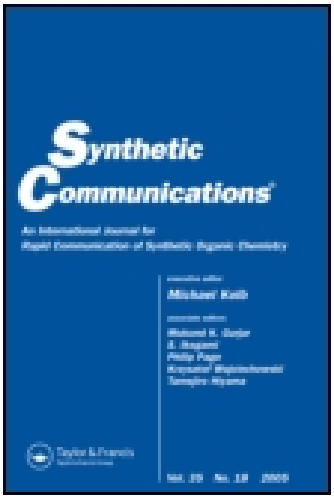

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Stereoselective Synthesis and Characterization of (Z)-(-)-4-(1′-Alkoxyl-1′-alkyloxycarbonyl-methylidene)-5(R)-[(1R)-menthyloxy]-γ-butyrolactones

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STEREOSELECTIVE SYNTHESIS AND CHARACTERIZATION OF (*Z*)-(−)-4-(1′-ALKOXYL-1′-ALKYLOXYCARBONYL-METHYLIDENE)-5(*R*)-[(1*R*)-MENTHYLOXY]-γ-BUTYROLACTONES

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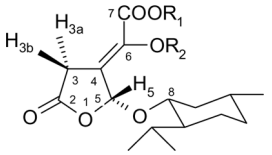
GRAPHICAL ABSTRACT



Abstract *A series of enantiomerically pure (*Z*)-(−)-4-(1′-alkyloxy-1′-alkyloxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactones were synthesized and characterized in good to excellent yields via* O*-alkylation of (4*R*,5*R*)-(−)-4-ethoxyoxalyl-5-[(1*R*)-menthyloxy]-γ-butyrolactone with alkyl halides in the presence of K_2CO_3 in acetone at room temperature.*

Keywords *O*-Alkylation; 4-methylidene-γ-butyrolactone; stereoselective synthesis

Many natural and unnatural molecules with the γ-butyrolactone moiety have been known to display a wide range of biological activities.[1–4] The methylidene-γ-butyrolactone fragment has also been found in many natural compounds.[5–8] There are three types of methylidene-γ-butyrolactones: 3-methylidene-, 4-methylidene-, and 5-methylidene-γ-butyrolactone. Among them, a large number of compounds possessing the 3-methylidene-γ-butyrolactone moiety are known to have various biological activities (e.g., antitumor,[9] antiplatelet,[10] insecticidal,[11] cardiovascular,[12] plant growth,[13] anti-inflammatary,[14] leishmanicidal,[15] and fungicidal,[16] activities), which have attracted considerable synthetic attention. However, little has been described about compounds possessing the 4-methylidene-butyrolactone moiety. In this article, the synthesis and characterization of compounds with the 4-methylidene γ-butyrolactone structural unit are reported.

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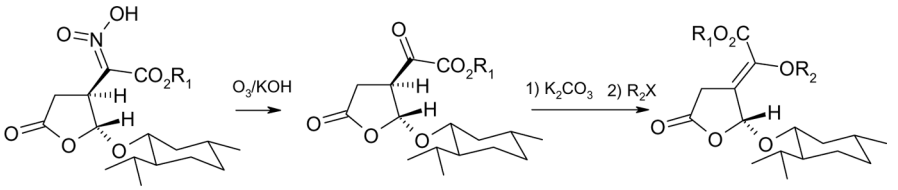

1 **2** **3**

1a R_1=Me **1b** R_1=Et **2a** R_1=Me **2b** R_1=Et **3m** R_1=R_2=Et

Scheme 1. Synthesis of 4-methylene-γ-butyrolactones **3a–n**.

A 4-methylidene-γ-butyrolactone structural unit is present in some furanoid terpenes[8] and sesquiterpenes.[17] The homogynolides A1 and B2 containing a novel 3-spiro-4-methylidene butyrolactone were found to possess antifeedant activity against certain types of beetle adults (*Sitophilus granarius*, *Tribolium confusum*) and larvae (*Trogoderma granarium*, *Tribolium confusum*).[18] A few methods of synthesizing the unit have been reported. One method involves the reaction of an enol ether with a carbene derived from diazomalonate as a key step.[19] The second method utilizes the thermally induced cyclization of a β,γ-epoxy ester.[20] The third method involves the [2,3]-sigmatropic rearrangement of the carbazate derivative for the total synthesis of (±)-bakkenolide, a furanoid terpenes.[21] The fourth method utilized the reductive cyclization of 2-bromoalkanal acetals.[22] Recently, in the study of an asymmetric synthesis of a natural product, we synthesized a key intermediate, the α-keto ester linked to γ-butyrolactone (**2b**),[23] which was obtained by a four-step procedure starting from furfural.[24] When we treated **2b** with iodoethane in the presence of K_2CO_3, the only product, the enantiomerically pure (*Z*)-(−)-4-ethoxycarbonyl-methylidene-5-(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (**3m**) (Scheme 1), was obtained, which apparently involves a number of stereoselective transformation in one pot. It appeared to be the first example of a stereoselective synthesis of optically pure 4-alkoxylcarbonyl-methylidene-γ-butyrolactone. We determined the configuration of this new compound based on NMR analysis.

RESULTS AND DISCUSSION

The nitronic acid **1a** or **1b** was synthesized via Michael addition to 5-(1*R*)-menthyloxy-3,4-unsaturated-γ-butyrolactone by methyl nitroacetate or ethyl nitroacetate.[24] The key intermediate (4*R*,5*R*)-(−)-4-ethoxyoxalyl-5-[(1*R*)-menthyloxy]-γ-butyrolactone (**2b**) was obtained via Nef reaction by treating **1b** with O_3 at 0 °C in methanol in the presence of KOH,[23] in which (4*R*,5*R*)-(−)-4-methoxyoxalyl-5[(1-*R*)-menthyloxy]-γ-butyrolactone (**2a**) was obtained as a by-product, resulting from the reaction of ester exchange with methanol. Use of ethanol as the solvent led to the formation of the only product **2b** and the acceleration of Nef reaction. The structure of **2a** was confirmed by ^{1}H NMR and ^{13}C NMR spectral and elemental analysis.

In the presence of K_2CO_3, **2b** was treated with iodoethane, generating the 4-(1′-ethoxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-menthyloxy-γ-butyrolactone (**3m**) as a single isomer. Its infrared (IR) spectrum showed very strong absorption at

1615 cm^{-1}(C=C) and 1735 cm^{-1} (C=O), which are the characteristic absorptions of an enol ether. Its ^1H NMR spectrum showed an H3 signal at δ 3.34 ppm and an H5 signal at δ 7.99 ppm, while those of **2b** emerged at 2.90 ppm and 5.80 ppm. Its ^{13}C NMR spectrum showed a C4 signal at δ 162.3 ppm and a C6 signal at δ 182.5 ppm, while those of **2b** emerged at 50.4 ppm and 189.5 ppm. Results of the elemental analysis were consistent with its structure.

In principle, the alkylation of α-keto ester **2** could produce four stereoisomers either from *R*/*S* *C*-alkylations at C4 or *E*/*Z* *O*-alkylations of the enolized α-keto. However, during the course of the reaction and after the workup, we obtained only a single *O*-alkylated product, which suggested a highly stereoselective *O*-alkylation of **2**. The configuration of the enol ether **3** was assigned to be *Z* on the basis of the nuclear Overhauser effect spectroscopy (NOESY) 1D spectrum in which strong NOEs among C5-H, C8-H, and C9-H (OCH_2 in OR_2) were observed.

This stereoselective *O*-alkylation reaction might result from the steric effect between the menthyloxy group and carbethoxy group and the formation of the enolate under basic conditions. In the presence of K_2CO_3, the enolization of α-keto ester **2** might readily occur as a result of the conjugation effect of the olefin and ester group; therefore, *O*-alkylation is preferred relative to *C*-alkylation. Because the carbethoxy group is much bigger than the hydroxy group after enolization, the carbethoxy group should be *trans* to the bulky menthyloxy group as a result of the steric effect, and therefore the *Z*-configuration is favored compared to the *E*-configuration.

Subsequently, we prepared a series of enantiomerically pure (*Z*)-(−)-4-(1′-alkoxy-1′-alkoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactones in 65–89% yields (Table 1). We found that the α-keto ethyl ester was almost as reactive as the α-keto methyl ester in the alkylation reaction. Acetone and dimethylformanide (DMF) are both effective solvents, but the former is easier to remove than the latter during reaction workup. It is interesting to note that no reaction was observed when secondary or tertiary alkyl halides were used under similar reaction conditions, and it is not surprising that the ease of the alkylation of **2** seems to follow the usual order: $RCH_2I > RCH_2Br > RCH_2Cl$.

Table 1. Synthesis of 4-methylidene-γ-butyrolactones **3a**–**n**

No.	R_1	R_2X	Time (d)	Yield (%)	Config.	$[\alpha]_{589}^{25}$ (acetone)
3a	CH_3CH_2	CH_3I	1	80	Z	−25.90 (c = 2.57)
3b	CH_3	CH_3I	1	80	Z	−28.30 (c = 2.51)
3c	CH_3CH_2	$CH_3CH_2CH_2Br$	2	72	Z	−30.20 (c = 4.30)
3d	CH_3	$CH_3(CH_2)_3Br$	2	68	Z	−25.46 (c = 2.96)
3e	CH_3CH_2	$CH_3(CH_2)_4$ Br	2	66	Z	−24.77 (c = 2.16)
3f	CH_3CH_2	$CH_2{=}CHCH_2Br$	1	89	Z	−27.10 (c = 1.09)
3g	CH_3	$CH_2{=}CHCH_2Br$	1	87	Z	−27.30 (c = 6.90)
3h	CH_3	$CH_3(CH_2)_4Br$	2	67	Z	−21.25 (c = 1.48)
3i	CH_3CH_2	$PhCH_2Br$	1.5	87	Z	−26.00 (c = 1.71)
3j	CH_3	$BrCH_2COOEt$	1.5	85	Z	−21.10 (c = 6.54)
3k	CH_3CH_2	$BrCH_2COOEt$	1.5	86	Z	−30.75 (c = 3.61)
3l	CH_3CH_2	$CH_3(CH_2)_{15}Br$	3	65	Z	−20.06 (c = 1.24)
3m	CH_3CH_2	CH_3CH_2Br	2	75	Z	−26.16 (c = 1.15)
3n	CH_3CH_2	$O_2NC_6H_4CH_2Br$	1	86	Z	−23.26 (c = 3.30)

In summary, a series of optically pure (*Z*)-(−)-4-(1′-alkoxy-1′-alkyloxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactones were synthesized in good yields under mild conditions via stereoselective *O*-alkylation of (5*R*,4*R*)-(−)-4-alkoxyoxalyl-5-[(1*R*)-menthyloxy]-γ-butyrolactone with primary alkyl halides. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, and NOESY 1D experiments. The biological activities of the new compounds obtained herein are currently under investigation.

EXPERIMENTAL

Unless otherwise indicated, all reagents and solvents were the best commercial grades available and were not purified further. ^{1}H NMR and ^{13}C NMR spectra were recorded on a DMX 300-MHz spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard with coupling constant (*J*) in hertz. IR spectra were performed on a Hitachi 260-50 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 spectrometer.

Nitronic acid (**1a** and **1b**) and α-keto ester **2** were prepared by Kang's methods.[23,24]

(4*R*,5*R*)-(−)-4-Ethoxyoxalyl-5-[(1*R*)-menthyloxy]-γ-butyrolactone (2b)

O_3 from an ozone generator was bubbled into a stirred solution of compound **1b** (6.0 g, 16.2 mmol) and KOH (1.0 g, 17.8 mmol) in 90 mL of ethanol at 0 °C. After 3 h, the reaction mixture was filtered, and the solvent was removed in vacuo. The residue was dissolved in 150 mL of ether and was washed with water (3 × 20 mL) and brine (2 × 30 mL). The solution was dried with anhydrous Na_2SO_4. Removal of solvent furnished the crude product, which was purified by flash chromatography on silica gel using 50% AcOEt–light petroleum ether, giving 4.3 g (80%) of **2b** as a colorless oil.

(4*R*,5*R*)-(−)-4-Methoxyoxalyl-5-[(1*R*)-menthyloxy]-γ-butyrolactone (2a)

Compound **2a** was prepared from nitronic acid **1a** in methanol using the same procedure as **2b**. Colorless oil; $[\alpha]_{589}^{20} = -138.1$ (c = 1.16, $CHCl_3$); IR (neat) 1792, 1761, 1750, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.68–1.30 (m, 14H), 1.55–1.75 (m, 2H), 2.01–2.22 (m, 2H), 2.79 (dd, 1H, *J* = 18.0, 4.8), 2.87 (dd, 1H, *J* = 18.0, 9.4), 3.45–3.65 (m, 1H), 3.82–4.02 (m, 1H), 3.89 (s, 3H), 5.87 (d, 1H, *J* = 2.2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ15.6, 20.9, 22.3, 23.2, 25.4, 29.5, 31.7, 34.3, 39.2, 47.7, 50.6, 63.2, 77.9, 99.1, 159.7, 173.6, 188.3. Anal. calcd. for $C_{17}H_{26}O_6$: C, 62.58; H, 7.98. Found: C, 62.55; H, 7.96.

General Procedure for Preparation of (Z)-(−)-4-(1′-Alkoxyl-1′-alkoxycarbonyl-methylidene)-5(R)-[(1R)-menthyloxy]-γ-butyrolactone (3)

Compound **2** (2.9 mmol) and finely ground anhydrous K_2CO_3 (0.5 g, 3.6 mmol) were mixed in acetone (20 mL) at room temperature. To this well-stirred suspension was added an alkyl halide (3 mmol). The progress of the reaction was monitored by

TLC. After being stirred at room temperature for the indicated time, ether (30 mL) was added. Then the mixture was filtered, and the solvent was removed from the filtrate in vacuo to give the crude product, which was further purified by flash chromatography on silica gel using a mixture of light petroleum ether and ethyl acetate (5:1), affording the compound **3**.

(*Z*)-(−)-4-(1′-Methoxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3a)

A colorless liquid; $[\alpha]_{589}^{25} = -25.9$ (c = 2.57, acetone); IR (neat) 1750, 1623 cm^{-1}; UV $\lambda_{max} = 326.5$ nm (acetone); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77–1.21 (m, 12H), 1.38 (t, 3H, $J = 7.2$), 1.42–1.58 (m, 2H), 1.65–1.80 (m, 2H), 1.89–2.10 (m, 2H), 3.35 (s, 2H), 3.65 (s, 3H), 3.79–3.92 (m, 1H), 4.32 (q, 2H, $J = 7.2$), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 15.7, 20.1, 21.4, 22.8, 25.3, 27.6, 31.0, 33.3, 41.2, 47.0, 51.3, 61.5, 86.5, 111.9, 162.9, 166.0, 170.3, 183.1. Anal. calcd. for $C_{19}H_{30}O_6$: C, 64.41; H, 8.47. Found: C, 63.95; H, 8.65.

(*Z*)-(−)-4-(1′-Methoxy-1′-methoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3b)

A colorless liquid; $[\alpha]_{589}^{25} = -28.3$ (c = 2.51, acetone); IR (neat) 1740, 1620 cm^{-1}; UV $\lambda_{max} = 268.4$ nm (EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78–1.22 (m, 12H), 1.42–1.58 (m, 2H), 1.65–1.80 (m, 2H), 1.88–2.11 (m, 2H), 3.35 (s, 2H), 3.65 (s, 3H), 3.88 (s, 3H), 3.79–3.93 (m, 1H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 20.6, 21.8, 23.2, 25.7, 28.0, 31.4, 33.7, 41.6, 47.4, 51.7, 52.5, 85.9, 112.5, 163.4, 166.5, 170.8, 182.0. Anal. calcd. for $C_{18}H_{28}O_6$: C, 63.53; H, 8.23. Found: C, 63.15; H, 8.53.

(*Z*)-(−)-4-(1′-Propyloxy-1′-ethoxycarbonyl-methylidene)–5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3c)

A colorless liquid; $[\alpha]_{589}^{25} = -30.2$ (c = 4.30, acetone); IR (neat): 1740, 1720 cm^{-1}; UV $\lambda_{max} = 267.5$ nm (EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77–1.18 (m, 16H), 1.38 (t, 3H, $J = 7.2$), 1.59–1.72 (m, 5H), 1.89–2.12 (m, 2H), 3.34 (s, 2H), 3.76–3.95 (m, 1H), 4.01 (t, 2H, $J = 6.6$), 4.33 (q, 2H, $J = 7.2$), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.1, 12.8, 15.0, 19.4, 20.7, 22.1, 24.6, 27.1, 30.3, 32.6, 40.5, 46.3, 60.8, 65.0, 75.5, 85.7, 111.4, 162.2, 165.1, 169.3, 182.4. Anal. calcd. for $C_{21}H_{34}O_6$: C, 65.97; H, 8.90. Found: C, 65.95; H, 9.25.

(*Z*)-(−)-4-(1′-Butoxy-1′-methoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3d)

A colorless liquid; $[\alpha]_{589}^{25} = -25.46$ (c = 2.96, acetone); IR (neat): 1730, 1610 cm^{-1}; UV $\lambda_{max} = 268.6$ nm (EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75–1.23 (m, 15H), 1.38–1.58 (m, 4H), 1.61–1.80 (m, 4H), 1.90–2.12 (m, 2H), 3.32 (s, 2H), 3.66 (s, 3H), 3.76–3.92 (m, 1H), 4.25–4.33 (m, 2H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 16.1, 19.1, 20.5, 21.8, 23.2, 25.7, 28.0, 30.5, 31.4, 33.7, 41.6, 47.4,

51.7, 65.6, 86.8, 112.4, 163.3, 166.1, 170.7, 183.2. Anal. calcd. for $C_{21}H_{34}O_6$: C, 65.97, H, 8.90. Found: C, 65.48, H, 9.25.

(*Z*)-(−)-4-(1′-Pentyloxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3e)

A colorless liquid; $[\alpha]_{589}^{25} = -24.77$ (c = 2.16, acetone); IR (neat): 1740, 1620 cm^{-1}; UV $\lambda_{max} = 268.2$ nm (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77–1.22 (m, 15H), 1.31–1.40 (m, 9H), 1.50–1.72 (m, 4H), 1.87–2.12 (m, 2H), 3.34 (s, 2H), 3.80–3.89 (m, 1H), 4.04 (t, 2H, $J = 6.7$), 4.33 (q, 2H, $J = 7.2$), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 13.7, 15.9, 20.3, 21.6, 21.9, 22.9, 25.4, 27.6, 27.9, 28.0, 31.1, 33.5, 41.4, 47.1, 61.7, 64.5, 86.6, 112.3, 163.0, 167.4, 170.3, 183.2. Anal. calcd. for $C_{23}H_{38}O_6$: C, 67.31; H, 9.27. Found: C, 66.8; H, 9.78.

(*Z*)-(−)-4-(1′-Allyloxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3f)

A colorless liquid; $[\alpha]_{589}^{25} = -27.1$ (c = 1.09, acetone); IR (neat) 1740, 1622 cm^{-1}; UV $\lambda_{max} = 268.9$ nm (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76–1.18 (m, 12H), 1.37 (t, 3H, $J = 7.1$), 1.32–1.50 (m, 2H), 1.52–1.72 (m, 2H), 1.90–2.10 (m, 2H), 3.38 (s, 2H), 3.81–3.88 (m, 1H), 4.33 (q, 2H, $J = 7.1$), 4.56 (d, 2H, $J = 5.5$), 5.80–5.96 (m, 1H), 5.19–5.33 (m, 2H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.67, 15.8, 20.3, 21.5, 22.9, 25.4, 27.8, 31.1, 33.5, 41.3, 47.1, 61.5, 64.8, 86.5, 112.0, 117.3, 131.8, 162.9, 166.0, 169.6, 183.1. Anal. calcd. for $C_{21}H_{32}O_6$: C, 66.32; H, 8.42. Found: C, 66.71; H, 8.15.

(*Z*)-(−)-4-(1′-Allyloxy-1′-methoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3g)

A colorless liquid; $[\alpha]_{589}^{25} = -27.30$ (c = 6.90, acetone); IR (neat): 1742, 1619 cm^{-1}; UV $\lambda_{max} = 269.2$ nm (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77–1.18 (m, 12H), 1.40–1.48 (m, 2H), 1.62–1.72 (m, 2H), 1.97–2.05 (m, 2H), 3.38 (s, 2H), 3.82–3.89 (m, 1H), 3.87 (s, 3H), 4.57 (q, 2H, $J = 5.1$), 5.15–5.33 (m, 2H), 5.80–6.00 (m, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 20.8, 22.0, 23.0, 25.6, 28.1, 31.3, 33.6, 41.5, 47.2, 52.5, 65.1, 86.9, 112.3, 117.7, 131.9, 163.3, 166.6, 170.0, 182.8. Anal. calcd. for $C_{20}H_{30}O_6$: C, 65.57; H, 8.19. Found: C, 65.25; H, 8.41.

(*Z*)-(−)-4-(1′-Pentyloxy-1′-methoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3h)

A colorless liquid; $[\alpha]_{589}^{25} = -21.25$ (c = 1.48, acetone); IR (neat): 1742, 1625 cm^{-1}; UV $\lambda_{max} = 268.5$ nm (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77–1.20 (m, 15H), 1.31–1.42 (m, 6H), 1.51–1.72 (m, 4H), 1.87–2.11 (m, 2H), 3.34 (s, 2H), 3.86 (s, 3H), 3.81–3.88 (m, 1H), 4.04 (t, 2H, $J = 6.7$), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 16.2, 20.6, 21.9, 22.3, 23.2, 25.8, 28.0, 28.2, 28.4, 31.6, 33.8, 41.7, 47.6, 52.7, 64.9, 87.0, 112.7, 163.6, 166.6, 170.6, 183.1. Anal calcd. for $C_{22}H_{36}O_6$: C, 66.67; H, 9.09. Found: C, 66.18; H, 9.45.

(*Z*)-(−)-4-(1′-Benzyloxy-1′-ethoxylcarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3i)

A colorless liquid; $[\alpha]_{589}^{25} = -26.0$ (c = 1.71, acetone); IR (neat): 1740, 1620 cm^{-1}; UV $\lambda_{max} = 326.4$ nm (acetone); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75–1.21 (m, 10H), 1.31–1.50 (m, 7H), 1.60–1.75 (m, 2H), 1.86–2.23 (m, 2H), 3.4 (s, 2H), 3.75–3.95 (m, 1H), 4.2–4.4 (m, 2H), 5.1 (s, 2H), 7.3 (s, 5H), 8.0 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 15.8, 20.2, 21.5, 22.8, 25.4, 27.9, 31.0, 33.4, 41.2, 47.0, 61.5, 65.8, 88.5, 111.9, 127.4 × 2, 127.5, 128.0 × 2, 135.6, 162.9, 166.0, 169.8, 183.2. Anal. calcd. for $C_{25}H_{34}O_5$: C, 69.77; H, 7.91. Found: C, 69.58; H, 7.79.

(*Z*)-(−)-4-(1′-Ethoxycarbonylmethyl-1′-methoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3j)

A colorless liquid; $[\alpha]_{589}^{25} = -21.1$ (c = 6.54, acetone); IR (neat): 1750, 1620 cm^{-1}; UV $\lambda_{max} = 326.1$ nm (acetone); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75–1.18 (m, 12H), 1.30 (t, 3H, $J = 7.2$), 1.21–1.55 (m, 2H), 1.61–1.80 (m, 2H), 1.85–2.1 (m, 2H), 3.43 (s, 2H), 3.84 (s, 3H), 3.80–3.95 (m, 1H), 4.2 (q, 2H, $J = 7.2$), 4.60 (s, 2H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 15.9, 20.5, 21.6, 22.9, 25.5, 27.6, 31.2, 33.5, 41.4, 47.1, 52.4, 60.7, 60.9, 86.9, 111.7, 163.2, 166.5, 167.3, 169.6, 182.8. Anal calcd. for $C_{21}H_{32}O_8$: C, 61.16; H, 7.76. Found: C, 61.05; H, 8.10.

(*Z*)-(−)-4-(1′-Ethoxycarbonylmethyl-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3k)

A colorless oil; $[\alpha]_{589}^{25} = -30.75$ (c = 3.61, acetone); IR (meat): 1750, 1620 cm^{-1}; UV $\lambda_{max} = 325.9$ nm (acetone); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75–1.18 (m, 12H), 1.29 (t, 3H, $J = 7.2$), 1.38 (t, 3H, $J = 7.2$), 1.22–1.55 (m, 2H), 1.62–1.80 (m, 2H), 1.86–2.11 (m, 2H), 3.43 (s, 2H), 3.80–3.95 (m, 1H), 4.2 (q, 2H, $J = 7.2$), 4.3 (q, 2H, $J = 7.2$), 4.6 (s, 2H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 15.7, 20.2, 21.4, 22.7, 25.3, 27.3, 29.2, 31.0, 33.4, 41.2, 47.0, 60.4, 60.7, 61.5, 86.6, 111.4, 162.6, 166.2, 167.1, 169.9, 182.9. Anal. calcd. for $C_{22}H_{34}O_8$: C, 61.97; H, 7.98; Found: C, 61.81; H, 7.89.

(*Z*)-(−)-4-(1′-Hexadecyloxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3l)

A colorless oil; $[\alpha]_{589}^{25} = -20.06$ (c = 1.24, acetone); IR (neat): 1740 (s), 1622 cm^{-1}; UV $\lambda_{max} = 267.7$ nm (EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75–1.18 (m,16H), 1.18–1.50 (m, 30H), 1.52–1.82 (m, 4H), 1.86–2.20 (m, 2H), 3.33 (s, 2H), 3.80–3.94 (m, 1H), 4.04 (t, 2H, $J = 6.6$), 4.32 (q, 2H, $J = 7.2$), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.8, 14.9, 17.0, 21.4, 22.6, 23.5, 26.6, 26.7, 29.4, 29.5, 30.1, 30.2, 30.3, 30.4, 30.5, 30.6 × 6, 32.2, 32.7, 34.8, 42.5, 48.3, 62.7, 65.6, 87.6, 113.4, 164.1, 167.1, 171.2, 184.3. Anal. calcd. for $C_{34}H_{60}O_6$: C, 72.34; H, 10.64. Found: C, 71.89; H, 11.05.

(*Z*)-(−)-4-(1′-Ethoxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3m)

A colorless liquid; $[\alpha]_{589}^{25} = -26.16$ (c = 1.15, acetone); IR (neat): 1735, 1615 cm^{-1}; UV $\lambda_{max} = 268.4$ nm (EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78–1.18 (m, 12H), 1.23 (t, 3H, $J = 7.2$), 1.37 (t, 3H, $J = 7.2$), 1.32–1.45 (m, 2H), 1.55–1.82 (m, 2H), 1.85–2.11 (m, 2H), 3.34 (s, 2H), 3.80–3.93 (m, 1H), 4.10 (q, 2H, $J = 7.2$), 4.32 (q, 2H, $J = 7.2$), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 13.0, 15.1, 19.4, 20.7, 22.1, 24.7, 27.1, 30.3, 32.7, 40.6, 46.4, 59.4, 60.8, 85.7, 111.4, 162.3, 165.2, 169.2, 182.5. Anal. calcd. for $C_{20}H_{32}O_6$: C, 65.22; H, 8.70. Found: C, 65.12; H, 8.90.

(*Z*)-(−)-4-(1′-*p*-Nitrobenzyloxy-1′-ethoxycarbonyl-methylidene)-5(*R*)-[(1*R*)-menthyloxy]-γ-butyrolactone (3n)

A colorless oil; $[\alpha]_{589}^{25} = -23.26$ (c = 3.30, acetone); IR (neat): 1750, 1620, 1521 cm^{-1}; UV $\lambda_{max} = 268$ nm (EtOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.74–1.18 (m, 12H), 1.41 (t, 3H, $J = 7.2$), 1.32–1.45 (m, 2H), 1.60–1.82 (m, 2H), 1.88–2.11 (m, 2H), 3.44 (s, 2H), 3.80–3.95 (m, 1H), 4.34 (q, 2H, $J = 7.2$), 5.21 (s, 2H), 7.51 (d, 2H, $J = 8.5$), 8.19 (d, 2H, $J = 8.5$), 8.03 (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.71, 15.9, 20.2, 21.5, 22.9, 25.6, 27.9, 31.1, 33.4, 41.3, 47.1, 61.7, 64.4, 86.8, 111.7, 123.3 × 2, 127.7 × 2, 143.2, 147.1, 162.9, 166.3, 169.6, 183.3; MS (FAB, m/z): 476 (M + 1). Anal. calcd. for $C_{25}H_{33}O_8N$: C, 63.16; H, 6.95; N, 2.95. Found: C, 62.95; H, 7.16; N, 2.78.

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