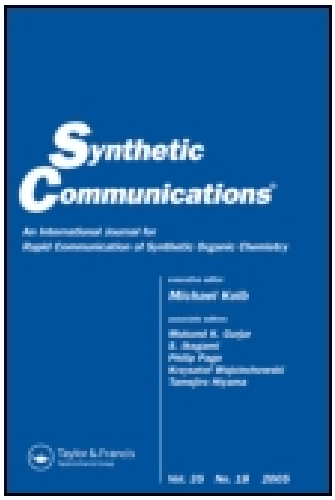

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# A CONVENIENT PREPARATION OF 1,2,3,4,5,6,7,8-OCTAHYDRO-NAPHTHALENE SKELETON. SYNTHESIS OF (±)-ISOCARIDIENE

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## ABSTRACT

Synthesis of isocaridiene, an isomeric compound of natural sesquiterpene caridiene, is described starting from myrcene. Dehydration of tertiary alcohol leading exclusively to isocaridiene was in agreement with the semiempirical and ab initio quantum mechanical calculations.

Caridiene (**1**)[1] is a new sesquiterpene isolated from *Pseudoterogorgonia americana*, a gorgonian collected in Havana, Cuba, whose structure was determined through careful analysis of its spectroscopic data. The occurrence of natural products having 1,2,3,4,5,6,7,8-octahydronaphthalene moiety as part of the molecule is becoming frequent nowadays, such as in

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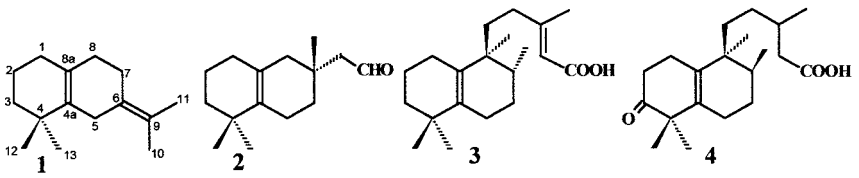
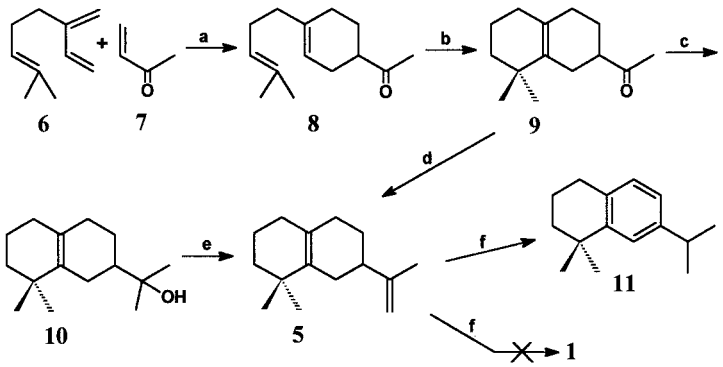
nanaimoal (**2**)[2,3] *ent*-halima-5(10), 13E-dien-15-oic acid (**3**),[4] salmantic acid (**4**),[5] and many others.




Continuing our interest in the synthesis of marine sesquiterpenoid,[6] we would like to describe here a straightforward synthesis of isocaridiene (**5**), an isomeric compound of **1**. The Diels-Alder reaction of myrcene (**6**) with methyl vinyl ketone (**7**) using $Me_2AlCl$ supported on silica gel as catalyst,[7] gave exclusively a known *para*-adduct **8**[8] in 72% yield (Scheme 1).




**a**. $(CH_3)_2AlCl$, Toluene (72%); **b**. HCOOH 99% (85%); **c**. $CH_3MgI$, $Et_2O$ (77%);
**d**. $CH_3P^+Ph_3Br^-$, *n*-BuLi, $Et_2O$ (70%); **e**. $POCl_3$, Py (78%); **f**. TsOH, Bz (55%)

***Scheme 1.***

Refluxing **8** in formic acid at 60°C for 8 h afforded a bicyclic methyl ketone **9** in 85%. The chemical shift of dimethyl group at C-4 appeared as a singlet at δ 0.98 and 0.99, and the methyl ketone as a singlet at δ 2.18. The $^{13}C$ NMR spectra showed 14 signals, two of them corresponding to tetra-substituted $sp^2$ carbon at δ 133.6 and 127.2, and a carbonyl carbon at δ 212.7. Treatment of **9** with methyl magnesium iodide furnished, as

expected, alcohol **10** in 77% yield. The IR spectra of **10** showed absorption at 3384 $cm^{-1}$ (ν O-H), and $^1$H NMR spectra showed two singlets at δ 0.97 and 0.99 corresponding to two methyl groups at C-4, and one singlet at δ 1.20 (6H) corresponding to two methyl groups at C-9. The $^{13}$C NMR analysis showed two chemical shifts at δ 127.2 and 134.5 corresponding to the tetrasubstituted $sp^2$ carbons, at δ 73.1 corresponding to carbinolic carbon, and chemical shifts of four methyl groups at δ 26.8, 27.1, 27.4 and 28.5. In order to obtain caridiene (**1**), compound **10** was submitted to the dehydration reaction in both acidic and basic conditions. In either case the reaction took place, affording isocaridiene (**5**) as the sole product, instead of the desirable **1**. The $^1$H NMR spectra of this compound showed three singlets at δ 0.97, 0.99 and 1.02 corresponding to the methyl groups, and two olefinic hydrogens at δ 4.71 as broad singlet. The structure of **5** was confirmed by analysis of $^{13}$C NMR spectra where the chemical shifts of $sp^2$ carbons of isopropenyl moiety appeared at δ 108.4 (=$CH_2$) and 151.1 (C). Compound **5** was also prepared through Wittig reaction of ketone **9** with methylenetriphenylphosphorane in 70% yield. Any attempts for isomerization of disubstituted olefin to the tetrasubstituted olefin, always lead to the known aromatized product **11**.[9] Thus isocaridiene (**5**), an isomeric compound of caridiene (**1**), was prepared in three steps from myrcene (**6**) in 43% overall yield. The sesquiterpenes **10** and **11** were also obtained in good yields.

The difficulty in the dehydration of **10** to give **1** was investigated by quantum mechanical calculations. The molecular geometries and total energies of compounds **1** and **5** were calculated in three different levels of theory: the semiempirical methods, the Hartree-Fock ab initio method and the density functional theory. The semiempirical calculations were carried out using the AMI[10] and PM3[11] methods. Stevens, Basch and Krauss[12] compact effective pseudopotential (CEP) was used at the Hartree-Fock ab initio level of theory with CEP-31G basis set in order to minimize computational efforts. The electronic correlation effects were included through the use of the density functional theory using the B3LYP functional[13] also with pseudopotential and the CEP-31G basis set. The Hartree-Fock calculations with the CEP-31G basis set were compared with those including polarization functions in all atoms, CEP-31G**, while the correlated calculations were also reproduced with the CEP-31G* basis set. The structures of all compounds were fully optimized at the three different levels of theory. All calculations were done using the Gaussian 94 program.[14]

Table 1 shows the difference between the total equilibrium energies of compounds **1** and **5** ($\Delta E = E_1 - E_5$). The semiempirical data indicate that compound **5** is more stable than **1** by approximately 5–7 kcal $mol^{-1}$, in agreement with the experimental observation. The ab initio results show an opposite tendency. The Hartree-Fock calculation suggests that

*Table 1.* Difference Between the Total Equilibrium Energies of Compounds **1** and **5**

| Method | Structure **1** (a.u.) | Structure **5** (a.u.) | $\Delta E = E_1 - E_5$ (kcal mol$^{-1}$) |
|---|---|---|---|
| Aml | − 0.0377535 | − 0.0455074 | 4.86 |
| Pm3 | − 0.0361915 | − 0.0471473 | 6.87 |
| Hf/cep-31g | − 96.0135370 | − 96.0088415 | − 2.95 |
| Hf/cep-31g** | − 96.2923434 | − 96.2881163 | − 2.65 |
| B3lyp/cep-31g | − 99.0117797 | − 99.0117166 | − 0.04 |
| B3lyp/cep-31g* | − 99.1477940 | − 99.1474149 | − 0.24 |
| B3lyp/cep-31g** | − 99.1825865 | − 99.1821601 | − 0.30 |

compound **1** is more stable than **5** by almost 3 kcal mol$^{-1}$. The inclusion of polarization functions diminishes the difference favoring structure **5**. The improvement of the Hartree-Fock calculation by the inclusion of electronic correlation effects reduces significantly the difference between the total energy of compounds **1** and **5**. The B3LYP calculations show almost no energetic difference between both compounds. The tendency from Hartree-Fock to the B3LYP energies suggests that higher level calculations should support the semiempirical results, confirming the greater stability of compound **5** with respect to **1**, in agreement with the experimental data. It must be emphasized that the ab initio results reflect only the differences between the total energy of molecules **5** and **1**, while the semiempirical results consider the differences between enthalpy of formation of both molecules.

## EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 1600 FT IR instrument. MS spectra were obtained at 70 eV on an HP-5990/5970 system equipped with a J and W Scientific DB-5 fused silica capillary column (30 m × 0.25 mm × 0.25 μm). $^{1}$H NMR and $^{13}$C NMR spectra were obtained with a Bruker AC 300. Elemental analyses were performed with a Perkin-Elmer 2400 CHN analyzer.

**1-[4-(4′-Methyl-3′-pentenyl)-3-cyclohexenyl] ethanone (8):** To a suspension of 125 mg of catalyst ($Me_2AlCl$/silica gel) in dry toluene (10 ml) was added methyl vinyl ketone (56.62 mg, 0.94 mmol) at 0°C, and mixture stirred for 20 min. Myrcene (**6**) (382.6 mg, 2.81 mmol) was then added to the mixture and after stirring for 2.5 h the solution was filtered, and residue washed several times with toluene. The solvent was removed under reduced pressure,

and residue purified by silica gel chromatography (*n*-hexane/diethyl ether, 8 : 2) to give 140.0 mg (72%) of **8**. IR (neat) $\nu = 2967$, 1711, 1438, 1372, 1353, 1165 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.68 (s, 3H), 1.70–2.08 (m, 9H), 2.17 (s, 3H), 2.30–2.70 (m, 2H), 5.09 (t, $J = 1.32$, 1H), 5.41 (bs, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 212.15 (C), 137.80 (C), 131.78 (C), 124.41 (CH), 119.17 (CH), 47.56 (CH), 37.59 ($CH_2$), 28.04 ($CH_3$), 27.97 ($CH_2$), 27.13 ($CH_2$), 26.45 ($CH_2$), 25.74 ($CH_3$), 25.04 ($CH_2$), 17.70 ($CH_3$); MS (*m*/*z*, relative intensity): 206 ($M^+$, 20), 163 (30), 93 (40), 43 (100); $C_{14}H_{22}O$ (206.3): Calcd C 81.50, H 10.75; found C 81.22, H 10.43.

**1,1-Dimethyl-7-acetyl-1,2,3,4,5,6,7,8-octahydronaphthalene (9):** A solution of **8** (52.8 mg, 0.26 mmol) in formic acid 99% (5 ml) was heated at 60°C for 8 h. After cooling at room temperature, $H_2O$ was added (20 ml), and solution extracted with diethyl ether (3 × 15 ml). The organic layer was washed with 1 N $NaHCO_3$ solution (10 ml), brine (2 × 10 ml), dried with anhydrous sodium sulfate, filtered, and solvent removed under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane) to give 44.8 mg (85%) of **9**. IR (neat) $\nu = 2927$, 1709, 1438, 1359, 1169 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 0.99 (s, 3H), 1.05–1.70 (m, 6H), 1.80–2.17 (m, 6H), 2.18 (s, 3H), 2.40–2.60 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 212.66 (C), 133.59 (C), 127.18 (C), 48.66 (CH), 39.70 ($CH_2$), 33.86 (C), 31.14 ($CH_2$), 30.53 ($CH_2$), 28.25 ($CH_3$), 28.09 ($CH_3$), 27.19 ($CH_3$), 26.33($CH_2$), 25.20 ($CH_2$), 19.28 ($CH_2$); MS (*m*/*z*, relative intensity): 206 ($M^+$, 70), 163 (80), 105 (50), 91 (100), 43 (90); $C_{14}H_{22}O$ (206.3): Calcd C 81.50, H 10.75; found C 81.31, H 10.53.

**1,1-Dimethyl-7-(propan-2′-ol-2′-yl)-1,2,3,4,5,6,7,8-octahydronaphthalene (10):** To a solution of methyl magnesium iodide (141.9 mg, 5.8 mmol of Mg and 82.9 mg, 5.8 mmol of methyl iodide) in dry diethyl ether (25 ml) at 0°C was added ketone **9** (120.3 mg, 0.58 mmol). After the mixture had been stirred for 4 h at 0°C, a saturated solution of $NH_4Cl$ (10 ml) was added and solution extracted with diethyl ether (3 × 20 ml). The combined organic layer was washed with brine (2 × 20 ml), dried with anhydrous sodium sulfate, filtered, and solvent removed under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane) to give 99.4 mg (77%) of **10**. IR (neat) $\nu = 3384$, 2967, 1459, 1380, 1138 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 0.99 (s, 3H), 1.20 (s, 6H), 1.30–2.20 (m, 14H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 134.52 (C), 127.25 (C), 73.07 (C), 46.15 (CH), 39.81 ($CH_2$), 33.90 (C), 31.94 ($CH_2$), 33.11 ($CH_2$), 28.51 ($CH_3$), 27.15 ($CH_3$), 27.12 ($CH_3$), 26.78 ($CH_3$), 25.76 ($CH_2$), 24.18 ($CH_2$), 19.36 ($CH_2$); MS (*m*/*z*, relative intensity): 222 ($M^+$, 10), 170 (10), 133 (10), 121 (30), 109 (40), 69 (50); $C_{15}H_{26}O$ (222.4): Calcd C 81.02, H 11.79; found C 80.89, H 11.47.

**1,1-Dimethyl-7-isopropenyl-1,2,3,4,5,6,7,8-octahydronaphthalene (isocaridiene-5).** *Procedure A*: To a solution of **10** (41.5 mg, 0.19 mmol) in

pyridine (1 ml) at 0°C was added phosphorous oxychloride (0.1 ml). After the mixture of the solution had been stirred for 4 h at room temperature, a solution of HCl 0.1N (10 ml) was added, and mixture extracted with diethyl ether ($3 \times 20$ ml), washed with brine (20 ml), dried with anhydrous sodium sulfate, filtered, and solvent removed under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane) to give 28.9 mg (78%) of **5**.

*Procedure B*: To a solution of triphenylphosphonium bromide (190.4 mg, 0.53 mmol) in diethyl ether (25 ml), at 0°C was added *n*-BuLi (0.21 ml, 0.53 mmol). After stirring for 30 min, a solution of ketone **9** (54.9 mg, 0.17 mmol) in diethyl ether (1 ml) was added. After stirring for 2 h at room temperature, the mixture was filtered, and residue washed several times with diethyl ether. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (*n*-hexane) to give 38.1 mg (70%) of **5**. IR (neat) $\nu = 2926$, 1642, 1458, 1358, 886 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.97 (s, 3H), 0.99 (s, 3H), 1.67 (s, 3H), 1.30–2.10 (m, 11H), 2.24 (t, $J = 6.23$ Hz, 1H), 2.70 (bs, 1H), 4.71 (bs, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 151.09 (C), 134.62 (C), 126.95 (C), 108.42 ($CH_2$), 42.27 (CH), 39.76 ($CH_2$), 33.81 (C), 31.46 ($CH_2$), 31.16 ($CH_2$), 30.09 ($CH_2$), 28.03 ($CH_2$), 27.11 ($CH_3$), 26.17 ($CH_3$), 20.98 ($CH_3$), 19.40 ($CH_2$); MS (*m*/*z*, relative intensity): 204 ($M^+$, 62), 161 (100), 133 (60), 105 (90), 91 (78), 79 (80), 41 (70); $C_{15}H_{24}$ (204.4): Calcd C 88.16, H 11.84; found C 88.02, H 11.49.

**1,1-Dimethyl-7-isopropyl-1,2,3,4-tetrahydronaphthalene (11):** To a solution of **5** (28.7 mg, 0.14 mmol) in benzene was added *p*-toluenesulphonic acid (3.5 mg, 0.02 mmol). After stirring for 3 h at room temperature, the mixture was diluted with diethyl ether (15 ml) and washed with 1N solution of $NaHCO_3$ ($2 \times 10$ ml), brine (15 ml), dried with anhydrous sodium sulfate, filtered, and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : diethyl ether 99 : 1) to give 15.9 mg (55%) of **11**. IR (neat) $\nu = 3386$, 3008, 2958, 1609, 1459, 1264, 739 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.24 (d, $J = 6.0$ Hz, 6H), 1.26 (s, 3H), 1.29 (s, 3H), 1.65 (m, 2H), 1.80 (m, 2H), 2.73 (t, $J = 6.59$, 2H), 2.86 (septet, $J = 6.0$ Hz, 1H), 6.97 (m, 2H), 7.18 (s, 1H); MS (*m*/*z*, relative intensity): 202 ($M^+$, 10), 187 (100), 145 (85), 128 (36), 117 (43), 91 (25), 77 (18), 43 (36); $C_{15}H_{22}$ (202.3): Calcd C 89.04, H 10.96; found C 88.76, H 10.63.

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