Stereoselective Synthesis of (±)-Echinolone

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A total and stereoselective synthesis of racemic echinolone (1), a juvenile hormone mimic, is reported. Reduction of the easily available (*E*)-ω-hydroxy ester **2** with Red-Al afforded diol **3** which, via the corresponding dichloride, was homologated in 75% yield into the chloride **5**. Its conversion into the title compound was achieved by conventional methods, including the quantitative deprotection of the carbonyl group with mercuric chloride–calcium carbonate in aqueous acetonitrile. The yields, except for the above mentioned reduction, are between 70 and 85%.

Echinolone has been obtained from the roots of *Echinacea angustifolia* by Jacobson, Redfern, and Mills.[1] It shows high juvenile hormone mimicking activity in the yellow meal worm, and it has considerable promise in insect control.[2] It was tentatively identified by the same authors as the (+) enantiomer of (*E*)-10-hydroxy-4,10-dimethyl-4,11-dodecadien-2-one (1).

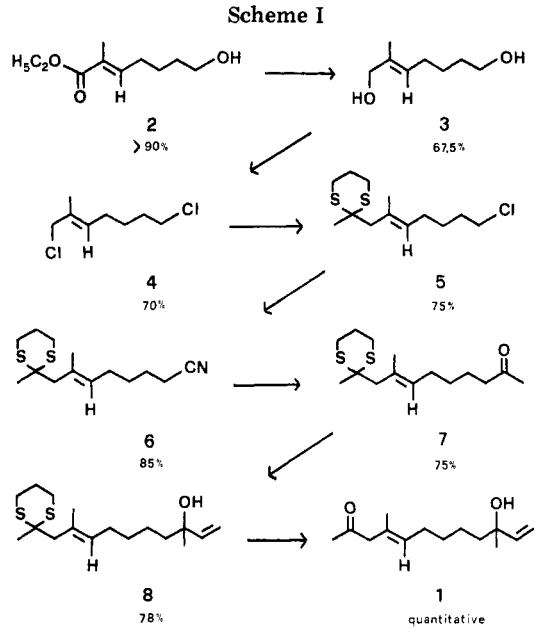
In the present paper we report a new stereoselective synthesis[3] of racemic (1), different from that already proposed by Cooke.[4]

This synthesis starts from the easily available (*E*)-ω-hydroxy ester **2**, obtained nearly quantitatively by condensation of 2-hydroxytetrahydropyran with α-(carboethoxy)ethylidenetriphenylphosphorane by the literature procedure:[5] IR (neat) 3400, 1710, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H, CH_3CH_2O), 1.80 (s, 3 H, methyl at double bond), 3.58 (t, J = 6 Hz, 2 H, CH_2OH), 4.15 (q, J = 7 Hz, 2 H, CH_3CH_2O), 6.70 (br t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 186 (M^+), 168 ($M^+ - H_2O$); R_f 0.23 (ethyl acetate–petroleum ether, 1:1); R_t 10.8 min (150 °C). The undesired Z isomer could be detected only in traces in the ^1H NMR spectrum of the crude ester **2** by the presence of a vinylic proton at δ 5.88 which disappears, however, after chromatographic purification.

The α,β-unsaturated ester **2** is selectively reduced by sodiumbis[2-methoxyethoxy]aluminum hydride (Red-Al)[6] to give the corresponding allylic alcohol **3** (Scheme I). This selective reduction could also be achieved with aluminum hydride. Red-Al is more advantageous, however, due to its great solubility and the reduction can be carried out in very controlled conditions.

Various methods were investigated to convert the allylic alcohol **3** to its corresponding dihalide **4**. We found that the diol **3** was readily transformed in excellent yields into the allylic chloride monomesylate. Methanesulfonyl chloride and a mixture of lithium chloride, dimethylformamide, and *S*-collidine at 0 °C were used to effect this transformation.[7] The displacement of the primary nonallyl mesyl group by chloride ion was then smoothly

Scheme I



achieved, using PTC (phase-transfer catalysis).

The displacement of the allylic chloride ion in **4** was selectively achieved in good yields by treatment with the carbanion of 2-methyl-1,3-dithiane at low temperature and afforded **5**.

The conversion of the chloride **5** into the tertiary allylic alcohol **8** involves conventional steps. By treatment with sodium cyanide in dimethyl sulfoxide, **5** was first converted into the corresponding nitrile **6**.

Addition of methyllithium in diethyl ether followed by acidic hydrolysis afforded the keto derivative **7**.

Grignard reagent prepared from vinyl bromide in tetrahydrofuran effected the conversion into the allylic alcohol **8**.

Finally the thioketal **8** was converted to the parent ketone (1) by mercuric chloride in aqueous acetonitrile in the presence of powdered carbonate.

The analytical data of **1** proved to be (*E*)-(±)-10-hydroxy-4,10-dimethyl-4,11-dodecadien-2-one. In addition a direct comparison of the IR and ^1H NMR spectra of **1** with the IR and ^1H NMR spectra (kindly supplied by Dr. Cooke) of the racemic echinolone synthetized by Cooke confirms that they are identical.

Experimental Section

General Procedures. Infrared spectra were recorded as films (neat) or in solutions (CCl_4) by using a Perkin-Elmer 257 spectrophotometer. ^1H NMR spectra were recorded with a Hitachi Perkin-Elmer R-24 spectrometer, using solutions in the solvent

(1) Jacobson, M.; Redfern, R. E.,; Mills, G. D., Jr. *Lloydia* **1975**, *38*, 473.
(2) *Chem. Eng. News* **1974**, *52*, Sept 23.
(3) Presented at the 8th conference on isoprenoids, Torun, Sept 1979.
(4) Cooke, M. P., Jr *J. Org. Chem.* **1979**, *44*, 2461. A nonstereoselective synthesis of 1 had been previously reported: Vig, O, P.; Sharma, S. D.; Bari, S. S.; Handa, V. K. *Indian J. Chem.* **1977**, *15B*, 1078.
(5) (a) Bergelson, L. D.; Shemyakin, M. M. *Tetrahedron* **1963**, 149. (b) Isler, O.; Gutmann, H.; Montavon, M.; Ruegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *40*, 1942. The yield of α-(carboethoxy)-ethylidenephosphorane was improved from 20% to 60% by prolonging the reaction time from 2 to 22 h.
(6) Walker, E. R. H. *Q. Rev., Chem. Soc.* **1976**, 23.
(7) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

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indicated with tetramethyl silane as internal standard. Mass spectra were recorded with a Varian Mat 112 spectrometer at 70 eV. GC analyses were carried out by using a 20 × 0.05 m column of 3% OV 1 on Chromosorb W (80–100 mesh) with nitrogen carrier gas at a 1 kg/cm^2 flow rate at the temperature indicated. TLC was performed by using plastic sheets of silica gel 60 F_{254}, 0.2-mm layer thickness. Merck 70–230-mesh silica gel was used for column chromatography. Combustion analytical data were performed for all new compounds and are in agreement with the proposed structures.

(*E*)-2-Methylhept-2-ene-1,7-diol (3). To a stirred, ice-cooled solution of **2** (42 g) in dry tetrahydrofuran (250 mL) was added dropwise a 70% solution (120 mL) of Red-Al in benzene. The reaction was stirred for 2 h at 0 °C and then treated sequentially with ethanol (50 mL) and ethanol–water (1:1, 50 mL). The solvent was evaporated under reduced pressure, and the residue was taken up in methanol–water (1:1) and filtered from the aluminum salts which were washed with aqueous methanol. The solution phase was reduced to small volume and extracted five times with ether. The dried extracts gave, after solvent removal under reduced pressure, 30 g of crude **3** which was purified either by distillation at 210 °C (1 mm) or by column chromatography on silica gel (silica–substance, 30:1, eluting with ether), affording 67.5% of pure **3**: IR (neat) 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H), 3.63 (t, J = 6 Hz, 2 H, CH_2OH), 4.00 (s, 2 H, allylic CH_2OH), 5.38 (t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 126 (M^+-H_2O), 95 (M^+-CH_2OH); R_f 0.1 (ethyl acetate–petroleum ether, 1:1); R_t 5.2 min (150 °C).

(*E*)-1,7-Dichloro-2-methylhept-2-ene (4). Lithium chloride (7.12 g) was melted in a two-necked flask under dry nitrogen. After the flask cooled, a solution of diol **3** (22 g) in dry dimethylformamide (300 mL) and dry *S*-collidine (44.5 mL) was added in one portion. To the well-stirred and ice-cooled reaction mixture was added 26.2 mL of methanesulfonyl chloride dropwise, and the vigorous stirring was continued for 2 h. The reaction mixture was slowly poured into ice–water and extracted with petroleum ether–ether (1:1). The combined organic extracts were washed with a saturated solution of copper(II) sulfate and water and dried (Na_2SO_4). Solvent removal gave the allylic chloride monomesylate (32.8 g) which was used for subsequent reaction: ^{1}H NMR (CCl_4) δ 1.75 (s, 3 H, methyl at double bond), 3.00 (s, 3 H, SO_2CH_3), 4.00 (s, 2 H, CH_2Cl), 4.20 (t, J = 6 Hz, 2 H, $CH_2OSO_2CH_3$), 5.55 (t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 146–144 ($M^+ - CH_3SO_3$), 109 ($M^+ - CH_3SO_3 - Cl$); R_f 0.56 (ethyl acetate–petroleum ether, 1:1); R_t 5.2 min (150 °C).

Crude allylic chloride monomesylate (32.8 g) in benzene (750 mL), a saturated aqueous solution (1.2 L) of potassium chloride (35 g in 100 mL of water), and tributylcetylphosphonium bromide (12 g) were refluxed with stirring for 2 h. The aqueous phase was renewed and refluxing continued for additional 3 h. The organic phase was then separated, washed with water, and dried (Na_2SO_4). Solvent removal under reduced pressure gave the dichloride **4** which was purified by column chromatography on silica gel (silica–substance, 8:1). Elution with 4:1 petroleum ether–ether afforded 19 g (70%) of **4**: ^{1}H NMR (CCl_4) δ 1.70 (s, 3 H, methyl at double bond), 3.45 (t, J = 6 Hz, 2 H, CH_2Cl), 3.90 (s, 2 H, allylic CH_2Cl), 5.45 (t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 184–182–180 (M^+), 147–145 ($M^+ - Cl$), 146–144 ($M^+ - HCl$), 133–131 ($M^+ - CH_2Cl$); R_f 0.85 (ethyl acetate–petroleum ether, 1:1); R_t 5.2 min (150 °C).

(*E*)-9-Chloro-4-methylnon-4-en-2-one Thioketal 5. A solution of 2-methyl-1,3-dithiane (13.1 g) in dry tetrahydrofuran (150 mL) was cooled to −30 °C under nitrogen atmosphere. A 2.2 N solution of *n*-butyllithium in hexane (60 mL) was added dropwise with stirring which was continued for 2 h at −30 °C. After the flask was cooled to −78 °C, a solution of dichloride **4** (17.7 g) in dry tetrahydrofuran (150 mL) was added dropwise. The mixture was allowed to warm at room temperature, diluted with ether, washed to pH 7 with water, and dried (Na_2SO_4). Solvent removal under reduced pressure afforded nearly pure **5** which could be further purified by column chromatography on silica gel. Elution with 6:4 ether–hexane gave 20 g of **5** (75%): ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3 H, CH_3), 1.75 (s, 3 H, methyl at double bond), 2.60 (s, 2 H, allylic CH_2), 2.7–2.9 (m, 4 H, CH_2S), 3.50 (t, J = 6 Hz, CH_2Cl), 5.20 (t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 205–203 ($M^+ - SCH_2CH_2CH_2$), 133 [$(CH_3C(SCH_2CH_2CH_2S)]^+$; R_f 0.5 (ethyl acetate–petroleum ether, 8:2); R_t 6.2 min (250 °C).

(*E*)-9-Cyano-4-methylnon-4-en-2-one Thioketal 6. **5** (13.5 g) and 3.6 g of sodium cyanide in dry dimethyl sulfoxide (120 mL) were stirred overnight at 90 °C under nitrogen. The mixture was cooled, diluted with a saturated solution of sodium sulfate, and extracted with chloroform. The dried extracts (Na_2SO_4), after solvent removal under reduced pressure, were filtered through silica gel, eluting with 6:4 ether–hexane, and afforded 11 g (85%) of pure nitrile **6**: IR (neat) 2250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H, CH_3), 1.80 (s, 3 H, methyl at double bond), 2.60 (s, 2 H, allylic CH_2), 2.80–3.00 (m, 4 H, CH_2S), 5.30 (t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 133 [$CH_3C(SCH_2CH_2CH_2S)]^+$; R_f 0.3 (ethyl acetate–petroleum ether, 8:2); R_t 8.1 min (250 °C).

(*E*)-4-Methylundeca-4-ene-2,10-dione Thioketal 7. **6** (10 g, 37 mmol) and 150 mmol of methyllithium in dry ether (500 mL) were refluxed for 15 h, with stirring and in a nitrogen atmosphere. The mixture was made slightly acidic by the dropwise addition of 0.1 N hydrochloric acid (3000 mL), stirred for 6 h over a water bath, and extracted with ether. Solvent removal of the dried (Na_2SO_4) extracts afforded crude **7** which was purified by column chromatography on silica gel. Elution with 4:1 hexane–ether gave 8 g (75%) of pure **7**: IR (CCl_4) 1710 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.65 (s, 3 H, CH_3), 1.80 (s, 3 H, methyl at double bond), 2.10 (s, 3 H, CH_3CO), 2.60 (s, 2 H, allylic CH_2), 2.80–3.00 (m, 4 H, CH_2S), 5.30 (t, J = 7 Hz, 1 H, vinylic proton); mass spectrum, m/e 133 [$CH_3C(SCH_2CH_2CH_2S)]^+$; R_f 0.52 (methylene chloride–ethyl acetate, 3:1); R_t 7.7 min (250 °C).

(*E*)-10-Hydroxy-4,10-dimethyldodeca-4,11-dien-2-one Thioketal 8. A solution of 8 g (28 mmol) of **7** in dry tetrahydrofuran (80 mL) was added to an excess (five times) of vinylmagnesium bromide at −20 °C, with stirring and in a nitrogen atmosphere. The mixture was stirred at −20 °C for 2 h and overnight at room temperature, then treated with aqueous ammonium chloride, and extracted with ether. The dried extracts (Na_2SO_4) gave, after concentration under reduced pressure, 11 g (78%) of nearly pure **8** which was used for the subsequent reaction: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3 H, allylic tertiary CH_3), 1.60 (s, 3 H, CH_3), 1.74 (s, 3 H, methyl at double bond), 2.60 (s, 2 H, allylic CH_2), 2.8–2.9 (m, 4 H, CH_2S), 5.00 (dd, J = 1, 10 Hz, 1 H, C**H**$_2$=CH), 5.16 (dd, J = 1, 18 Hz, 1 H, C**H**$_2$=CH), 5.25 (t, J = 7 Hz, 1 H, vinylic proton), 5.90 (dd, J = 10, 18 Hz, 1 H, C**H**=CH$_2$); mass spectrum, m/e 133 [$CH_3C(SCH_2CH_2CH_2S)]^+$; R_f 0.48 (methylene chloride–ethyl acetate, 3:1); R_t 10.5 min (250 °C).

(±)-Echinolone (1). **8** (1 g), 1.8 g of mercuric chloride, and 0.66 g of powdered calcium carbonate in aqueous acetonitrile (250 mL) were refluxed for 5 h, with stirring, in a nitrogen atmosphere. Most of the solvent was evaporated under reduced pressure and the residue taken up in water and extracted with ether. Pure **1** was quantitatively obtained either by bulb-to-bulb distillation at 150 °C (0.2 mm) or by column chromatography on silica gel (silica–substance, 100:1), eluting with 3:1 methylene chloride–ethyl acetate: IR (CCl_4) 3450, 1715, 1650 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 s, 3 H, tertiary CH_3), 1.62 (s, 3 H, methyl at double bond), 2.07 (s, 3 H, CH_3CO), 3.05 (s, 2 H, CH_2COCH_3), 5.00 (dd, J = 1, 10 Hz, 1 H, C**H**$_2$=CH), 5.20 (dd, J = 1, 18 Hz, 1 H, C**H**$_2$=CH), 5.32 (t, J = 7 Hz, 1 H, vinylic proton), 5.95 (dd, J = 10, 18 Hz, 1 H, C**H**=CH$_2$); mass spectrum, m/e 148 ($M^+ - CH_3 - H_2O - CH_3CO$), 133 (148 − CH_3), 111 [$(CH_3COCH_2C(CH_3)=CHCH_2)^+$]; R_f 0.4 (methylene chloride–ethyl acetate, 3:1); R_t 1.2 min (250 °C).

Registry No. 1, 66521-02-6; 2, 74844-86-3; 3, 74868-68-1; 3 allylic chloride monomesylate, 74844-87-4; 4, 74868-69-2; 5, 74844-88-5; 6, 74844-89-6; 7, 74844-90-9; 8, 74868-70-5; 2-methyl-1,3-dithiane, 6007-26-7.