

An Alternative Synthetic Access to *cis*-4*a*-Methyloctahydrophenanthrene, a Biomarker of Sergipe-Alagoas Basin Petroleum in Brazil

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cis-4*a*-Methyloctahydrophenanthrene (**1**) foi preparado em 8 etapas (23% rendimento total) a partir do ácido 2-bromofenilacético (**3**) e cicloexano-1,3-diona (**6**). Uma reação de acoplamento do tipo Michael Heck com alta diastereosseletividade *cis* foi a etapa chave na montagem do esqueleto tricíclico. O composto **1** foi utilizado como padrão cromatográfico o que permitiu identificação inequívoca de um biomarcador minoritário presente no petróleo de Carmópolis, Bacia de Sergipe-Alagoas, Brasil.

cis-4*a*-Methyloctahydrophenanthrene (**1**) was prepared in 8 steps (23% overall yield) from 2-bromophenyl)acetic acid (**3**) and cyclohexane-1,3-dione (**6**). A highly *cis*-diastereoselective Michael-type Heck coupling served as the key step in the assembly of the tricyclic skeleton. This compound **1** was used as gas chromatography standard which allowed the unequivocal identification of a minor biomarker present in Carmópolis oil from the Sergipe-Alagoas Basin in Brazil.

Keywords: *cis*-4*a*-Methyloctahydrophenanthrene, biomarker, Carmópolis petroleum, Sergipe-Alagoas Basin

Introduction

GC/MS analyses of Brazilian petroleum¹ (Carmópolis oil field, Sergipe-Alagoas Basin, Brazil) disclosed the presence of several acids and hydrocarbons possessing alkyl-substituted monoaromatic sterane, and methyloctahydrophenanthrene (biodegraded monoaromatic sterane) skeletons, most of which require non-commercial standards for full characterization. Confirming the presence of both biomarkers, **1** and **2**, possessing *cis* A/B-ring configuration, in the studied oils, would provide evidence for the low maturity level of the petroleum and of a common diagenetic precursor for **1** and **2** (Figure 1).²

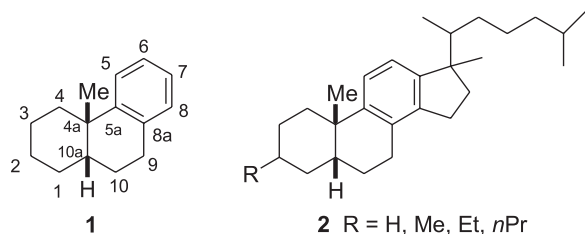


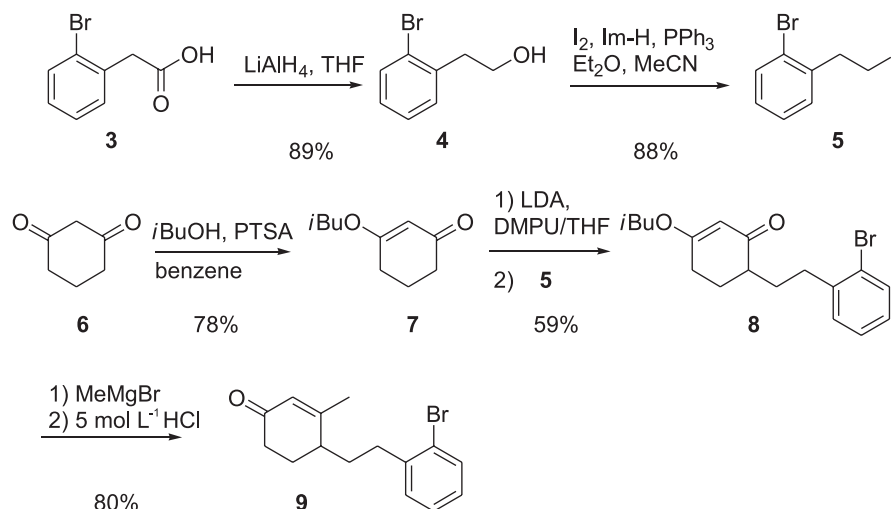
Figure 1. Two biomarkers detected in Brazilian petroleum.

Preparation of *cis*-4*a*-methyloctahydrophenanthrene (**1**) has already been accomplished along several routes.² Notwithstanding these reports we proposed a new synthetic strategy assess *cis*-diastereomer **1** which would easily be extended to the synthesis of **2**.

Results and Discussion

The most attractive synthetic strategy based on a retrosynthetic analysis called for the insertion of the arylpalladium bromide intermediate formed from the aryl bromide unit in **9** into the tethered cyclohexenone moiety (Scheme 1). This would correspond to the carbopalladation step of an intramolecular Heck reaction, one of the most versatile palladium-catalyzed carbon-carbon bond-forming processes, that has been widely applied for the construction of complex carbon skeletons,³ and works particularly well with an electron-acceptor-substituted alkene partner. However, since the intramolecular carbopalladation in **9** generates a quaternary center, the intermediate cannot undergo β -hydride elimination, and must take the course of an overall conjugate addition, as has previously been observed for β -substituted enones.⁴ According to literature precedence,⁵ *cis*-configuration of the formed product could be expected.

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Scheme 1. Synthetic route to the pivotal intermediate **9**

The pivotal intermediate **9**⁶ was easily prepared in three steps from 1,3-cyclohexanedione (**6**) and 1-bromo-2-(2-iodoethyl)benzene (**5**) in 37% yield. The latter was obtained from (2-bromophenyl)acetic acid (**3**) in two steps with 78% overall yield (Scheme 1).

Applying typical conditions for a Heck reaction (Table 1), *i.e.* exposing **9** in DMF solution to a mixture of Pd(OAc)₂ as catalyst, triphenylphosphine as ligand, tetrabutylammonium bromide as phase transfer catalyst (Jeffery's conditions⁷) and methanol/triethylamine as a proton source, at 80 °C for 12 h, gave a dark mixture, from which, by filtration through a pad of Celite, distribution between diethyl ether and water, and flash chromatography over silica gel of the residue from the ether solution, the cyclization product **10** was isolated. The yield, which was 36% in the first attempt (entry 1, Table 1), was only slightly

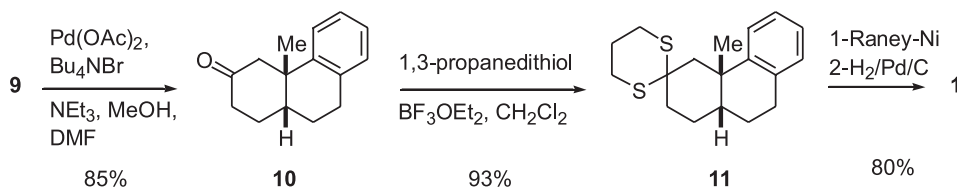
improved by using twice as much Pd(OAc)₂ with the same amount of PPh₃, yet was significantly higher with a decreased amount of PPh₃ or none at all present in the catalyst cocktail (entries 3 and 4).

Careful spectroscopic characterisation of the tricyclic compound **10**⁸ on the basis of one- and two-dimensional ¹H- and ¹³C-NMR spectra, revealed that only a single diastereomer had formed, and it was established as the *cis*-fused tricycle **10** by differential NOE experiments, *e.g.* irradiation at δ 0.87 corresponding to the methyl group on C-4a enhanced the signal of 10a-H (δ 1.20 undegassed sample) by 1.5%. From the ketone **10**, the target compound **1**⁹ was obtained in two steps with 72% overall yield by transformation to the dithiane **11** and its reductive desulfurization with Raney nickel (Scheme 2). It is worth mentioning that the desulfurization produced a mixture

Table 1. Optimization of the reaction conditions for the intramolecular Heck-type reaction of compound **9**

Entry	Equiv. of 9	Pd(OAc) ₂ (mol%)	Ligand	Ligand (mol%)	Equiv. Bu ₄ NBr	Equiv. Et ₃ N:MeOH	Yield 10 (%)
1	1	5	PPh ₃	20	0.4	10:5	36 ^a
2	1	10	PPh ₃	20	0.4	10:5	40 ^a
3	1	10	PPh ₃	10	0.4	10:5	71 ^b
4	1	10	–	–	0.4	10:5	85 ^b

^a Debrominated **9** was the major by-product. ^b Only traces of debrominated **9** were isolated.



Scheme 2. Transformation of compound **9** into the biomarker **1**

of **1** with other unsaturated hydrocarbons. The crude mixture was hydrogenated, without any attempt to purify its components, to produce almost pure **1**. In an alternative attempt, **10** was reduced with sodium borohydride to furnish a mixture of equatorial and axial alcohols which could be mesylated, however, reductive removal of the mesyloxy groups by treatment with LiAlH_4 failed.

Compound **1** was coinjected with the neutral aromatic fraction from one of the samples from the Carmopolis oil field from Sergipe-Alagoas Basin, Brazil, and it indeed coeluted with one of the components (relative retention index 1617).¹⁰

Conclusion

This investigation demonstrates not only the presence of *cis*-4a-methyloctahydrophenanthrene, biomarker **1**, in the Carmopolis oil from Sergipe-Alagoas Basin, possessing a *cis*-decalin moiety, but also that the Michael-type Heck reaction proceeds in high yields and with total *cis* stereoselectivity during the intramolecular 1,4-conjugate addition of an arylpalladium bromide intermediate to an α,β -unsaturated ketone with no hydrogen substituent at the β -position. These results add a new application to the vast repertoire of palladium-catalyzed reactions.

Experimental

2-(2-Bromophenyl)ethanol (4). To a solution of (2-bromophenyl)acetic acid (**3**) (0.511 g, 2.4 mmol) in THF at 0 °C was added LiAlH_4 (68 mg, 1.8 mmol). The mixture was heated under reflux for 1 h. The reaction mixture was cooled to 0 °C and treated with 0.5 mol L⁻¹ HCl (20 mL). The organic fraction was extracted with ether, the combined ethereal solutions were washed with NaHCO_3 and brine, dried over MgSO_4 , and concentrated under reduced pressure furnishing 0.431 g (89%) of the alcohol **4** as a pale yellow oil. ¹H NMR (300 MHz, CDCl_3) δ 3.03 (t, *J* 6.9 Hz, 2 H), 3.89 (t, *J* 6.9 Hz, 2 H), 7.07–7.13 (m, 1 H), 7.23–7.29 (m, 2 H), 7.56 (d, *J* 8.5 Hz, 1 H). ¹³C NMR (75 MHz, CDCl_3) δ 39.3, 62.1, 124.7, 127.5, 128.2, 131.3, 133.0, 137.8. MS (EI) *m/z* (%): 202 (14) [M^+], 200 (14) [M^+], 171 (50), 169 (48), 121 (50), 91 (100), 63 (24). IR (film) ν_{max} /cm⁻¹: 3367, 3057, 2939, 2882, 1646, 1567, 1471, 1439, 1156, 1041, 749, 659.

2-(2'-Bromophenyl)iodoethane (5). To a solution of the alcohol **4** (0.148 g, 0.74 mmol), triphenylphosphine (0.340 g, 1.30 mmol), and imidazol (0.092 g, 1.35 mmol) in ether/ acetonitrile (20/10 mL) kept at 0 °C was added iodine (0.380 g, 1.5 mmol) with stirring. After 30 min the reaction

was complete. The organic fraction was extracted with ether, and the ethereal solution washed with saturated Na_2SO_3 solution and brine, dried over MgSO_4 and distilled under pressure furnishing 0.203 g (88%) of the iodide **5** as a colorless oil. ¹H NMR (300 MHz, CDCl_3) δ 3.27–3.40 (m, 4 H), 7.11–7.16 (m, 1 H), 7.22–7.30 (m, 2 H), 7.55 (d, *J* 8.0 Hz, 1 H). ¹³C NMR (75 MHz, CDCl_3) δ 3.2, 40.6, 124.1, 127.6, 128.6, 130.7, 133.1, 139.8. MS (EI) *m/z* (%): 312 (4) [M^+], 310 (4) [M^+], 185 (77), 183 (75), 104 (100), 77 (62), 51 (29). IR (film) ν_{max} /cm⁻¹: 3055, 2959, 2856, 1567, 1469, 1440, 1235, 1173, 1087, 1046, 1025, 942, 904, 750, 723, 658, 619, 532.

3-Isobutoxycyclohex-2-en-1-one (7). Into a two-neck round-bottomed flask connected to a Dean-Stark apparatus, containing 1,3-cyclohexanedione (3.887 g, 34.7 mmol) and *p*-toluenesulfonic acid monohydrate (0.275 g, 1.4 mmol), was added benzene (80 mL) and isobutyl alcohol (30 mL, 324 mmol). The mixture was heated so that the azeotrope started to distill off. After all the water had been removed by azeotropic distillation, the reaction mixture was cooled down to room temperature, washed with 5% KOH solution, water and brine, dried over MgSO_4 . Distillation under reduced pressure furnished 4.52 g (78%) of compound **7** as a colorless oil. ¹H NMR (500 MHz, CDCl_3) δ 0.98 (d, *J* 6.5 Hz, 6 H), 1.96–2.08 (m, 3 H), 2.33 (t, *J* 7.0 Hz, 2 H), 2.43 (t, *J* 6.5 Hz, 2 H), 3.60 (d, *J* 6.5 Hz, 2 H), 5.33 (s, 1 H). ¹³C NMR (75 MHz, CDCl_3) δ 19.1, 21.1, 27.6, 28.7, 36.3, 73.9, 102.7, 175.0, 195.2. MS (EI) *m/z* (%): 168 (3) [M^+], 113 (64), 84 (100), 69 (18), 57 (68), 41 (73). IR (film) ν_{max} /cm⁻¹: 2960, 2875, 1651, 1606, 1476, 1384, 1329, 1223, 1185, 1136, 1006, 955, 865, 823, 760, 606.

6-[2'-(2'-Bromophenyl)ethyl]-3-isobutoxycyclohexen-2-en-1-one (8). To a solution of diisopropylamine (0.17 mL, 1.2 mmol) in THF (5 mL) kept under argon at –20 °C, was added *n*-butyllithium (1.2 mmol). The mixture was stirred for 1 h, cooled down to –78 °C, and 3-isobutoxycyclohex-2-en-1-one (**7**) (0.205 g, 1.2 mmol) was added via syringe. The enolate solution was stirred for 20 min, and 0.6 mL of DMPU was added. The reaction mixture was stirred for an additional 40 min, and 2-(2'-bromophenyl)iodoethane (**5**) (0.268 g, 0.86 mmol in 3 mL of THF) was added slowly. The mixture was warmed to room temperature. The organic fraction was extracted with ether, the ethereal solution was washed with water and brine, dried over MgSO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel afforded 0.177 g (59%) of the enone **8** as a colorless oil. ¹H NMR (500 MHz, CDCl_3) δ 0.97 (d, *J* 7.0 Hz, 6 H), 1.65–1.73 (m, 1 H), 1.81–1.88 (m, 1 H), 1.97–2.07 (m, 1 H),

2.12–2.21 (m, 2 H), 2.24–2.30 (m, 1 H), 2.42–2.52 (m, 2 H), 2.78 (ddd, *J* 13.5, 10.5 and 5.5 Hz, 1 H), 2.86 (ddd, *J* 13.5, 11.0 and 5.5 Hz, 1 H), 3.59 (dd, *J* 6.3 and 1.5 Hz, 2 H), 5.32 (s, 1 H), 7.04 (td, *J* 7.5 and 1.5 Hz, 1 H), 7.23 (td, *J* 7.5 and 1.5 Hz, 1 H), 7.29 (dd, *J* 7.5 and 1.5 Hz, 1 H), 7.51 (dd, *J* 7.5 and 1.5 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ 19.1, 26.4, 27.7, 28.0, 30.0, 33.6, 44.8, 74.8, 102.3, 124.4, 127.5, 127.6, 130.5, 132.7, 141.5, 177.0, 201.1. HRMS (EI) *m/z* (%): 271.2072 (15) [M⁺ – Br]; 215.1355 (6); 168.1340 (100); 112.0634 (96); 84.0678 (6); 57.0727 (9). IR (film) ν_{\max} /cm⁻¹: 3031, 2958, 2933, 2872, 1654, 1608, 1496, 1471, 1545, 1384, 1368, 1223, 1195, 1178, 994, 833, 752, 699.

4-[2'-(2''-Bromophenyl)ethyl]-3-methylcyclohex-2-*en*-1-*one* (**9**). To a solution of compound **8** (0.108 g, 0.31 mmol) in THF (10 mL), kept under argon at 0 °C, was added methylmagnesium bromide (0.5 mmol). After 30 min no more starting material was detected by TLC. The reaction mixture was treated with saturated NH₄Cl solution (10 mL), and the organic phase was extracted with ether (2 × 15 mL). After separation of the phases, 2 mol L⁻¹ HCl (20 mL) was added to the organic fraction, and the biphasic mixture was stirred overnight. Afterwards the organic phase was washed with saturated Na₂CO₃ solution, water and brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by chromatography on silica gel afforded 0.072 g (80%) of compound **9** as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 1.68–1.82 (m, 1 H), 1.86–1.96 (m, 1 H), 1.97 (d, *J* 1.1 Hz, 3H), 2.01–2.21 (m, 2 H), 2.29–2.39 (m, 2 H), 2.53 (ddd, *J* 16.8, 11.2 and 5.5 Hz, 1 H), 2.73 (ddd, *J* 13.2, 10.9 and 5.8 Hz, 1 H), 2.93 (ddd, *J* 13.2, 11.2 and 5.1 Hz, 1 H), 5.85 (s, 1 H), 7.06–7.11 (m, 1 H), 7.22–7.29 (m, 2 H), 7.54 (d, *J* 7.7 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ 23.0, 26.1, 31.1, 33.8, 34.7, 39.4, 124.6, 127.1, 127.9, 128.2, 130.6, 133.3, 141.2, 165.8, 200.0. HRMS (EI) *m/z* (%): 294.0432 (2), 292.0463 (2) [292.04628 Calcd. for C₁₅H₁₇BrO, M⁺], 279.0227 (4), 277.0252 (5), 213.1254 (6), 183.9665 (82), 181.9686 (84), 123.0737 (11), 95.0425 (100), 67.0457 (10). IR (film) ν_{\max} /cm⁻¹: 3026, 2943, 2864, 1668, 1625.

4a-Methyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-3-*one* (**10**). In a two-neck round-bottomed flask was added under argon palladium acetate (9.2 mg, 0.041 mmol), triphenylphosphine (10.8 mg, 0.041 mmol), tetrabutylammonium bromide (52 mg, 0.16 mmol), triethylamine (0.6 mL, 4.3 mmol) and anhydrous DMF (5 mL). Argon was bubbled through the solution for 5 min which turned orange-brown. MeOH (0.1 mL, 2.4 mmol) and compound **9** (120 mg, 0.41 mmol, predissolved in 2

mL of DMF) was added to the mixture. Argon was bubbled through the solution for an additional 5 min. The mixture was heated to 80 °C and stirred at this temperature for 16 h. After this period the reaction mixture was cooled down to room temperature and filtered through a pad of Celite. The organic fraction was extracted with ether, and the ethereal solution washed with water, dried over MgSO₄ and concentrated under reduced pressure. Purification by chromatography on silica gel afforded 62 mg (71%) of compound **10** as a colorless solid. ¹H NMR (500 MHz, C₆D₆) δ 0.87 (s, 3 H), 1.08–1.15 (m, 1 H), 1.17–1.22 (m, 1 H), 1.26–1.31 (m, 2 H), 1.35–1.42 (m, 1 H), 1.71–1.80 (m, 2 H), 1.93 (dd, *J* 14.0 and 1.5 Hz, 1 H), 2.31 (d, *J* 14.0 Hz, 1 H), 2.35 (t, *J* 6.5 Hz, 2 H), 6.68–6.70 (m, 1 H), 6.76 (td, *J* 7.5 and 1.5 Hz, 1 H), 6.79 (td, *J* 7.5 and 1.5 Hz, 1 H), 6.90 (dd, *J* 7.5 and 1.5 Hz, 1 H). ¹³C NMR (125 MHz, C₆D₆) δ 24.5, 28.4, 28.5, 29.6, 38.6, 40.1, 42.1, 52.7, 126.2, 126.4, 126.6, 129.5, 134.9, 143.1, 208.0. HRMS (EI) *m/z* (%): 214.13562 (74) [214.13577 Calcd. for C₁₅H₁₈O, M⁺], 199.11010 (66), 181.09578 (19), 157.09092 (100), 141.05952 (54), 129.05886 (49), 115.04248 (29), 91.04068 (13), 77.02362 (7). IR (film) ν_{\max} /cm⁻¹: 3103, 2929, 2877, 1712, 1598, 1491, 1446, 1316, 1295, 1244, 1120, 763, 736.

4a-Methylspiro-(1,3-dithiane[2:3]-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthrene) (**11**). To a solution of compound **10** (10 mg, 0.047 mmol) and 1,3-propanedithiol (6 μL, 0.06 mmol) in CH₂Cl₂ (5 mL), kept under argon at 0 °C, was added freshly distilled BF₃OEt₂ (6 μL, 0.048 mmol) via syringe. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was treated with saturated NaHCO₃ solution, and the organic fraction was extracted with CH₂Cl₂, the CH₂Cl₂ solution was washed with water, dried over MgSO₄ and concentrated under reduced pressure. Purification by chromatography on silica gel afforded 13.2 mg (93%) of compound **11** as a colorless solid. ¹H NMR (500 MHz, C₆D₆) δ 1.33 (s, 3 H), 1.63–1.74 (m, 2 H), 1.78–2.06 (m, 7 H), 2.41–2.49 (m, 2 H), 2.66–2.76 (m, 4 H), 2.95 (ddd, *J* 17.0, 11.0 and 6.0 Hz, 1 H), 3.02 (ddd, *J* 14.1, 11.0 and 3.0 Hz, 1 H), 7.04 (d, *J* 7.0 Hz, 1 H), 7.08 (td, *J* 7.0 and 1.5 Hz, 1 H), 7.13 (td, *J* 7.0 and 1.5 Hz, 1 H), 7.41 (d, *J* 7.0 Hz, 1 H). ¹³C NMR (75 MHz, C₆D₆) δ 24.3, 25.0, 25.7, 26.5, 26.6, 26.7, 34.3, 35.9, 37.9, 41.2, 49.0, 50.4, 125.5, 126.9, 129.3, 134.6, 143.5. MS (EI) *m/z* (%): 304 (84) [M⁺], 289 (100), 197 (72), 181 (60), 157 (90), 141 (61), 129 (100), 115 (58), 106 (50), 91 (38), 41 (44).

cis-4*a*-Methyl-1,2,3,4,4*a*,10,10*a*-octahydrophenanthrene (**1**). To a solution of compound **11** (13.2 mg,

0.043 mmol) in ethanol (5 mL) was added Raney-Ni (100 mg, 1.7 mmol). The mixture was kept under reflux during 12 h. After this period the reaction mixture was filtered through a pad of Celite, and the organic fraction was extracted with CH_2Cl_2 . The CH_2Cl_2 solution was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by chromatography on silica gel afforded 7 mg (80%) of compound **1** as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 1.24 (s, 3 H, Me), 1.24–1.25 (m, 1 H, 2-H), 1.34–1.43 [m, 3 H, (1,3,4)-H], 1.46–1.71 [m, 5 H, (1,2,3,10,10a)-H], 1.99–2.05 (m, 1 H, 10-H), 2.13–2.17 (m, 1 H, 4-H), 2.76 (ddd, J 17.5, 6.5 and 5.0 Hz, 1 H, 9-H), 2.87 (ddd, J 17.5, 9.0 and 6.5 Hz, 1 H, 9-H), 7.04–7.09 [m, 2 H, (7,8)-H], 7.12–7.15 (m, 1 H, 6-H), 7.28 (d, J 8.0 Hz, 1 H, 5-H). ^{13}C NMR (125 MHz, CDCl_3) δ 22.9 (C-2), 24.4 (C-10), 25.1 (C-1), 27.1 (C-9), 28.1 (C-3), 31.7 (Me), 37.5 (C-4a), 38.2 (C-4), 41.2 (C-10a), 125.1 (C-7), 125.8 (C-6), 126.0 (C-5), 129.3 (C-8), 136.0 (C-_{quat}). HRMS (EI) m/z (%): 200.15652 (37) [200.15650 calcd. for $\text{C}_{15}\text{H}_{20}$, M^+], 185.13450 (100), 157.10363 (35), 143.08707 (32), 129.07359 (27), 117.07365 (34), 91.05856 (11), 69.07265 (7).

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- RI exp. = Relative Retention Index calculated applying the Van den Dool and Kratz equation (van den Dool, H.; Kratz, P. D.; *J. Chromatogr.* **1963**, *11*, 463); t = traces. GC-MS-Analyses were carried out using a HP-5990/5970 system equipped with a J&W Scientific DB-5 fused silica capillary column (30 m \times 0.25 mm \times 0.25 mm); column temperatures were programmed from 90 to 300 °C at 3.5 °/min. Helium was used as carrier gas at 1 mL/min, and SIM detection mode was used.

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