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Synthesis of enantiopure (*R*)-(−)-massoialactone through ruthenium-SYNPHOS® asymmetric hydrogenation

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Abstract—Total synthesis of enantiopure (*R*)-(−)-massoialactone was achieved. The key step includes the asymmetric hydrogenation of an achiral β-keto ester using a ruthenium-SYNPHOS® catalyst to set the hydroxyl function in a stereocontrolled manner with excellent enantioselectivity (>99% ee). Ring closing metathesis (RCM) in the presence of Grubbs' catalyst allows the final construction of the six-membered lactone.

1. Introduction

Saturated and unsaturated aliphatic δ-lactones occur in several food flavours and essential oils.[1] Owing to their specific odour impression and low threshold concentration, they play an important role as flavouring materials; therefore practical syntheses of these δ-lactones are in great demand whereas the α,β-unsaturated δ-lactone (or 5,6-dihydro-2-(2*H*)-pyranone) moiety is present in a number of bioactive natural products, such as hexadecanolide[2] (*R*)-goniothalamin[3] (Fig. 1).

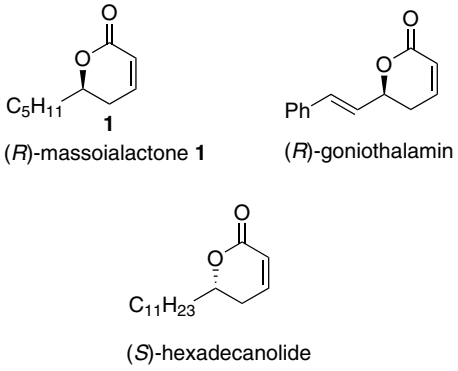

Figure 1.

(*R*)-(−)-6-Pentyl-5,6-dihydro-2*H*-pyran-2-one named (*R*)-massoialactone **1** is the allomone of the two species of formicine ants of the genus *camponotus*, collected in Western Australia.[4] In 1937, Abe isolated (−)-massoialactone **1** for the first time from the bark oil of *Cryptocarya massoia*, which had been used for many centuries as a constituent of native medicine.[5] It has also been isolated from jasmine flowers[6] as well as from cane molasses (in which it is a flavour component).[7] This lactone has also been shown to occur in *Hierochloe odorata* and *Hierochloe australis*, both being commonly used in vodka production.[8] In addition to various methods for the synthesis of the racemic massoialactone **1**,[9] a number of enantioselective syntheses[10] have been reported in the literature, based on the chiral pool as the starting material, chiral induction or chromatographic resolution of diastereomeric derivatives of the lactone precursor.[11] Recently, we succeeded in designing a new atropisomeric diphosphine named SYNPHOS® with relevant stereoelectronic properties.[12] As part of our research programme aimed at developing stereocontrolled syntheses of naturally occurring bioactive compounds in enantiopure form,[13] we herein report a new application of the SYNPHOS® ligand to the total synthesis

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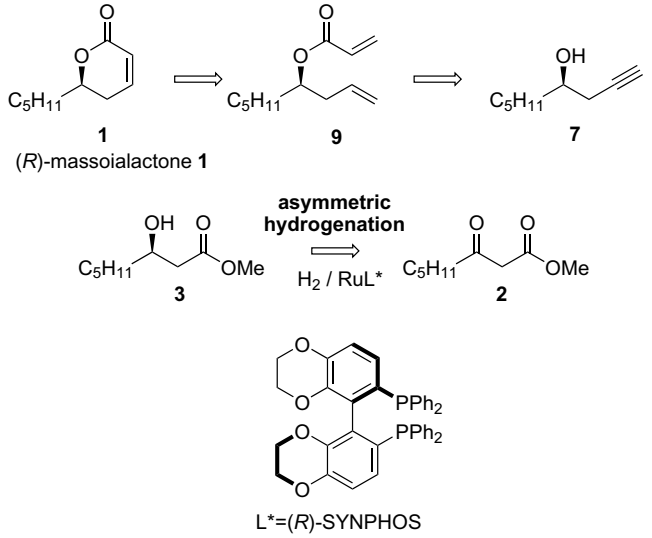
of (*R*)-(−)-massoialactone **1** from commercially available inexpensive hexanoic acid as the starting material.

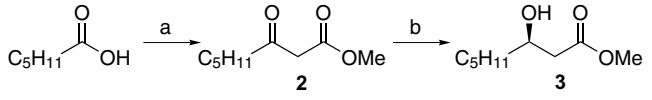
2. Results and discussion

Retrosynthetically, target compound **1** (Scheme 1) would result from compound **9** through ring-closing metathesis (RCM)[14] for the final construction of the six-membered unsaturated lactone **1**. The key step for massoialactone **1** would be a catalytic asymmetric hydrogenation reaction of β-keto ester **2** based upon SYNPHOS® as the chiral ligand, which would set the configuration of the hydroxyl group with high enantioselectivity.



Scheme 1. Retrosynthetic analysis for (*R*)-massoialactone **1**.

The synthesis of the required β-hydroxy ester **3** began with the commercially available hexanoic acid (Scheme 2), which was converted into β-keto ester **2** using Masamune's procedure.[15] Thus, the addition of *N*,*N*′-carbonyldiimidazole to hexanoic acid followed by treatment with magnesium salt of monomethyl malonic acid afforded methyl-3-oxooctanoate **2** in 82% yield.



Scheme 2. Reagents and conditions: (a) ImCOIm, THF, rt, 6 h then $Mg(O_2CCH_2CO_2Me)_2$, THF, rt, 16 h, 82% yield; (b) H_2 (bar), *T* (°C), [Ru-((*R*)-SYNPHOS)] catalyst, MeOH, 24 h.

The asymmetric hydrogenation of β-keto ester **2** was carried out in methanol for 24 h by using in situ generated [$RuBr_2$((*R*)-SYNPHOS)] catalyst (*R*)-**10** prepared from a mixture of Ru(COD)(η^3-methylallyl)$_2$ and SYNPHOS® by addition of 2.2 equiv of HBr according to our convenient procedure.[16a] Preliminary studies were first conducted in MeOH at 50 °C under a low pressure of hydrogen (5 bar) for 24 h by varying the catalyst loading (0.25–0.75 mol %, Table 1). In all cases, excellent enantiofacial discrimination was observed and β-hydroxy ester **3** was obtained in an enantiomerically pure form (entries 1–3, ee >99%), while no complete conversions were achieved when 0.25 and 0.5 mol % of Ru-SYNPHOS catalyst were used (entries 1 and 2, 85% and 94% conv.). By increasing the catalyst loading to 0.75 mol %, total conversion was obtained (entry 3, 100% conv., Table 1).

Afterwards, the reaction was optimized regarding both the catalyst loading and reaction times and we performed a comparative examination of Ru-SYNPHOS catalysts (Fig. 2) with both in situ generated [$RuBr_2$((*R*)-SYNPHOS)] (*R*)-**10** and [(RuCl((*R*)-SYNPHOS))$_2$(μ-Cl)$_3$][NH_2Me_2] (*R*)-**11** obtained from a mixture of [$RuCl_2$(*p*-cymene)]$_2$ and (*R*)-SYNPHOS® in the presence of NH_2Me_2·HCl in toluene at 100 °C for 7 h.[16b] The hydrogenation of methyl 3-oxooctanoate **2** was conducted in methanol under strictly identical conditions to ensure complete conversions (10 bar H_2, 50 °C, 0.5 mol % of Ru-catalyst). In this case, the [$RuBr_2$((*R*)-SYNPHOS)] (*R*)-**10** complex demonstrated extremely high rates (30 min) affording (*R*)-3-hydroxy octanoate **3** with excellent 96% yield and 99% ee determined by HPLC analysis. Comparable results were obtained but in 2 h by using [(RuCl((*R*)-SYNPHOS))$_2$(μ-Cl)$_3$][NH_2Me_2] (*R*)-**11** (96% yield and 99% ee).

The absolute configuration of β-hydroxy ester **3** was assigned to be (*R*) by considering the stereochemical model proposed for the hydrogenation reaction of functionalized ketones with ruthenium-arylphosphine catalysts.[12a,17]

Afterwards, β-hydroxy ester **3** was protected as its *tert*-butyl dimethylsilyl ether **4** by using *tert*-butyl dimethylsilyl triflate in the presence of 2,6-lutidine affording methyl (*R*)-(−)-3-(*tert*-butyl-dimethyl-silyloxy)octanoate **4** with excellent yield (Scheme 3, 94% yield). Dibal-H reduction of **4** in dichloromethane at −78 °C proceeded smoothly to furnish (*R*)-(−)-3-(*tert*-butyl-dimethyl-silyloxy)octanal **5** in 71% yield. The transformation of the corresponding aldehyde **5** into (*R*)-4-(*tert*-butyl-dimethyl-silyloxy)-non-1-yne **6** with dimethyl-1-diazo-2-oxopropylphosphonate according to the method of Ohira–Bestmann[18] gave only a poor yield out of alkyne **6** because of formation of the

Table 1. Ru-Catalyzed asymmetric hydrogenation of **2**

Entry	Ru-Catalyst (*R*)-**10**	Mol (%)	*P* (bar)	*T* (°C)	Conv[a] (%)	ee[b] (%)
1	[$RuBr_2$((*R*)-SYNPHOS)]	0.25	5	50	85	>99
2	[$RuBr_2$((*R*)-SYNPHOS)]	0.5	5	50	94	>99
3	[$RuBr_2$((*R*)-SYNPHOS)]	0.75	5	50	100	>99

[a] Measured by ^{1}H NMR (300 MHz).
[b] Determined by HPLC analysis, Chiralcel OD-H column.

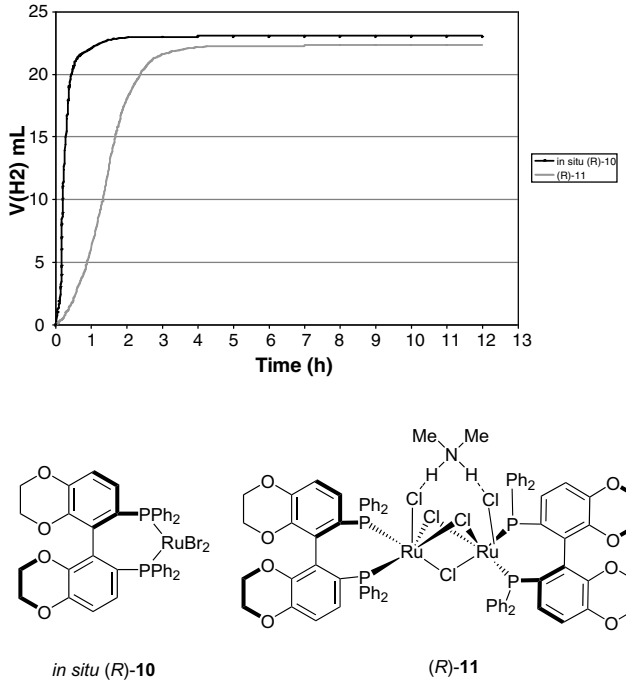
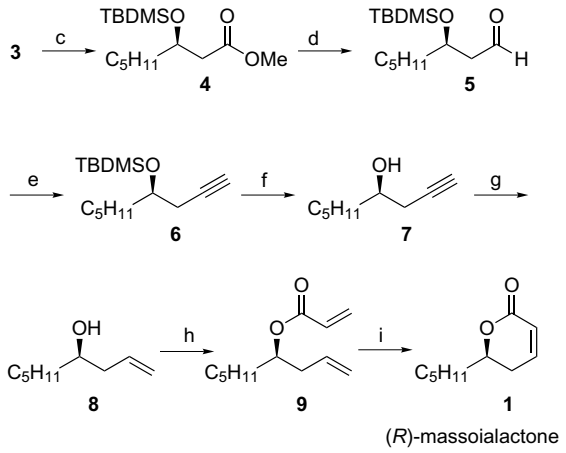


Figure 2. Kinetics of hydrogen uptake versus time for the Ru-SYNPHOS asymmetric hydrogenation of **2** using (*R*)-**10** (ee >99%) and (*R*)-**11** (ee >99%).



Scheme 3. Reagents and conditions: (c) 2,6-lutidine, TBDMSOTf, CH_2Cl_2, −25 to −15 °C, 45 min, 94%; (d) DIBAL-H, CH_2Cl_2, −78 °C, 4 h, 71%; (e) LDA, $TMSCHN_2$, THF, −78 °C, 1 h at −78 °C then 2 h at −10 °C, 87%; (f) Bu_4NF (1 M in THF), 2 h, rt, 95%; (g) $Pd/BaSO_4$, quinoline, EtOAc, H_2 (1 bar), rt, 2 h, 74%; (h) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 8 h, 82%; (i) $(PCy_3)_2Ru(Cl)_2{=}CH{-}Ph$ (25 mol %), CH_2Cl_2, $Ti(i\text{-}PrO)_4$, reflux, 6 h, 78%.

product of elimination. The method of Ohira–Shioiri[19] using trimethyl silyldiazomethane allowed us to obtain alkyne **6** in 87% yield. Removal of the protecting groups of alkyne **6** with TBAF in THF afforded the deprotected alcohol **7** in 95% yield. Lindlar hydrogenation of the triple bonds furnished the desired homoallylic alcohol **8** in 74% yield. Esterification of **8** with acryloyl chloride in the presence of triethylamine provided the corresponding acryloyl ester **9** in 82% yield. Finally, the formation of α,β-unsaturated lactone **1** was achieved by ring-closing metathesis of homoallylic alcohol **9** derived acrylate ester.

Exposure of diene ester **9** to Grubbs' catalyst ([bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride]) and a catalytic amount of $Ti(i\text{-}PrO)_4$ under high dilution (2.5×10^{-3} M) in anhydrous degassed dichloromethane at reflux afforded (−)-massoialactone **1** in 78% yield (Scheme 2). Spectral data of **1** were found to be in agreement with the reported literature data {$[\alpha]_D^{25} = -110.8$ (*c* 1, $CHCl_3$), Lit.[10f] $[\alpha]_D^{25} = -110.7$ (*c* 1, $CHCl_3$)]}.

3. Conclusion

In summary, we have developed a total synthesis of enantiopure (*R*)-(−)-massoialactone based upon catalytic asymmetric hydrogenation that proceeds in nine steps and 20% overall yield from commercially available hexanoic acid. The results obtained in this work demonstrated that high reaction rates and selectivities could be achieved at low catalyst loading on a multigram scale. We have demonstrated that SYNPHOS® ligand can be efficiently used in this transformation. This flexible strategy should allow the preparation of other lactones derivatives from inexpensive starting material.

4. Experimental

4.1. General methods

Dichloromethane was distilled from calcium hydride and tetrahydrofuran from sodium-benzophenone. Acetone for the catalyst preparation was distilled over potassium carbonate. Other solvents were used without any purification. Triethylamine was distilled from potassium hydroxide. All air and/or water sensitive reactions were carried out under an argon atmosphere unless otherwise noted. ^1H NMR spectra were recorded on Avance 300 at 300 MHz or Avance 400 at 400 MHz; ^{13}C NMR spectra were recorded on Avance 300 at 75 MHz or Avance 400 at 100 MHz. Chemical shifts (δ) are reported in ppm downfield relative to internal Me_4Si. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplicities (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; qu, quintet; o, octet; m, multiplet; and br, broad). Mass spectra were determined on a Nermag R10-10C instrument. Ionization was obtained by chemical ionization with ammonia (DCI/NH_3) or by electrospray (on a API 3000 PE Sciex instrument). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium lamp). HPLC analyses of compound **3** were performed on a Waters 600 system with a Chiralcel OD-H column.

4.2. Methyl 3-oxooctanoate 2

To a suspension of hexanoic acid (13.92 g, 120 mmol) in dry tetrahydrofuran (140 mL) was added *N*,*N*′-carbonyldiimidazole (23.4 g, 144 mmol) under argon in small portions. After evolution of the gas, the reaction mixture was stirred at room temperature for 8 h. Under vigorous

stirring, the bis(monomethylmalonate) magnesium salt (37.2 g, 144 mmol) was poured progressively into this solution. After 36 h at room temperature, the mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the resulting mixture was acidified to pH 4 with 10% hydrochloric acid and extracted with diethyl ether (3×200 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (200 mL), dried over magnesium sulfate and condensed under reduced pressure to give the crude product, which was purified by silica gel column chromatography using cyclohexane/ethyl acetate (9:1) as eluent to give the pure β-keto ester **2** (12.8 g, 62% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 3.74$ (s, 3H), 3.45 (s, 2H), 2.53 (t, $J = 7.4$ Hz, 2H), 1.61–1.66 (m, 2H), 1.30–1.34 (m, 6H), 0.91 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 202.8$, 167.7, 52.2, 48.9, 42.9, 31.1, 23.1, 22.3, 13.8. MS (EI, 70 eV): m/z 172 (M^+, 4%), 129 (10%), 116 (60%), 43 (100%).

4.3. Methyl (*R*)-(−)-3-hydroxyoctanoate 3

In situ preparation of [$RuBr_2$((*R*)-SYNPHOS)] (*R*)-**10**: A dry 10-mL round bottom flask tube was equipped with a magnetic stirrer bar, a stopper and connected to a supply of vacuum/argon. The flask was charged with 48 mg (0.15 mmol) of Ru(COD)(η^3-methylallyl)$_2$ and 105 mg (0.165 mmol) of (*R*)-SYNPHOS, then evacuated and filled with argon. Degassed anhydrous acetone (15 mL) was introduced via a syringe under a stream of argon. Methanolic HBr (1.83 mL, 2.2 equiv, 0.18 mol L^{-1}) was added dropwise to the solution. The mixture was degassed with three vacuum/argon cycles and stirred for 30 min at room temperature under a stream of argon. The orange precipitate was concentrated under vacuum. The crude orange-brown solid (*R*)-**10** was used as the catalyst in the hydrogenation reaction without further purification. (*R*)-3-Hydroxy octanoate **3**: 5.16 g (30 mmol) of methyl-3-oxooctanoate **2** and 20 mL of methanol were introduced in a 50 mL round bottom flask equipped with a magnetic stirrer. The system was connected to a supply of vacuum/argon and the solution carefully degassed by three vacuum/argon cycles. In situ generated [$RuBr_2$((*R*)-SYNPHOS)] catalyst (*R*)-**10** (0.5 mol %) was added. The orange solution was degassed by another vacuum/argon cycle. Under a flow of argon, the solution was introduced via a cannula in a 50 mL stainless steel autoclave, which was connected to a 1,590,000 TOP INDUSTRIE[20] parallel hydrogenation system equipped with a central mechanical stirrer and a gas consumption control and display system (TOP VIEW software). The atmosphere of the autoclave was purged three times with argon (8 bar) and twice with hydrogen (10 bar). The temperature of the autoclave was adjusted to 50 °C under a hydrogen pressure of 1 bar (stirring 200 rpm). The autoclave was then filled with hydrogen (20 bar, stirring 200 rpm). The stirring rate was adjusted to 1200 rpm and the hydrogen uptake was monitored. After total conversion of the substrate (end of hydrogen uptake), the autoclave was adjusted to room temperature and atmospheric pressure and finally purged three times with argon (8 bar, stirring 200 rpm). The contents were drained off and the autoclave was rinsed with methanol (20 mL). The methanol was distilled off in vacuo and the crude reaction mixture was purified by silica gel chromatography (cyclohexane: ethyl acetate (60:40)) to afford (*R*)-3-hydroxy octanoate **3** as a colourless oil, which was dried under reduced pressure to give 5.01 g of **3** (96%, ee >99%). ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 3.92$–4.08 (m, 1H), 3.71 (s, 3H), 2.8 (br, 1H), 2.37–2.55 (m, 2H), 1.41–1.48 (m, 2H), 1.27–1.35 (m, 6H), 0.89 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 173.4$, 68.1, 51.6, 41.1, 36.5, 31.6, 25.1, 22.5, 13.9. MS (DCI, NH_3): m/z 192 (100%, $[M+NH_4]^+$), 175 (50%, $[M+H]^+$), 157 (10%, $[M-H_2O+H]^+$). MS (EI, 70 eV): m/z 175 ($[M+H]^+$, 4%), 103 ($[M-C_5H_{11}]^+$, 100%), 71 ($[C_5H_{11}]^+$, 50%), 43 (60%). $[\alpha]_D^{25} = -26$ (*c* 1.0, $CHCl_3$). HPLC: Chiralcel OD-H, 95:5 hexane/*iso*-propanol, 1.0 mL/min, $\lambda = 215$ nm, t_R 6.65 min for (*R*) and 7.61 min for (*S*). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found C, 61.99; H, 10.44.

4.4. Methyl (*R*)-(−)-3-(*tert*-butyl-dimethyl-silyloxy)octanoate 4

Under argon, to a solution of methyl (*R*)-3-hydroxy octanoate **3** (1.74 g, 1 mmol) and 2,6-lutidine (4.65 mL) in CH_2Cl_2 (10 mL) at −25 °C was added *tert*-butyl dimethylsilyl triflate (4.74 mL) and the mixture was stirred for 45 min allowing the temperature to rise to −15 °C. The solution was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent was removed in vacuo. Purification by flash chromatography (80 g of silica gel, cyclohexane/ethyl acetate: 100/0 to 95/5) afforded 2.8 g of **4** (94% yield) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 4.02$–4.16 (m, 1H), 3.63 (s, 3H), 2.41 (d, $J = 7.2$ Hz, 2H), 1.43–1.48 (m, 2H), 1.25–1.26 (m, 6H), 0.82–0.87 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 172.3$, 69.5, 51.4, 42.5, 37.6, 31.8, 25.7, 24.6, 22.5, 17.9, 13.9, −4.5, −4.8. MS (DCI, NH_3): m/z 306 (10%, $[M+NH_4]^+$), 289 (100%, $[M+H]^+$). MS (EI, 70 eV): m/z 289 ($[M+H]^+$, 4%), 273 ($[M-CH_3]^+$, 20%), 231 ($[M-C_4H_9]^+$, 100%). $[\alpha]_D^{21} = -21.1$ (*c* 1.0, $CHCl_3$).

4.5. (*R*)-(−)-3-(*tert*-Butyl-dimethyl-silyloxy)octanal 5

To a stirred solution of the protected ester **4** (1.19 g, 4 mmol) in dry dichloromethane (25 mL) cooled to −78 °C, a solution of diisobutylaluminium hydride (1.0 M solution in dichloromethane) (4.8 mL) was added slowly under argon and the mixture was stirred at the same temperature for 2 h followed by another addition of DIBAL-H (2.4 mL, 0.5 equiv). Stirring was continued for 1.5 h (reaction monitored by TLC), then methanol (5 mL) was added to quench the excess of DIBAL-H and the reaction mixture was stirred for 1 h at −78 °C. Diluted HCl was added and the temperature let to rise. Extraction with ethyl acetate, then CH_2Cl_2 followed by drying over Na_2SO_4 and purification by flash chromatography (18 g of silica gel, cyclohexane/ethyl acetate: 90/10) afforded 0.8 g of aldehyde **5** (71% yield) as a clear liquid. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 9.75$ (br, 1H), 4.08–4.16 (m, 1H), 2.44–2.46 (m, 2H), 1.37–1.48 (m, 2H), 1.23–1.26 (m, 6H), 0.80–0.85 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 202.4$, 68.2, 50.8, 37.8, 31.7, 25.7,

24.7, 22.5, 17.9, 13.9, −4.4, −4.7. MS (DCI, NH_3): m/z 276 (10%, $[M+NH_4]^+$), 259 (100%, $[M+H]^+$). MS (EI, 70 eV): m/z 259 ($[M+H]^+$, 1%), 201 ($[M-C_4H_9]^+$, 80%), 101($[M-CH_2COH-(SiMe_2C(CH_3)_3)]^+$, 100%). $[\alpha]_D^{21} = -5.5$ (c 1, $CHCl_3$). HRMS m/z (M+): calcd for $C_{14}H_{30}O_2Si$, 258.2015; found, 258.2017.

4.6. (*R*)-4-(*tert*-Butyl-dimethyl-silyloxy)-non-1-yne 6

Under argon at −78 °C, to a solution of LDA (2.4 mmol, 1.2 equiv) in THF (3 mL) was added a solution of trimethylsilyldiazomethane in Et_2O (2 M, 1.2 mL, 2.4 mmol) and the mixture was stirred for 30 min. Then a solution of the protected aldehyde **5** (516 mg, 2 mmol) in THF (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h at −78 °C. Afterwards the temperature was raised between −10 and 0 °C and the solution was kept for stirring for 2 h, then quenched with saturated aqueous NH_4Cl. Extraction was done with Et_2O and ethyl acetate followed by drying over $MgSO_4$ and purification by flash chromatography (32 g of silica gel, cyclohexane/ethyl acetate: 9/1) to furnish 441 mg of alkyne **6** (87% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 3.68$–3.80 (m, 1H), 2.24 (ddd, $J = 16.8$ Hz, $J = 5.4$ Hz, $J = 2.7$ Hz, 2H), 1.89 (t, $J = 2.7$ Hz, 2H), 1.49–1.60 (m, 2H), 1.21–1.23 (m, 6H), 0.80–1.84 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 81.9$, 71.1, 69.8, 36.6, 31.9, 27.4, 25.9, 24.8, 22.7, 18.1, 14.1, −4.4, −4.6. MS (DCI, NH_3): m/z 272 (10%, $[M+NH_4]^+$), 255 (100%, $[M+H]^+$). MS (EI, 70 eV): m/z 255 ($[M+H]^+$, 2%), 215 ($[M-C_2H_5]^+$, 60%), 73 (100%). $[\alpha]_D^{25} = -17.8$ (c 1.0, $CHCl_3$). HRMS m/z (M+): calcd for $C_{15}H_{30}OSi$, 254.2066; found, 254.2061.

4.7. (*R*)-(+)-Non-1-yn-4-ol 7

Under argon at room temperature, to a solution of silyl ether **6** (254 mg, 1 mmol) in THF (50 mL) was added 1.2 mL of tetrabutylammoniumfluoride (TBAF) as a 1 M solution in THF. The solution was stirred for 2 h, then the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, and extracted with diethyl ether and ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtrated and concentrated. Purification by flash chromatography on silica gel (cyclohexane/ethyl acetate: 100/0 to 95/5) afforded 133 mg (95% yield) of the deprotected alcohol **7** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 3.65$–3.68 (m, 1H), 2.36 (ddd, $J = 16.8$ Hz, $J = 5.4$ Hz, $J = 2.7$ Hz, 2H), 2.05 (t, $J = 5.4$ Hz, 2H), 1.95 (br, 1H), 1.43–1.48 (m, 2H), 1.34–1.39 (m, 6H), 0.90 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 80.1$, 70.8, 69.9, 36.2, 31.7, 27.3, 25.3, 22.6, 14.1. MS (DCI, NH_3): m/z 158 (100%, $[M+NH_4]^+$), 140 (5%, $[M-H_2O+NH_4]^+$), MS (EI, 70 eV): m/z 140 ($[M+H]^+$, 2%), 83 (75%), 55 (100%). $[\alpha]_D^{25} = +23.0$ (c 1, $CHCl_3$).

4.8. (*R*)-(+)-Non-1-en-4-ol 8

To a stirred solution of (4*R*)-non-1-yn-4-ol **7** (100 mg, 0.71 mmol) in EtOAc (10 mL) was added palladium 5 wt % on $BaSO_4$ poisoned with lead (Lindlar cat.) (10 mg). After 10 min, the reaction mixture was treated with quinoline (91 μL, 0.71 mmol) and stirring was continued for 3 h under a balloon of H_2. The reaction mixture was filtered through Celite (eluting with EtOAc) and concentrated in vacuo. Flash chromatography (cyclohexane/ethyl acetate: 100/0 to 96/4) afforded (4*R*)-non-1-en-4-ol **8** (74 mg, 73%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 5.70$–5.90 (m, 1H), 5.10 (dd, $J = 16.9$ Hz, $J = 1.1$ Hz, 1H, *trans*) 5.14 (dd, $J = 10.1$ Hz, $J = 1.1$ Hz, 1H, *cis*) 3.80–4.05 (m, 1H), 2.10–2.32 (m, 2H), 1.20–1.50 (m, 8H + OH), 0.92 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 136.3$, 121.1, 71.7, 42.0, 37.5, 29.7, 25.4, 22.7, 14.1. $[\alpha]_D^{25} = +5.2$ (c 1, $CHCl_3$). HRMS m/z (M+): calcd for $C_9H_{18}O$, 142.1358; found, 142.1360.

4.9. (*R*)-Non-1-en-4-yl acrylate 9

Acryloyl chloride (0.19 mL, 2.3 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **8** (50 mg, 0.35 mmol) and triethylamine (0.5 mL, 2.85 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred overnight and during that time the temperature was allowed to warm to room temperature. Saturated $NaHCO_3$ solution was added to quench the excess of acryloyl chloride and the resulting mixture was partitioned between Et_2O (100 mL) and water (30 mL). The organic layer was washed with saturated NH_4Cl, dried over Na_2SO_4 filtered and evaporated. The residue was purified by silica gel column chromatography using hexane/ethyl acetate (99:1) as eluent to give the title compound **9** (56 mg, 82%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 6.20$–6.24 (m, 1H), 6.16–6.19 (m, 1H), 5.84–5.88 (m, 2H), 5.22–5.26 (m, 1H), 5.10–5.15 (m, 1H), 4.11–4.16 (m, 1H), 2.18–2.22 (m, 2H), 1.28–1.35 (m, 8H), 0.89 (t, $J = 6.7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 171.4$, 131.0, 128.3, 123.7, 118.6, 73.2, 39.9, 32.1, 31.9, 31.3, 25.7, 24.1, 18.3. $[\alpha]_D^{25} = +9.5$ (c 1.0, $CHCl_3$). HRMS m/z (M+): calcd for $C_{12}H_{20}O_2$, 196.1463; found, 196.1464.

4.10. (*R*)-(−)-6-Pentyl-5,6-dihydro-2*H*-pyran-2-one 1

Grubbs' catalyst [bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride] (16.4 mg, 0.002 mmol) was dissolved in 5 mL of CH_2Cl_2 and added dropwise to a refluxing solution of the above acrylic ester **9** (49 mg, 0.25 mmol) in 100 mL of CH_2Cl_2. Refluxing was continued for 6 h by which time all of the starting material was consumed (TLC). The solvent was removed under vacuum and the crude product purified by silica gel column chromatography (hexane/ethylacetate, 90:10) to obtain 31.6 mg (78%) of **1** as a pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz, 27 °C): $\delta = 6.82$ (ddd, $J = 9.6$ Hz, $J = 5.4$ Hz, $J = 3.1$ Hz, 1H), 5.92 (ddd, $J = 9.6$ Hz, $J = 2.3$ Hz, $J = 1.3$ Hz, 1H), 4.72–4.77 (m, 1H), 2.18–2.28 (m, 2H), 1.72–1.84 (m, 4H), 1.31–1.41 (m, 4H), 0.95 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 27 °C): $\delta = 166.5$, 146.1, 121.1, 77.8, 37.5, 31.9, 29.7, 25.3, 22.7, 14.1. $[\alpha]_D^{25} = -110.8$ (c 1.0, $CHCl_3$) {Lit.[10f] $[\alpha]_D^{25} = -110.7$ (c 1, $CHCl_3$)}. HRMS m/z (M+): calcd for $C_{10}H_{16}O_2$, 168.1150; found, 168.1151.

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