Organocatalytic Enantioselective Approach to the Synthesis of Verbalactone and (*R*)-Massoialactone

Anand Harbindu, Pradeep Kumar*

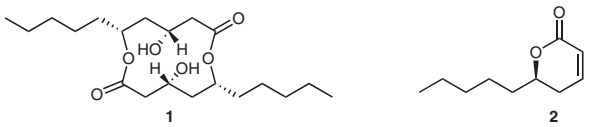
Division of Organic Chemistry, National Chemical Laboratory, Pune 411008, India
Fax +91(20)25902629; E-mail: pk.tripathi@ncl.res.in

Received 15 March 2011

Abstract: The organocatalytic enantioselective synthesis of verbalactone and (*R*)-massoialactone is described. The requisite stereogenic centers of the target molecules were constructed using L-proline-catalyzed α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination. Yamaguchi macrolactonization and ring-closing metathesis were employed as key steps in the syntheses.

Key words: L-proline, α-aminoxylation, Horner–Wadsworth–Emmons olefination, Yamaguchi macrolactonization, ring-closing metathesis, verbalactone, massoialactone

Verbalactone (**1**, Figure 1), isolated by Mitaku and co-workers in 2001 from the roots of *Verbascum undulatum*,[1] displays interesting antibacterial activity against various Gram-positive and Gram-negative bacteria. Verbalactone is a novel macrocyclic symmetrical dimeric lactone and is the first natural product in which the unique 1,7-dioxacyclododecane ring system was found. The complex molecular architecture and interesting biological activity has stimulated many synthetic chemists[2] worldwide towards the total synthesis of lactone **1**. Barua and co-workers reported the first total synthesis of verbalactone in 2004 in which Barbier–Grignard and Sharpless asymmetric dihydroxylation reactions were employed as the key transformations.[2a] Subsequently, Sharma and Reddy reported another convergent strategy for the synthesis of verbalactone starting from L-malic acid.[2b] Meanwhile, several other reported syntheses for verbalactone were mainly based on using either the chiral-pool starting material or stereoselective methods to generate the stereogenic centers and subsequent Yamaguchi esterification to bring about macrocyclization.[2c–g]



1 2

Figure 1 Structures of verbalactone (**1**) and massoialactone (**2**)

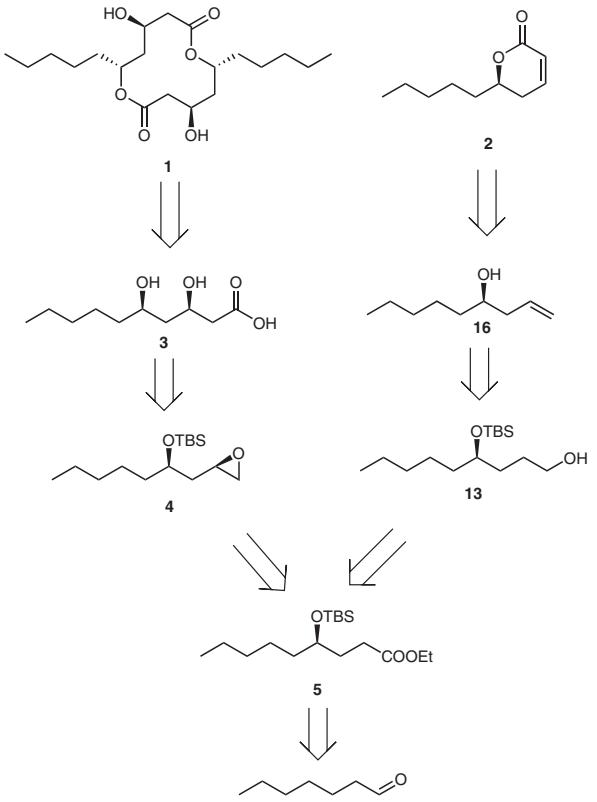
Massoialactone[3,4] (**2**, Figure 1) was isolated for the first time in 1937 by Abe[5] from the bark of *Cryptocarya massoia*. It is skin irritant and produces systolic standstill in frog heart muscle. This lactone has also been isolated from cane molasses[6] and jasmine blossoms[7] as a flavor substance. In 1968 it was isolated from the secretion of two species of formicine ants of the genus *Componotus* collected in western Australia.[8] Various methods for the synthesis of massoialactone utilizing either the chiral pool as starting material, asymmetric synthesis or the chromatographic resolution of the diastereomeric derivatives of the lactone precursor have been reported.[9]

As a part of our ongoing research program aimed at developing the enantioselective synthesis of biologically active natural products,[10] we have recently developed a novel and efficient protocol for 1,3-polyols based on iterative use of proline-catalyzed tandem α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehydes.[11] Now, we have further extended the synthetic utility of this protocol to synthesize two natural products, verbalactone and (*R*)-massoialactone, in a most concise and efficient manner.

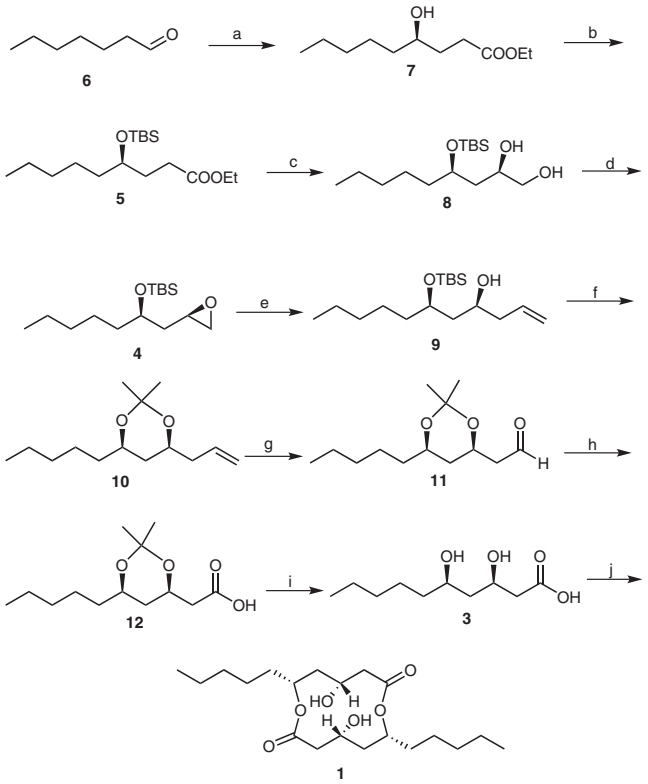
Our retrosynthetic route to verbalactone (**1**) is outlined in Scheme 1. Verbalactone (**1**) can simply be synthesized using Yamaguchi's macrolactonization of (3*R*,5*R*)-3,5-dihydroxydecanoic acid (**3**) which in turn could be obtained from epoxide **4**. Epoxide **4** could easily be derived from *tert*-butyldimethylsilyl-protected γ-hydroxy ester **5** which in turn could be synthesized from *n*-heptanal (**6**) via L-proline-catalyzed α-aminoxylation and HWE olefination.

As shown in Scheme 2, commercially available *n*-heptanal (**6**) was subjected to sequential α-aminoxylation using nitrosobenzene as the oxygen source and L-proline as a catalyst and subsequent HWE olefination using triethyl phosphonoacetate, followed by reductive hydrogenation using a catalytic amount of palladium on carbon, to furnish the γ-hydroxy ester **7** in 68% yield and 97% ee.[12] The free hydroxy group of γ-hydroxy ester **7** was protected as the *tert*-butyldimethylsilyl (TBS) ether using *tert*-butyldimethylsilyl chloride to furnish compound **5** in 94% yield. With protected γ-hydroxy ester **5** in hand, the stage was set for introduction of another hydroxy group at the α-position. Thus, diisobutylaluminum hydride reduction of ester **5** furnished the corresponding aldehyde which was then subjected to α-aminoxylation using L-proline as a catalyst, followed by sodium borohydride reduction and subsequent palladium on carbon reduction, to give the protected 1,3-*syn*-diol **8** in 78% yield. ^{1}H NMR analysis revealed the diastereomeric purity of **8** to be >95% de. The primary hydroxy group of **8** was converted into the tosyl derivative using *p*-toluenesulfonyl chloride, triethyl-

SYNTHESIS 2011, No. 12, pp 1954–1959
Advanced online publication: 17.05.2011
DOI: 10.1055/s-0030-1260051; Art ID: C28811SS



Scheme 1 Retrosynthetic route to verbalactone (**1**) and massoialactone (**2**)



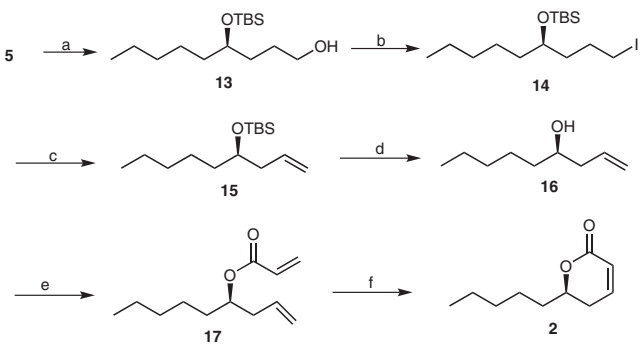
Scheme 2 *Reagents and conditions*: (a) (i) nitrosobenzene, L-proline, DMSO, then HWE salt, DBU, LiCl, MeCN; (ii) H_2, Pd/C, EtOAc, 68% (over two steps); (b) TBSCl, imidazole, CH_2Cl_2, 14 h, 94%; (c) (i) DIBAL-H, CH_2Cl_2, –78 °C; (ii) nitrosobenzene, L-proline, DMSO; (iii) $NaBH_4$, MeOH; (iv) H_2, Pd/C, EtOAc, 78%; (d) (i) TsCl, Et_3N, *n*-Bu_2SnO, CH_2Cl_2; (ii) K_2CO_3, MeOH, r.t., 82%; (e) vinylmagnesium bromide, CuI, THF, –20 °C, 12 h, 89%; (f) (i) TBAF, THF, 2 h; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 0 °C, 92%; (g) (i) OsO_4, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH–H_2O (1:1), 0 °C, 24 h; (ii) silica-supported $NaIO_4$, CH_2Cl_2, r.t., 1 h, 82% (over two steps); (h) H_2O_2, $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH–H_2O (3:1), 0 °C to r.t., 3 h, 84%; (i) CSA, MeOH, r.t., 1 h, 80%; (j) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, r.t., then DMAP, toluene, reflux, 53%.

amine and a catalytic amount of dibutyltin oxide; subsequent base treatment furnished the epoxide **4**. Epoxide **4** was treated with vinylmagnesium bromide in the presence of copper(I) iodide to give the homoallylic alcohol **9**. Deprotection of the TBS group and subsequent treatment of the resulting 1,3-*syn*-diol with 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate gave the isopropylidene derivative **10**. Dihydroxylation of **10** followed by oxidative cleavage using silica-supported sodium periodate gave aldehyde **11** which on subsequent oxidation resulted in the formation of acid **12** in good yield. Deprotection of the isopropylidene group was achieved with catalytic 10-camphorsulfonic acid (5 mol%) in methanol to provide (3*R*,5*R*)-3,5-dihydroxydecanoic acid (**3**).

The pH during the deprotection of isopropylidene **12** was crucial and had to be carefully controlled as the formation of monomeric lactone at higher acidic pH was noted in previous reports. Thus, a citric acid–sodium hydroxide buffer solution (pH 6) was used during the workup.[2a,c] Compound **3** was found to be unstable as, on standing for longer time, lactonization to form monomeric lactone was the major pathway. Consequently, acid **3** without any further purification was directly subjected to Yamaguchi macrolactonization to afford verbalactone (**1**) in 53% yield.

Towards the synthesis of massoialactone (**2**, see Scheme 1 for the retrosynthetic route), the TBS-protected γ-hydroxy ester **5** was subjected to diisobutylaluminum hydride reduction to furnish the corresponding alcohol **13** in 83% yield (Scheme 3). Alcohol **13** was converted into the iodo derivative **14** which, on reaction with potassium *tert*-butoxide in dimethyl sulfoxide (KtBD)[13] in benzene, afforded the TBS-protected homoallylic alcohol **15** in 69% yield. TBS deprotection of **15** in 88% yield followed by esterification of resultant alcohol **16** with acryloyl chloride in the presence of triethylamine gave **17** in 82% yield. Subsequent ring-closing metathesis of acrylate **17** under reflux in high dilution conditions using first generation Grubbs' catalyst and a catalytic amount of titanium(IV) isopropoxide provided (*R*)-massoialactone (**2**) in good yield. The physical and spectroscopic data of **2** were in accord with those described in the literature.[9f]

In summary, concise and efficient total syntheses of verbalactone and (*R*)-massoialactone with high enantioselectivities have been accomplished in which the stereocenters were generated by means of L-proline-catalyzed α-aminoxylation and Horner–Wadsworth–Emmons olefination. The synthetic approach is amenable for other



Scheme 3 *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 83%; (b) I_2, Ph_3P, imidazole, THF, MeCN, r.t., 2 h, 72%; (c) 1 N KtBD, benzene, r.t., 30 min, 69%; (d) TBAF, THF, r.t., 2 h, 88%; (e) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 6 h, 82%; (f) $(Cy_3P)_2Ru(Cl)_2$=CHPh (20 mol%), Ti(O-*i*-Pr)$_4$, CH_2Cl_2, reflux, overnight, 86%.

macrolactones of this class. Currently, work is in progress in this direction.

All reactions were carried out under an inert atmosphere, unless otherwise stated, following standard syringe–septa techniques. Solvents were dried and purified by conventional methods prior to use. Column chromatography was performed on silica gel (60 and 230 mesh) using PE (petroleum ether) or a PE–EtOAc mixture as eluent. PE refers to the fraction boiling in the 60–80 °C range. Optical rotations were measured on a JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker AC-200 and AC-400 spectrometers at 200 MHz or 400 MHz (^{1}H) and 50 MHz or 100 MHz (^{13}C); $SiMe_4$ was used as the internal standard. ESI-MS were obtained using an API-Q-Star Applied Biosystems spectrometer. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer.

Ethyl (*R*)-4-Hydroxynonanoate (7)

To a soln of *n*-heptanal (**6**; 3.0 g, 26.3 mmol) and nitrosobenzene (2.81 g, 26.3 mmol) in anhyd DMSO (40 mL) was added L-proline (1.2 g, 10.5 mmol) at 20 °C. The mixture was vigorously stirred for 30 min under argon (the color of the reaction mixture changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) soln of triethyl phosphonoacetate (15.65 mL, 78.9 mmol), DBU (11.77 mL, 78.9 mmol) and LiCl (3.35 g, 78.9 mmol) in MeCN (40 mL) was added quickly at 0 °C. The resulting mixture was allowed to warm to r.t. over 1 h, and the reaction was quenched by the addition of ice pieces. The MeCN was evaporated under reduced pressure. The remaining mixture was then poured into H_2O (100 mL) and extracted with Et_2O (5 × 100 mL). The combined organic layer was washed with H_2O (3 × 50 mL) and brine (3 × 50 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to give crude product which was directly subjected to the next step without purification.

To the crude allylic alcohol in EtOAc (20 mL) was added Pd/C (10%; catalytic amount) under hydrogenation conditions and the reaction mixture was stirred overnight. On completion of the reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (PE–EtOAc, 19:1) to give (*R*)-**7** as a yellow-colored liquid; yield: 3.61 g (68%).

IR ($CHCl_3$): 3432, 2934, 1713, 1465, 1177 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84–0.90 (m, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.32–1.38 (m, 3 H), 1.36–1.44 (m, 4 H), 1.52–1.94 (m, 4 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 3.54–3.63 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 22.3, 24.7, 27.8, 28.7, 31.6, 35.3, 60.3, 71.0, 177.0.

ESI-MS: *m*/*z* = 225 [M + Na]$^+$.

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.11; H, 10.81.

Ethyl (*R*)-4-(*tert*-Butyldimethylsilyloxy)nonanoate (5)

To a stirred soln of alcohol **7** (3 g, 14.83 mmol) in CH_2Cl_2 (40 mL) was added imidazole (1.99 g, 29.68 mmol). Then, TBSCl (2.90 g, 19.29 mmol) was added at 0 °C and the mixture was stirred at r.t. for 14 h. The reaction was quenched with sat. aq NH_4Cl and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extract was washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product (PE) provided **5** as a colorless liquid; yield: 4.42 g (94%).

$[\alpha]_D^{25}$ –8.96 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$): 2856, 1725, 1463, 1258 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.04 (s, 6 H), 0.89 (s, 12 H), 1.22–1.32 (m, 9 H), 1.37–1.43 (m, 2 H), 1.59–1.90 (m, 2 H), 2.32–2.40 (m, 2 H), 3.66–3.72 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, –4.5, 14.0, 14.2, 18.0, 22.6, 24.8, 25.8, 30.0, 31.7, 31.9, 36.9, 60.2, 71.1, 174.0.

ESI-MS: *m*/*z* = 339 [M + Na]$^+$.

Anal. Calcd for $C_{17}H_{36}O_3Si$: C, 64.50; H, 11.46. Found: C, 64.74; H, 11.58.

(2*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)nonane-1,2-diol (8)

To a soln of ester **5** (4.0 g, 12.64 mmol) in CH_2Cl_2 (60 mL) was added 1.87 M DIBAL-H in toluene (7.44 mL, 13.90 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred at this temperature for 40 min. Then, a sat. soln of tartaric acid in H_2O (15 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give aldehyde as a colorless liquid, which was directly used in the next step without further purification.

To the crude aldehyde (3.98 g, 14.62 mmol) was added nitrosobenzene (1.54 g, 14.62 mmol) in anhyd DMSO (40 mL), which was followed by the addition of L-proline (0.67 g, 5.85 mmol) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, which was followed by dilution of the mixture with anhyd MeOH (30 mL) and careful addition of excess $NaBH_4$ (2.22 g, 58.38 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic soln of Et_2O and 2 M aq HCl. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phase was dried (Na_2SO_4), concentrated and passed through a silica gel plug (PE–EtOAc, 4:1) to give aminoxy alcohol.

The crude aminoxy alcohol (4.26 g) was dissolved in EtOAc (30 mL). To the solution was added a catalytic amount of 10% Pd/C and the mixture was stirred in a hydrogen atmosphere (60 psi) for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite® pad and concentrated. The crude product was purified by silica gel chromatography (PE–EtOAc, 7:3) to give pure diol **8** as a colorless liquid; yield: 2.86 g (78%).

$[\alpha]_D^{25}$ –14.98 (*c* 0.9, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.91 (s, 12 H), 1.22–1.32 (m, 6 H), 1.46–1.56 (m, 2 H), 1.59–1.66 (m, 2 H), 2.28 (br s, 1 H), 3.47 (dd, *J* = 6.2, 11.0 Hz, 1 H), 3.62 (dd, *J* = 3.7, 11.0 Hz, 1 H), 3.83–4.01 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.7, –4.0, 13.9, 17.9, 22.5, 24.3, 25.7, 31.9, 37.9, 38.9, 66.9, 71.3, 73.1.

ESI-MS: *m*/*z* = 313 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{34}O_3Si$: C, 62.01; H, 11.80. Found: C, 61.95; H, 11.47.

(2*R*)-2-[(2*R*)-2-(*tert*-Butyldimethylsilyloxy)heptyl]oxirane (4)

To a mixture of diol **8** (1.00 g, 3.44 mmol) in anhyd CH_2Cl_2 (15 mL) was added *n*-Bu_2SnO (0.49 g, 1.72 mmol), followed by the addition of TsCl (0.66 g, 3.44 mmol) and Et_3N (0.53 mL, 3.79 mmol), and the mixture was stirred at r.t. under N_2. The reaction was monitored by TLC and, after completion, was quenched by adding H_2O. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phase was washed with H_2O (2 × 30 mL), dried (Na_2SO_4) and concentrated.

To this crude mixture in MeOH (15 mL) at 0 °C was added K_2CO_3 (1.03 g, 3.78 mmol) and the resulting mixture was stirred at r.t. for 1 h. After completion of the reaction (as indicated by TLC), the reaction was quenched by the addition of ice pieces and the MeOH was evaporated. The concentrated mixture was then extracted with EtOAc (3 × 30 mL), and the combined organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated. Column chromatography of the crude product (PE–EtOAc, 96:4) gave epoxide **4** as a colorless liquid; yield: 0.77 g (82%).

$[\alpha]_D^{25}$ +4.2 (*c* 2.0, $CHCl_3$).

IR ($CHCl_3$): 3041, 2926, 2854, 1465, 1255, 1070, 835, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 12 H), 1.27–1.37 (m, 6 H), 1.48–1.57 (m, 2 H), 1.60–1.80 (m, 2 H), 2.46 (dd, *J* = 2.7, 5.1 Hz, 1 H), 2.74–2.79 (m, 1 H), 3.00–3.09 (m, 1 H), 3.85 (quin, *J* = 5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, –4.5, 14.0, 18.0, 22.6, 25.1, 25.8, 31.9, 37.1, 40.1, 46.8, 49.5, 70.3.

ESI-MS: *m*/*z* = 273 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 65.87; H, 11.63.

(4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)undec-1-en-4-ol (9)

To a stirred soln of epoxide **4** (0.50 g, 1.83 mmol) and CuI (35 mg, 0.18 mmol) in anhyd THF (5 mL) was added 1 M vinylmagnesium bromide in THF (392 mg, 3.67 mL, 3.67 mmol) dropwise over a period of 30 min at –20 °C and the mixture was stirred for 12 h. The mixture was allowed to warm to 0 °C, before the reaction was quenched with sat. NH_4Cl soln (2 mL). The layers were separated; the aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined ethereal extract was washed with brine (2 mL) and dried (Na_2SO_4). Evaporation of the solvent and silica gel column chromatographic purification of the crude product (PE–EtOAc, 19:1) gave pure compound **9** as a colorless oil; yield: 0.49 g (89%).

(4*S*,6*R*)-4-Allyl-2,2-dimethyl-6-pentyl-1,3-dioxane (10)

To a stirred soln of compound **9** (400 mg, 1.33 mmol) in anhyd THF (7 mL) was added 1 M TBAF in THF (1.46 mL, 1.46 mmol) at r.t. After completion of the reaction (2 h), some ice flakes were added to the mixture which was then extracted with EtOAc (3 × 20 mL). The combined organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure to afford crude diol which was directly used for the next step.

To a soln of the crude diol (248 mg) in anhyd CH_2Cl_2 (10 mL) and 2,2-dimethoxypropane (0.33 mL, 2.66 mmol) was added a catalytic amount of PPTS and activated 3-Å molecular sieves (0.2 g) at 0 °C, after which the reaction mixture was stirred at r.t. for 30 min. After completion of the reaction, the molecular sieves were removed by filtration. Sat. aq $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried (Na_2SO_4). The solvent was removed under reduced pressure to afford crude compound **10** as a colorless syrup. Purification of the crude product by silica gel column chromatography (PE–EtOAc, 9:1) gave **10** as a colorless liquid; yield: 277 mg (92%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3 H), 1.40 (s, 3 H), 1.44 (s, 3 H), 1.02–1.57 (m, 10 H), 2.07–2.39 (m, 2 H), 3.73–3.94 (m, 2 H), 5.04–5.14 (m, 2 H), 5.71–5.92 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 19.8, 22.5, 24.6, 30.2, 31.8, 36.4, 40.9, 68.6, 68.9, 98.3, 116.9, 134.2.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 73.43; H, 10.27. Found: C, 73.57; H, 10.43.

2-[(4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl]acetaldehyde (11)

To a mixture of $K_3Fe(CN)_6$ (0.87 g, 2.65 mmol) and K_2CO_3 (0.37 g, 2.65 mmol) in *t*-BuOH–H_2O (1:1, 8 mL) cooled at 0 °C was added 0.1 M OsO_4 in toluene (0.035 mL, 0.4 mol%). After the mixture was stirred at 0 °C for 5 min, olefin **10** (0.20 g, 0.884 mmol) was added in one portion. The mixture was stirred at 0 °C for 24 h and then the reaction was quenched with solid Na_2SO_3. Stirring was continued for 45 min and then the solution was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with 10% KOH soln (20 mL) and then brine (2 × 30 mL), dried (Na_2SO_4) and concentrated to give crude diol (0.23 g) as a colorless, syrupy liquid which was pure enough for the next step.

To a vigorously stirred suspension of silica gel supported $NaIO_4$ reagent (1.77 g) in CH_2Cl_2 (400 mL) was added a soln of the crude diol (0.23 g, 0.883 mmol) in CH_2Cl_2 (20 mL). On completion of the reaction (1 h, monitored by TLC), the reaction mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with $CHCl_3$. Removal of solvent and silica gel column chromatography of the crude product (PE–EtOAc, 15:1) afforded aldehyde **11** as a colorless liquid; yield: 165 mg (82%).

$[\alpha]_D^{25}$ –134.2 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.4 Hz, 3 H), 1.38 (s, 3 H), 1.47 (s, 3 H), 1.1–1.7 (m, 10 H), 2.50 (ddd, *J* = 1.7, 5.1, 16.4 Hz, 1 H), 2.59 (ddd, *J* = 2.3, 7.3, 16.4 Hz, 1 H), 3.80–3.89 (m, 1 H), 4.35–4.45 (m, 1 H), 9.79 (t, *J* = 1.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.7, 22.6, 24.5, 30.1, 31.7, 36.3, 49.9, 64.7, 68.8, 98.7, 201.1.

ESI-MS: *m*/*z* = 229 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.50; H, 10.87.

2-[(4*R*,6*R*)-2,2-Dimethyl-6-pentyl-1,3-dioxan-4-yl]acetic Acid (12)

To an ice-cold soln of aldehyde **11** (20 mg, 87.6 mmol) in *t*-BuOH–H_2O (3:1, 6 mL) was added successively $NaH_2PO_4{\cdot}2H_2O$ (48 mg, 306.58 μmol), 30% aq H_2O_2 (0.10 mL) and $NaClO_2$ (15.84 mg, 175.18 μmol). The reaction mixture was gradually warmed to r.t. and stirred for 3 h. After completion of the reaction, the mixture was diluted with EtOAc (10 mL) and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to afford the crude product, which on purification over silica gel (light PE–EtOAc, 1:1) afforded acid **12** as a colorless oil; yield: 18 mg (84%).

$[\alpha]_D^{25}$ +13.3 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.7 Hz, 3 H), 1.40 (s, 3 H), 1.44 (s, 3 H), 1.24–1.54 (m, 10 H), 2.46 (dd, *J* = 15.4, 5.6 Hz, 1 H), 2.58 (dd, *J* = 15.4, 6.8 Hz, 1 H), 3.79–3.88 (m, 1 H), 4.26–4.35 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 19.8, 22.5, 24.5, 30.2, 31.8, 36.3, 41.4, 65.8, 68.9, 99.3, 176.2.

ESI-MS: *m*/*z* = 267 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.83; H, 9.67.

Verbalactone (1)

A soln of acid **12** (120 mg, 0.49 μmol) and CSA (5.70 mg, 24.6 μmol) in anhyd MeOH (10 mL) was stirred at r.t. for 1 h. A citric acid–sodium hydroxide buffer soln (pH 6) was added and the mixture was extracted with EtOAc (5 × 20 mL). The combined extract was dried (Na_2SO_4) and concentrated to afford deprotected **3** (80 mg) as a colorless syrup which was found to be unstable (on standing it undergoes lactonization to form monomeric lactone) and was directly taken for the next reaction without further purification.

To a soln of seco acid **3** (24 mg, 117.5 μmol) in THF (4 mL) was added Et_3N (18.02 μL, 129.24 μmol) at r.t. The mixture was treated with 2,4,6-trichlorobenzoyl chloride (18.36 μL, 117.5 μmol) and stirred at r.t. for 2 h. The mixture was diluted with anhyd toluene (4 mL), then added dropwise over a period of 3 h to a refluxing soln of DMAP (187.7 mg, 1.536 mmol) in anhyd toluene (40 mL). After completion of the addition, the mixture was refluxed for an additional hour and then concentrated under reduced pressure to provide crude product which on purification over silica gel (light PE–EtOAc, 5:1) furnished verbalactone (**1**); yield: 11 mg (53%).

$[\alpha]_D^{25}$ +8.7 (*c* 0.9, $CHCl_3$) [Lit.[1] $[\alpha]_D^{20}$ +7.3 (*c* 0.9, $CHCl_3$)].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 6 H), 1.16–1.31 (m, 12 H), 1.45–1.60 (m, 4 H), 1.97 (td, *J* = 15.1, 4.5 Hz, 2 H), 2.02–2.10 (ddd, *J* = 14.5, 9.7, 3.1 Hz, 2 H), 2.67 (d, *J* = 3.6 Hz, 4 H), 3.73 (br s, 2 H), 4.03–4.08 (m, 2 H), 4.90–4.97 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.4, 25.4, 31.3, 31.6, 36.2, 39.4, 64.7, 72.5, 172.9.

ESI-MS: *m*/*z* = 373 $[M + H]^+$.

(*R*)-4-(*tert*-Butyldimethylsilyloxy)nonan-1-ol (13)

To a soln of ester **5** (3.0 g, 9.48 mmol) in CH_2Cl_2 (40 mL) was added 1.87 M DIBAL-H in toluene (12.67 mL, 23.69 mmol) at –78 °C under argon atmosphere. The reaction mixture was stirred at this temperature for 2 h. Then, a sat. soln of tartaric acid in H_2O (10 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification over silica gel (light PE–EtOAc, 9:1) afforded alcohol **13** as a colorless oil; yield: 2.16 g (83%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.91 (s, 12 H), 1.20–1.27 (m, 6 H), 1.45–1.67 (m, 6 H), 3.55–3.77 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.5, 14.0, 18.0, 22.6, 25.1, 25.8, 31.9, 33.3, 36.4, 41.9, 63.1, 72.1.

ESI-MS: *m*/*z* = 297 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{34}O_2Si$: C, 65.63; H, 12.48. Found: C, 65.31; H, 12.57.

(*R*)-4-(*tert*-Butyldimethylsilyloxy)-1-iodononane (14)

To a cooled (0 °C), stirred soln of Ph_3P (2.10 g, 8.01 mmol) in THF–MeCN (6:5, 30 mL) were added imidazole (0.60 g, 8.74 mmol) and I_2 (2.03 g, 8.01 mmol). The mixture was stirred for 2 h and then a soln of alcohol **13** (2 g, 7.29 mmol) in THF (10 mL) was added at 0 °C. The mixture was stirred for 2 h, then diluted with 10% aq $Na_2S_2O_3$ (40 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, then used without purification for the next step.

(*R*)-4-(*tert*-Butyldimethylsilyloxy)non-1-ene (15)

To the crude iodo compound **14** (2.8 g, 7.29 mmol) dissolved in benzene (25 mL) was added 1 N KtBD (10.4 mL, 10.4 mmol) and the mixture was stirred at r.t. for 30 min. Then, the mixture was poured into H_2O and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography (PE) afforded **15** as a colorless liquid; yield: 1.29 g (69%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.90 (s, 12 H), 1.27–1.45 (m, 8 H), 2.18–2.25 (m, 2 H), 3.63–3.74 (m, 1 H), 5.00–5.09 (m, 2 H), 5.72–5.93 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.5, –4.4, 14.0, 18.1, 22.6, 25.0, 25.8, 31.9, 36.7, 41.9, 72.0, 116.5, 135.5.

ESI-MS: *m*/*z* = 257 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{32}OSi$: C, 70.24; H, 12.57. Found: C, 69.88; H, 12.83.

(*R*)-Non-1-en-4-ol (16)

To a stirred soln of compound **15** (500 mg, 1.95 mmol) in anhyd THF (10 mL) was added 1 M TBAF in THF (2.15 mL, 2.15 mmol) at r.t. After completion of the reaction (2 h), some ice flakes were added to the mixture which was then extracted with EtOAc (3 × 15 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford crude homoallylic alcohol. Purification of the crude product by silica gel column chromatography (PE–EtOAc, 9:1) gave **16** as a colorless liquid; yield: 244 mg (88%).

$[\alpha]_D^{25}$ +12.5 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$): 3351, 2926, 2854, 1641, 1589, 1457, 1378, 1259, 1156, 999, 836 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.4 Hz, 3 H), 1.26–1.47 (m, 8 H), 1.70 (br s, 1 H), 2.09–2.19 (m, 1 H), 2.27–2.35 (m, 1 H), 3.65–3.69 (m, 1 H), 5.12–5.16 (m, 2 H), 5.77–5.91 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 25.2, 31.8, 36.7, 41.8, 70.7, 117.6, 134.9.

(*R*)-Non-1-en-4-yl Acrylate (17)

Acryloyl chloride (0.95 g, 0.86 mL, 10.55 mmol) was added dropwise under argon to a soln of homoallylic alcohol **16** (1.5 g, 10.55 mmol) and Et_3N (4.27 g, 5.9 mL, 42.18 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at 0 °C for 6 h. Then, the mixture was filtered through a pad of Celite® and poured into H_2O (15 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layer was washed with brine (2 × 20 mL), dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography (PE–EtOAc, 19:1) afforded **17** as a colorless liquid; yield: 1.70 g (82%).

$[\alpha]_D^{25}$ +19.93 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 2956, 2930, 2859, 1742, 1725, 1640, 1620, 1549, 1406, 1296, 1271, 1195, 1048, 986, 917, 809 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.18–1.29 (m, 8 H), 2.33–2.37 (m, 2 H), 4.96–5.11 (m, 3 H), 5.72–5.83 (m, 2 H), 6.10 (dd, *J* = 10.5, 17.2 Hz, 1 H), 6.42 (d, *J* = 18 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.9, 31.6, 33.5, 38.6, 73.6, 117.5, 128.9, 130.0, 132.7, 165.4.

(*R*)-Massoialactone (2)

Grubbs' catalyst (0.169 g, 0.20 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to a refluxing soln of acrylate **17** (0.200 g, 1.02 mmol) and Ti(O-*i*-Pr)$_4$ (8.6 mg, 0.03 mmol) in anhyd CH_2Cl_2 (50 mL). Refluxing was continued overnight, by which time all the starting material had been consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (PE–EtOAc, 4:1) to afford **2** as a colorless oil; yield: 0.147 g (86%).

$[\alpha]_D^{25}$ –114.5 (*c* 1, $CHCl_3$) [Lit.[9i] $[\alpha]_D^{25}$ –113.6 (*c* 1, $CHCl_3$)].

IR (neat): 2931, 2860, 1725, 1630, 1466, 1388, 1251, 1155, 1118, 1059, 1039, 955, 815 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.9 Hz, 3 H), 1.26–1.34 (m, 5 H), 1.64–1.82 (m, 3 H), 2.32–2.38 (m, 2 H), 4.41–4.45 (m, 1 H), 6.04 (d, *J* = 10 Hz, 1 H), 6.87–6.90 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.4, 24.5, 29.4, 31.5, 34.8, 78.0, 121.5, 144.9, 164.4.

ESI-MS: *m*/*z* = 169 $[M + H]^+$.

References

(1) Magiatis, P.; Spanakis, D.; Mitaku, S.; Tsitsa, E.; Mentis, A.; Harvala, C. *J. Nat. Prod.* **2001**, *64*, 1093.

(2) (a) Gogoi, S.; Barua, N. C.; Kalita, B. *Tetrahedron Lett.* **2004**, *45*, 5577. (b) Sharma, G. V. M.; Reddy, C. G. *Tetrahedron Lett.* **2004**, *45*, 7483. (c) Allais, F.; Louvel, M. C.; Cossy, J. *Synlett* **2007**, 451. (d) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Synth. Commun.* **2008**, *38*, 3129. (e) Wu, J. Z.; Gao, J.; Ren, G. B.; Zhen, Z. B.; Zhang, Y. H.; Wu, Y. K. *Tetrahedron* **2009**, *65*, 289. (f) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Helv. Chim. Acta* **2009**, *92*, 1840. (g) Salunke, G. B.; Shivakumar, I.; Gurjar, M. K. *Tetrahedron Lett.* **2009**, *50*, 2048.

(3) Meijer, Th. M. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 191.

(4) Crombie, L. *J. Chem. Soc.* **1955**, 2535.

(5) Abe, S. *J. Chem. Soc. Jpn.* **1937**, *58*, 246.

(6) Hashizumi, T.; Kikuchi, N.; Sasaki, Y.; Sakata, I. *Agric. Biol. Chem.* **1968**, *32*, 1306.

(7) Kaiser, P.; Lamparsky, D. *Tetrahedron Lett.* **1976**, 1659.

(8) Cavill, G. W. K.; Clark, D. V.; Whitefield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819.

(9) (a) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761. (b) Bennett, F.; Knight, D. W.; Fenton, G. *Heterocycles* **1989**, *29*, 639. (c) Bonini, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron: Asymmetry* **1992**, *3*, 29. (d) Fournier, L.; Gaudel-Siri, A.; Kocieński, P. J.; Pons, J.-M. *Synlett* **2003**, 107. (e) Fournier, L.; Kocieński, P. J.; Pons, J.-M. *Tetrahedron* **2004**, *60*, 1659. (f) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849. (g) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445. (h) Sabitha, G.; Gopal, P.; Yadav, J. S. *Synth. Commun.* **2007**, *37*, 1495. (i) Touati, R.; Ratovelomanana-Vidal, V.; Ben Hassine, B.; Genet, J. P. *Tetrahedron: Asymmetry* **2006**, *17*, 3400. (j) Mori, K. *Agric. Biol. Chem.* **1976**, *40*, 1617.

(10) (a) Harbindu, A.; Kumar, P. *Synthesis* **2010**, 1479. (b) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843. (c) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207. (d) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6571. (e) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397. (f) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935. (g) Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195. (h) Chowdhury, P. S.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 7018. (i) Kumar, P.; Pandey, M.; Gupta, P.; Naidu, S. V.; Dhavale, D. D. *Eur. J. Org. Chem.* **2010**, 6993.

(11) Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611.

(12) The enantiomeric excess(ee) of **7** was determined by derivatizing its precursor α,β-unsaturated γ-hydroxy ester with Mosher's acid and analyzing the ^{19}F NMR spectrum. The ee was found to be >97%.

(13) Wood, N. F.; Chang, F. C. *J. Org. Chem.* **1965**, *30*, 2054.