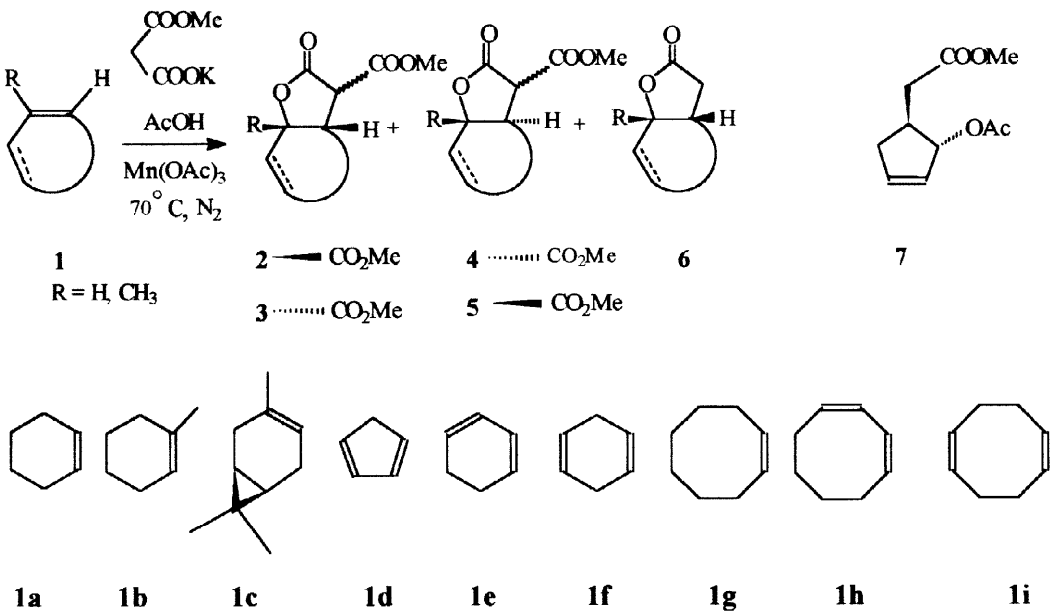

Table 1. Addition of Potassium Monomethyl Malonate on Cycloalkenes and -alkadienes **1a-i**. Relative Ratio of *cis*-Fused **(2+3+6)** to *trans*-Fused **(4+5)** Lactones.

Entry	1	Time (min)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	(2+3+6) : (4+5)	Yield (%)[a]
1	a	30	69	13	18	-	-	82 : 18	32
2	b	50	47	-	32	-	21	68 : 32	21
3	c	20	35	-	-	-	65	100 : 0	57[b]
4	d	10	100	-	-	-	-	100 : 0	8[c]
5	e	30	100	-	-	-	-	100 : 0	41
6	f	20	90	10	-	-	-	100 : 0	11
7	g	15	18	-	76	6	-	18 : 82	70
8	h	15	7	-	82	11	-	7 : 93	70
9	i	15	-	-	100	-	-	0 : 100	40

[a] Chromatographic yield of lactones based on the consumed starting olefin.[b] 40% of the starting material was recovered.[c] With 2% of the *trans*-carbomethoxyacetate 7 and 18% (estimated by GPC) of a complex mixture of four carbomethoxyacetates whose structure could not be established.

Structural determination :

Our results are summarized in Table 1. When compared with the addition of acetic acid on the same substrates, the reaction is always cleaner (the formation of mono- and diacetates is totally suppressed) and shorter, and the overall yield greatly enhanced.[26]

For each entry, the major α-carbomethoxy-γ-lactone could always be obtained as a pure product by chromatography and its structure determined by NMR and, whenever possible (**4g-i**), by X-ray crystallography.[27] The relative configuration of the minor isomers (which could not be obtained in a pure state) has been assigned by NMR and, in the more complex cases, by chemical correlations (catalytic hydrogenation, carbomethoxylation or decarbomethoxylation) with bicyclic lactones whose configurations had already been elucidated.

Cyclopentadiene :

A single epimer of a *cis*-fused bicyclic lactone is obtained, albeit in a very low yield (entry 4).

Six-membered rings :

Overall, the addition of monomethyl malonate leads to a mixture of two or three γ-lactones (entries 1-3, 6). Concerning the ring junction, the diastereoselectivity is only moderate with cyclohexene **1a** since 82% of *cis*-fused (**2a+3a**) and 18% of *trans*-fused (**4a**) bicyclic lactones are obtained (entry 1). It further decreases (68:32) with the introduction of an angular methyl (1-methylcyclohexene **1b**, entry 2). On the contrary, it reaches 100% when using cyclohexa-1,3-diene **1e** and cyclohexa-1,4-diene **1f**. With respect to the relative configuration of the carbomethoxy group to the adjacent ring junction, the *trans* relationship is the major one. It increases from 87% with **1a** to 90% with **1f** and 100% with **1b** and **1e**. Furthermore, the diastereoselectivity is total in the last case as only the $1\beta,6\beta,7\alpha$ epimer **2e** is formed (entry 5).

The reaction with (1*S*)-Δ^3-carene **1c** affords the uncarbomethoxylated γ-lactone **6c** as the main product (entry 3). For lactones **6c** and **2c**, the regioselectivity is the one expected: the oxygen atom of the lactone moiety is linked to the carbon bearing the angular methyl, contrary to the findings of Chabudzinski.[28] Moreover, the NMR data and NOESY experiments show that the cyclopropane ring and the lactone moiety are in a *trans* relationship. For this olefin, the diastereoselectivity is therefore complete.

It should also be noted that the uncarbomethoxylated lactones **6b** and **6c** (entries 2,3) do not arise from the direct addition of acetic acid onto olefins **1b** and **1c** but from an *in situ* decarbomethoxylation of lactones **2b** and **2c**: when the reaction was performed for the same duration depicted in Table 1, but without monomethyl malonate, no lactone **6b** or **6c** could be detected; furthermore, when lactones **2b** and **2c** were submitted to the reaction conditions, lactones **6b** and **6c** were formed.

Eight-membered rings :

Cyclooctene **1g** and cycloocta-1,3-diene **1h** lead to three bicyclic lactones (two *trans*-fused epimers and one *cis*-fused epimer) while cycloocta-1,5-diene **1i** gives a single (*trans*-fused) bicyclic lactone (entries 7-9).

We find here the same trend observed by us with six-membered rings *i.e.* the introduction of a supplementary intracyclic double bond notably increases the diastereoselectivity (from 18:82 to 0:100).

As unsaturated lactones can be quantitatively hydrogenated, this opens up an indirect access to diastereomerically pure saturated bicyclic lactones (**2a** from **2e**, **4g** from **4i**). Likewise, in most cases, the *cis*-fused lactones **6** (six-membered rings) and their *trans*-fused counterparts (eight-membered rings) can readily be prepared in good yield (70-80%) by decarbomethoxylation of the corresponding carbomethoxylated lactones **2** and **4**, respectively.[29]

CONCLUSION

With cycloalkenes, we verified the same progression observed by Fristad *i.e.* when the size of the ring increases, the proportion of *trans*-fused products increases too. We have also shown that cycloalkadienes lead to a significantly higher stereoselectivity which could be explained by the presence of an extra double bond thereby reducing conformational flipping. An angular methyl decreases this stereoselectivity but Δ^3-carene, which possesses an angular methyl, leads to **2c** (and the corresponding decarbomethoxylated γ-lactone **6c**) with 100% stereoselectivity, the cyclopropane ring seeming to play the same role as a double bond.

Moreover, by using monomethyl malonate and an appropriate cyclic diene, not only bicyclic lactones can be prepared in fair to good yield but it is also possible to obtain a total control of the relative configurations for the three new stereocentres formed during the reaction.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 297 apparatus, neat or in $CHCl_3$. ^{1}H-NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 250 MHz, using TMS as internal standard in $CDCl_3$. Chemical shifts are reported in parts per million and are given in δ units; coupling constants are given in Hertz. We used the following symbols to report the multiplicity and shape of signals: s (singlet), d (doublet), t (triplet), m (multiplet). ^{13}C-NMR spectra were recorded on the same spectrometer, operating at 62 MHz. Mass spectra were recorded using a HP 5987 instrument. Melting points were determined in capillary tubes using an Electrothermal IA 9100 apparatus. The progress of chromatographic separations was monitored by TLC on silica gel plates (Merck Kieselgel 60 F_{254}). Column flash chromatography was performed on silica gel (Merck Kieselgel 60H).

General procedure for the preparation of α-carbomethoxy-γ-lactones 2-5- A two-necked 50 ml round-bottomed flask equipped with a reflux condenser was charged with olefin (2 mmol), potassium monomethyl

malonate (780 mg, 5 mmol) and $Mn(OAc)_3.2H_2O$ (1.180 g, 4.4 mmol) in glacial acetic acid (20 ml). The solution was stirred for 20 min at room temperature under a stream of N_2 then placed in an oil bath at 70°C. The reaction turned from dark brown to light yellow in 10-50 min. After cooling, the reaction mixture was poured into brine (80 ml) and extracted with Et_2O (4x20 ml). The organic layer was washed with a saturated $NaHCO_3$ solution to remove acetic acid and dried over $MgSO_4$. Removal of the solvent under reduced pressure at room temperature afforded an oily residue which was flash chromatographed (eluent: hexane-Et_2O gradient).

General procedure for hydrogenation - A two-necked 25 ml round-bottomed flask was charged with unsaturated γ-lactone (0.2 mmol) and 10% palladium on activated carbon (20 mg) in MeOH (3 ml). The mixture was stirred for 36 h at room temperature under H_2 (1 atm) then filtered through a Celite pad. Removal of the solvent under reduced pressure afforded 0.2 mmol of the pure saturated γ-lactone.

General procedure for decarbomethoxylation - A 10 ml round-bottomed flask equipped with a reflux condenser was charged with α-carbomethoxy-γ-lactone (0.89 mmol), NaCl (79 mg, 1.35 mmol) and H_2O (30 µl, 1.66 mmol) in DMF or DMSO (2 ml). The mixture was stirred for 3-5h (depending on the substrate) at 150°C. It was then cooled, poured into brine (10 ml) and extracted with Et_2O (4x5 ml). The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure at room temperature afforded an oily residue which was flash chromatographed (eluent: hexane-Et_2O gradient) to give pure γ-lactones (70-80% yield).

General procedure for carbomethoxylation - A two-necked 50 ml round-bottomed flask equipped with a reflux condenser was charged with γ-lactone (0.98 mmol, obtained by $Mn(OAc)_3$-promoted addition of acetic acid on the appropriate olefin)[26] and NaH (190 mg, 4.9 mmol) previously washed with hexane, in freshly distilled dimethyl carbonate (8 ml). The suspension was stirred for 5-7 h at 90°C under N_2. It was then cooled in an ice bath and H_2O (10 ml) was added dropwise. After extraction with Et_2O (4x10 ml), the organic layer was washed with 10% HCl (3x10 ml) then with H_2O (3x10 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure at room temperature afforded an oily residue which was flash chromatographed (eluent: hexane-Et_2O gradient) to give pure α-carbomethoxy-γ-lactones (70-80% yield).

(1β, 6β, 9α)-9-carbomethoxy-7-oxabicyclo[4.3.0]nonan-8-one (2a)[15, 30, 31]

IR, ν_{max} cm^{-1} ($CHCl_3$) 1780 (C=O, γ-lactone), 1735 (C=O, ester); ^1H NMR, δ ppm 1.36-1.62 (m, 5H), 1.70-1.88 (m, 3H), 2.78-2.88 (m, 1H), 3.36 (d, ^3J 5.5 Hz, 1H), 3.79 (s, 3H), 4.73 (ddd, ^3J 10.6, 5.3, 5.3 Hz, 1H); ^{13}C NMR, δ ppm 20.32, 21.98, 26.22, 28.03, 39.07, 52.94, 53.12, 78.36, 167.84, 172.09. Mp = 35°C. Anal. Found C, 60.38; H, 7.11%. Calc. for $C_{10}H_{14}O_4$ C, 60.59; H, 7.12%.

(1β, 6β, 9β)-9-carbomethoxy-7-oxabicyclo[4.3.0]nonan-8-one (3a)[32]

IR, ν_{max} cm^{-1} (film) 1780 (C=O, γ-lactone), 1735 (C=O, ester); ^1H NMR, δ ppm 3.72 (d, ^3J 7.1Hz, 1H), 3.81 (s, 3H), 4.47-4.55 (m, 1H); ^{13}C NMR, δ ppm 19.30, 22.88, 25.45, 29.66, 38.88, 52.35, 52.75, 77.46.

(1α, 6β, 9β)-9-carbomethoxy-7-oxabicyclo[4.3.0]nonan-8-one (4a)

IR, ν_{max} cm^{-1} (film) 1780 (C=O, γ-lactone), 1735 (C=O, ester); ^1H NMR, δ ppm 1.17-1.67 (m, 4H), 1.72-1.82 (m, 2H), 1.82-2.07 (m, 2H), 2.37 (m, 1H), 3.31 (d, ^3J 12.9 Hz, 1H), 3.82 (s, 3H), 3.87 (td, ^3J 9.9, 9.9, 3.8 Hz, 1H); ^{13}C NMR, δ ppm 23.83, 24.93, 27.41, 29.96, 48.31, 52.80, 83.06, 167.99, 171.43. Anal. Found C, 60.38; H, 7.11%. Calc. for $C_{10}H_{14}O_4$ C, 60.59; H, 7.12%.

(1β, 6β, 7α)-1-methyl-7-carbomethoxy-9-oxabicyclo[4.3.0]nonan-8-one (2b)[31]

IR, ν_{max} cm^{-1} (film) 1780 (C=O, γ-lactone), 1735 (C=O, ester); ^1H NMR, δ ppm 1.20-2.03 (m, 8H), 1.45 (s, 3H), 2.66-2.77 (m, 1H), 3.57 (d, ^3J 12.8 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR, δ ppm 19.77, 22.57, 24.08, 24.11, 35.36, 45.04, 50.17, 52.84, 84.34, 168.34, 171.01. Anal. Found C, 62.20; H, 7.51%. Calc. for $C_{11}H_{16}O_4$ C, 62.25; H, 7.60%.

(1β, 6α, 7β)-1-methyl-7-carbomethoxy-9-oxabicyclo[4.3.0]nonan-8-one (4b)[31]

IR, ν_{max} cm^{-1} (film) 1780 (C=O, γ-lactone), 1735 (C=O, ester); ^1H NMR, δ ppm 1.24 (s, 3H), 1.20-2.03 (m, 8H), 2.41-2.47 (m, 1H), 3.35 (d, ^3J 13.8 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR, δ ppm 18.57, 22.95, 25.26, 36.83, 50.48, 52.75, 85.11, 168.47, 171.38. Anal. Found C, 62.20; H, 7.51%. Calc. for $C_{11}H_{16}O_4$ C, 62.25; H, 7.60%.

***cis*-1-methyl-9-oxabicyclo[4.3.0]nonan-8-one (6b)**

IR, ν_{max} cm^{-1} (film) 1770 (C=O, γ-lactone); ^1H NMR, δ ppm 1.04-1.87 (m, 8H), 1.12 (s, 3H), 1.93-2.02 (m, 1H), 2.10 (dd, ^2J 16.9, ^3J 7.8 Hz, 1H), 2.31 (dd, ^2J 16.9, ^3J 7.5 Hz, 1H); ^{13}C NMR, δ ppm 21.35, 22.06, 25.68, 26.60, 34.84, 35.35, 40.40, 85.23, 176.90. Anal. Found C, 69.99; H, 9.09%. Calc. for $C_9H_{14}O_2$ C, 70.10; H, 9.15%.

(1*S*, 3*S*, 5*R*, 7*S*, 8*R*)-1,4,4-trimethyl-8-carbomethoxy-10-oxatricyclo[5.3.0.$0^{3,5}$]decan-9-one (2c)

IR, ν_{max} cm^{-1} (film) 3025 (C-H, cyclopropane), 1770 (C=O, γ-lactone), 1740 (C=O, ester); ^1H NMR, δ ppm 0.60-0.75 (m, 2H), 0.84-0.94 (m, 1H), 0.97-1.03 (m, 1H), 1.00 (s, 3H), 1.05 (s, 3H), 1.46 (s, 3H), 1.83-2.02 (m, 1H), 2.13-2.22 (m, 1H), 2.69-2.74 (m, 1H), 3.64 (d, ^3J 5.7 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR, δ ppm 14.58,

16.72, 17.39, 18.83, 22.11, 28.15, 28.57, 29.98, 42.75, 53.08, 53.93, 86.53, 169.10, 171.12 ; $[\alpha]^{24}_D$ = -14.9° (c 2.08, MeOH). Anal. Found C, 66.55; H, 7.88%. Calc. for $C_{14}H_{20}O_4$ C, 66.63; H, 7.99%.

(1*S*, 3*S*, 5*R*, 7*S*)-1,4,4-trimethyl-10-oxatricyclo[5.3.0.0^{3,5}]decan-9-one (6c)

IR, ν_{max} cm^{-1} (film) 3020 (C-H, cyclopropane), 1750 (C=O, γ-lactone); ^{1}H NMR, δ ppm 0.61-0.77 (m, 2H), 0.81-0.96 (m, 1H), 0.98-1.03 (m, 1H), 1.00 (s, 3H), 1.05 (s, 3H), 1.39 (s, 3H), 1.76 (dd, ^2J 15.0, ^3J 6.9 Hz, 1H), 2.15 (dd, ^2J 15.1, ^3J 6.8 Hz, 1H), 2.29-2.38 (m, ^3J 11.1, 4.6 Hz, 1H), 2.48 (dd, ^2J 18.6, ^3J 4.6 Hz, 1H), 2.94 (dd, ^2J 11.1, ^3J 11.1 Hz, 1H); ^{13}C NMR, δ ppm 14.59, 16.34, 17.76, 18.54, 22.80, 28.21, 28.51, 30.03, 35.62, 37.45, 86.53, 176.65 ; $[\alpha]^{24}_D$ = +16.0° (c 2.08, MeOH). Anal. Found C, 74.10; H, 9.29%. Calc. for $C_{12}H_{18}O_2$ C, 74.19; H, 9.34%.

(1β, 4α, 5β)-4-carbomethoxy-2-oxabicyclo[3.3.0]oct-7-en-3-one (2d)

IR, ν_{max} cm^{-1} (film) 1775 (C=O, γ-lactone), 1740 (C=O, ester), 1615 (C=C); ^{1}H NMR, δ ppm 2.33 (dddd, ^2J 17.5, ^3J 4.4, 2.2, ^4J 2.2 Hz, 1H), 2.76 (dddd, ^2J 17.5, ^3J 7.9, 3.9, ^4J 1.7 Hz, 1H), 3.32 (d, ^3J 6.6 Hz, 1H), 3.44 (m, 1H), 3.75 (s, 3H), 5.53 (ddd, ^3J 7.4, 0.9, ^4J 0.9 Hz, 1H), 5.81-5.86 (m, 1H), 6.01-6.07 (m, 1H); ^{13}C NMR, δ ppm 38.60, 40.33, 53.32, 54.05, 88.85, 129.10, 137.06, 168.53, 171.91. Anal. Found C, 59.25; H, 5.50%. Calc. for $C_9H_{10}O_4$ C, 59.34; H, 5.53%.

***trans*-1-acetoxy-2-carbomethoxymethyl cyclopent-4-ene (7)**

IR, ν_{max} cm^{-1} (film) 1740 (C=O, ester), 1615 (C=C); ^{1}H NMR, δ ppm 1.81 (ddd, ^2J 14.4, ^3J 7.4, 5.3 Hz, 1H), 1.96 (s, 3H), 2.06 (ddd, ^2J 14.4, ^3J 7.4, 5.3 Hz, 1H), 2.20-2.41 (m, 2H), 3.17-3.27 (m, 1H), 3.62 (s, 3H), 5.59-5.69 (m, 1H), 5.77-5.82 (m, 1H), 5.93-6.01 (m, 1H); ^{13}C NMR, δ ppm 21.39, 37.00, 39.78, 40.87, 51.77, 79.81, 130.07, 140.96, 171.16, 172.84.

(1β, 6β, 7α)-7-carbomethoxy-9-oxabicyclo[4.3.0]non-2-en-8-one (2e)[30]

IR, ν_{max} cm^{-1} ($CHCl_3$) 1785 (C=O, γ-lactone), 1735 (C=O, ester); ^{1}H NMR, δ ppm 1.57 -1.71 (m, 1H), 1.78-1.83 (m, 1H), 2.09-2.20 (m, 2H), 2.98-3.07 (m, 1H), 3.42 (d, ^3J 6.6 Hz, 1H), 3.82 (s, 3H), 5.03 (ddd, ^3J 6.3, 3.3, ^4J 1.5 Hz, 1H), 5.84 (dddd, ^3J 10.2, 3.3, ^4J 2.0, 2.0 Hz, 1H), 6.10 (dddd, ^3J 10.2, 3.9, 3.9 ^4J 1.0 Hz, 1H); ^{13}C NMR, δ ppm 21.61, 22.34, 37.93, 51.34, 53.04, 75.16, 123.22, 133.62, 167.95, 171.35 ; Mp = 73°C. Anal. Found C, 61.52; H, 6.18%. Calc. for $C_{10}H_{12}O_4$ C, 61.22; H, 6.16%.

(1β, 6β, 9α)-9-carbomethoxy-7-oxabicyclo[4.3.0]non-3-en-8-one (2f)

IR, ν_{max} cm^{-1} (film) 1775 (C=O, γ-lactone), 1735 (C=O, ester); ^{1}H NMR, δ ppm 1.96-2.56 (m, 4H), 3.05 (ddd, ^3J 15.6, 8.1, 4.8 Hz, 1H), 3.32 (d, ^3J 8.1 Hz, 1H), 3.74 (s, 3H), 4.83 (dt, ^3J 6.9, 4.8, 4.8 Hz, 1H), 5.61-5.81

(m, 2H); ^{13}C NMR, δ ppm 25.32, 27.61, 36.65, 52.53, 52.95, 76.32, 124.16, 125.02, 167.90, 171.52. Anal. Found C, 61.31; H, 6.13%. Calc. for $C_{10}H_{12}O_4$ C, 61.22; H, 6.16%.

(1β, 6β, 9β)-9-carbomethoxy-7-oxabicyclo[4.3.0]non-3-en-8-one (3f)

IR, ν_{max} cm^{-1} (film) 1775 (C=O, γ-lactone), 1735 (C=O, ester); ^{1}H NMR, δ ppm 1.96-2.56 (m, 4H), 2.75-2.87 (m, 1H), 3.30 (d, ^3J 12.9 Hz, 1H), 3.71 (s, 3H), 4.44-4.56 (m, 1H), 5.61-5.81 (m, 2H); ^{13}C NMR, δ ppm 21.91, 26.81, 35.90, 51.78, 52.53, 76.09, 123.03, 124.74, 167.53, 171.17. Anal. Found C, 61.31; H, 6.13%. Calc. for $C_{10}H_{12}O_4$ C, 61.22; H, 6.16%.

(1β, 8β, 11α)-11-carbomethoxy-9-oxabicyclo[6.3.0]undecan-10-one (2g)[15, 32]

IR, ν_{max} cm^{-1} (film) 1785 (C=O, γ-lactone), 1745 (C=O, ester); ^{1}H NMR, δ ppm 2.90-3.03 (m, 1H), 3.29 (d, ^3J 10.3 Hz, 1H), 3.81 (s, 3H), 4.81 (m, 1H); ^{13}C NMR, δ ppm 43.29, 53.00, 84.25, 171.06, 168.22.

(1α, 8β, 11β)-11-carbomethoxy-9-oxabicyclo[6.3.0]undecan-10-one (4g)[15, 30]

IR, ν_{max} cm^{-1} ($CHCl_3$) 1785 (C=O, γ-lactone), 1745 (C=O, ester); ^{1}H NMR, δ ppm 1.23-1.34 (m, 1H), 1.38-1.54 (m, 3H), 1.54-1.62 (m, 1H), 1.66-1.81 (m, 4H), 1.84-1.90 (m, 1H), 1.90-2.05 (m, 1H), 2.18-2.28 (m, 1H), 2.74-2.88 (m, 1H), 3.32 (d, ^3J 6.3 Hz, 1H), 3.82 (s, 3H), 4.44 (ddd, ^3J 8.0, 8.0, 2.9 Hz, 1H); ^{13}C NMR, δ ppm 21.90, 24.22, 26.61, 27.28, 33.35, 34.39, 44.85, 52.98, 55.50, 84.94, 168.18, 170.60; Mp = 78°C. Anal. Found C, 63.60; H, 8.04%. Calc. for $C_{12}H_{18}O_4$ C, 63.70; H, 8.02%.

(1α, 8β, 11α)-11-carbomethoxy-9-oxabicyclo[6.3.0]undecan-10-one (5g)[32]

IR, ν_{max} cm^{-1} (film) 1785 (C=O, γ-lactone), 1745 (C=O, ester); ^{1}H NMR, δ ppm 2.56-2.59 (m, 1H), 3.61 (d, ^3J 8.9 Hz, 1H), 3.82 (s, 3H), 4.63-4.73 (m, 1H); ^{13}C NMR, δ ppm 28.34, 29.69, 34.11, 52.53, 54.13, 86.23. Anal. Found C, 63.60; H, 8.04%. Calc. for $C_{12}H_{18}O_4$ C, 63.70; H, 8.02%.

(1β, 8β, 9α)-9-carbomethoxy-11-oxabicyclo[6.3.0]undec-2-en-10-one (2h)[32]

IR, ν_{max} cm^{-1} (film) 1795 (C=O, γ-lactone), 1750 (C=O, ester); ^{1}H NMR, δ ppm 3.19 (d, ^3J 13.0 Hz, 1H), 5.31 (ddd, ^3J 10.4, 6.1, ^4J 1.2 Hz, 1H); ^{13}C NMR, δ ppm, 79.17, 125.58, 134.94, 168.13, 171.57. Anal. Found C, 64.06; H, 7.23%. Calc. for $C_{12}H_{16}O_4$ C, 64.27; H, 7.19%.

(1β, 8α, 9β)-9-carbomethoxy-11-oxabicyclo[6.3.0]undec-2-en-10-one (4h)[30]

IR, ν_{max} cm^{-1} ($CHCl_3$) 1795 (C=O, γ-lactone), 1750 (C=O, ester); ^{1}H NMR, δ ppm 1.28-1.45 (m, 2H), 1.60-2.02 (m, 4H), 2.18-2.25 (m, 2H), 2.44-2.59 (m, 1H), 3.32 (d, ^3J 12.8 Hz, 1H), 3.82 (s, 3H), 4.96 (ddd, ^3J 10.6, 5.7, ^4J 1.3 Hz, 1H), 5.68 (tdd, ^3J 10.8, 7.5, ^4J 1.3 Hz, 1H), 5.85 (dd, ^3J 10.8, 5.7 Hz, 1H); ^{13}C NMR,

δ ppm 23.62, 24.97, 27.03, 27.76, 50.15, 52.96, 53.86, 81.62, 128.92, 130.05, 167.78, 171.06 ; Mp = 105°C. Anal. Found C, 64.06; H, 7.23%. Calc. for $C_{12}H_{16}O_4$ C, 64.27; H, 7.19%.

(1β, 8α, 9α)-9-carbomethoxy-11-oxabicyclo[6.3.0]undec-2-en-10-one (5h)[32]

IR, ν_{max} cm^{-1} (film) 1795 (C=O, γ-lactone), 1750 (C=O, ester); ^1H NMR, δ ppm 3.54 (d, ^3J 8.6 Hz, 1H), 3.80 (s, 3H), 5.35-5.42 (m, 1H); ^{13}C NMR, δ ppm 23.80, 24.14, 24.81, 27.84, 28.62, 49.10, 52.96, 82.19, 129.35, 129.84. Anal. Found C, 64.06; H, 7.23%. Calc. for $C_{12}H_{16}O_4$ C, 64.27; H, 7.19%.

(1α, 8β, 11β)-11-carbomethoxy-9-oxabicyclo[6.3.0]undec-4-en-10-one (4i) [30]

IR, ν_{max} cm^{-1} ($CHCl_3$) 1790 (C=O, γ-lactone), 1750 (C=O, ester); ^1H NMR, δ ppm 1.37-1.52 (m, 1H), 1.56-1.66 (m, 1H), 1.91-2.04 (m, 1H), 2.15-2.45 (m, 5H), 2.78-2.91 (m, 1H), 3.36 (d, ^3J 11.0 Hz, 1H), 3.82 (s, 3H), 4.38 (ddd, ^3J 10.6, 8.5, 4.0 Hz, 1H), 5.62-5.79 (m, 2H); ^{13}C NMR, δ ppm 21.12, 24.04, 31.84, 33.38, 44.30, 53.05, 54.62, 84.36, 129.59, 129.66, 168.16, 170.68 ; Mp = 83°C. Anal. Found C, 64.22; H, 7.16%. Calc. for $C_{12}H_{16}O_4$ C, 64.27; H, 7.19%.

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