Asymmetric Total Syntheses of (*R*)-(–)-Argentilactone and (*S*)-5-Hexadecanolide

Gowravaram Sabitha,* Narjis Fatima, R. Swapna, J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax +91(40)27160512; E-mail: sabitha@iictnet.org

Received 20 April 2006; revised 5 May 2006

Abstract: The simple and efficient asymmetric syntheses of (*R*)-(–)-argentilactone and (*S*)-5-hexadecanolide were achieved from the same starting material by a similar strategy. The key intermediates for both molecules were chiral 5-hydroxyalk-2-en-6-ynoates.

Key words: lactones, total synthesis, natural products, argentilactone, hexadecanolide

6-Alkyl-substituted δ-lactones and α,β-unsaturated δ-lactones (5,6-dihydro-2*H*-pyran-2-ones) are key structural units of many natural products[1] as well as valuable synthetic intermediates to other chiral molecules of considerable interest. These lactones are known to exhibit a wide range of biological activities such as plant-growth inhibition, antifeedant, antifungal, and antitumor properties,[2] and comprise structural moieties frequently present in, e.g., insect pheromones, cardenolides, and lignans.[3] Argentilactone (**1**) belongs to this family, having an alkyl side chain at the C6 position and with a *cis* double bond at C7–C8. This lactone was first isolated in 1977 from the rhizomes of *Aristolochia argentia* by Ruveda and coworkers.[4] It showed both antileishmanial[5] and cytotoxic activity[6] against P-388 mouse leukemia cells. Later it was also isolated from the methanolic extract of a Brazilian medicinal plant, *Chorisia crispiflora*,[6] which is one of the folk medicines used for rheumatism and menorrhalgia. This compound was also found to be present in the hexane extract of *Annona haematantha*.[5] Recently, argentilactone was isolated as the main constituent from the essential oil of *Hyptis ovalifolia* Benth,[7] and showed strong *in vitro* antifungal activity against dermatophytes. Therefore, argentilactone (**1**) could be an interesting molecule for the development of new drugs against dermatophytes. The natural form of argentilactone has the *R*-configuration, and is used as a starting material for the synthesis of pheromones.[8] A δ-lactone (*S*)-5-hexadecanolide (**2**) was isolated from the mandibular glands of the oriental hornet, *Vespa orientalis*[9] as a pheromone to stimulate the workers to construct queen cells. This lactone is also found in some fruits, such as apricots and peaches. Both **1** and **2** have chiral lactone units in their structure.

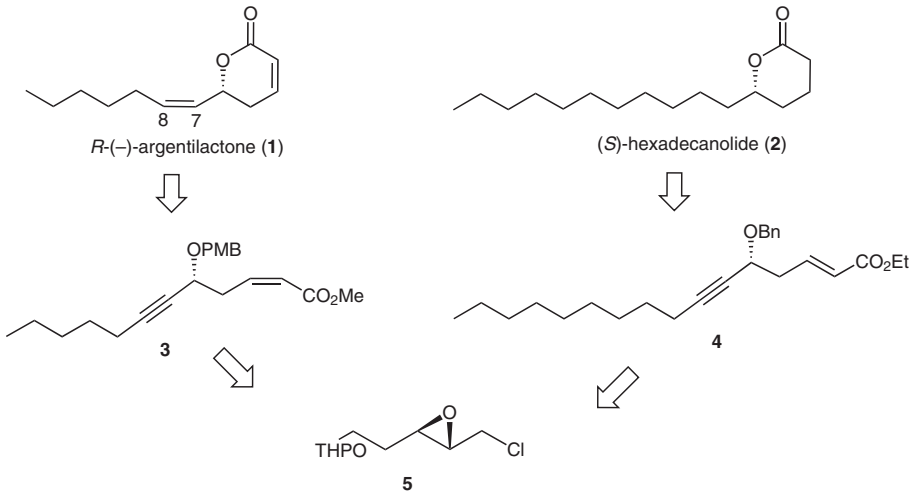
The important biological activities of argentilactone (**1**) and hexadecanolide (**2**) have led to a number of synthetic procedures being reported[10,11] for both the racemic and optically active forms. Most of the reported synthetic routes for argentilactone (**1**) employ Wittig olefination of the pyrancarbaldehyde with the corresponding hexylidenetriphenylphosphorane to produce the (*Z*)-alkene (C7–C8). In continuation of our studies on the synthesis of naturally occurring lactones,[12,13] we became interested in the total synthesis of argentilactone (**1**) and hexadecanolide (**2**) by using a similar strategy. It is important to mention that these two molecules **1** and **2** can be made from the same starting material, and via two chiral 5-hydroxyalk-2-en-6-ynoates **3** and **4** (Scheme 1).

The synthesis of argentilactone (**1**) (Scheme 2) began with the known 2,3-epoxy chloride **5**.[14] 2,3-Epoxy chloride **5** was directly converted into an alkylated chiral alkynol **6**[14] in 81% yield in a one-pot procedure consisting of subjecting 2,3-epoxy chloride **5** to a base-induced opening with lithium metal in liquid ammonia in tetrahydrofuran, and treatment of the resultant alkynol without isolation with 1-bromopentane at –78 °C. The spectral data of alkynol **6** was in good agreement with the assigned structure. The secondary hydroxy group of alkynol **6** was protected as its *p*-methoxybenzyl ether by reaction of alkynol **6** with *p*-methoxybenzyl bromide and sodium hydride in dry tetrahydrofuran at room temperature; this afforded compound **7**[15] in 88% yield. Deprotection of the tetrahydropyran-2-yl group in **7** was achieved with the use of pyridinium *p*-toluenesulfonate in methanol[16] at room temperature, affording primary alcohol **8** in 67% yield; it was characterized by IR, ^{1}H NMR, and mass spectroscopy.

The oxidation of the primary hydroxy group in alcohol **8** with pyridinium dichromate in dichloromethane afforded aldehyde **9**[17] in 64% yield. Aldehyde **9** underwent Still's modification of the Horner–Wadsworth–Emmons[18] reaction in the presence of sodium hydride and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate in dry tetrahydrofuran at –78 °C; this gave α,β-unsaturated ester **3**, predominantly as the *Z*-isomer, as characterized by ^{1}H and ^{13}C NMR spectroscopy, in 85% yield. In the ^{1}H NMR spectrum, resonances at δ 5.83, a doublet of triplets (J = 1.8, 11.5 Hz), and at δ 6.38, a doublet of triplets (J = 6.8, 11.5 Hz), confirmed the *Z*-geometry of the double bond. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane–water (CH_2Cl_2–H_2O, 9:1)[19] was used to deprotect ether **3**, removing the *p*-methoxybenzyl group, and giving secondary alcohol **10** in 55% yield. The cyclization of hydroxy ester **10** was achieved in refluxing

SYNTHESIS 2006, No. 17, pp 2879–2884
Advanced online publication: 25.07.2006
DOI: 10.1055/s-2006-942518; Art ID: Z08006SS
© Georg Thieme Verlag Stuttgart · New York

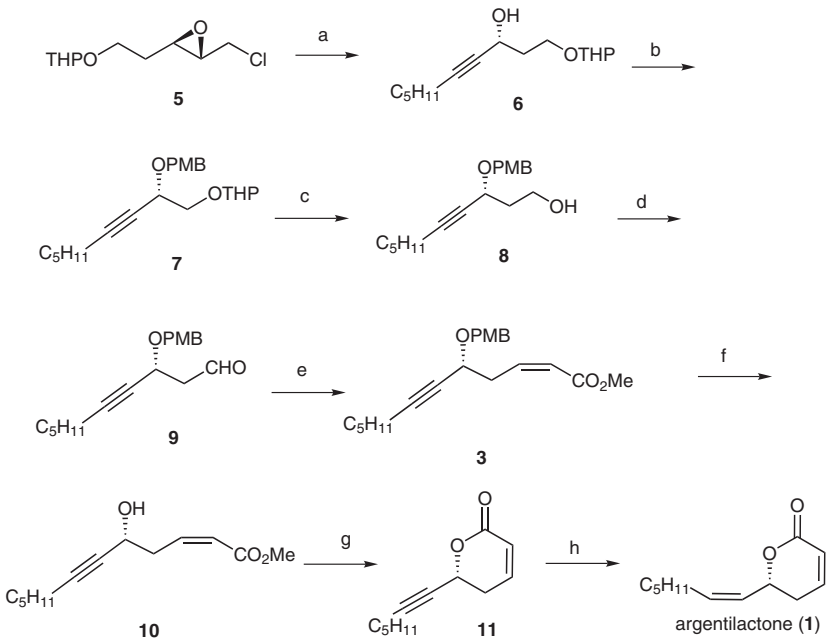
Downloaded by: University of Arizona Library. Copyrighted material.



Scheme 1 Retrosynthetic strategy for (*R*)-(–)-argentilactone and (*S*)-5-hexadecanolide from the same starting material

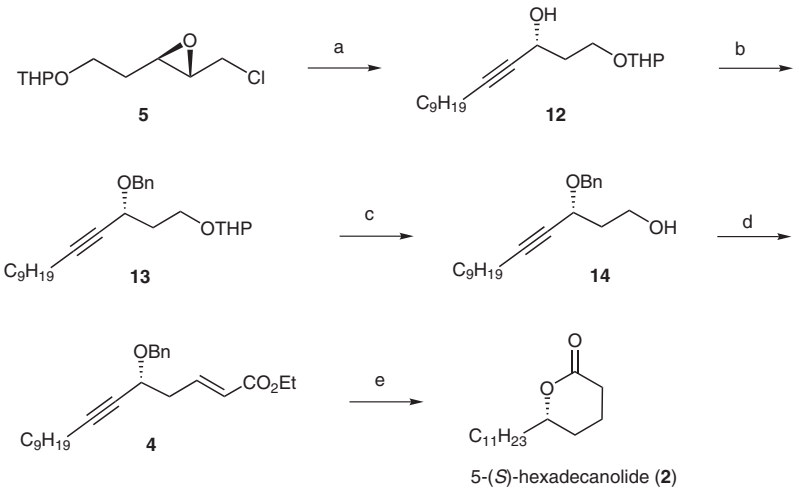
benzene containing catalytic amount of *p*-toluenesulfonic acid,[20] to afford lactone **11** in 68% yield. Finally, the partial hydrogenation of the triple bond over 5% palladium–calcium carbonate gave the target molecule, (*R*)-(–)-argentilactone (**1**), in 60% yield, and with optical rotation $[\alpha]_D^{25}$ –19.5 (*c* 0.5, EtOH) {Lit.[4] $[\alpha]_D^{25}$ –21.1 (*c* 2.25, EtOH)}. The optical purity of the product was estimated to be 86%. The ^{1}H and ^{13}C NMR, IR, and mass spectroscopic data of this synthesized compound were identical to those of the natural product.

By a similar strategy, (*S*)-5-hexadecanolide was synthesized in a short procedure, also starting from 2,3-epoxy chloride **5**. The procedure is shown in Scheme 3. Epoxy chloride **5** was subjected to base-induced opening by lithium amide in liquid ammonia at –78 °C, and treated with 1-bromononane to give the chiral alkynol **12** directly in a one-pot procedure in 70% yield. The secondary hydroxy group of alkynol **12** was protected as its benzyl ether by treatment of alkynol **12** with sodium hydride and benzyl bromide in dry tetrahydrofuran[15] at room temperature; this gave benzyl ether **13**[15] in 96% yield. Subsequently, deprotection of the tetrahydropyran-2-yl group by use of pyridinium *p*-toluenesulfonate in methanol[16] furnished primary alcohol **14** in 96% yield. Alcohol **14** was oxidized to the corresponding aldehyde, which, without isolation, was further treated with the two-carbon Wittig ylide



Scheme 2 Synthesis of (*R*)-(–)-argentilactone. *Reagents and Conditions:* (a) Li/liq NH_3, $Fe(NO_3)_3$ (cat.), $Me(CH_2)_4Br$, dry THF, 81%; (b) NaH, PMBBr, THF, 0 °C to r.t., 88%; (c) PPTS, MeOH, r.t., 67%; (d) PDC, CH_2Cl_2, reflux, 3–4 h, 64%; (e) $(F_3CCH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, 1 h, 85%; (f) DDQ, CH_2Cl_2–H_2O, r.t., 2.5 h, 55%; (g) PTSA, benzene, reflux, 2 h, 68%; (h) 5% Pd–$CaCO_3$, quinoline, EtOAc, H_2, r.t, 2 h, 60%.

Downloaded by: University of Arizona Library. Copyrighted material.



Scheme 3 Synthesis of (*S*)-5-hexadecanolide. *Reagents and Conditions:* (a) Li/liq NH_3, $Fe(NO_3)_3$ (cat.), $Me(CH_2)_8Br$, dry THF, 70%; (b) NaH, BnBr, THF, 0 °C to r.t., 98%; (c) PPTS, MeOH, r.t., 96%; (d) $(COCl)_2$, DMSO, Et_3N, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, –78 °C, 70%; (e) 10% Pd/C (cat.), H_2, EtOH, 12 h, 70%.

(ethoxycarbonylmethylene)triphenylphosphorane, to furnish the α,β-unsaturated ester **4**[21] in 70% yield.

Finally, the synthesis of target molecule **2** was completed in a single-pot four-reaction sequence. Treatment of ester **4** over 10% palladium–carbon in ethanol under hydrogen yielded (*S*)-5-hexadecanolide (**2**) in 70% yield, by in situ removal of the benzyl protecting group, saturation of the double and triple bonds, followed by cyclization (Scheme 3). The synthetically obtained compound showed IR, ^1H, and ^{13}C NMR spectral data and an optical rotation {$[\alpha]_D^{25}$ –27.10 (*c* 1, $CHCl_3$)} in good agreement with those of the natural lactone.

In summary, we have demonstrated efficient, scalable, and stereoselective total syntheses of (*R*)-argentilactone and (*S*)-5-hexadecanolide in eight and five steps, respectively, in good yields by utilizing chiral 5-hydroxyalk-2-en-6-ynoates as key intermediates.

Reactions were conducted under a N_2 atmosphere in anhydrous solvents such as CH_2Cl_2, THF, CCl_4, benzene, and EtOAc. All reactions were monitored by TLC on silica-coated plates (Merck 60 F-254) and with visualization under UV light. Light PE of the distillation range 60–80 °C was used. Yields refer to chromatographically and spectroscopically (^1H, ^{13}C NMR) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator.^1H NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) instruments, and $CDCl_3$ was the solvent. Chemical shift values (δ) were reported in ppm relative to tetramethylsilane (δ 0.0) as internal standard. Mass spectra were recorded under electron impact at 70 eV on an LC-MSD (Agilent Technologies) instrument. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. Optical rotations were measured with a JASCO DIP-370 polarimeter at 20 °C.

(*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)dec-4-yn-3-ol (6)

To freshly distilled NH_3 (50 mL) in a 100-mL two-neck round-bottomed flask fitted with a cold-finger condenser was added a catalytic amount of $Fe(NO_3)_3$. The piecewise addition of Li metal (0.244 g, 81.6 mmol) followed at –78 °C, and the resulting grey suspension was stirred for 30 min. Epoxide **5** (3 g, 13.6 mmol) in dry THF (25 mL) was added to this over 15 min, and the mixture was then stirred for 2 h at the same temperature. Then 1-bromopentane (4.13 mL, 32.6 mmol) was added dropwise to the mixture. The mixture was stirred at the same temperature for 6 h, and the reaction was quenched by the addition of solid NH_4Cl; then the NH_3 was allowed to evaporate. The reaction mixture was extracted with H_2O and EtOAc. The combined organic layers were washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4); this gave pure **6** as a clear, colorless liquid.

Yield: 2.8 g (81%); $[\alpha]_D^{25}$ –6.72 (*c* 1, $CHCl_3$).

IR (neat): 3420, 3933, 2362, 1617, 1352, 1032, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.77–3.67 (m, 1 H), 3.58–3.66 (t, *J* = 6.0 Hz, 1 H), 3.11–3.25 (m, 1 H), 2.88–3.05 (m, 1 H), 2.81–2.72 (m, 1 H), 2.68–2.56 (m, 1 H), 2.05 (br s, OH, 1 H), 1.34–1.27 (td, *J* = 2.2, 7.5 Hz, 2 H), 1.5–2.0 (m, 8 H,), 1.2–1.4 (m, 6 H), 0.01–0.06 (t, *J* = 6.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.83, 80.71, 64.65, 64.53, 62.12, 61.94, 37.39, 30.99, 30.49, 28.31, 25.31, 22.11, 19.35, 18.62, 13.88.

MS (EI, 70 eV): *m*/*z* = 254 $[M + Na]^+$.

2-{(*R*)-3-[(4-Methoxybenzyl)oxy]dec-4-ynyloxy}tetrahydro-2*H*-pyran (7)

Alcohol **6** (0.8 g, 3.1 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of freshly activated NaH (0.223 g, 9.3 mmol) in dry THF (30 mL) at 0 °C. After the mixture had stirred for 30 min, PMBBr (0.636 g, 3.1 mmol) in dry THF (10 mL) was added. After completion of the reaction (3 h), the mixture was quenched with sat. aq NH_4Cl soln and extracted with EtOAc. The organic layer was washed with H_2O and brine soln, dried (anhyd Na_2SO_4), and concentrated in vacuo; purification by column chromatography (silica gel) afforded **7** as a viscous liquid.

Yield: 1.03 g (88%); $[\alpha]_D^{25}$ +21.72 (*c* 1, $CHCl_3$).

IR (neat): 3418, 1615, 1513, 1353, 1248, 1121, 1034, 772, 618 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.19 (m, 2 H), 6.87–6.79 (d, *J* = 8.3 Hz, 2 H), 4.67 (d, *J* = 11.2 Hz, 1 H), 4.55 (m, 1 H), 4.40 (t, *J* = 11.2 Hz, 1 H), 4.2 (m, 1 H), 3.78 (s, 3 H), 3.52–3.38 (m, 2 H),

Downloaded by: University of Arizona Library. Copyrighted material.

2.30–2.17 (td, *J* = 7.2, 5.6 Hz, 2 H), 2.06–1.29 (m, 2 H), 1.3–1.5 (m, 14 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.80, 129.93, 129.70, 129.62, 114.25, 113.73, 113.69, 98.89, 98.68, 76.57, 73.79, 70.32, 70.16, 65.56, 64.96, 63.34, 62.14, 55.25, 36.02, 30.58, 25.46, 19.47, 14.08.

MS (EI, 70 eV): *m*/*z* = 374 $[M + Na]^+$.

(*R*)-3-[(4-Methoxybenzyl)oxy]dec-4-yn-1-ol (8)

A cat. amount of PPTS was added to a stirred soln of **7** (3.25 g, 8.6 mmol) in MeOH (30 mL). The mixture was stirred at r.t. for ca. 2 h, and then the MeOH was removed under reduced pressure. The crude residue was purified by column chromatography (silica gel); this gave **8** as a viscous liquid.

Yield: 1.7 g (67%); $[\alpha]_D^{25}$ +53.5 (*c* 1, $CHCl_3$).

IR (neat): 3416, 1617, 1219, 772, 617 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.18 (d, *J* = 9.0 Hz, 2 H), 6.85–6.80 (d, *J* = 8.3 Hz, 2 H), 4.71–4.39 (AB q, *J* = 11.3 Hz, 2 H), 4.24 (m, 1 H), 3.80 (s, 3 H), 3.88–3.64 (m, 2 H), 2.28–2.21 (dt, *J* = 1.5, 6.8 Hz, 2 H), 1.97–1.89 (q, *J* = 5.2, 10.5 Hz, 2 H), 1.61–1.49 (m, 2 H), 1.44–1.23 (m, 4 H), 0.93 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.33, 129.65, 113.85, 87.54, 78.25, 70.14, 67.25, 60.30, 55.25, 38.24, 31.06, 29.69, 28.38, 22.16, 18.67, 14.10.

MS (EI, 70 eV): *m*/*z* = 292 $[M + H]^+$.

(*R*)-3-[(4-Methoxybenzyl)oxy]dec-4-ynal (9)

PDC (0.972 g, 2.5 mmol) was added to a soln of **8** (0.5 g, 1.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture was refluxed for 3–4 h. The progress of the reaction was monitored by TLC. Removal of the solvent afforded a gummy material, which was filtered through Celite with Et_2O and concentrated. The residue was purified by column chromatography (PE–EtOAc); this gave **9** as a liquid.

Yield: 0.323 g (64%); $[\alpha]_D^{25}$ +24.72 (*c* 1, $CHCl_3$).

IR (neat): 3419, 2931, 1616, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.90 (s, 1 H), 7.84 (d, 2 H), 7.01 (d, 2 H), 4.42–4.47 (AB q, *J* = 11.3 Hz, 2 H), 3.92 (s, 3 H), 4.12 (m, 1 H), 2.76–2.66 (dd, *J* = 8.3, 1.5 Hz, 1 H), 2.62–2.58 (dd, *J* = 5.2, 1.5 Hz, 1 H), 2.30–2.21 (t, *J* = 6.0 Hz, 2 H), 1.63–1.30 (m, 6 H), 0.99–0.91 (t, *J* = 6.8 Hz, 3 H).

MS (EI, 70 eV): *m*/*z* = 288 $[M + H]^+$.

Methyl (*Z*,*R*)-5-[(4-Methoxybenzyl)oxy]dodec-2-en-6-ynoate (3)

To a stirred suspension of NaH (0.82 g, 3.4 mmol) in dry THF (20 mL) at 0 °C under N_2 was added bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (0.594 g, 1.8 mmol) in dry THF (10 mL). After the mixture had stirred for 30 min at 0 °C, it was cooled to –78 °C, and then a soln of aldehyde **9** (0.5 g, 1.7 mmol) in dry THF (20 mL) was added dropwise. After stirring for 1 h, the mixture was diluted with Et_2O (5 mL) and the reaction was quenched by the slow addition of H_2O (4 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The organic extract was washed with brine soln, dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel); this gave α,β-unsaturated ester **3** as a viscous liquid.

Yield: 0.419 g (85%).

IR (neat): 3418, 2932, 1722, 1605, 1513, 1440, 1172, 1083, 1034, 823, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.20 (d, *J* = 8.2 Hz, 2 H), 6.84–6.79 (d, *J* = 8.7 Hz, 2 H), 6.38 (dt, *J* = 6.8, 11.5 Hz, 1 H), 5.83 (dt, *J* = 1.8, 11.5 Hz, 1 H), 4.69–4.37 (AB q, *J* = 11.3 Hz, 2 H), 4.1 (m, 1 H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.07–3.01 (dt, *J* = 2.0, 6.8 Hz, 2 H), 2.26–2.19 (dt, *J* = 2.0, 6.9 Hz, 2 H), 1.59–1.30 (m, 6 H), 0.96–0.89 (t, *J* = 6.7 Hz, 3 H).

Methyl (*Z*,*R*)-5-Hydroxydodec-2-en-6-ynoate (10)

To a stirred soln of ester **3** (0.12 g, 0.3 mmol) in CH_2Cl_2 (4.5 mL) and H_2O (0.5 mL) was added DDQ (0.081 g, 0.3 mmol) at r.t. The mixture was stirred for 2.5 h at r.t. before being quenched by the addition of sat. aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried (anhyd Na_2SO_4) and then concentrated in vacuo. The crude product was purified by column chromatography (silica gel); this gave ester **10** as a pure yellow oil.

Yield: 0.44 g (55%).

IR (neat): 3417, 1618, 1353 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.45–6.39 (m, 1 H), 5.94–5.90 (td, *J* = 1.5 Hz, 1 H), 4.51–4.43 (m, 1 H), 3.72 (s, 3 H), 3.05–2.97 (m, 2 H), 2.23–2.14 (td, *J* = 5.2, 6.7 Hz, 2 H), 2.06 (br s, OH, 1 H), 1.57–1.23 (m, 6 H), 0.91 (t, *J* = 6.7 Hz, 3 H).

(*R*)-6-(Hept-1-ynyl)-5,6-dihydro-2*H*-pyran-2-one (11)

To a stirred soln of ester **10** (1.0 g, 4.4 mmol) in dry benzene (10 mL) was added a cat. amount of PTSA under a N_2 atmosphere. The mixture was refluxed for 2 h, the solvent was removed under vacuum, and the reaction was quenched with aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 × 20 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel); this gave lactone **11** as a yellow liquid.

Yield: 0.58 g (68%); $[\alpha]_D^{25}$ +24.5(*c* 0.5, $CHCl_3$).

IR (neat): 2930, 1730, 1617, 1381, 1243, 1053, 816, 760, 617 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (m, 1 H), 6.08–6.02 (dt, *J* = 1.5, 2.2 Hz, 1 H), 5.18–5.12 (m, 1 H), 2.66–2.60 (m, 2 H), 2.2–2.26 (td, *J* = 5.2, 1.5, 2 H), 1.59–1.21 (m, 6 H), 0.97–0.91 (t, *J* = 6.9, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 162.99, 149.09, 121.50, 115.76, 67.59, 30.93, 30.66, 29.67, 27.90, 22.10, 18.56, 13.90.

MS (EI, 70 eV): *m*/*z* = 192 $[M + H]^+$..

(*Z*,*R*)-6-[Hept-1-enyl]-5,6-dihydro-2*H*-pyran-2-one [(*R*)-Argentilactone; 1]

To a soln of lactone **11** (0.3 g, 1.5 mmol) in EtOAc, quinoline and the Lindlar catalyst (5% Pd/$CaCO_3$) were added, and the mixture was stirred at r.t. under a H_2 atmosphere for 6 h. After completion of the reaction, the mixture was filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel); this gave **1** as a colorless liquid.

Yield: 0.18 g (60%); $[\alpha]_D^{25}$ –19.5 (*c* 0.5, $CHCl_3$).

IR (neat): 2361, 1721, 1381, 1243, 1022, 816, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.88–6.80 (ddd, *J* = 3.0, 5.4, 9.8 Hz, 1 H), 6.05–5.99 (ddd, *J* = 1.3, 2.4, 9.8 Hz, 1 H), 5.69–5.48 (m, 2 H), 5.23–5.13 (ddd, *J* = 4.7, 8.0, 10.3 Hz, 1 H), 2.43–2.31 (m, 2 H), 2.02–2.01 (m, 2 H), 1.47–1.20 (m, 6 H), 0.90 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 164.23, 144.85, 135.63, 126.44, 121.67, 73.78, 31.39, 29.94, 29.07, 27.76, 22.49, 13.97.

MS (EI, 70 eV): *m*/*z* = 194 $[M + H]^+$.

(*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)tetradec-4-yn-3-ol (12)

To freshly distilled NH_3 (50 mL) in a 100-mL two-neck round-bottomed flask fitted with a cold-finger condenser was added a catalytic amount of $Fe(NO_3)_3$. The piecewise addition of Li metal (0.380

Downloaded by: University of Arizona Library. Copyrighted material.

g, 54.5 mmol) followed at –78 °C, and the resulting grey suspension was stirred for 30 min. Epoxide **5** (2 g, 9.09 mmol) in dry THF (10 mL) was added to this over 15 min, and the mixture was then stirred for 2 h at the same temperature. Then 1-bromononane (3.76 g, 18.2 mmol) was added dropwise. The mixture was stirred at the same temperature for 6 h, and the reaction was quenched by the addition of solid NH_4Cl; then the NH_3 was allowed to evaporate. The reaction mixture was extracted with H_2O and EtOAc. The combined organic layers were washed with H_2O (1 × 30 mL) and brine (1 × 30 mL), and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4); this gave pure **12** as a clear, colorless liquid.

Yield: 1.8 g (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.75 (d, *J* = 12.0 Hz, 1 H), 4.56 (t, *J* = 3.7 Hz, 1 H), 4.22 (m, 1 H), 3.81 (m, 2 H), 3.47 (m, 2 H), 2.23 (td, *J* = 2.2, 6.7 Hz, 2 H), 158–1.48 (m, 2 H), 1.43–1.27 (m, 19 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

MS (EI, 70 eV): *m*/*z* = 333 [M$^+$ + Na].

2-[(*R*)-3-(Benzyloxy)tetradec-4-ynyloxy]tetrahydro-2*H*-pyran (13)

Alcohol **12** (2 g, 6.0 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of freshly activated NaH (0.31 g, 12.9 mmol) in dry THF (50 mL) at 0 °C, under a N_2 atmosphere. After the mixture had stirred for 30 min at 0 °C, BnBr (1.21 g, 7.0 mmol) was added dropwise. The mixture was stirred for 6 h at 0 °C, and quenched with sat. KBr soln. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O and brine soln and then dried (anhyd Na_2SO_4). The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel); this gave **13** as a viscous liquid.

Yield: 2.52 g (98%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 5 H, Ar), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.45 (d, *J* = 12.1 Hz, 1 H), 4.56 (t, *J* = 3.7 Hz, 1 H,), 4.22 (m, 1 H), 3.81 (m, 2 H), 3.47 (m, 2 H), 2.23 (td, *J* = 2.2, 6.7 Hz, 2 H) 1.58–1.48 (m, 2 H), 1.43–1.27 (m, 19 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

MS (EI, 70 eV): *m*/*z* = 423 [M$^+$ + Na].

(*R*)-3-(Benzyloxy)tetradec-4-yn-1-ol (14)

A cat. amount of PPTS was added to a stirred soln of **13** (2 g, 5.0 mmol) in MeOH (10 mL) under a N_2 atmosphere. After stirring for 12 h at r.t., the mixture was quenched with solid $NaHCO_3$, which was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, PE–EtOAc, 6:4); this gave **14** as a yellow liquid.

Yield: 1.5 g (96%); $[\alpha]^{25}_D$ +74.52 (*c* 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 5 H, Ar), 4.79 (d, *J* = 1.3 Hz, 1 H), 4.45 (d, *J* = 11.3 Hz, 1 H), 4.27 (m, 1 H), 3.69–3.67 (m, 2 H), 2.22 (td, *J* = 2.2, 6.7 Hz, 2 H), 2.13 (m, 1 H), 1.98 (q, *J* = 6.1 Hz, 2 H), 1.61–1.22 (m, 14 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 137.70, 128.48, 128.42, 128.02, 127.78, 126.93, 87.61, 78.11, 70.49, 68.07, 60.24, 38.18, 31.87, 29.50, 29.26, 29.08, 28.86, 28.65, 22.64, 18.67, 14.08.

MS (EI, 70 eV): *m*/*z* = 339 [M$^+$ + Na].

Ethyl (*E*,*R*)-5-(Benzyloxy)hexadec-2-en-6-ynoate (4)

Dry DMSO (0.9 mL, 12.6 mmol) was added to a stirred soln of oxalyl chloride (0.55 mL, 6.3 mmol) in dry CH_2Cl_2 (10 mL) at –78 °C under a N_2 atmosphere. After the mixture had stirred for 20 min at –78 °C, a soln of alcohol **14** (1 g, 3.1 mmol) in dry CH_2Cl_2 (5 mL) was added slowly. After 45 min, Et_3N (2.6 mL, 18.9 mmol) was added and the mixture was allowed to warm to 0 °C, and stirred for 15 min at 0 °C. (Ethoxycarbonylmethylene)triphenylphosphorane (2.2 g, 6.3 mmol), dissolved in dry CH_2Cl_2 (10 mL), was added slowly and the mixture was stirred for 6 h at r.t. and then the reaction was quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic layers were washed with H_2O and brine and dried (anhyd Na_2SO_4). The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel); this gave α,β-unsaturated ester **4** as a viscous liquid.

Yield: 0.86 g (70%); $[\alpha]_D^{25}$ +50.60 (*c* 1, $CHCl_3$).

IR (neat): 3030, 2927, 2855, 2230, 1721, 1657, 1171, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5 H, Ar), 6.94 (dt, *J* = 6.8, 15.8 Hz, 1 H), 5.85 (d, *J* = 15.8 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.46 (d, *J* = 12.1 Hz, 1 H), 4.17 (q, *J* = 6.7 Hz, 2 H), 4.12–4.09 (m, 1 H), 2.62–2.56 (m, 2 H), 2.24 (td, *J* = 1.5, 6.8 Hz, 2 H), 1.58–48 (m, 2 H), 1.43–1.27 (m, 15 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.29, 143.98, 137.87, 130.19, 128.36, 128.04, 127.98, 127.69, 123.79, 87.89, 70.29, 67.38, 60.17, 38.90, 31.89, 29.50, 29.30, 29.15, 28.89, 28.72, 28.66, 22.67, 18.71, 14.29, 14.08.

MS (EI, 70 eV): *m*/*z* = 384 [M$^+$].

(*S*)-6-Undecyl-5,6-dihydro-2*H*-pyran-2-one [(*S*)-5-Hexadecanolide; 2]

A cat. amount of Pd/C (10%) was added to a soln of ester **4** (0.5 g, 1.3 mmol) in dry EtOH (5 mL), and the mixture was stirred at r.t. under a H_2 atmosphere for 6 h. Then the mixture was filtered, washed with EtOAc, and the filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, PE–EtOAc, 6:4); this gave **2** as a colorless liquid.

Yield: 0.23 g (70%); $[\alpha]_D^{25}$ –27.10 (*c* 1, $CHCl_3$).

IR (neat): 2921, 2852, 1727, 1465, 1251, 1044 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.27–4.19 (m, 1 H) 2.60–2.35 (m, 2 H), 1.95–1.26 (m, 24 H), 0.89 (t, *J* = 6.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.97, 80.59, 35.85, 31.89, 29.62, 29.59, 29.54, 29.48, 29.46, 29.41, 29.30, 27.79, 24.91, 22.67, 18.48, 14.08.

MS (EI, 70 eV): *m*/*z* = 255 [M$^+$ + 1].

Acknowledgement

N.F. thanks the IICT (IICT Communication No: 060301) and R.S. thanks the CSIR for financial support.

References

(1) (a) Siegel, S. M. *Phytochemistry* **1976**, *15*, 566. (b) Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 431. (c) Davies-Coleman, M. T.; Rivett, D. E. A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1.

(2) (a) Fujita, T.; Nishimura, H.; Kaburagi, K.; Mizutani, J. *Phytochemistry* **1994**, *36*, 23. (b) Nyandat, E.; Rwekika, E.; Galeffi, C.; Palazzino, G.; Nicoletti, M. *Phytochemistry* **1993**, *33*, 1493. (c) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoeckli-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265. (d) Pereda-Miranda, R.; Garcia, M.; Delgado, G. *Phytochemistry* **1990**, *29*, 2971.

(3) (a) Fukusaki, E.; Senda, S.; Nakazono, Y.; Omata, T. *Tetrahedron* **1991**, *47*, 6223. (b) Mori, K. *Tetrahedron* **1989**, *45*, 3233. (c) Rao, Y. S. *Chem. Rev.* **1976**, *78*, 625.

Downloaded by: University of Arizona Library. Copyrighted material.

(4) Priestap, H. A.; Bonafede, J. D.; Ruveda, E. A. *Phytochemistry* **1977**, *16*, 1579.
(5) Waechter, A. I.; Ferreria, M. E.; Fournet, A.; Rojas de Arias, A. *Planta Med.* **1997**, *63*, 433.
(6) Matsuda, M.; Endo, Y.; Fushiya, S.; Endo, T.; Nozoe, S. *Heterocycles* **1994**, *38*, 1229.
(7) de Oliveira, C. M. A.; Silva, M. R. R.; Kato, L.; da Silva, C. C.; Ferreira, H. D.; Souza, L. K. H. *J. Braz. Chem. Soc.* **2004**, *15*, 1.
(8) Sala, L. F.; Cravero, R. M.; Signorella, S. R.; Gonzalez-Sierra, M.; Ruveda, E. A. *Synth. Commun.* **1987**, *17*, 1287.
(9) Ikan, R.; Gottlieb, R.; Bergmann, E. D.; Ishay, J. *J. Insect. Physiol.* **1969**, *15*, 1709.
(10) (a) Hansen, T. V. *Tetrahedron: Asymmetry* **2002**, *13*, 547. (b) Fatima, A.; de Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2004**, *12*, 5437. (c) Chidambaram, N.; Satyanarayana, K.; Chandrasekharan, S. *Tetrahedron Lett.* **1989**, *30*, 2429. (d) Carretero, J. C.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 2059. (e) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *27*, 5201. (f) Fehr, C.; Galindo, J.; Ohloff, G. *Helv. Chim. Acta* **1981**, *64*, 1247. (g) Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281. (h) de Fatima, A.; Pilli, R. A. *ARKIVOC* **2003**, *(x)*, 118; www.arkat-usa.org.
(11) (a) Salladie, G.; Matloubi-Mogliadam, F. *J. Org. Chem.* **1982**, *47*, 91. (b) Bin, S.; Chao-Xin, Z.; Gui-Min, Z.; Ying, L.; Yu-Lin, L.; Li-Zeng, P. *Chin. J. Chem.* **2005**, *23*, 1228; and references cited therein. (c) Yamada, H.; Sugai, T.; Ohta, H.; Yoshikawa, S. *Agric. Biol. Chem.* **1990**, *54*, 1579. (d) Kayser, M. M.; Chen, G.; Stwart, J. D. *J. Org. Chem.* **1998**, *63*, 7103. (e) Alphand, V.; Arcjelas, A.; Furstoss, R. *J. Org. Chem.* **1990**, *55*, 347. (f) Utaka, M.; Watabu, H.; Takeda, A. *J. Org. Chem.* **1987**, *52*, 4363. (g) Yamamoto, Y.; Sakancoto, A.; Nishioka, T.; Oda, J.; Fukazawa, Y. *J. Org. Chem.* **1991**, *56*, 1112. (h) Kosugi, H.; Konta, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1983**, 211. (i) Naoshima, Y.; Hasegawa, H.; Saeki, T. *Agric. Biol. Chem.* **1987**, *51*, 3417. (j) Sabitha, G.; Reddy, E. V.; Yadagiri, K.; Yadav, J. S. *Synthesis* **2006**, in press.
(12) Sabitha, G.; Sudhakar, K.; Mallikarjun Reddy, N.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567.
(13) Sabitha, G.; Bhikshapathy, M.; Yadav, J. S. *Synth. Commun.* **2006**, in press.
(14) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033.
(15) Marco, J. L.; Hueso-Rodriquez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459.
(16) Corey, E. J.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.
(17) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(18) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
(19) Harika, K.; Yoshika, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(20) Dale, L. B.; Ichikawa, S.; Zhong, W. *J. Am. Chem. Soc.* **2001**, *123*, 4161.
(21) Garegg, P. J.; Samuelsen, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

Downloaded by: University of Arizona Library. Copyrighted material.