Total Synthesis of the Marine Sesquiterpenoid Raikovenal through a Novel Utilization of the Bicyclo[3.2.0]heptenone Approach

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Introduction

In 1994, Pietra and co-workers[1] isolated from the marine ciliate *Euplotes raikovi* Amagaliev, stock Morl, collected along Atlantic coasts near Casablanca, the architecturally unusual sesquiterpenoid **1** termed raikovenal and its putative biogenetic precursor (preraikovenal). The structure and relative stereochemistry of **1** were deduced on the basis of extensive NMR studies. The main part of the molecular array is the bicyclo[3.2.0]-heptane core with the five-carbon side chain, the hydroxylated α,β-unsaturated aldehyde, in a strictly defined geometric setting.

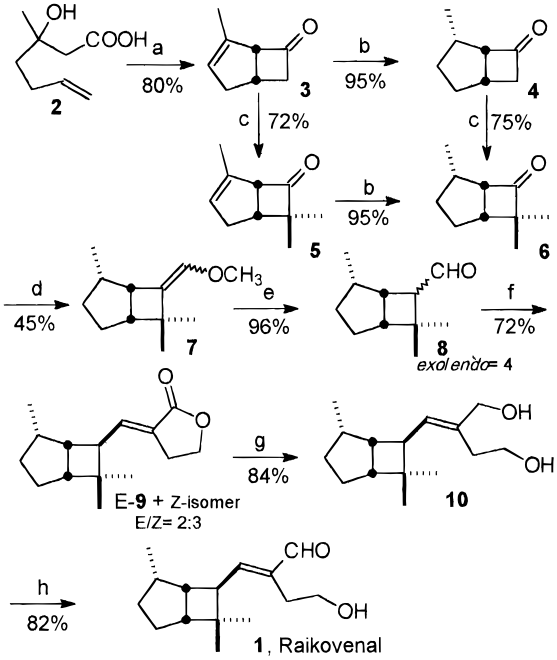
Whereas the effectiveness of raikovenal in favoring adaptive radiation of marine ciliate *E. raikovi* was clearly demonstrated,[1] no synthesis of this interesting marine natural product has been reported until now.

Recently, an efficient approach to the stereoselective synthesis of natural products based on the practical preparation and selective utilization of bicyclo[3.2.0]hept-3-en-6-ones[2,3] has been devised and developed in our laboratories. In this paper we present (Scheme 1) the stereoselective synthesis of racemic raikovenal through the application of this bicyclization methodology.

Results and Discussion

Our synthetic approach starts with 4-methylbicyclo-[3.2.0]hept-3-en-6-one (**3**), easily available in nearly 80% yield by the intramolecular bicyclization of 3-hydroxy-3-methyl-6-heptenoic acid.[3,4] The palladium-catalyzed hydrogenation of compound **3** followed by bismethylation of the C7 gave the 4-*endo*-7,7-trimethylbicyclic derivative **6** in 71% yield. Alternatively, compound **6** can be obtained by palladium-catalyzed hydrogenation of filifolone[5,6] (4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-one, **5**)

Scheme 1. The Total Synthesis of Marine Sesquiterpenoid Raikovenal through the Bicyclo[3.2.0]heptenone Approach



a: Ac_2O, AcOK, Δ, H_2O. b: H_2 (3 atm), Pd(C). c: NaH, THF, MeI. d: (i) Me_3SiCH_2OMe, *sec*-BuLi, THF; (ii) $SOCl_2$, Py, THF. e: HCO_2H. f: α-Diethylphosphonate-γ-butyrolactone, LiCl, DBU, THF. g: DIBAH, Et_2O, -70°C. h: MnO_2, CH_2Cl_2, 0°C.

which can be prepared by bismethylation of **3**.[2] It is relevant to point out that racemic 4-methylbicyclo[3.2.0]-hept-3-en-6-one (**3**) as well as racemic filifolone (**5**) have been efficiently resolved into their enantiomerically pure forms,[7] thus allowing this strategy to be applicable to the synthesis of both enantiomers of raikovenal.

Carbonyl homologation of **6** to obtain the aldehyde **8** was revealed to be the crucial step of our synthetic sequence. This conversion was achieved by reaction at low temperature of the bicyclic ketone **6** with the in-situ generated (methoxy(trimethylsilyl)methyl)lithium[8] (MT-MSMLi, Magnus reagent) followed by treatment of the diastereoisomeric β-alkoxysilane intermediates with thionyl chloride and pyridine. The diastereoisomeric enol ethers **7** were isolated in only a 45% yield and almost quantitatively converted into a mixture of bicyclic aldehydes **8** (*exo*/*endo* = 4:1) by hydrolysis with formic acid. The low yield of the carbonyl homologation can be ascribed to two concomitant factors: the hampering effect

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(5) Filifolone (4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-one), the first monoterpene reported to have the bicyclo[3.2.0]heptane ring, was isolated always in scalemic mixtures: D-filifolone from the Australian plant *Zieria smithii* Andrews, and L-filifolone in the Arizonan sage *Artemisia filifolia* Torrey: Torrance, S. J.; Steelink, C. *J. Org. Chem.* **1974**, *39*, 1068.

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of the geminal methyls on the carbon adjacent to the carbonyl group that amplify the hindrance due to the wedge shape of the bicyclic compound, and the tendency of the intermediates to undergo fragmentations and rearrangements through the formation of unstable tertiary carbon ions.

We chose the Horner−Wadsworth-Emmons[9] (HWE) modification introduced by Masamune, Roush et al.[10] to perform the olefination of the aldehydes **8** with the γ-butyrolactone residue to complete the building of the raikovenal skeleton. This modification has been depicted as particularly useful in reactions with aldehydes or phosphonates that can undergo epimerization or aldol-type reactions under standard conditions to furnish products with a high (*E*)-selectivity. Actually, when the mixture of the aldehydes **8** was treated with γ-butyrolactone-α-diethylphosphonate[11] in tetrahydrofuran in the presence of LiCl and DBU we obtained the (*E*)-**9** and (*Z*)-**9** isomers (71% yield, *E*/*Z* = 2:3), both with the *exo*-disposition on the bicyclo[3.2.0]heptane system. This fact indicated the absence of (*E*)-selectivity of the reaction and that the epimerization of the *endo*-aldehyde took place in the presence of DBU. Any attempt to increase the (*E*)/(*Z*) ratio was unsuccessful. The use of acetonitrile, recommended in the original paper as solvent, furnished lower yields and almost the same (*E*)/(*Z*) ratio.

The two isomers **9** were easily separated by flash column chromatography. The DIBAH reduction of each compound, performed at −70 °C, revealed that only the (*E*)-isomer undergoes reduction and that, instead of the corresponding lactol, the diol **10** is obtained in 84% yield. In the same reaction conditions, as well as at higher temperature, the (*Z*)-**9** isomer was always recovered unchanged. This fact makes it possible to perform the reduction with DIBAH directly on the mixture of (*E*)-**9** and (*Z*)-**9**, it being more convenient to isolate the diol **10** from the lactone (*Z*)-**9** by flash column chromatography. To minimize the drawback of the low yield of the homologation, the latter could, in principle, be recycled to the aldehyde **8** by an oxidative cleavage of the carbon−carbon double bond. The synthesis was completed with the selective MnO_2 oxidation of the allylic hydroxy group of **10** that furnished (82% yield) racemic raikovenal (**1**) as an oil with the same physical chemical and spectroscopic properties recorded on the natural product and reported in the literature.[1]

Conclusion

We have accomplished the first stereoselective total synthesis of racemic raikovenal taking advantage from a practical preparation of the mainframework of this marine natural sesquiterpenoid: the bicyclo[3.2.0]heptane structure. The availability of enantiomerically pure forms of compound **3** as well as of filifolone (**5**) make this procedure a formal EPC synthesis[12] of both enantiomers of raikovenal.

Experimental Section

General. Melting points were obtained with a Büchi apparatus and are uncorrected. Yields refer to isolated products. Proton and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, in $CDCl_3$ solvent. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in hertz. Signal multiplicities were established by DEPT experiments. Flash chromatographic separations were performed using Merck silica gel 60 (70−230 mesh ASTM). For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. All solvents were dried and purified by standard methods prior to use. Reactions involving alkyllithiums and DIBAH were run under argon or nitrogen. Compounds **3** and **5** were prepared following the procedures already reported.[3,4]

4-*endo*-Methylbicyclo[3.2.0]heptan-6-one (4). Palladium on carbon (10%, 1.82 g) was added to a solution of the bicyclic ketone **3** (7 g, 57.4 mmol) in ethyl acetate (30 mL) at room temperature. The reaction vessel was evacuated by aspirator and thoroughly purged with hydrogen (three times), and the resulting heterogeneous mixture was stirred under hydrogen at 3 atm. The reaction mixture was monitored by TLC analysis (petroleum ether: dichloromethane 3:2) using vanillin reagent[13] to test the progress of the reaction. After 3 h, the hydrogen was evacuated, the catalyst filtered off on Celite, and the filtrate concentrated under reduced pressure to give the crude product **4** (6.73 g, 95%) as a colorless oil. IR (liquid film): ν 2935, 2864, 1768 cm^{-1}. ^1H NMR: δ 3.49−3.30 (m, 1H), 3.13 (ddd, J = 4.8; J = 9.0; J = 18.2, 1H), 2.92−2.73 (m, 1H), 2.50 (ddd, J = 1.1; J = 3.4; J = 18.2, 1H), 2.21−2.02 (m, 2H), 2.01−1.73 (m, 2H), 1.51−1.30 (m, 1H),1.13 (d, J = 6.8, 3H). ^{13}C NMR: δ 213.8, 69.52, 60.79, 52.05, 39.71, 33.40, 29.84, 15.83. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.42; H, 9.79.

4-*endo*-7,7-Trimethylbicyclo[3.2.0]heptan-6-one (6). The bismethylation of bicyclic ketone **4** was performed according to the synthetic protocol previously described.[3] A solution of bicyclic ketone **4** (9.00 g, 72.5 mmol) dissolved in THF (50 mL) was slowly added at room temperature to a suspension of NaH (4.35 g, 182 mmol, 2.5 equiv) in THF (100 mL) containing MeI (18.1 mL, 290 mmol, 4 equiv), and the mixture was stirred overnight. During the first hour, the evolution of hydrogen was observed and the increase in temperature to 40 °C was controlled with a water bath. The color of the reaction mixture turned to brown, and after 1 h a white product began to precipitate. The reaction was monitored by GC and TLC (petroleum ether/diethyl ether 9:1) as eluant. After 12 h, the reaction was stopped by adding diethyl ether (250 mL) and water (50 mL). The organic layer was washed with water (3 × 30 mL) and dried (Na_2SO_4). The solvent was evaporated at ambient pressure, and the residue was purified by distillation to give pure **6** (8.27 g, 75%) as a pale yellow oil: bp (kugelrohr) = 145 °C/15 mmHg. IR (liquid film): ν 2954, 2866, 1764 cm^{-1}. ^1H NMR: δ 3.54 (dd, J = 1.1, J = 7.6, 1H), 2.46 (dd, J = 1.1, J = 7.7, 1H), 2.18−1.92 (m, 1H), 1.91−1.76 (m, 2H), 1.75−1.61 (m, 2H), 1.18 (s, 3H), 1.17 (d, J = 6.7, 3H), 0.94 (s, 3H). ^{13}C NMR: δ 221.2, 65.44, 59.03, 43.20, 38.83, 35.43, 28.20, 26.02, 15.61, 15.32. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.93; H, 10.53.

Preparation of 4-*endo*-7,7-Trimethylbicyclo[3.2.0]heptan-6-one (6) by Hydrogenation of Filifolone (5). The title compound **6** was prepared by hydrogenation of filifolone (**5**) according to the typical procedure described before for the hydrogenation of compound **3**. Filifolone (7.0 g, 46.6 mmol) was dissolved in ethyl acetate (30 mL), and palladium on carbon (10%, 1.8 g) was added. The reaction with hydrogen was performed at 3 atm and gave the pure ketone **6** (6.73 g, 95%). All the spectroscopic data are in agreement with those reported before.

(*E*)- and (*Z*)-6-(Methoxymethylidene)-4-*endo*-7,7-trimethylbicyclo[3.2.0]heptane (7). (Methoxymethyl)trimethylsilane (6.1 mL, 39.5 mmol) in dry THF (30 mL) was cooled to −78 °C, and *sec*-butyllithium (30.4 mL, 39.5 mmol, 1.3 M in hexanes) was slowly added. The mixture was warmed at −25 °C and held

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at this temperature for 1.5 h to complete formation of (methoxy-(trimethylsilyl)methyl)lithium.[8] The above pale yellow solution was cooled to −35 °C, and the bicyclic ketone **6** (3.0 g, 19.70 mmol) was added. The mixture was slowly allowed to warm to 25 °C over 2 h, dry pyridine (4.7 mL, 60.0 mmol) was added, the resulting mixture was cooled to 0 °C, and thionyl chloride (2.9 mL, 39.5 mmol) dissolved in THF (10 mL) was slowly added. The deep brown mixture was allowed to react at room temperature and under magnetic stirring for 16 h, diethyl ether (150 mL) was added, and the mixture was quenched with saturated aqueous ammonium chloride (2 × 20 mL), water (3 × 30 mL), and saturated aqueous sodium chloride solution (2 × 20 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give (1.69 g, 45%) a mixture of (*E*)- and (*Z*)-**7** (*E*:*Z* = 3:2) as an oil. Spectra were recorded on a sample of the isomeric mixture. ^{1}H NMR: δ 5.76 and 5.56 (two singlets, 1:3 ratio for (*Z*) and (*E*) isomers, 3H), 3.47 and 3.45 (two singlets, 3:1 ratio for (*E*) and (*Z*) isomers, 3H), 3.13 (dd, J = 1.0, J = 7.5, 1H), 2.21 (dd, J = 0.9, J = 7.6, 1H), 1.97−1.31 (m, 5H), 1.20 and 1.17 (two singlets, 1:3 ratio for the (*Z*) and (*E*) isomers, 3H), 1.08 (s, 3H), 1.03 (d, J = 6.5, 3H). ^{13}C NMR: (*E*)-isomer: δ 140.0, 126.7, 59.58, 47.48, 44.26, 40.02, 37.48, 34.33, 29.56, 27.81, 19.55, 15.04. (*Z*)-isomer: δ 137.2, 127.6, 59.08, 48.11, 45.88, 41.43, 38.83, 34.98, 32.94, 27,62, 20,83, 16,38. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.01; H, 11.08.

4-*endo*-7,7-Trimethylbicyclo[3.2.0]heptane-6-carbaldehyde (8). The mixture of enol ethers (*E*)- and (*Z*)-**7** (1.10 g, 6.1 mmol) was stirred with 90% formic acid (10 mL) at room temperature for 1 h. The mixture was poured into a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 30 mL), dried (Na_2SO_4), and filtered. Evaporation of the residue gave the aldehyde **8** (0.97 g, 96%) as a 4:1 mixture of the *exo* and *endo* isomers at C6. IR (liquid film): ν 2947, 2862, 1707 cm^{-1}. ^{1}H NMR: δ 10.8 and 9.78 (two d: d, J = 6.0, *endo* and d, J = 1.8, *exo*, 1H), 3.00 (m, 1H), 2.69 and 2.49 (two dd: dd, J = 6.0, J = 10.1, *endo* and dd, J = 1.7, J = 7.5, *exo*, 1H), 2.14 (dd, J = 7.9, J = 8.4, 1H), 1.97−1.41 (m, 6H), 1.14 (s, 3H), 1.06 (s, *exo*) and 1.04 (s, *endo*)(two singlets, 3H), 0.82 (d, J = 6.4, 3H). ^{13}C NMR: *exo* isomer: δ 204.9, 53.32, 48.08, 47.42, 39.00, 36.54, 34.32, 27.44, 27.22, 24.68, 14.08; *endo* isomer: δ 206.3, 56.22, 48.08, 46.56, 38.68, 36.18, 34.56, 28.31, 27.22, 24.83, 14.56. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.38; H, 19.87.

(1α,4*β*,5α,6α,*E*)- and (1α,4*β*,5α,6α,*Z*)-2-[(4,7,7-Trimethylbicyclo[3.2.0]hept-6-yl)methylidene]butyrolactone (9). To a suspension of LiCl (0.30 g, 7.0 mmol) in dry THF (25 mL), stirred under nitrogen at room temperature, were added γ-butyrolactone-α-diethylphosphonate[11] (1.54 g, (6.94 mmol), DBU (0.66 g, 4.33 mmol), and finally the aldehyde **8** (0.48 g, 2.9 mmol). The progress of the reaction was followed by TLC and judged completed after 16 h. The reaction mixture was diluted with diethyl ether (50 mL) and quenched with water (20 mL). The usual workup provided compound **9** (0.480 g, 71%) as a mixture of (*E*) and (*Z*) isomers (*Z*/*E* = 1.5), separated by flash column chromatography (petroleum ether/diethyl ether 4:1) to obtain the two isomers as solids. (*Z*)-**9**: mp 84−86 °C; IR (KBr): ν 2930, 2867, 1737, 1654, 1169, 1084, 1024 cm^{-1}. ^{1}H NMR: δ 6.30 (td, J = 2.2, J = 10.9, 1H), 4.29 (t, J = 7.4, 2H), 3.77 (dd, J = 7.0, J = 11.0, 1H), 2.91 (m, 2H), 2.37 (q, J = 6.7, 1H), 2.18 (t, J = 7.7, 1H), 1.95−1.29 (m, 5H), 1.06 (s, 3H), 0.90 (s, 3H), 0.87 (d, J = 6.4, 3H). ^{13}C NMR: δ 170.2(s), 146.7(d), 122.8(s), 65.48(t), 47.10(d), 46.37(d), 39.38(s), 38.65(d), 37.34(d), 34.47(t), 29.73(t), 27.58(q), 27.37(t), 24.36(q), 14.01(q). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.80; H, 9.41. (*E*)-**9**: mp 99−101 °C; IR (KBr): ν 2948, 2862, 1745, 1660, 1185, 1023 cm^{-1}. ^{1}H NMR: δ 6.82 (td, J = 2.8, J = 10.4, 1H), 4.36 (t, J = 7.5, 2H), 2.84 (tdd, J = 2.5, J = 2.5, J = 7.4, 2H), 2.54 (m, 1H), 2.34−2.17 (m, 2H), 1.98−1.17 (m, 5H), 1.09 (s, 3H), 0.90 (s, 3H), 0.85 (d, J = 6.3). ^{13}C NMR: δ 171.1 (s), 143.2 (d), 124.4 (s), 65.73 (t), 47.02 (d), 45.53 (d), 43.32 (d), 39.01 (s), 36.68 (d), 34.57 (t), 27.77 (q), 27.27 (t), 25.91 (t), 24.93 (q), 14.37 (q). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.40.

(1α,4*β*,5α,6α,*E*)-2-[(4,7,7-Trimethylbicyclo[3.2.0]hept-6-yl)methylidene]butane-1,4-diol (10). A solution of DIBAH (1 M, 5.5 mL, 5.5 mmol) in *n*-hexane diluted with dried diethyl ether (20 mL) was added to a stirred solution of (*E*)-**9** (0.260 g, 1.10 mmol) dissolved in diethyl ether (20 mL) at −70 °C. Stirring was continued for 2 h. Then water was added, and the stirred mixture was allowed to warm to 0 °C. A solution of HCl (10%) was added until the aluminates were completely dissolved. The organic phase was washed again with the HCl solution, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to obtain the diol **10** (0.222 g, 84%) as a white solid: mp 66−68 °C. IR (KBr): ν 3430, 2944, 1283 cm^{-1}. ^{1}H NMR: δ 5.55 (d, J = 9.3, 1H), 4.02 (s, 2H), 3.88−3.65 (m, 2H), 2.47−2.25 (m, 3H), 2.14 (dd, J = 0.8, J = 7.5, 1H), 1.89−1.65 (m, 3H), 1.55−1.30 (m, 3H), 1.10 (s, 3H), 0.85 (s, 3H), 0.83 (d, J = 4.7, 3H). ^{13}C NMR: δ 135.8 (s), 133.7 (d), 68.68 (t), 62.40 (t), 46.61 (d), 46.24 (d), 39.62 (d), 37.51 (s), 36.76 (d), 34.38 (t), 32.84 (t), 27.02 (q), 26.92 (t), 23.95 (q), 14.00 (q). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.63; H, 10.85.

(1α,4*β*,5α,6α,*E*)-4-Hydroxy-2-[(4,7,7-trimethylbicyclo[3.2.0]-hept-6-yl)methylidene]butanal (1, raikovenal). The diol **10** (0.220 g, 0.92 mmol) was dissolved in dichloromethane (10 mL), and the solution was cooled to 0 °C with an ice bath before adding MnO_2 (1.0 g) under magnetic stirring. After 2 h at 0 °C, the temperature was allowed to rise at room temperature. The progress of the reaction was monitored by TLC (petroleum ether/diethyl ether 2:3) and was judged complete after 20 h. The mixture was filtered on Celite, and the dichloromethane was evaporated under reduced pressure to give pure raikovenal (0.180 g, 82%) as an oil. IR (liquid film): ν 3414, 2950, 2865, 1764, 1625, 1146 cm^{-1}. ^{1}H NMR: δ 9.40 (s, 1H), 6.64 (d, J = 10.5, 1H), 3.60 (t, J = 6.7, 2H), 2.64 (dd, J = 6.6, J = 10.4, 1H), 2.61−2.27 (m, 3H), 2.26−2.21 (dd, J = 0.6, J = 7.7, 1H), 1.90−1.58 (m, 3H); 1.62−1.31 (m, 3H), 1.10 (s, 3H), 0.93 (s, 3H), 0.84 (d, J = 6,5, 3H). ^{13}C NMR: δ 196.1 (d), 159.8 (d), 139.6 (s), 61.79 (t), 46.75 (d), 45.69 (d), 41.11 (d), 38.91 (s), 36.76 (d), 34.20 (t), 28.29 (t), 27.21 (q), 26.91 (t), 24.08 (q), 13.84 (q). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.12; H, 10.21.

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