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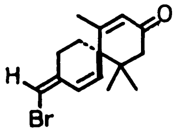
TOTAL SYNTHESIS OF (±)-(Z)-9-(BROMOMETHYLENE)-1,5,5-TRIMETHYLSPIRO[5.5]UNDECA-1,7-DIEN-3-ONE, A BROMINATED SESQUITERPENE OF CHAMIGRANE TYPE

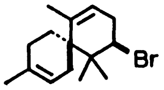
Haruki NIWA, Yoshifumi YOSHIDA, Takashi HASEGAWA, and Kiyoyuki YAMADA*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464

The first total synthesis of (±)-(Z)-9-(bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one, a chamigrane sesquiterpene having a novel bromomethylene group is described.

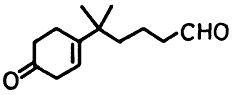
A number of halogenated sesquiterpenes of chamigrane type have been isolated from the red algae of the genus Laurencia.[1)] Nevertheless, the synthetic studies on these halogenated sesquiterpenes are very limited and only 10-bromo-α-chamigrene has so far been synthesized.[2)] In this communication, we wish to report a total synthesis of another brominated sesquiterpene of chamigrane type, (Z)-9-(bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one (1) isolated from Laurencia majuscula HARVEY by Suzuki and Kurosawa,[3)] in racemic form.



1



10-bromo-α-chamigrene



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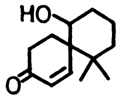
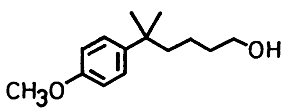


3

One of the key steps in the present synthesis is a spiroannelation of a cyclohexenone aldehyde 2 into the spiro[5.5]undecenone derivative 3.[4)] The preparation of 2 started from anisole. The Friedel-Crafts reaction[5)] of anisole with 5-methyl-1,5-hexanediol[6,7)] ($AlCl_3$, 0 °C for 3 h and then room temp for 20 h) gave the desired para alkylation product 4,[7)] bp 114-115 °C (0.1 mmHg) (99%[8)]). Birch reduction of 4 (Li-t-BuOH-liq. NH_3, ether) and subsequent hydrolysis of the resulting enol ether [$(CO_2H)_2$, H_2O-DME, room temp, 25 h] gave the cyclohexenone alcohol 5[7)] (colorless oil, 68% from 4). Swern oxidation[9)] of 5 [DMSO-$(COCl)_2$-Et_3N, CH_2Cl_2, -60 °C to room temp, 20 min] afforded the desired aldehyde 2[7)] (colorless oil, 75%).

The spiroannelation of 2 was effected on treatment with 6 M HCl-DME (1:10) (reflux, 1 h) to produce a ca. 5:1 mixture of the desired spiro enone 3 and the side product 6 (97% combined yield), which could not be separated chromatographically. The mixture of 3 and 6 was oxidized directly with PCC[10)] (CH_2Cl_2, room temp, 2 h) to yield the spiro diketone 7[7)] (colorless oil, 73% from 2) and the tricyclic diketone 8[7)] (mp 78.5-80.0 °C, 14% from 2). The site specific reaction of 7 with dibromomethyllithium[11)] (THF, -78 °C, 10 min) afforded a single adduct 9[7,12)] (mp 153-156 °C, 98%). Reduction of 9 with Zn-AcOH[13)] (CH_2Cl_2, room temp, 2 h) provided an inseparable 1:1 mixture of the bromomethylene ketones, (Z)-10 and (E)-10 (70%), which was reacted with methyllithium (THF, -78 °C, 1 h) to give the



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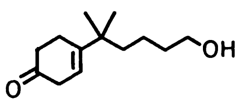

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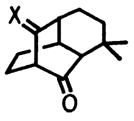
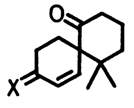


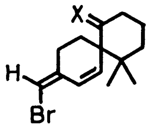
6 X =$<^{\mathrm{H}}_{\mathrm{OH}}$

8 X = O



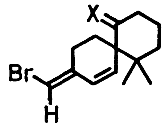
7 X = O

9 X =$<^{\mathrm{OH}}_{\mathrm{CHBr_2}}$



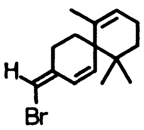
(Z)-10 X = O

(Z)-11 X =$<^{\mathrm{OH}}_{\mathrm{CH_3}}$

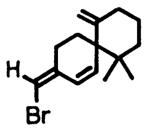


(E)-10 X = O

(E)-11 X =$<^{\mathrm{OH}}_{\mathrm{CH_3}}$



endo-12



exo-12

(Z)-bromomethylene alcohol (Z)-11[7,12,14] (colorless oil, 46%) and the (E)-isomer (E)-11[7,12,14] (colorless oil, 47%). Dehydration of (Z)-11 was performed with $SOCl_2$-pyridine (toluene, -78 °C, 20 min) to give a 3:1 mixture of the olefins, endo-12 and exo-12 (99% combined yield).[15] Finally, the mixture of endo-12 and exo-12 was oxidized with 3,5-dimethylpyrazole-CrO_3 complex[16] (CH_2Cl_2, -20 °C to -10 °C, 1 h) to give (±)-1[7] [colorless oil, 30% from (Z)-11]. The spectral properties (IR and ^{1}H NMR) of the synthetic 1 were completely identical with those of the natural 1.

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4) K. Yamada, M. Aratani, Y. Hayakawa, H. Nakamura, H. Nagase, and Y. Hirata, J. Org. Chem., 36, 3653 (1971).
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6) This diol was easily prepared from δ-valerolactone by reaction with CH_3MgI (ether, reflux, 4 h) in 55% yield after distillation [bp 95-97 °C (1.5 mmHg)].
7) Satisfactory spectral (IR, ^{1}H NMR, and mass) and analytical (microanalyses or high resolution mass spectra) data were obtained for this compound.
8) All yields refer to the materials purified by silica gel column chromatography.
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12) Stereochemistry of the hydroxyl group of this compound was not determined.
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14) Stereochemistry of the two isomers, (Z)-11 and (E)-11 was assigned by converting the former isomer to the natural 1 in racemic form, which was previously proved to have the Z-configuration as to the bromomethylene group.[3]
15) Isolation of endo-12 in pure form failed owing to partial isomerization of the bromomethylene group (Z→E) during separation. Thus, the final oxidation was performed without separation of the mixture of endo-12 and exo-12.
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