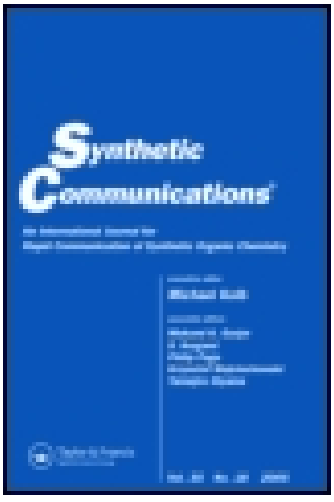

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Versatile Approach for the Asymmetric Synthesis of (R)- and (S)-Massoialactones

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Versatile Approach for the Asymmetric Synthesis of (*R*)- and (*S*)-Massoialactones

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Abstract: A general synthetic approach to both enantiomers, (*R*)- and (*S*)-massoialactones, has been devised from commercially available (*S*)-butane-1,2,4-triol.

Keywords: chiral lactones, enantiomers, massoialactone, natural products

INTRODUCTION

The 6-substituted chiral δ-lactone moiety is present in a number of natural products and exhibits significant bioactivities.[1] Massoialactone (**1**) belongs to this family, first isolated from the bark oil of *Cryptocarya massoia* by Abe in 1937.[2] Later this lactone was also isolated as a flavor substance from cane molasses[3] and jasmine flowers.[4] The *R* enantiomer has been identified as the defense secretion of two species of formicin ants of the genus *Camponotus*.[5]

Several methods for the synthesis of (*R*)-massoialactone have been reported[6] either from a chiral pool starting material,[7] hydrolytic kinetic resolution,[8] or the resolution of racemic mixtures of the lactone precursor,[9] whereas methods for the synthesis of (*S*)-massoialactone are rare.[10] The lactone **1** has been used for many centuries as a constituent of native medicines. A general synthetic route to the enantiomerically pure lactones would be of value because these lactones are synthetically versatile

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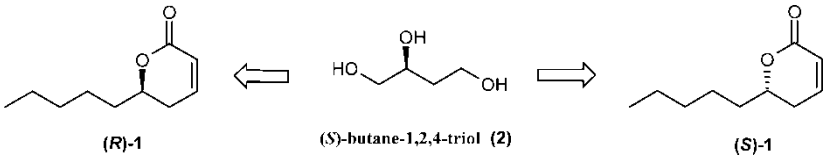
precursors to other chiral molecules of considerable interest. Recently we have been interested in the development of practical and concise enantioselective approaches to naturally occurring biologically important lactones.[11] As a consequence, we herein describe a general synthetic approach that affords both isomers, natural (*R*)-**1** and unnatural (*S*)-**1** massoialactones. The synthesis of both natural (*R*)- and (*S*)-**1** massoialactones started from commercially available (*S*)-butane-1,2,4-triol (**2**) by manipulating the reactions. The retrosynthetic plan for the synthesis of both isomers is illustrated in Scheme 1.

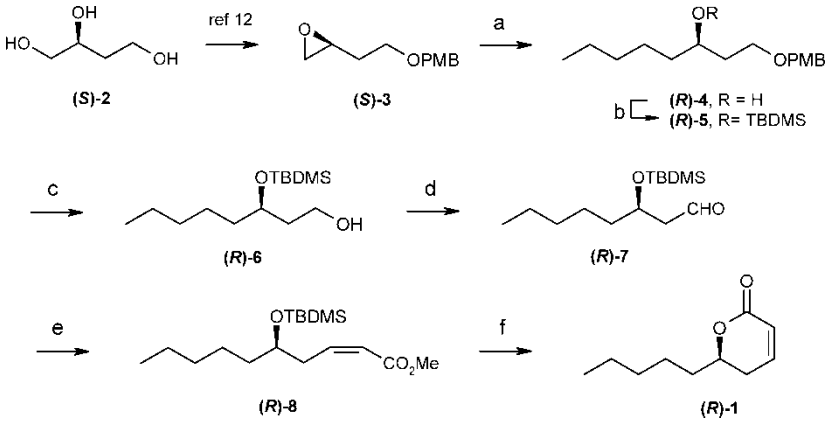
RESULTS AND DISCUSSION

The known (*S*)-epoxide **3**[12] (Scheme 2) could be derived from (*S*)-butane-1,2,4-triol **2**. Selective opening of epoxide (*S*)-**3** with CuI and *n*-BuLi[12] furnished (*R*)-**4** in 87% yield. The secondary hydroxyl group in compound **4** was protected as tert-butyldimethylsilyl (TBDMS) ether (*R*)-**5** using TBDMSCl, imidazole in CH_2Cl_2 (74%). Oxidative deprotection of the para-methoxybenzyl (PMB) group using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aq. CH_2Cl_2 gave the primary alcohol (*R*)-**6** in 80% yield, which on oxidation with iodoxybenzoic acid (IBX) in dimethylsulphoxide (DMSO) furnished the corresponding aldehyde (*R*)-**7** (68%).[6e,6g,13] A modified Still's Horner–Wadsworth–Emmons reaction of (*R*)-**7** using methyl(bistrifluoroethyl) phosphonoacetate in the presence of NaH in THF gave *Z*-unsaturated ester (*R*)-**8,** exclusively. Subsequent cyclization of Z-ester using a catalytic amount of *p*-TsOH in methanol and benzene furnished the target molecule, (*R*)-**1**, in 76% yield by in situ deprotection of TBDMS group. The ^1H and ^{13}C NMR data and optical rotation value of synthetic (*R*)-**1**, $[\alpha]_D$ −113.5 (*c* 1, $CHCl_3$), lit.[8] $[\alpha]_D$ −115.2 (*c* 1, $CHCl_3$), were in good accordance with the literature data.

Similarly, the synthesis of (*S*)-massoialactone began with the known (*R*)-epoxide **3**[12] with the required stereogenic center, derived from (*S*)-butane-1,2,4-triol **2**. The same set of reactions were carried out as shown in Scheme 2. Thus, selective opening of epoxide (*R*)-**3** with CuI and *n*-BuLi furnished (*S*)-**4** in 86% yield, which was protected as its TBDMS ether (*S*)-**5**. The deprotection of the PMB group in (*S*)-**5** using DDQ (84%) and



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: a) CuI, *n* BuLi, dry ether, −20°C, 1.5 h, 87%; b) TBDMSCl, imidazole, DCM, 0°C, 2 h, 74%; c) DDQ, DCM:H_2O rt, 3 h, 80%; d) IBX, DMSO, DCM, 2 h, 68%; e) $H_3COOCCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, 1 h, 85%; f) PTSA/MeOH, 30 min, benzene, 1 h, 76%.

subsequent oxidation with IBX afforded the aldehyde (S)-**7** in 67% yield. Homologation of (*S*)-**7** with methyl(bistrifluoroethyl) phosphonoacetate in the presence of NaH in THF gave *Z*-unsaturated ester (*S*)-**8** (89%). Finally, the deprotection of TBDMS group and lactonization was effected in one step by treatment with *p*-TSOH in methanol to give unnatural (*S*)-**1** in 74% yield. The physical and spectroscopic data of (*S*)-**1** were in full agreement with the literature data.[9]

In conclusion, we have developed a simple and new synthetic route for both isomers, (*R*)- and (*S*)-massoialactones **1**, from (S)-**2**, employing a divergent strategy. A general and simple reaction sequence and high-yielding steps to provide the targets from the same starting material, (*S*)-butane-1,2,4-triol, renders our strategy a good alternative to the known methods.

EXPERIMENTAL

All solvents were distilled before use. Dry solvents were prepared according to the standard procedures. All reactions were carried out under an N_2 atmosphere and monitored by thin-layer chromatography (TLC) on silica gel (60–120 mesh, Merck). NMR spectra were recorded on Bruker (300 MHz ^{1}H, 75 MHz ^{13}C) and Varian (200 MHz ^{1}H, 50 MHz ^{13}C) NMR spectrometers using $CDCl_3$ as solvent. ESI-mass spectra were recorded with LC-MSD-Trap-SL (Agilent technologies). IR spectra were recorded with Fourier Transform Infra Red (FTIR) (Thermo Nicolet Nexus 670 spectrometer). Optical rotations were measured with Jasco DIP-370 Polarimeter at 20°C.

(3*R*)-1-[(4-Methoxybenzyl)oxy]octan-3-ol ((*R*)-4)

To a stirred mixture of copper (I) iodide (9.13 g, 48.08 mmol) in dry ether (40 mL), *n*-butyllithium (37.56 mL, 60.09 mmol, 1.6 M solution in *n*-hexane) was added at −20°C and stirred for 0.5 h. Then, a solution of epoxide (*S*)-**3** (5 g, 24.03 mmol) in dry ether (20 mL) was added and stirred at the same temperature for 1 h. The reaction mixture was quenched with aq. NH_4Cl solution (20 mL) and allowed to stir for 15 min. The organic layer was separated, and aq. layer was washed with ethyl acetate (2 × 40 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography to afford (R)-**4** (5.53 g, 87%) as a liquid. $[\alpha]_D$ +3.79 (*c* 1, $CHCl_3$). IR (neat): 3459, 2931, 2860, 1093, 822, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 2H, $J = 8.3$ Hz), 6.82 (d, 2H, $J = 8.3$ Hz), 4.43 (s, $\underline{CH_2}$-O, -PMB), 3.79 (s, 3H, -O-$\underline{Me}$), 3.53–3.76 (m, 3H, $\underline{CH}$-OH, CH_2-OPMB), 2.74 (brs, 1H, -O$\underline{H}$), 1.68 (q, 2H, $J = 6.0$ Hz, HO-CH2-$\underline{CH2}$-CH2-OPMB), 1.24–1.49 (m, 8H, aliphatic), 0.89 (t, 3H, $J = 6.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 159.15, 129.96, 129.23, 113.78, 72.91, 71.52, 68.94, 55.16, 37.35, 36.29, 31.86, 25.21, 22.61, 13.99; LCMS: 289 (M + Na).

(3*S*)-1-[(4-Methoxybenzyl)oxy]octan-3-ol ((*S*)-4)

Compound (S)-**4** was similarly obtained in 86% yield from epoxide (*R*)-**3**: liquid, $[\alpha]_D$ −3.72 (*c* 1, $CHCl_3$).

Tert-butyl[((1*R*)-1-2-[(4-methoxybenzyl)oxy]ethylhexyl)oxy] dimethyl silane ((*R*)-5)

To a stirred solution of alcohol (*R*)-**4** (5.0 g, 18.79 mmol) and imidazole (2.5 g, 37.59 mmol) in dry DCM (35 mL), TBDMSCl (3.399 g, 22.55 mmol) was added portionwise at 0°C. The reaction mixture was stirred at the same temperature for 2 h and then quenched with water (20 mL). The dichloromethane (DCM) layer was separated, and the aqueous layer was extracted with additional DCM (2 × 20 mL). Combined organic layers were washed with water and brine solution and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, and the residue was purified by silica-gel column chromatography to afford (*R*)-**5** (5.3 g, 74%) as a colorless liquid. $[\alpha]_D$ −8.33 (*c* 0.85, $CHCl_3$); IR (neat): 2931, 2857, 1249, 1093, 835, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, 2H, $J = 8.3$ Hz), 6.82 (d, 2H, $J = 8.3$ Hz), 4.37 (Abq, 2H, $J = 11.3$ Hz, O-$\underline{CH_2}$-O-PMB), 3.79 (s, 3H, -$\underline{OMe}$), 3.76–3.83 (m, 1H, $\underline{CH}$-O-TBS), 3.45 (dt, 2H, $J = 3.0$ Hz, $\underline{CH_2}$-O-PMB), 1.6–1.74 (m, 2H, TBS-O-CH-$\underline{CH_2}$-CH_2-O-PMB),

1.23–1.43 (m, 8H, aliphatic), 0.89 (t, 3H, $J = 6.0$ Hz terminal CH_3), 0.87 (s, 9H), 0.03 (s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 158.98, 129.13, 113.5, 72.46, 69.34, 66.87, 55.13, 37.44, 36.81, 31.95, 25.78, 24.57, 22.49, 17.93, 13.89, −4.51, −4.76; LCMS: 403 (M + Na).

Tert-butyl[((1*S*)-1-2-[(4-methoxybenzyl)oxy]ethylhexyl)oxy] dimethyl silane ((*S*)-5)

Compound (*S*)-**5** was similarly obtained in 77% yield from (*S*)-**4**: liquid, $[\alpha]_D$ +8.83 (*c* 0.85, $CHCl_3$).

(3*R*)-3-[1-(Tert-butyl)-1,1-dimethylsilyl]oxyoctan-1-ol ((*R*)-6)

To a stirred solution of compound (*R*)-**5** (5.0 g, 13.15 mmol) in 36 mL of aq. DCM (DCM–H_2O, 9:1), DDQ (5.97 g, 26.31 mmol) was added, and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was washed with 5% aq. $NaHCO_3$ solution (35 mL). The layers were separated, and the aqueous layer was extracted twice with DCM. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography using silica gel to give alcohol (*R*)-**6** (2.75 g, 80% yield) as a liquid. $[\alpha]_D$ −17.09 (*c* 1, $CHCl_3$); IR (neat): 3464, 2929, 2858, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.6–3.94 (m, 3H, -CH-O-TBS, -CH_2-OH), 2.15 (brs, 1H, -OH), 1.69–1.89 (m, 2H), 1.56–1.68 (m, 2H), 1.21–1.55 (m, 6H), 0.90 (s, 9H), 0.88 (t, 3H, $J = 6.0$ Hz), 0.09 (s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 72.00, 60.28, 37.62, 36.74, 31.91, 25.78, 24.99, 22.58, 17.92, 13.96, −4.45, −4.77; LCMS: 261 (M + 1).

(3*S*)-3-[1-(Tert-butyl)-1,1-dimethylsilyl]oxyoctan-1-ol ((*S*)-6)

Compound (*S*)-**6** was similarly obtained in 84% yield from (*S*)-**5**: liquid, $[\alpha]_D$ +17.82 (*c* 1, $CHCl_3$).

(3R)-3-[1-(Tert-butyl)-1,1-dimethylsilyl]oxyoctanal ((*R*)-7)

To a stirred solution of IBX (4.56 g, 16.92 mmol) in DMSO (2.2 mL), alcohol (*R*)-**6** (2.2 g, 8.46 mmol) was added in dry DCM (15 ml). The reaction mixture was allowed to stir at room temperature for 2 h. DCM was removed from the reaction mixture under reduced pressure, then diethylether (20 ml) was added to reaction mixture and filtered through Celite®. The filter cake was washed with DCM and water. The layers were separated, and the aqueous phase was

extracted with DCM. The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography using silica gel to give the aldehyde (*R*)-**7** (1.48 g, 68%). $[\alpha]_D^{25}$ −5.0 (*c* 1, $CHCl_3$), lit.[6g] −5.83 (*c* **1**, $CHCl_3$); IR (neat): 2929, 1714, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.78 (t, -CHO, $J = 2.2$ Hz), 4.07–4.20 (m, 1H, -CH-O-TBS), 2.45–2.52 (m, 2H, CH_2-CHO), 1.22–1.56 (m, 8H, aliphatic), 0.91 (t, 3H, CH_3, $J = 6.0$ Hz), 0.87 (s, 9H, *t*Bu), 0.07 (s, 6H, 2 × CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 202.43, 68.24, 50.75, 37.82, 31.75, 25.68, 24.76, 22.56, 17.95, 13.94, −4.46, −4.47.

(3S)-3-[1-(Tert-butyl)-1,1-dimethylsilyl]oxyoctanal ((*S*)-7)

Compound (*S*)-**7** was similarly obtained in 62% yield from (*S*)-**6**: liquid, $[\alpha]_D^{25}$ +5.9 (*c* 1, $CHCl_3$), lit.[14] −6.7 (*c* 1, $CHCl_3$).

Methyl (*Z*, 5*R*)-5-[1-(Tert-butyl)-1,1-dimethylsilyl]oxy-2-decenoate ((*R*)-8)

To a stirred suspension of NaH (0.11 g, 4.58 mmol) in dry THF (10 mL), a solution of methyl(bistrifluoroethyl) phosphonoacetate (1.602 g, 5.03 mmol) in THF (5 mL) was added at 0°C. After 0.5 h, a solution of aldehyde (1 g, 3.87 mmol) in dry THF (10 mL) was added and stirred. After 2 h, EtOAc (15 ml) and water (20 ml) were added to the reaction mixture and stirred for a few min; the organic layer was separated and the aq. layer was washed with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel to get Z-unsaturated ester (1.03 g, 85% yield). $[\alpha]_D$ +7.35 (*c* 0.85, $CHCl_3$); IR (neat): 1722, 1685, 1083, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.30–6.40 (m, 1H), 5.78–5.84 (dt, 1H), 3.69 (s, 3H, -COOMe), 3.71–3.82 (m, 1H, CH-O-TBS), 2.7–2.93 (m, 2H, allylic), 1.22–1.47 (m, 8H, aliphatic), 0.88 (t, 3H, $J = 6.0$ Hz), 0.90 (s, 9H, *t*Bu), 0.04 (s, 6H, 2 × CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): 166.79, 147.31, 120.22, 71.46, 50.96, 37.15, 36.35, 31.89, 25.81, 25.0, 22.61, 18.0, 14.0, −4.6; LCMS: 315 (M + 1).

Methyl (*Z*, 5*S*)-5-[1-(Tert-butyl)-1,1-dimethylsilyl]oxy-2-decenoate ((*S*)-8)

Compound (*S*)-**8** was similarly obtained in 89% yield from (*S*)-**7**: liquid $[\alpha]_D$ −9.21 (*c* 0.85, $CHCl_3$).

(6*R*)-6-Pentyl-5,6-dihydro-2H-2-pyranone ((*R*)-1)

To a stirred solution of ester (*R*)-**8** (0.92 g, 2.93 mmol) in MeOH (15 mL), a pinch of PTSA was added. The reaction mixture was allowed to stir for 30 min at room temperature. Methanol was removed in vacuum, and then benzene (15 ml) was added to the reaction mixture and stirred for 1 h at room temperature. Followed by TLC, the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel to give a lactone (*R*)-**1** (0.372 g, 76%). $[\alpha]_D$ −113.5 (*c* 1, $CHCl_3$), lit.[6e] $[\alpha]_D$ −110.7 (*c* 1, $CHCl_3$); IR (neat): 2933, 1725, 1617, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.80–6.87 (m, 1H), 5.96–6.02 (m, 1H), 4.33–4.44 (m, 1H), 2.27–2.35 (m, 2H), 1.25–1.86 (m, 8H), 0.91 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.57, 144.99, 121.43, 78.0, 34.79, 31.54, 29.35, 24.47, 22,46, 13.94; LCMS: 191 (M + Na).

(6*S*)-6-Pentyl-5,6-dihydro-2H-2-pyranone ((*S*)-1)

Compound (*S*)-**1** was similarly obtained in 74% yield from (*S*)-**8**: liquid, $[\alpha]_D$ +104.8 (*c* 0.41, $CHCl_3$), lit.[9] $[\alpha]_D$ +109.6 (*c* 2.0, $CHCl_3$).

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