Sesquiterpene Synthesis. Studies Relating to the Synthesis of (±)-Dugesialactone

P. A. Zoretic,*† J. L. Ferrari, C. Bhakta, F. Barcelos, and B. Branchaud

Department of Chemistry, Southeastern Masschusetts University, North Dartmouth, Massachusetts 02747

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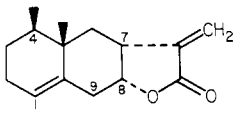
Racemic 1, the structure previously proposed for dugesialactone, was synthesized and was shown not to correspond to natural dugesialactone.

Recently Bohlmann and Zdero[1] reported the isolation of a new sesquiterpene, dugesialactone, from *Dugesia mexicana* Gray. The structure of dugesialactone, based on NMR studies, was deduced to be 1. It has also been postulated that the ring juncture stereochemistry depicted in 1 appears to be an exception to that found in sesquiterpene lactones isolated from higher plants on the basis of biogenetic considerations.[2] Natural compounds containing an α-methylene-γ-butyrolactone moiety have become of interest, since they possess considerable biological activity as antitumor agents,[3] allergenic agents,[4] growth inhibitors,[5] and antibacterial agents.[6] Herein we report our unambiguous synthesis of 1, which was found not to be identical with natural dugesialactone.[7] The synthesis of the key synthon 6, which contains the necessary functionality for further elaboration into 1, is outlined in Scheme I.



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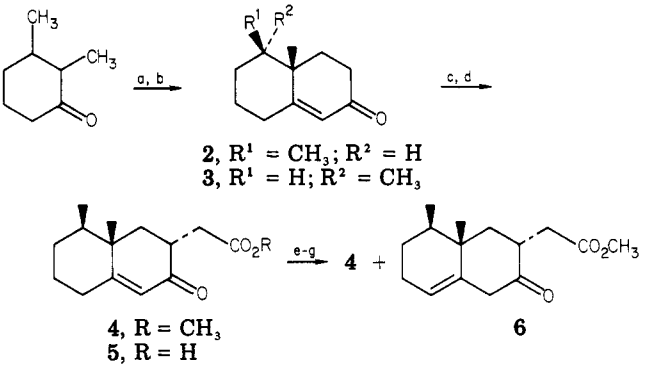
Reaction[8] of 2,3-dimethylcyclohexanone and methyl vinyl ketone in the presence of sulfuric acid[9,10] in benzene at 0–5 °C and subsequent cyclization with sodium methoxide[11] afforded a 33% yield of octalones 2 and 3 in a ratio ≥9:1 as determined by ^{13}C NMR analysis. The necessary two-carbon extension to eventually form the lactone moiety was introduced at this stage via a kinetic enolate-alkylation reaction.[12,13] Treatment of octalones 2 and 3 with 1.1 equiv of LDA in THF at −78 °C and concomitant alkylation with methyl bromoacetate in the presence of HMPA afforded a 74% yield of essentially pure ester 4 contaminated with a small amount of the trans isomer. Subsequent saponification and recrystallization of the resulting acids afforded pure keto acid 5 [mp 126.5–127 °C (lit.[14] mp 127.5–128 °C)]. Deconjugation of the α,β double bond to the β,γ isomer was effected through a dianion reaction. Thus, reaction of keto acid 5 with 6.5 equiv of potassium *tert*-butoxide[15] in *tert*-butyl alcohol at room temperature, subsequent acidification with a 0.15 M Na_2HPO_4 solution,[15,16] and esterification of the resulting acids with base-free diazomethane in ether afforded a 96% yield of an isomeric mixture of the β,γ-olefinic keto ester 6 and the α,β-olefinic keto ester 4 in an 80:20 ratio as determined by NMR analysis.

Hydride reduction (Scheme II) of the 80:20 mixture of keto esters with L-Selectride in THF at −78 °C followed by acidification and subsequent chromatography afforded the cis lactone 7 as the minor component and the isomeric cis lactone 8 (85%, mp 103.5–104.5 °C) as the major product. Irradiation of the vinyl proton in 7 caused the apparent triplet at δ 4.65 to collapse to a doublet at δ 4.65 ($J_{7,8}$ = 5 Hz). Likewise, irradiation of the C-9 protons in

Scheme I[a]



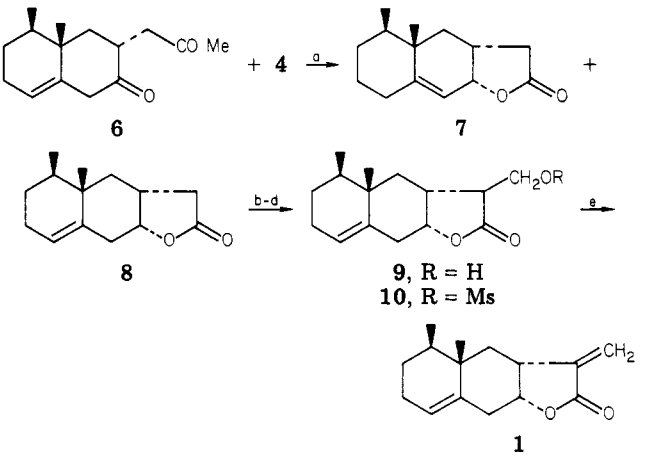
2, $R^1 = CH_3$; $R^2 = H$
3, $R^1 = H$; $R^2 = CH_3$

4, R = CH_3
5, R = H

6

[a] (a) MVK, PhH, H_2SO_4, 0–5 °C; (b) NaOMe, MeOH; (c) 1.1 equiv of LDA, THF, −78 °C, then $BrCH_2CO_2Me$, HMPA (−78 °C to room temp); (d) aqueous NaOH–MeOH, then H^+; (e) 6.5 equiv of *t*-BuOK, *t*-BuOH; (f) 0.15 M Na_2HPO_4; (g) CH_2N_2.

Scheme II[a]



6 7

8

9, R = H
10, R = Ms

1

[a] (a) $LiB(CHMeC_2H_5)_3H$, THF, −78 °C; (b) LDA, THF, −78 °C; (c) HCHO (gas), −20 °C; (d) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0–5 °C; (e) DBU, PhH, room temperature.

† To whom correspondence should be addressed at the Department of Chemistry, East Carolina University, Greenville, NC 27834.

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(7) After comparing synthetic 1 with natural dugesialactone via ^1H NMR studies at 270 MHz, Professor Bohlmann has concluded that the stereochemistry in the natural compound should be trans rather than cis (private communication, F. Bohlmann).

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8 caused the apparent quartet at δ 4.52 to collapse to a doublet at δ 4.52 with $J_{7,8}$ = ~5 Hz. The coupling constants are indicative of the assigned cis ring juncture stereochemistry in 7 and 8, respectively.

Reaction of 8 with LDA at −78 °C and subsequent trapping of the resulting enolate with gaseous formaldehyde[17] gave a 76% yield of the α-hydroxymethylene lactone 9 (mp 133–135.5 °C). Treatment of 9 with methanesulfonyl chloride in methylene chloride between −5 and −10 °C in the presence of triethylamine afforded a quantitative yield of mesylate 10 (mp 89.5–90 °C). Subsequent reaction of 10 and DBU in benzene at room temperature followed by chromatography afforded a 78% yield of pure[7] 1 [mp 95.5–96.2 °C; NMR (PhD_6) δ 3.70–4.05 (m, CHOCO, unresolved)]. Irradiation of the C-9 hydrogens in 1 caused the unresolved multiplet at δ 3.70–4.05 to collapse to a doublet at δ 3.93 ($J_{7,8}$ = 4–5 Hz). This coupling constant is in excellent agreement with the assigned cis ring juncture stereochemistry in 1.

Currently we are exploring the application of the described synthetic methodology to related terpenoids and to the possible synthesis of some of the stereoisomers of 1.

Experimental Section

Methyl (2β,8α,8aα)-α-(1,5,6,7,8,8a-Hexahydro-8,8a-dimethyl-3(2*H*)-oxonaphthyl)acetate (4). Diisopropylamine (2.0 g, 19.9 mmol) in 15 mL of dry THF was cooled to 0 °C. A hexane solution of 2.3 M *n*-BuLi (8.65 mL, 19.9 mmol) was added with a syringe under N_2; the reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. A mixture (≥9:1) of octalones 2 and 3 (2.96 g, 16.6 mmol) in 20 mL of dry THF containing HMPA (3.56 g, 19.9 mmol) was added over a 30-min period and the reaction mixture was stirred at −78 °C for an additional 30 min. Methyl bromoacetate (2.54 g, 16.6 mmol) in 10 mL of dry THF was added dropwise over a 10-min period and the reaction mixture was stirred at −78 °C for 3 h and then at room temperature for 3 days. The reaction mixture was poured into an aqueous HCl solution (380 mL of H_2O and 120 mL of 10% HCl) and extracted with three 300-mL portions of ether. The organic solution was washed with two 150-mL portions of H_2O, dried ($MgSO_4$), and concentrated in vacuo, giving an oil. The oil was chromatographed on silica gel G, and elution with ether–hexane solutions afforded (3.1 g, 74%) of essentially pure ester 4 containing a small amount of the trans isomer: NMR (CCl_4) δ 5.61 (s, 1 H), 3.66 (s, 3 H), 1.22 (s, 3 H, angular methyl), 0.96 (m, 3 H, unresolved); IR (neat) 1665, 1740 cm^{-1}.

(2β,8α,8aα)-α-(1,5,6,7,8,8a-Hexahydro-8,8a-dimethyl-3-(2*H*)-oxonaphthyl)acetic Acid (5). A sodium hydroxide solution (12.3 g, 0.307 mol) in 40 mL of H_2O and 4-(dimethylamino)pyridine (5.3 g, 0.043 mol) were added to the octalone esters 2 and 3 (12.9 g, 0.052 mol) in 40 mL of methanol, and the resulting reaction mixture was stirred at room temperature for 5 days. The reaction mixture was poured into 225 mL of water and extracted with three 150-mL portions of ether. The aqueous solution was then acidified with HCl, extracted with three 200-mL portions of CH_2Cl_2, dried ($MgSO_4$), and concentrated in vacuo, giving 10 g of a semisolid. Chromatography on silica gel and elution with ether–hexane solutions afforded 8.0 g (66%) of a mixture of acids enriched with acid 5. Recrystallization from ethyl acetate afforded 4.4 g (36%) of pure 5: mp 126.5–127 °C (lit.[13] mp 127.5–128 °C).

Methyl (2β,8α,8aα)-α-(1,2,6,7,8,8a-Hexahydro-8,8a-dimethyl-3(4*H*)-oxonaphthyl)acetate (6). Potassium *tert*-butoxide (2.96 g, 26.4 mmol) in 30 mL of *tert*-butyl alcohol was deaerated with N_2. Acid 5 (0.94 g, 3.98 mmol) in 25 mL of *t*-BuOH (deaerated with N_2) was added and stirring was continued at room temperature for 1.5 h. The reaction mixture was added dropwise to 380 mL of a 0.15 M NaH_2PO_4 solution with stirring. The resulting reaction mixture was extracted with four 200-mL portions of ether. The organic solution was dried ($MgSO_4$) and concentrated in vacuo (apply very little heat) to approximately 200 mL. The resulting ether solution was cooled to 0 °C and base-free CH_2N_2 was added dropwise with stirring until a yellow color persisted. The reaction mixture was diluted with 250 mL of ether, washed with two 50-mL portions of H_2O, dried ($MgSO_4$), and concentrated in vacuo at 15 mm and then at 0.01 mm for 1 h to afford (0.90 g, 96%) of an 80:20 mixture of 6 and 4 as determined by NMR analysis: NMR ($CDCl_3$) δ 5.62 (s), 5.15–5.40 (m), 3.61 (s), 1.20 (s, angular methyl), 0.96 (m, second methyl unresolved). The isomeric ketones were not characterized further but were subjected directly to hydride reduction.

(3aβ,4aα,5α,9aβ)-3a,4,4a,5,6,7,8,8a,9a-Octahydro-4a,5-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (7) and (3aβ,4aα,5α,9aβ)-3a,4,4a,5,6,7,9,9a-Octahydro-4a,5-dimethylnaphtho[2,3-*b*]furan-2(3*H*)-one (8). The 80:20 ratio of esters 6 and 4 (900 mg, 3.6 mmol) in 10 mL of dry THF was cooled to −78 °C and a THF solution of 1 M L-Selectride (3.78 mL, 3.78 mmol) was added dropwise via syringe over a 10-min period. The reaction was stirred at −78 °C for an additional 1.7 h and then methanol (8 mL) was added; and stirring was continued for 5 min. The reaction mixture was diluted with 60 mL of ether; 40 mL of 10% HCl was added and the heterogeneous mixture was shaken for 15 min. The organic layer was separated and the aqueous solution was extracted with two 100-mL portions of ether. The combined organic solution was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo, giving an oil. Chromatography on silica gel G and elution with ether–hexane solutions gave 60 mg of 7 [NMR ($CDCl_3$) δ 5.53 (d), 4.65 (apparent t), 0.96 (s, angular methyl), 0.93 (m, second methyl unresolved); irradiation of the vinyl proton at δ 5.53 caused the apparent triplet at δ 4.65 to collapse to a doublet at δ 4.65 ($J_{7,8}$ = 5 Hz)] and 538 mg (85%) of 8 [mp 103.5–104.5 °C; NMR ($CDCl_3$) δ 5.43–5.51 (m), 4.52 (apparent q), 0.94 (s), 0.91 (m, second methyl unresolved); irradiation of the C-9 protons caused the apparent quartet at δ 4.52 to collapse to a doublet at δ 4.52 ($J_{7,8}$ = ~5 Hz; IR (KBr) 1760 cm^{-1}].

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.34.

(3α,3aβ,4aα,5α,9aβ)-3a,4,4a,5,6,7,9,9a-Octahydro-4a,5-dimethyl-3-(hydroxymethyl)naphtho[2,3-*b*]furan-2(3*H*)-one (9). Diisopropylamine (0.155 g, 1.53 mmol) in 3 mL of dry THF was cooled to 0 °C. A hexane solution of 2.45 M *n*-butyllithium (0.625 mL, 1.53 mmol) was added via a syringe under N_2; the reaction mixture was stirred for an additional 20 min and then cooled to −78 °C. Lactone 8 (280 mg, 1.27 mmol) in 4 mL of dry THF was added dropwise via a syringe over a 30-min period and stirring was continued at −78 °C for 30 min. The reaction mixture was then allowed to warm to −20 °C and was stirred at −20 °C for 20 min. Gaseous formaldehyde [generated from paraformaldehyde (1.1 g) at 150 °C] was passed into the reaction mixture via a N_2 stream over a 2-h period. The reaction mixture was diluted with 40 mL of ether, extracted with brine, dried ($MgSO_4$), and concentrated in vacuo, giving an oil. Chromatography of the oil on silica gel G and elution with ether–hexane solutions gave (240 mg, 76%) of 9: mp 133–135.5 °C; NMR ($CDCl_3$) δ 5.25–5.62 (m, 1 H), 4.58–4.95 (m, 1 H), 3.65–4.11 (m, 2 H); IR (KBr) 3560 (s), 3400 (br), 1775 cm^{-1}.

(3α,3aβ,4aα,5α,9aβ)-3a,4,4a,5,6,7,9,9a-Octahydro-4a,5-dimethyl-3-[((methylsulfonyl)oxy)methyl]naphtho[2,3-*b*]-

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furan-2(3*H*)-one (10). Dry triethylamine (107 mg, 0.147 mL, 1.05 mmol) was added via a syringe to alcohol **9** (220 mg, 0.88 mol) in 3.7 mL of CH_2Cl_2 at −5 °C to −10 °C under N_2 with stirring. The reaction mixture was stirred for 5 min and methanesulfonyl chloride (111 mg, 0.075 mL, 0.97 mmol) was added dropwise via a syringe over a 10-min period. The reaction mixture was stirred between 0 and −10 °C for 2.75 h, diluted with 100 mL of CH_2Cl_2, and washed with 15 mL of cold H_2O, 20 mL of 10% HCl, 20 mL of 10% $NaHCO_3$, and 15 mL of brine. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford a quantitative yield of **10**: mp 89.5–90 °C; NMR ($CDCl_3$) δ 5.30–5.58 (m, 1 H), 4.59–4.92 (m, 1 H, CHOCO, unresolved), 4.42 (d, 2 H), 3.06 (s, 3 H); IR (KBr) 1765, 1340, 1360 cm^{-1}.

(3aβ,4aα,5α,9aβ)-3a,4a,5,6,7,9,9a-Octahydro-4a,5-dimethyl-3-methylenenaphtho[2,3-*b*]furan-2(3*H*)-one (1). DBU (0.191 g, 0.188 mL, 1.26 mmol) was added via a syringe over a 10-min period to sulfonate **10** (330 mg, 1.01 mol) in 4.5 mL of dry benzene under N_2 with stirring at room temperature. The reaction mixture was stirred for 3 h and then diluted with 150 mL of ether. The organic solution was washed with 10 mL of cold H_2O, 15 mL of cold 10% HCl, and 10 mL of cold brine, dried ($MgSO_4$), and concentrated in vacuo, giving an oil. Chromatography on silica gel G and elution with hexanes and ether–hexane solutions afforded (183 mg, 78%) of **1**: mp 95.5–96.2 °C; NMR (PhD_6) δ 6.01 (d, 1 H, J = ~1 Hz, H-13), 5.10–5.40 (m, 1 H, H-1), 4.96 (d, 1 H, J = 1 Hz, H-13), 3.70–4.05 (m, 1 H), 2.10–2.60 (m), 1.65–2.0 (m), 0.85–1.60 (m, 5 H), 0.67 (d, J = 6 Hz), 0.63 (s, 6 H); irradiation of the C-7 and C-9 hydrogens caused the multiplet at δ 3.70–4.05 to collapse to a singlet at δ 3.93; irradiation of the C-9 hydrogens caused the multiplet at δ 3.70–4.05 to collapse to a doublet at δ 3.93 ($J_{7,8}$ = 4–5 Hz); IR (CH_2Cl_2) 1770 cm^{-1}; mass spectrum m/e 232 (M), 217, 190, 145, 119, 105, 91, 79.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.79; H, 8.58.

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Registry No. (±)-**1**, 80656-02-6; (±)-**2**, 20536-80-5; (±)-**3**, 20536-77-0; (±)-**4**, 80594-80-5; (±)-**5**, 33118-42-2; (±)-**6**, 80594-81-6; (±)-**7**, 80594-82-7; (±)-**8**, 80594-83-8; (±)-**9**, 80594-84-9; (±)-**10**, 80594-85-0.

Synthesis of Chiral Dipeptides by means of Asymmetric Hydrogenation of Dehydro Dipeptides

Iwao Ojima,* Tetsuo Kogure, Noriko Yoda, Tadashi Suzuki, Momoko Yatabe, and Toshiyuki Tanaka

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

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Asymmetric hydrogenation of various dehydro dipeptides was carried out by using rhodium complex catalysts with a variety of chiral diphosphine ligands. The efficiency of chiral diphosphine ligands as well as the effect of the chiral center in the substrate on the catalytic asymmetric induction was studied. It was found that extremely high stereoselectivities for producing the *S,S*, *R,S*, *S,R*, or *R,R* isomer were achieved with the proper choice of chiral ligands although a considerably large double asymmetric induction was observed in some cases. Pyrrolidinodiphosphines, e.g., Ph-CAPP, *p*-BrPh-CAPP, BPPM, CBZ-Phe-PPM, and diPAMP, exhibited excellent stereoselectivities, whereas chiraphos, prophos, and BPPFA only gave poor results especially for the reaction of *N*-acyldehydro dipeptide which had a free carboxylic acid terminus. Stereoselective dideuteration was also successfully performed.

It is well-known that the general methods for the formation of peptide linkage are based on the coupling of two optically active amino acid components by using, e.g., the acyl chloride method, the acyl azide method, the mixed anhydride method, the carbodiimide method, and the enzyme method. These methods have been developed for the synthesis of naturally occurring polypeptides with minimum racemization.

Recently, it has been shown that significant modification of biological activities can be effected through inversion of configuration at one or more chiral centers or through replacement of one or more "natural" amino acid residue(s), by "unnatural" amino acid components in a biologically active polypeptide such as enkephalin, vasopressin, angiotensin II, gonadoliberin, and other hormones.[1] As an approach to the synthesis of chiral olgio- and polypeptides with desired structures, it is important to develop a facile device which gives a chiral building block for peptide synthesis other than the simple preparation of "unnatural" amino acids. As precursors of modified peptides, dehydro peptides are interesting candidates since catalytic asymmetric hydrogenation, in principle, can convert the dehydro amino acid residue into the amino acid residue with either *R* or *S* configuration. In this context, the asymmetric hydrogenation of dehydro dipeptides giving chiral dipeptides is a significant model reaction. We reported the preliminary results on the asymmetric synthesis of dipeptides by means of asymmetric hydrogenation catalyzed by chiral rhodium complexes in 1980,[2] and in the same year Kagan et al.,[3] and Onuma et al.[4] also reported similar results independently. Now, we will describe here a full account of our research on this approach to the synthesis of chiral dipeptides.

Results and Discussion

As the homogeneous asymmetric hydrogenation of dehydro-α-amino acids catalyzed by rhodium complexes with chiral diphosphine ligands has turned out to be quite effective for the synthesis of chiral α-amino acids,[5] it would

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