Organoselenium-Assisted Route to Conjugated Dienoic Macrolides. Synthesis of (Z)-Dodec-3-en-12-olide, a Pheromone of the Flat Grain Beetle Cryptolestes pusillus (Coleoptera: Cucujidae)

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Oxidative elimination of the arylseleno group in (E)-2-(4-methoxyphenylseleno)dodec-4-en-12-olide gave (Z,4E)-dodeca-2,4-diene-12-olide which on 1,4-cis-hydrogenation over (η⁶-naphthalene)tricarboxylchromium afforded the title pheromone. (E)-2-(4-Methoxyphenylseleno)dodec-4-en-12-olide was best prepared by macrolactonization of the corresponding α-hydroxy acid.

Access to (Z)-olefinic macrolides (e.g., the pheromones of cucujid beetles) remained limited until PPh₃-DEAD was introduced as a reagent for macrolactonization, and was applied to pheromone synthesis by Boden et al. Whether chemical or enzymatic, most synthetic schemes leading to (Z)-olefinic macrolides have involved a lactonization of the corresponding hydroxy acid in the final step. Having developed effective syntheses of (Z)-olefinic insect pheromones by 1,4-cis-hydrogenation of conjugated dienes over (η⁶-arene)tricarboxylchromium catalysts, we thought it would be interesting to examine a similar approach to (Z)-olefinic macrolides such as compound 1 (Scheme 1). The required 2,4-dienolides 2, we reasoned, could be obtained by oxidative elimination of an ArSe group from the corresponding α-arylseleno olefinic macrolide 3. Similar transformations have recently been carried out in acyclic systems using an improved procedure for selenation of esters. Thus, the protocol for preparing cis-olefinic macrolides (Scheme 1) would require α-hydroxy-γ-alkenoic acids as starting materials.

Results and discussion

Readily available 8-hydroxyoctyl tert-butyldimethylsilyl ether (4) was used as the starting material in the synthesis of compound 1, the major component of the aggregation pheromone of the flat grain beetle Cryptolestes pusillus (Coleoptera: Cucujidae) (Scheme 2). The remaining primary alcohol was then electrochemically oxidized in a TEMPO mediated reaction to give aldehyde 5 (88%). Although PCC oxidation also affords the desired aldehyde in high yield, the electrochemical approach is environmentally more attractive. Subsequent addition of vinylmagnesium bromide, treatment of the resulting alcohol 6 with trimethyl orthoacetate and E-stereoselective Claisen–Johnson rearrangement afforded the key intermediate 7 in 61% overall yield.

Scheme 1. i. H₂-(arene)Cr(CO)₉; ii. H₂O₂–THF.

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Scheme 2. i, NaBr–NaHCO₃aq–CH₂Cl₂–4-AcNH-TEMPO (−2 V, 2.0 F mol⁻¹), rt; ii, H₂C==CHMgBr–THF; iii, MeClOMe₃–EtCO₂H (cat.), 115 °C; iv Bu₄NF–THF; rt; v, (a) KOH–H₂O–MeOH, rt; (b) HCl aq; vi, Ph₂P–DEAD–MePh; vii, (a) LDA–THF, −78 °C (b) (4-MeOC₆H₄)₂Se; viii, H₂O₂–THF, rt; ix, H₂(η⁶-naphthalene)Cr(CO)₅–THF, 45 °C, 40 atm.

Compound 7 was further transformed in two ways, differing in the order of the α-arylseleation and macrocyclization steps. Removal of the silyl protective group and saponification of the ester afforded the unsaturated acid 8 in 68% yield. Subsequent lactonization proceeded without affecting the double bond geometry to give (E)-dodec-4-en-12-olide (9) in moderate yield (31%). Final α-(4-methoxyphenyl)seleation of compound 9 afforded the selenated lactone 10 in 73% yield (15% based on 7).

α-(4-Methoxyphenyl)seleation of compound 7 afforded the O-silylated unsaturated ester 11 in 65% yield. Removal of the silyl protective group (74% yield) and saponification of the ester (81% yield) gave the unsaturated acid 12b. Lactonization under Mitsunobu conditions afforded the α-selenated lactone 10 in 63% yield (25% based on 7). Thus, the latter route is clearly the more efficient one.

Oxidative elimination of the arylseleno moiety in compound 10 proceeded cleanly (91% yield) to afford (2Z,4E)-dodeca-2,4-dien-12-olide (13). The configurational assignment is based on decoupling experiments [δ 5.56 (d, J₁₂,₁₃=11.1 Hz, 2-H), 6.64 (dd, J₁₂,₁₃=J₁₃,₁₄=11.1 Hz, 3-H), 7.30 (dd, J₁₃,₁₄=16.0, J₁₄,₁₅=11.1 Hz, 4-H), 6.11 (t, J₁₄,₁₅=16.0, J₁₅,₁₆=4.3 Hz, 5-H)]. These values are in good agreement with those reported for acyclic (2Z,4E)-methyl deca-2,4-dienoate. The transition state for syn-elimination to a (2Z)-double bond is apparently conformationally less strained than the one affording the (2E)-isomer. (η⁶-Naphthalene)tricarbonylchromium is usually the catalyst of choice for 1,4-cis-hydrogenation of 1,3-dienes. Whereas other (η⁶-arene)tricarbonylchro-

Scheme 3.
to (Z)-alk-3-ene-ω- or (Z)-alk-3-ene-(ω−1)-olide semiochemicals of cucujid grain beetles. The unoptimized overall yield of pheromone I from silyl ether 4 was 10.5% over the nine steps used.

**Experimental**

All melting points are uncorrected. NMR spectra were recorded for samples in CDCl₃ at 299.903 MHz (¹H) and at 75.419 MHz (¹³C) using a Varian XL-300 spectrometer. Multiplicities of signals in the ¹H NMR spectra are given as observed. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. Bis(4-methoxyphenyl) diselenide and (η⁶-naphthalene)Cr(CO)₅ (Ref. 16) were prepared according to the literature. THF, i-Pr₂NH, pyridine, toluene and CH₂Cl₂ were purified by conventional procedures and redistilled prior to use. 1,8-Octadecanediol, tert-butylidimethylchlorosilane, trimethyl orthoacetate, diethyl azodicarboxylate (DEAD) and triphenylphosphine were used as purchased. 8-(tert-Butyldimethylsilyloxy)-1-octanol (4) was prepared in 59% yield, essentially (pyridine was used as solvent instead of dichloromethane) as described.

8-(tert-Butyl)dimethylsiloxyoctanol (5). An undivided glass cell, equipped with a magnetic stirring bar and an outer cooling jacket, was charged with compound 4 (1.54 g, 6 mmol), 4-acetamido-2,2,6,6-tetramethyl piperidin-1-oxyl (4-AcNH-TEMPO) (0.3 g) in CH₂Cl₂ (15 mL), and a solution of NaBr (25%) and NaHCO₃ (5%) in water (20 mL). The cathode (stainless steel, 17 × 25 mm) and anode (graphite plate, 13 × 25 mm) were immersed, at a distance of 10 mm, into the upper aqueous layer of the biphasic system. The mixture was then electrolysed under a constant current of 150 mA at ambient temperature with moderate magnetic stirring of the lower phase. The electrolysis was continued until the consumption of starting material was practically complete (TLC monitoring). This required 2.0 F mol⁻¹, based on alcohol 4, and was accompanied by a colour change in the organic phase. The lower organic layer was separated, filtered, dried (MgSO₄), and concentrated to leave essentially pure aldehyde 5 as a yellowish oil (1.355 g, 88%). This was immediately used in the next step without further purification. ¹H NMR spectral data of the material were in good agreement with literature data.

**Methyl (E)-12-(tert-butyl)dimethylsiloxydoced-4-enoate (7).** To a stirred solution of vinylmagnesium bromide (30 mmol) in THF (15 mL), a solution of aldehyde 5 (4.71 g, 18.5 mmol) in THF (10 mL) was added dropwise at 30°C. After 2 h of additional stirring, the reaction mixture was quenched with an aqueous solution of NH₄Cl and extracted with Et₂O. The extracts were dried (MgSO₄) and concentrated under vacuum. The residue was co-evaporated with toluene, and the resulting crude vinyl carbinol 6 was used in the following step without purification. The material was heated with MeC(OMe)₃ (25 mL) and propionic acid (0.2 ml) for 5 h until no more methanol distilled off. The reaction mixture was then concentrated under reduced pressure and the remainder was stirred with HOAc-acidified brine for 5 min and then neutralized with solid NaHCO₃. After extraction with benzene, drying over MgSO₄ and evaporation of the solvent, column chromatography (elution with pentane-EtOAc 9 : 1) afforded the title compound as a colourless oil. Yield: 3.9 g (61%). ¹H NMR: δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.28 (m, 8 H), 1.49 (m, 2 H), 1.95 (m, 2 H), 2.39–2.34 (m, 5 H), 3.58 (t, 2 H, J = 6.6 Hz), 3.65 (s, 3 H), 5.41 (m, 2 H). ¹³C NMR: δ −5.3 (q), 18.4 (s), 25.7 (t), 26.0 (q), 27.9 (t), 29.1 (t), 29.3 (t), 29.4 (t), 32.5 (t), 32.8 (t), 34.2 (t), 51.4 (q), 63.3 (t), 127.8 (d), 131.8 (d), 173.7 (s). Analysis: calc. for C₁₈H₃₈O₂Si: C, 66.61; H, 11.18. Found: C, 66.40; H, 11.70.

(E)-12-Hydroxydoced-4-enoic acid (8). To a solution of ester 7 (0.855 g, 2.5 mmol) in THF (25 mL) tetrabutylammonium fluoride (2.65 mmol, 2.65 ml of a 1 M solution in THF) was added, and the mixture was stirred for 5 h at ambient temperature. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (using a gradient of pentane and 10 → 40% EtOAc as the eluent) to afford crude (E)-methyl 12-hydroxydoced-4-enoate. The ester was dissolved in MeOH (6 ml) and treated with KOH (0.4 g) in water (2 mL) at ambient temperature over 1 h. Methanol was removed in vacuo, the residue was diluted with brine (5 ml) and unconverted material was taken up in Et₂O. The aqueous layer was acidified with 2 M HCl and extracted with Et₂O. The extract was washed with brine, dried (Na₂SO₄) and evaporated to afford the title compound (0.366 g, 68%) as white crystals, m.p. 60–61°C. ¹H NMR: δ 1.30 (m, 8 H), 1.56 (m, 2 H), 1.98 (q, 2 H, J₅,₆ = J₆,₇ = 6.6 Hz), 2.33 (m, 2 H), 2.41 (m, 2 H), 3.64 (t, 2 H, J = 6.6 Hz), 5.30 (br s, 2 H), 5.43 (m, 2 H). Analysis: calc. for C₁₁H₁₂O₃: C, 67.26; H, 10.35. Found: C, 67.44; H, 10.51.

(E)-Dodec-4-en-12-olide (9). A solution of acid 8 (0.354 g, 1.65 mmol) in a mixture of THF (10 ml) and toluene (45 ml) was added over 7 h to a stirred solution of Ph₃P (2.157 g, 8.27 mmol) and DEAD (1.451 g, 1.31 ml, 8.41 mmol) in toluene (257 ml) under N₂ with a syringe pump. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (using a gradient of pentane and 0 → 5% Et₂O as the eluent) to give 0.099 g (31%) of the title compound as a colourless oil. ¹H NMR: δ 1.28 (m, 4 H), 1.40 (m, 4 H), 1.64 (m, 2 H), 2.01 (q, 2 H, J₅,₆ = J₆,₇ = 5.5 Hz), 2.38 (m, 4 H), 4.12 (m, 2 H), 5.41 (dt, 1 H, J = 15.5 and 6.2 Hz), 5.52 (dt, 1 H, J = 15.5 and 6.2 Hz). ¹³C NMR: δ 24.7 (t), 26.5 (t), 27.0 (t), 27.1 (t), 28.1 (t), 31.6 (t), 34.6 (t), 64.5 (t), 128.5 (d), 132.7 (d), 173.9 (s).
Procedure A. To a stirred solution of i-Pr₂NH (0.091 g, 0.9 mmol) in THF (1.1 ml) at -78 °C, a solution of n-BuLi in hexane (0.46 ml 1.55 M, 0.72 mmol) was added dropwise. After 10 min, a solution of macrolide 9 (0.071 g, 0.36 mmol) in THF (0.4 ml) was added over 5 min, and the mixture was stirred for an additional 30 min. The solution of the lithium enolate thus formed was then transferred via cannula at -78 °C into a stirred solution of bis-(4-methoxyphenyl) diselenide (0.18 g, 0.48 mmol) in THF (1.1 ml), and stirring was continued for another 40 min. The reaction mixture was quenched with HOAc (0.2 ml) and neutralized with aqueous NaHCO₃. After extraction with Et₂O, drying (Na₂SO₄) and concentration, column chromatography (using pentane containing 2→5% Et₂O as the eluent) afforded 0.102 g (73% of lactone 10 as a viscous oil. ¹H NMR: δ 1.2-1.44 (m, 8 H), 1.5-1.75 (m, 2 H), 1.97 (m, 2 H), 3.61 (dd, 1 H, J = 11.1 and 4.8 Hz), 3.80 (s, 3 H), 3.82 (ddd, 1 H, J = 11.1, 7.7 and 3.1 Hz), 4.40 (ddd, 1 H, J = 11.1, 7.3 and 3.1 Hz), 5.38 (dm, 2 H, J₆₋₅ = 15.7 Hz), 5.52 (dt, 1 H, J₅₋₆ = 15.7, J₆₋₇ = 7.0 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 7.54 (d, 2 H, J = 8.6 Hz). ¹³C NMR: δ 24.5 (t), 26.6 (t), 26.7 (t), 27.0 (t), 27.1 (t), 31.8 (t), 35.2 (t), 43.2 (d), 55.2 (q), 65.0 (t), 114.6 (d), 117.8 (s), 126.9 (d), 134.5 (d), 138.0 (d), 160.2 (s), 173.0 (s). Analysis: calc. for C₁₉H₂₆O₂Se: C, 59.84; H, 6.87. Found: C, 59.78; H, 6.73.

Procedure B. A solution of acid 12b (0.196 g, 0.49 mmol) in toluene (17 ml) was introduced by syringe pump over 6 h into a stirred solution of Ph₃P (0.64 g, 2.45 mmol) and DEAD (0.435 g, 2.50 mmol) in toluene (77 ml) at ambient temperature under an atmosphere of N₂. The mixture was concentrated in vacuo, after which column chromatography (using pentane containing 0→5% Et₂O as the eluent) afforded 0.119 g (63%) of lactone 10, identical with the material obtained by using procedure A.

Methyl (E)-12-hydroxy-2-(4-methoxyphenylseleno) dodec-4-enoate (12a). A solution of ester 11 (0.819 g, 1.55 mmol) in THF (15 ml) was treated with tetra-n-butylammonium fluoride (1.7 mmol, 1.7 ml of an 1 M solution in THF) at ambient temperature for 4 h. Removal of the solvent under reduced pressure and subsequent column chromatography (10%, then 30% EtOAc in pentane) afforded 0.475 g (74%) of the title compound as a viscous oil. ¹H NMR: δ 1.28 (m, 9 H), 1.54 (m, 2 H), 1.95 (q, J₆₋₅ = J₅₋₆ = 7.0 Hz, 2 H), 2.41 (m, 2 H), 2.51 (m, 1 H), 3.52 (dd, 1 H, J = 9.3 and 6.7 Hz), 3.53 (t, 2 H, J = 6.6 Hz), 3.61 (s, 3 H), 3.80 (s, 3 H), 5.33 (dt, 1 H, J = 15.1 and 6.2 Hz), 5.48 (dt, 1 H, J = 15.1 and 7.2 Hz), 6.83 (d, 2 H, J = 8.8 Hz), 7.50 (d, 2 H, J = 8.8 Hz). ¹³C NMR: δ = 5.3 (q), 18.3 (s), 25.7 (t), 26.0 (q), 29.0 (t), 29.2 (t), 32.5 (t), 34.8 (t), 43.1 (d), 51.9 (q), 55.2 (q), 63.3 (t), 114.6 (d), 117.5 (s), 125.9 (d), 134.0 (d), 138.2 (d), 160.3 (s), 173.0 (s). Analysis: calc. for C₃₉H₄₈O₃Se: C, 59.18; H, 8.41. Found: C, 59.46; H, 8.92.

(E)-12-Hydroxy-2-(4-methoxyphenylseleno) dodec-4-enoic acid (12b). A solution of ester 12a (0.25 g, 0.6 mmol) in MeOH (2 ml) was stirred to homogeneity at ambient temperature with a 20% aqueous solution of KOH (1 ml) over 5 h. The solution was then diluted with saturated sodium chloride solution (brine) and extracted with Et₂O to remove unsaponified material. The aqueous phase was acidified with 2 M HCl and extracted with Et₂O. The extracts were washed with brine, dried (Na₂SO₄), and concentrated to give 0.196 g (81%) of the title compound as a viscous, colourless oil. ¹H NMR: δ 1.29 (m, 8 H), 1.55 (m, 2 H, J = 7.2 Hz), 1.97 (m, 2 H), 2.45 (m, 2 H), 3.49 (dd, 1 H, J = 9.7 and 6.6 Hz), 3.64 (t, 2 H, J = 6.6 Hz), 3.80 (s, 3 H), 4.86 (br s, 2 H), 5.36 (dt, 1 H, J = 15.4 and 6.4 Hz), 5.49 (dt, 1 H, J = 15.4 and 6.5 Hz), 6.83 (d, 2 H, J = 8.7 Hz), 7.54 (d, J = 8.7 Hz). ¹³C NMR: δ 25.3 (t), 28.2 (t), 28.7 (t), 32.0 (t), 34.7 (t), 42.7 (d), 55.2 (q), 62.9 (t), 114.7 (d), 117.5 (s), 126.1 (d), 134.0 (d), 138.1 (d), 160.4 (s), 176.8 (s).

(Z,4E)-Dodeca-2,4-dien-12-olide (13). To a solution of lactone 10 (0.102 g, 0.267 mmol) in THF (3 ml), a 30% aqueous solution of H₂O₂ (0.3 ml) was added, and the mixture was stirred at ambient temperature for 3 h. Pentane (10 ml) was then added and the reaction mixture was neutralized with aqueous NaHCO₃. The organic layer was separated, dried (Na₂SO₄) and concentrated; the residue was subjected to column chromatography (5% Et₂O in pentane) to afford 0.047 g (91%) of dionolide 14 as white crystals, m.p. 38-39 °C, Rₖ 0.59 (EtOAc-
hexane = 2:8). ¹H NMR: δ 1.42 (m, 4 H), 1.68 (m, 6 H), 2.25 (m, 2 H), 4.18 (m, 2 H), 5.56 (d, 1 H, J₂₃=11.1 Hz), 6.11 (dt, 1 H, J₆₋₅=16.0, J₅₋₆=4.3 Hz), 6.64 (t, 1 H, J₂₃=11.1 Hz), 7.30 (dd, 1 H, J₄₋₅=16.0, J₅₋₆=11.1 Hz). ¹³C NMR: δ 23.8 (t), 24.2 (t), 24.3 (t), 27.5 (t), 27.6 (t), 29.9 (t), 65.2 (t), 117.8 (d), 126.5 (d), 140.8 (d), 142.6 (d), 167.3 (s). Analysis: calc. for C₁₉H₁₈O₂: C, 74.19; H, 9.34. Found: C, 74.27; H, 9.45.

(Z)-Dodec-3-en-12-olide (1). A solution of dienolide 13 (0.040 g, 0.20 mmol) and (R⁻)-naphthalene-tricarboxylonychromium (0.25 g, 4.7 mmol) in THF (10 ml) was placed in a stainless steel autoclave under an atmosphere of argon. The vessel was sealed and filled/evacuated three times with H₂ (at 10 atm) to remove traces of O₂. The hydrogen pressure was then adjusted to 40 atm, and hydrogenation was carried out at 45–50°C for 2 h. The autoclave was rinsed with ether, and the resulting solution filtered and concentrated under reduced pressure. Column chromatography (using pentane containing 0–5% Et₂O as the eluent) gave 0.026 g (65%) of the title phenolone 1 as a colourless oil. ¹H NMR and ¹³C NMR data were in close agreement with the literature.³

(2E,4E)-12-Hydroxydodeca-2,4-dienoic acid (15). Methyl (E)-12-hydroxy-2-(4-methoxysphenoxy)dec-4-enoate (12a) (0.221 g, 0.53 mmol) was treated with 30% H₂O₂ (0.3 ml) in THF (3 ml) as described for the preparation of compound 13. Column chromatography (using pentane containing 5–40% Et₂OAc as the eluent) afforded 0.117 g (79%) of (2E,4E)-methyl 12-hydroxydodeca-2,4-dienoate as a yellowish oil. ¹H NMR: δ 1.32 (m, 9 H), 1.42 (m, 2 H), 2.16 (q, 2 H, J₆₋₅=J₅₋₆=6.1 Hz), 3.63 (t, 2 H, J₆₋₅=6.3 Hz), 3.72 (s, 3 H), 5.78 (d, 1 H, J = 15.6 Hz), 6.12 (m, 2 H), 7.26 (dd, 1 H, J = 15.6 and 10.3 Hz). ¹³C NMR: δ 25.6 (t), 28.6 (t), 29.1 (t), 29.2 (t), 32.7 (t), 32.9 (t), 51.4 (q), 63.0 (t), 118.6 (d), 128.3 (d), 144.8 (d), 145.4 (d), 167.8 (s).

Saponification of the ester (0.117 g, 0.52 mmol) was then performed as described for the preparation of acid 8 to afford 0.100 g (92%) of the title compound as white crystals. ¹H NMR: δ 1.33 (m, 8 H), 1.57 (m, 2 H), 2.18 (q, 2 H, J₆₋₅=J₅₋₆=5.8 Hz), 3.64 (t, 2 H, J = 6.6 Hz), 5.40 (br s, 2 H), 5.78 (d, 1 H, J = 15.4 Hz), 6.19 (m, 2 H), 7.34 (dm, 1 H, J = 15.4 Hz).

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