

Practical Total Synthesis of (\pm)-Strigol

Dee W. Brooks,* H. S. Bevinakatti, Eileen Kennedy, and Jim Hathaway

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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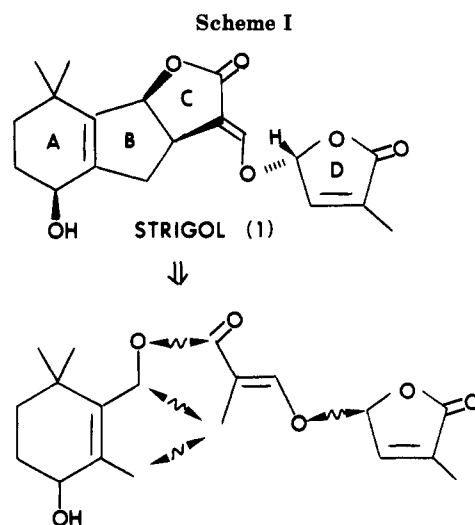
An improved total synthesis of racemic strigol (1) and 4'-epistrigol (21) from α -ionone in 10 (4.4% overall yield) or 12 steps (6.8% overall yield) by recycling isomer 16 is described which is applicable on a multigram scale with a minimum of purification steps. The synthetic scheme also allows efficient access to many analogues for evaluation of structure-activity relationships.

Strigol (1) was isolated in small amounts from root exudates of cotton (*Gossypium hirsutum* L.) and identified by Cook and co-workers.¹ Strigol was found to be a potent seed germination stimulant for *striga* species and similar parasitic plants in the genus *Orobancha*.² It is presently the most potent seed germination stimulant known for witchweed, which causes considerable economic loss acting upon important crops of the Gramineae family such as corn, sorghum, and sugarcane.³ This weed is particularly prevalent in the Eastern Hemisphere but has also emerged as a problem in North and South Carolina.⁴ Laboratory results show almost complete germination of witchweed by (\pm)-strigol at concentrations of 10^{-9} M.⁵ Usually, witchweed seeds will remain dormant in the soil for many years, until favorable conditions prevail which often include exposure to some type of chemical stimulant released by the roots of a host plant. The concept of using a biosynthetic product or chemical to break dormancy and stimulate germination of weed seed has important implications for weed control. The premise developed is that inducing germination of witchweed in the absence of a host plant will result in starvation of the seedling. Field tests with ethylene⁶ and simple synthetic analogues of strigol⁷ have shown that this idea has merit.

Several partial⁸ and two total syntheses^{9,10} of (\pm)-strigol have been reported. The interest in field testing strigol, which is not readily available from natural sources, provides impetus to develop a practical synthesis applicable on a multigram scale. In addition, the availability of synthetic intermediates prepared enroute to strigol can form a basis for the elucidation of structure-activity relationships which might provide a lead to the preparation of simpler analogues of strigol with potent activity. The simple analogues of strigol which have been evaluated as witchweed seed germination stimulants, thus far, have all exhibited much less activity.⁵

Results and Discussion

The total synthesis of (\pm)-strigol (1) developed by Sih and co-workers⁹ formed the basis for our efforts to devise



an improved practical synthesis. The general synthetic plan involves consecutive (A + B + C + D)-ring formation and the connection of four key bonds as shown in Scheme I. Our total synthesis of (\pm)-strigol is outlined in Scheme II and is described as follows.

Commercially available α -ionone (2) was chosen as the starting material as it contained the required carbon framework and functionality appropriate for elaboration to an A-ring intermediate. Treatment of 2 with 4 equiv of 30% peracetic acid in acetic acid at 0 °C in the presence of sodium acetate provided a 9:1 ratio of isomeric epoxides 3a and 3b in 94% yield. The enone functionality was removed by ozonolysis in methanol at -78 °C and subsequent reductive treatment with zinc and acetic acid¹¹ gave the aldehydes 4a and 4b in 86% yield after vacuum distillation.

Oxidative cleavage of the enone in 3a,b was investigated in some detail before the present optimized procedure was developed. We reported previously^{8d} the application of the Lemieux procedure on a strigol A-ring precursor, but this method was not practical on a large scale. Attempts to cleave the enone with potassium permanganate under phase-transfer conditions¹² gave complex product mixtures. Ozonolysis in methanol at -78 °C followed by reductive workup with dimethyl sulfide¹³ gave a complicated mixture of products which included 4a and 4b in 28% yield. Ozonolysis followed by oxidative treatments such as sodium metaperiodate,¹⁴ chromic acid,¹⁵ or alkaline aqueous

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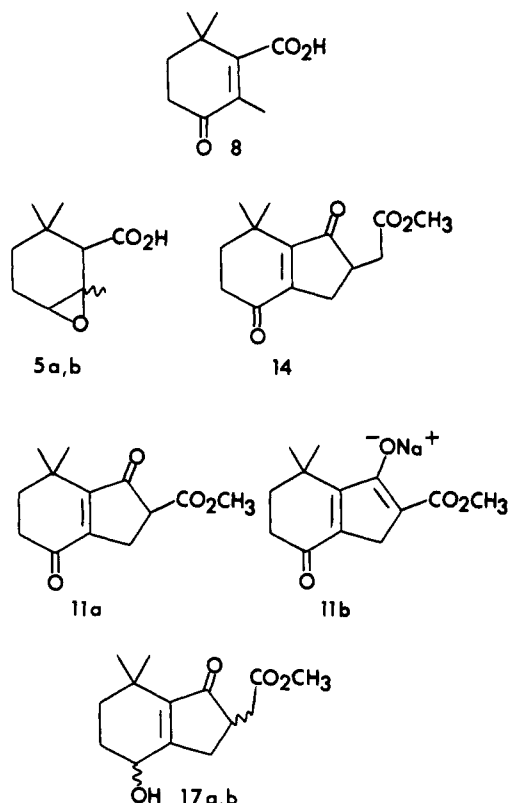
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hydrogen peroxide¹⁶ gave low yields (<20%) of the acids **5a** and **5b**.



Epoxide opening with pyrrolidine in ether at room temperature⁹ gave the hydroxy aldehyde **6** in 90% yield. Careful selective oxidation of the hydroxy group with Jones' reagent¹⁷ provided the keto aldehyde **7** in 88% yield, which was susceptible to slow oxidation to the acid **8** in the presence of air. In fact, a carbon tetrachloride solution of **7** left exposed to air at 0 °C for 2 weeks provided keto acid **8**, which crystallized out of solution in 95% yield. However, a neat film of **7** left at room temperature gave a complex mixture of products including **8** in 55% yield. Attempts to prepare **8** by treatment with excess Jones' reagent gave poor yields (<50%).^{8c,9}

The keto aldehyde **7** could be directly converted to the bromomethyl ester **10** by a one-pot reaction. Treatment of **7** with *N*-bromosuccinimide¹⁸ (2.1 equiv) in carbon tetrachloride at 70 °C in the presence of a sun lamp for 2–3 h provided the bromo acid bromide **9**, which was not isolated but treated with excess methanol at 0 °C for 6 h, to give **10** in 83% yield. This result circumvents the troublesome oxidation step of previous synthetic studies.^{8c,9}

For the formation of the B-ring unit, we investigated the procedures reported by Sih⁹ and soon realized that the condensation reaction of the bromo ester **10** with the sodium salt of dimethyl malonate was very dependent upon the reaction conditions and yields varied from 15% to 85%. Systematic optimization of the reaction conditions and amounts of reagents employed finally provided a reproducible one-pot procedure for the preparation of the diester **12** from **10**. The bromo ester **10** (1 equiv) was added dropwise to a mixture of sodium hydride (2.5 equiv) and dimethyl malonate (1.2 equiv) in tetrahydrofuran at

–10 °C and the mixture was then stirred under nitrogen for 24 h at 25 °C. Aqueous acidic workup of an aliquot from the reaction verified the formation of the keto ester **11a** which in the reaction mixture would exist as the sodium salt **11b**; therefore, methyl bromoacetate (1.5 equiv) was added, and the mixture was stirred for 48 h at 25 °C. Aqueous workup gave crude material which was purified by chromatography (silica gel, 10–30% ethyl acetate in hexane) to give the diester **12** in 82% yield. On large-scale reactions the crude material was used without purification in the next step. Acid-catalyzed hydrolysis and decarboxylation of crude **12** gave the acid **13** in 64% yield after recrystallization from ether. The ester **14** could be readily obtained directly from crude **12** in 70% yield by heating at 120 °C for 6 h with lithium chloride in *N*-methylpyrrolidone containing a trace of water. Numerous attempts were made to devise a method for reduction of either the acid **13** or the ester **14** to the lactone isomers **15** and **16**. Reduction of the cyclohexanone carbonyl proceeded smoothly with NaBH₄, LiBH₄, and 9-BBN to give **17a,b**, but attempts to further reduce the hindered cyclopentanone carbonyl either failed or resulted in complicated mixtures. Repeating the reduction advocated by Sih using diisobutylaluminum hydride gave a 45% yield of the isomeric lactones **15** and **16** in a 1:1 ratio. We were very pleased to finally find a simple alternative for this reduction involving the use of a reducing reagent consisting of NaBH₄ and CeCl₃.¹⁹ When the homogeneous aqueous solution of the sodium salt of the acid **13** was mixed with an aqueous solution of 1 equiv of CeCl₃ a yellowish precipitate formed. Subsequent addition of excess NaBH₄ (6 equiv) effected smooth reduction within 2 h at 25 °C to provide, after acidification to pH 1 with 6 N HCl and extraction with dichloromethane, a 75% yield of a 1:1 mixture of **15** and **16**. Also, the reduction of the salt of acid **13** derived directly from the acid hydrolysis and decarboxylation step without recrystallization gave good yields of **15** and **16**. The desired isomer **15** crystallized from an ether solution of the isomeric mixture. The action of CeCl₃ in promoting the reduction of the sodium salt of **13** is very interesting. The acid **13** was not cleanly reduced by this method.

The undesired hydroxy lactone isomer **16** was salvaged for the synthesis of strigol by first oxidation with pyridinium chlorochromate in dichloromethane to the keto lactone **18**, followed by stereoselective reduction with sodium borohydride to give the desired isomer **15** (76%) and **16** (14%). Reduction of **18** with LiAl(O₂C₄H₉)₃ gave a similar ratio of products.

Formylation of the hydroxy lactone **15** by treatment with NaH and ethyl formate proceeded to give **19** which was then subjected to *O*-alkylation with the bromobutenolide **20**⁹ using excess potassium carbonate in *N*-methylpyrrolidone providing a mixture of (±)-strigol (35%) and (±)-4'-epistrigol (39%), which were separated by chromatography (silica gel, 0–30% ethyl acetate in dichloromethane).

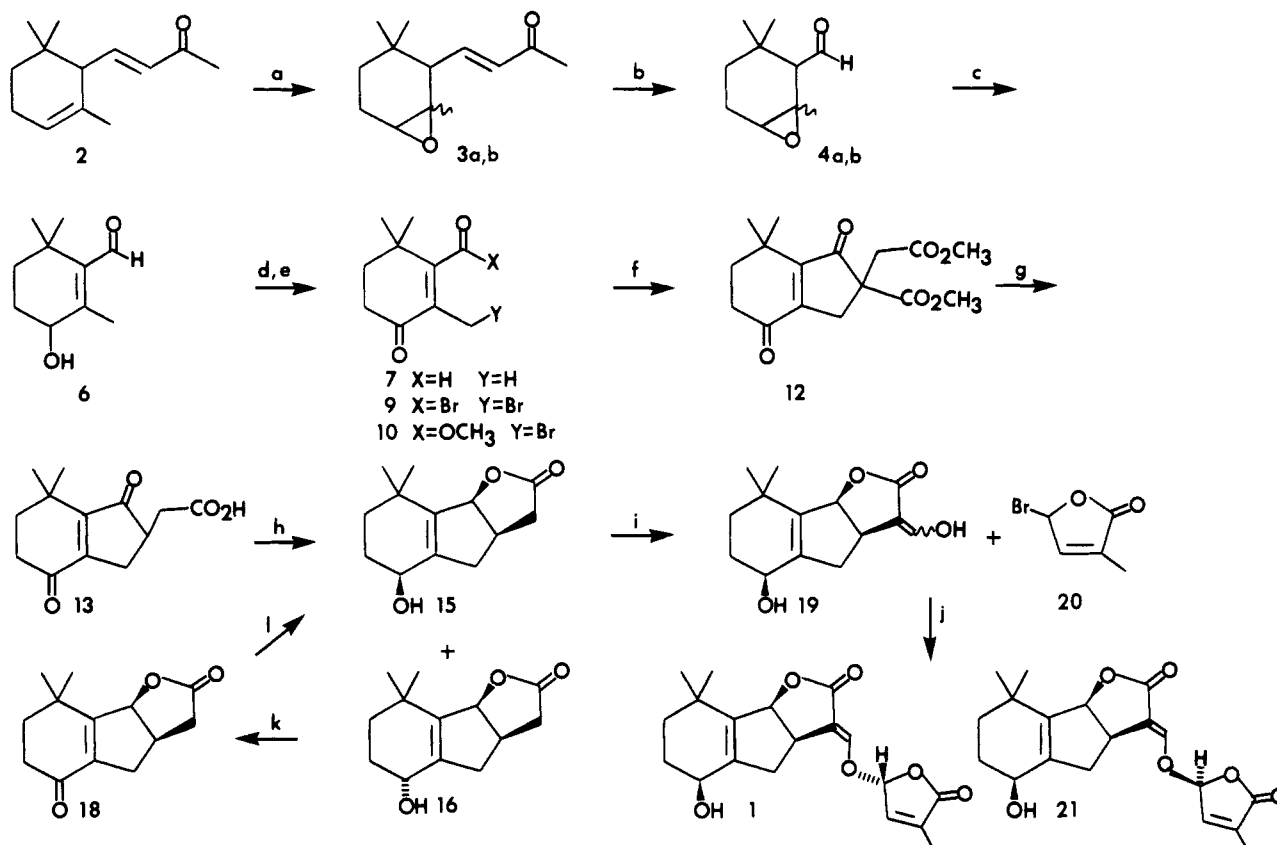
In summary, a total synthesis of (±)-strigol has been accomplished in 10 steps and 4.4% overall yield from α-ionone or 12 steps and 6.8% overall yield if recycling of **16** is considered. The synthesis proceeds with a minimum of purification steps and one chromatographic separation necessary at the final step to separate (±)-strigol and (±)-4'-epistrigol. The methods and reagents used are amenable to scale-up and thus the capability to make multigram amounts of (±)-strigol for field testing is now

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Scheme II^a

^a (a) $\text{CH}_3\text{CO}_2\text{H}$, $\text{CH}_3\text{CO}_2\text{H}$, 0 °C, 94%; (b) (i) O_3 , CH_3OH , -78 °C, (ii) Zn , $\text{CH}_3\text{CO}_2\text{H}$, -30 to 25 °C, 86%; (c) pyrrolidine, ether, 25 °C, 90%; (d) Jones' reagent;¹⁷ (e) (i) NBS, CCl_4 , 70 °C, (ii) CH_3OH , 0 °C, 83%; (f) (i) NaH , $\text{CH}_2(\text{CO}_2\text{CH}_3)_2$, THF, -10 to 25 °C, (ii) $\text{BrCH}_2\text{CO}_2\text{CH}_3$, 25 °C, 82%; (g) 6 N HCl, $\text{CH}_3\text{CO}_2\text{H}$, 100 °C, 64%; (h) $\text{CeCl}_3(\text{H}_2\text{O})_7$, NaBH_4 , 0 °C, 75% 15 and 16 (1:1); (i) NaH , EtOCHO , ether, 25 °C, 93%; (j) K_2CO_3 , NMP, 25 °C, 39% 21 and 35% 1; (k) PCC, CH_2Cl_2 , 25 °C, 74%; (l) $\text{CeCl}_3(\text{H}_2\text{O})_7$, NaBH_4 , 0 °C, 76% 15.

available. The synthetic scheme also allows efficient access to many analogues of the A-, AB-, ABC-, ABCD-ring, or other combination structures for evaluation of structure-activity relationships.

Experimental Section

General Methods. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F-254 plates (0.25 mm) and visualized with a *p*-anisaldehyde solution (1350 mL of ethanol, 50 mL of concentrated H_2SO_4 , 15 mL of glacial acetic acid, 37 mL of *p*-anisaldehyde) followed by heating. Solvents were evaporated on a Buchi Rotovapor R110 at aspirator pressure (ca. 20 mm). Infrared (IR) spectra were recorded on a Perkin-Elmer 710B spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer R-32 and Nicolet 470 for proton spectra and a Varian XL-200 for carbon spectra using deuteriochloroform as solvent and reporting chemical shifts in parts per million (δ) downfield relative to tetramethylsilane. Mass spectra were obtained via electron impact (EI, 70 eV) or chemical ionization (CI, CH_4) using a Finnigan 4121 GC-MS spectrometer. Several compounds have been previously prepared by different methods, which are referenced after the compound name. The spectral data acquired in this study were consistent with previously reported data, and only pertinent additional spectral data are included.

4-(2,6,6-Trimethyl-2,3-epoxycyclohexan-1-yl)-3-buten-2-one (3a,b).^{3d} α -Ionone (90% tech, 100 g, 0.52 mol) was added dropwise to a stirred solution of 30% peracetic acid (270 mL, 2 mol) in acetic acid at 0 °C containing sodium acetate (8 g, 0.1 mol). After 3 h the excess peracetic acid was quenched with 20% aqueous Na_2SO_3 (200 mL), and the reaction mixture was neutralized with 20% aqueous NaOH and extracted with dichloromethane (2 \times 300 mL). The organic extract was washed with saturated aqueous NaHCO_3 , water, and saturated aqueous NaCl and dried over Na_2SO_4 .

Filtration and evaporation of the solvent at reduced pressure gave 101 g (94%) of an isomeric mixture of 3a and 3b (9:1) as a colorless oil.

2,3-Epoxy-2,6,6-trimethylcyclohexane-1-carboxaldehyde (4a,b).⁹ A solution of 3a,b (101 g, 0.49 mol) in methanol (930 mL) at -78 °C under nitrogen was treated with excess ozone (ozonized oxygen was generated by a Wellsbach Model T-23 ozonizer operating at an oxygen pressure of 8 psi and a flow rate of 0.015 ft³/min and bubbled into the reaction mixture for 8 h). The excess ozone (blue color) was removed by introducing a stream of nitrogen into the reaction mixture. The reaction mixture was cooled at -30 °C, zinc (52 g, 0.8 mol) was added, and with stirring a solution of 50% aqueous acetic acid (200 mL) was added dropwise over 1 h (the reduction is exothermic!) and then the mixture was allowed to warm gradually to room temperature over 1 h. Filtration of the zinc and evaporation of the methanol gave a liquid residue, which was dissolved in water (2.5 L) and extracted with dichloromethane (3 \times 400 mL). The organic extract was washed with saturated aqueous NaHCO_3 , water, and saturated aqueous NaCl and dried over MgSO_4 . Filtration and evaporation of the solvent at reduced pressure gave a clear yellow oil, which was purified by vacuum distillation (bp 55–61 °C, 0.2–0.3 mm) to give 63.1 g (86%) of 4a,b.

3-Hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxaldehyde (6)⁹ was prepared according to the procedure in ref 9.

3-Oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxaldehyde (7).⁹ Jones' reagent¹⁶ (34 mL) was added dropwise to a stirred solution of 6 (20 g, 0.12 mol) in degassed acetone (160 mL) under nitrogen at 0 °C. After the mixture was stirred for 15 min, the excess oxidant was destroyed by addition of isopropyl alcohol. Water (100 mL) was added and the acetone was evaporated. The residue was extracted with ethyl acetate (3 \times 50 mL), and the combined extracts were washed with 5% aqueous Na_2CO_3 and saturated aqueous NaCl, dried over MgSO_4 , and filtered, and the solvent was evaporated at reduced pressure to give 17.4 g (88%) of 7,

which was used immediately in the next transformation.

Methyl 3-(Bromoethyl)-6,6-dimethyl-3-oxocyclohex-1-ene-1-carboxylate (10).⁹ A mixture of **7** (17.3 g, 0.10 mol) and *N*-bromosuccinimide (37.2 g, 0.21 mol) dissolved in carbon tetrachloride (350 mL) was heated at 70 °C under a nitrogen atmosphere with illumination of a 275-W tungsten lamp. After 3 h, the reaction mixture was cooled to 0 °C and methanol (100 mL) was added with stirring. After 6 h, the solvents were removed under reduced pressure. Carbon tetrachloride (100 mL) was added to the residue and the mixture was filtered. The solids were washed with carbon tetrachloride (2 × 25 mL), and the combined filtrate was concentrated by evaporation of the solvent to give 30 g (100%) of **10**. This material was used directly in the next reaction. Purification of the product of a smaller scale reaction by chromatography (silica gel, 10–30% ethyl acetate in hexane) gave pure **10** in 83% yield.

1,4-Dioxo-7,7-dimethyl-4,5,6,7-tetrahydro-2-indanacetic Acid (13).⁹ A 60% oil dispersion of sodium hydride (10.9 g, 0.27 mol) was washed twice with dry hexane under nitrogen, and then tetrahydrofuran (500 mL) was added, the mixture was cooled to -10 °C, and a solution of dimethyl malonate (15.8 g, 0.12 mol) in tetrahydrofuran (50 mL) was added dropwise. After stirring for 10 min, a solution of bromo ester **10** (30 g, 0.10 mol) in tetrahydrofuran (50 mL) was added dropwise. After the addition, the cooling bath was removed and stirring was continued at room temperature for 24 h; then methyl bromoacetate (15.4 mL, 0.163 mol) was added dropwise and the mixture was stirred for an additional 48 h. Water (200 mL) was added and the mixture was extracted with ether (3 × 100 mL). The combined ether extracts were washed with 5% aqueous Na₂CO₃ (50 mL), water, and saturated aqueous NaCl, dried over MgSO₄, and filtered, and the solvent was evaporated to give 31.1 g of crude diester **17**, which was used directly in the next reaction. A smaller scale run from 4.4 g of **10** gave an 82% yield of pure **12** after chromatography (silica gel, 10–30% ethyl acetate in hexane). **12**: ¹H NMR (90 MHz) δ 1.33 (s, 6), 1.97 (t, *J* = 7 Hz, 2), 2.5–2.7 (m, 2), 3.0–3.2 (m, 2), 3.67 (s, 3), 3.70 (s, 3), 3.79 (s, 2); ¹³C NMR (50 MHz) δ 24.68 (CH₃), 24.99 (CH₃), 32.13 (C), 34.31 (CH₂), 35.11 (CH₂), 37.80 (CH₂), 37.92 (CH₂), 51.78 (CH₃), 52.93 (CH₃), 56.00 (C), 156.32 (C=), 156.66 (C=), 169.61 (C=O), 170.58 (C=O), 198.52 (C=O), 204.08 (C=O).

A mixture of crude **12** (15 g, 0.049 mol) in glacial acetic acid and 6 N HCl (75 mL, 1:1) was heated under nitrogen, and over 3 h solvent was removed by slow distillation (methanol formed). After the mixture was cooled to room temperature, water was added (400 mL) and the mixture was extracted with ethyl acetate (4 × 100 mL). The combined organic extracts were washed with water (50 mL) and saturated aqueous NaCl, and the solvents were evaporated to give 11.1 g (97%) of crude acid **13** as a red residue, which was used directly in the next reaction.

The residue could be purified by dissolving it in a minimum amount of hot ether and leaving this to crystallize overnight to give **13** as pale yellow crystals. The filtrate was evaporated and dissolved in a minimum amount of dichloromethane and then added to a small neutral alumina column, eluted first with dichloromethane to remove impurities, and the desired acid was eluted with 2% acetic acid in methanol. Evaporation of the solvent from this fraction and recrystallization from ether gave a further crop of crystals resulting in a total yield of 64%. **13**: mp 136–137 °C; ¹H NMR (90 MHz) δ 1.35 (s, 3), 1.37 (s, 3), 2.00 (t, *J* = 6.8 Hz, 2), 2.4–3.1 (m, 7), 9.24 (br, 1); ¹³C NMR (50 MHz) δ 24.98 (CH₃), 25.42 (CH₃), 29.21 (CH₂), 32.20 (C), 34.50 (CH₂), 35.33 (CH₂), 38.21 (CH₂), 42.12 (CH), 156.29 (C=), 158.27 (C=), 177.27 (C=O), 199.34 (C=O), 209.77 (C=O).

Methyl 1,4-Dioxo-7,7-dimethyl-4,5,6,7-tetrahydro-2-indanacetate (14). A mixture of **12** (0.62 g, 2 mmol) and lithium chloride (0.14 g) in *N*-methylpyrrolidone (10 mL) containing water (1 mmol) was stirred at 120–125 °C for 6 h. The reaction mixture was poured into water (100 mL), acidified with 2 N HCl, and extracted with ether (3 × 30 mL). The ether extracts were combined and washed with water and saturated aqueous NaCl, dried over MgSO₄, and filtered, and the solvent was evaporated. The residue was chromatographed (silica gel, 10–30% ethyl acetate in hexane) to give 0.35 g (70%) of pure **14** as an oil. **14**: ¹H NMR (90 MHz) δ 1.32 (s, 6), 1.92 (t, *J* = 6.8 Hz, 2), 2.4–3.1 (m, 7), 3.65 (s, 3); ¹³C NMR (50 MHz) δ 25.00 (CH₃), 25.42 (CH₃), 29.18 (CH₂),

32.18 (C), 34.18 (CH₂), 35.35 (CH₂), 38.24 (CH₂), 42.37 (CH), 51.84 (CH₃), 156.24 (C=), 158.17 (C=), 171.85 (C=O), 199.15 (C=O), 209.92 (C=O).

1,4-Dihydroxy-7,7-dimethyl-4,5,6,7-tetrahydroindan-2-acetic Acid Lactones (15 and 16).⁹ A stirred suspension of crude diketo acid **13** (11 g, 0.047 mol) in water (500 mL) was neutralized with 1 N NaOH (55 mL) and then a solution of CeCl₃(H₂O)₇ (17.4 g, 0.047 mol) in water (50 mL) was added. To the suspension was added dichloromethane (200 mL), and the solution was cooled to 0 °C. An aqueous solution of NaBH₄ (10.6 g, 0.28 mol), in 50 mL of H₂O was added dropwise. After 2 h, 6 N HCl was carefully added dropwise (to destroy the excess NaBH₄) until the mixture became clear (pH 1). The two-phase mixture was separated, and the aqueous layer was extracted further with dichloromethane (3 × 150 mL). The combined organic extracts were washed with water (200 mL) and saturated aqueous NaCl, dried over MgSO₄, and filtered, and the solvent was evaporated under reduced pressure to give 6.7 g of crude product. Purification by flash chromatography (silica gel, ether) gave 3.8 g (37%) of a mixture of pure isomers **15** and **16** (1:1). Note that this yield represents an overall yield from **6** since no intermediate compounds were purified. The isomers could be separated by chromatography (silica gel, 10% dichloromethane in ether) or the desired isomer **15** could be selectively recrystallized from an ether solution of the mixture.

A smaller scale reduction of pure diketo acid **13** (10 mmol) gave the isomers **15** and **16** (1:1) in 75% combined yield after purification by chromatography (silica gel, 10% dichloromethane in ether). **15**: mp 142–144 °C; ¹H NMR (90 MHz) δ 1.09 (s, 3), 1.16 (s, 3), 1.4–3.2 (m, 9), 4.23 (t, *J* = 5.2 Hz, 1), 5.6 (d, *J* = 7.6 Hz, 1); ¹³C NMR (50 MHz) δ 27.38 (CH₃), 27.48 (CH₃), 29.54 (CH₂), 32.25 (C), 34.48 (CH), 35.84 (CH₂), 36.77 (CH₂), 38.49 (CH₂), 66.93 (CH), 89.76 (CH), 141.08 (C=), 142.49 (C=), 177.40 (C=O). **16**: ¹H NMR (90 MHz) δ 1.08 (s, 3), 1.12 (s, 3), 1.3–3.2 (m, 9), 4.16 (t, *J* = 5.0 Hz, 1), 5.49 (d, *J* = 7 Hz, 1).

1-Hydroxy-4-oxo-7,7-dimethyl-4,5,6,7-tetrahydroindan-2-acetic Acid Lactone (18). To a stirred suspension of pyridinium chlorochromate (3.87 g, 18 mmol) in dichloromethane (25 mL) was added a solution of **16** (2.66 g, 12 mmol) in dichloromethane (10 mL). After 2 h, ether (75 mL) was added and the mixture was stirred for 1 h and then filtered through Celite, and the solids were washed with ether. Evaporation of the solvent gave 1.98 g (74%) of **18**, which was used directly in the next reaction. Purification could be effected by recrystallization from ether. **18**: IR (Nujol) cm⁻¹, 1775 (C=O), 1676 (C=O); ¹H NMR (470 MHz) δ 1.26 (s, 3), 1.28 (s, 3), 1.8–2.0 (m, 2), 2.2–2.6 (m, 4), 2.7–2.9 (m, 2), 3.15 (m, 1), 5.63 (d, *J* = 7.6 Hz, 1); ¹³C NMR (50 MHz), δ 25.78 (CH₃), 26.36 (CH₃), 33.13 (C), 34.11 (CH), 34.83 (CH₂), 35.01 (CH₂), 35.18 (CH₂), 38.58 (CH₂), 88.82 (CH), 160.42 (C=), 162.56 (C=), 176.03 (C=O), 197.76 (C=O).

Reduction of Keto Lactone 18. To a stirred solution of **18** (0.66 g, 3 mmol) in ethanol (20 mL) was added CeCl₃(H₂O)₇ (1.12 g, 3 mmol) followed by addition of NaBH₄ (0.114 g, 3 mmol). After 1 h, the mixture was quenched by dropwise addition of 1 N HCl to pH 1 and then the solvents were evaporated. The residue was partitioned between water (20 mL) and dichloromethane (30 mL), the phases were separated, and the aqueous phase was further extracted with dichloromethane (30 mL). The combined organic extract was washed with aqueous saturated NaCl, dried over MgSO₄, and filtered, and the solvents were evaporated to give 0.63 g of crude product. Recrystallization from ether gave 0.51 g (76%) of the desired hydroxy lactone **15**.

(±)-Strigol (1) and (±)-4'-Epistrigol (21).⁹ To a stirred solution of NaH (0.63 g, 60% in oil, 15.8 mmol, washed with dry hexane before use) in ether (30 mL) at 25 °C under nitrogen was added dropwise a solution of hydroxy lactone **15** (1.17 g, 5.27 mmol) in ether (10 mL) followed by ethyl formate (5 mL). After 24 h the mixture was acidified with 1 N HCl and extracted with ethyl acetate (3 × 25 mL). The organic extract was washed with water (25 mL) and aqueous saturated NaCl (25 mL), dried over MgSO₄, and filtered, and the solvent was evaporated at reduced pressure to give 1.23 g (93%) of **19** as a pale yellow solid. This product could be used directly in the next step without further purification.

To a stirred solution of hydroxymethylene lactone **19** (1.23 g, 4.92 mmol) and anhydrous K₂CO₃ (1.38 g), in dry *N*-methyl-

pyrrolidone (25 mL) under nitrogen at 25 °C was added bromobutenolide **20** (1.57 g, 8.9 mmol). After 24 h the mixture was poured into 1 N HCl (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with water (50 mL) and saturated aqueous NaCl, dried over MgSO₄, and filtered, and the solvent was evaporated at reduced pressure to give 2.18 g of crude product. Chromatography (silica gel, gradient elution with dichloromethane to 30% ethyl acetate in dichloromethane gave first 0.66 g (39%) of (±)-4'-epistrigol (**21**) as a white solid and then 0.60 g (35%) of (±)-strigol (**1**) as a white solid.

(±)-Strigol (**1**): mp 202–205 °C (ethyl acetate–hexane); ¹H NMR (470 MHz) δ 1.09 (s, 3), 1.16 (s, 3), 1.44 (dt, *J* = 12.4, 2.5 Hz, 1), 1.56 (ddd, *J* = 12.4, 6.7, 2.8 Hz, 1), 1.68 (m, 1), 1.78 (br, 1, OH), 1.98 (m, 1), 2.01 (br s, 3), 2.70 (m, 2), 3.64 (m, 1), 4.11 (br t, *J* = 6.49 Hz, 1), 5.50 (br d, *J* = 7.84 Hz, 1), 6.16 (br s, 1), 6.93 (br s, 1), 7.45 (d, *J* = 2.29 Hz, 1); ¹³C NMR (50 MHz) δ 10.73 (CH₃), 27.53 (CH₃), 27.65 (CH₃), 29.69 (CH₂), 32.37 (C), 36.63 (CH), 36.96 (CH₂), 37.86 (CH₂), 67.28 (CH), 88.00 (CH), 100.65 (CH), 113.65 (C=), 135.73 (C=), 141.15 (CH=), 142.41 (C=), 142.66 (C=), 150.72 (CH=), 170.38 (C=O), 171.54 (C=O).

(±)-4'-Epistrigol (**21**): mp 178–180 °C (ethyl acetate–hexane); ¹H NMR (470 MHz) δ 1.08 (s, 3), 1.15 (s, 3), 1.44 (dt, *J* = 12.5, 2.6 Hz, 1), 1.55 (ddd, *J* = 12.5, 6.7, 2.9 Hz, 1), 1.67 (m, 1), 1.77

(br, 1, OH), 1.98 (m, 1), 2.01 (t, *J* = 1.2 Hz, 3), 2.69 (m, 2), 3.63 (m, 1), 4.08 (br t, *J* = 6.59 Hz, 1), 5.50 (br d, *J* = 7.94 Hz, 1), 6.16 (t, *J* = 1.2 Hz, 1), 6.93 (t, *J* = 1.2 Hz, 1), 7.44 (d, *J* = 2.5 Hz, 1); ¹³C NMR δ 10.73 (CH₃), 27.56 (CH₃), 27.65 (CH₃), 29.63 (CH₂), 32.35 (C), 36.57 (CH), 37.04 (CH₂), 37.96 (CH₂), 69.24 (CH), 88.04 (CH), 100.47 (CH), 113.75 (C=), 135.82 (C=), 141.18 (CH=), 142.17 (C=), 142.92 (C=), 150.40 (CH=), 170.32 (C=O), 171.57 (C=O).

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Registry No. **1**, 51820-11-2; **2**, 127-41-3; **3** (isomer I), 84107-27-7; **3** (isomer II), 84107-28-8; **4** (isomer I), 94425-37-3; **4** (isomer II), 94425-38-4; **5** (isomer I), 84057-28-3; **5** (isomer II), 84107-29-9; **6**, 60078-92-4; **7**, 18378-66-0; **8**, 51823-74-6; **9**, 94348-18-2; **10**, 51799-97-4; **11a**, 60078-95-7; **12**, 94348-19-3; **13**, 59488-99-2; **14**, 61343-45-1; **15**, 51800-01-2; **16**, 51820-15-6; **17** (isomer I), 94348-20-6; **17** (isomer II), 94348-21-7; **18**, 59518-85-3; **19**, 94480-17-8; **20**, 59488-94-7; **21**, 52389-58-9; dimethyl malonate, 108-59-8; methyl bromoacetate, 96-32-2; ethyl formate, 109-94-4.

Synthetic Approach to the Amphilectane Diterpenes: The Use of Nitriles as Terminators of Carbocation–Olefin Cyclizations

Robert V. Stevens[†] and Kim F. Albizati*¹

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

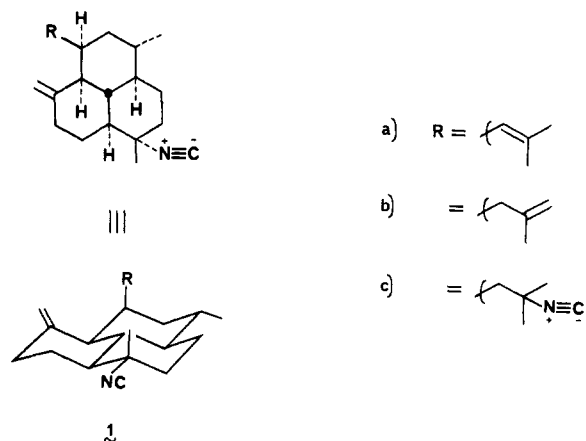
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A biomimetic approach to the synthesis of tricyclic terpenoid isonitriles from marine sponges is described which involves carbocation–olefin cyclization of polyolefinic precursors terminated by the stereoselective formation of a carbon–nitrogen bond. The key intermediate **8** was produced in racemic and optically pure form and was subjected to a cuprate addition–aldol trapping sequence to produce the olefinic substrates **15–17**. Cyclization of **16** and **17** was successful utilizing mercury(II) nitrate in nitrile solvents to produce bicyclic amides **28–33** after reductive cleavage of the carbon–mercury bond. Transformation of the mercuri halide group in the intermediate organomercurial amides **37** and **40** to several types of functionality provided potential intermediates for the synthesis of amphilectane diterpenes.

Carbocation–olefin cyclization provides the means to introduce or transform functionality while simultaneously forming carbon–carbon and carbon–heteroatom bonds in a stereocontrolled fashion.^{2,3} A major thrust in this area has been the formulation of new initiators and terminators of the cyclization process, thus expanding the functionalization aspect of the transformation. While oxygen nucleophiles have been used very successfully in this regard, nitrogen nucleophiles as terminators are rare,⁴ despite their obvious potential for the synthesis of nitrogenous heterocycles. We wish to describe our findings in this area within the context of our work in the field of marine natural products synthesis.

The amphilectane diterpenes are a group of nine tri- and tetracyclic isonitrile-containing metabolites isolated from the tropical marine sponges *Hymeniacidon amphilecta* and an unidentified *Adocia* species.⁵ Three of the compounds possess the common structure **1** differing only in the four-carbon side chain at C-1. In general, the metabolites display in vitro antimicrobial activity and “in

vivo...marked toxicity”.^{5a} Our desire was to synthesize **1a–c**



in optically pure form by combining the concepts of the

[†] Deceased March 9, 1984.

(1) Current address The Scripps Institution of Oceanography, La Jolla, CA.