70. A Stereoselective Synthesis of (±)-*cis*-γ-Irone

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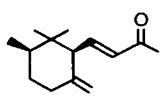
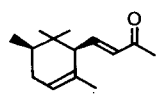
(±)-*cis*-γ-Irone (**1**), a main constituent of natural iris oil, has been stereoselectively synthesized from methyl (2*E*)-3-[(2,2,4-trimethyl-3-cyclohexen-1-yl)methoxy]-2-propenoate (**3**) (6 steps, overall yield 14%). The *cis*-configuration as well as the exocyclic position of the double bond of **1** were secured by the thermal ene reaction of the β-(alkenyloxy)acrylate **3** yielding the 3-oxabicyclo[3.3.1] nonane derivative **5**.

Introduction. – The synthesis of irones has attracted considerable attention over the last 10 years [1–9]. Interestingly, it was only recently that syntheses of *cis*-γ-irone (**1**), which is one of the principal constituents of natural iris oil [5] [10], have been disclosed [2] [3]. Both of these approaches, however, are not stereoselective and consequently rely on the separation of diastereoisomeric intermediates[1]).



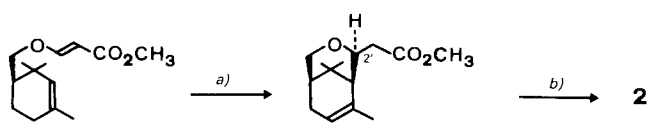
1



2

We recently described a synthesis of (±)-*cis*-α-irone (**2**), based on the acid-catalyzed cyclization of the readily available β-(alkenyloxy)acrylate **3** to the 3-oxabicyclo-[3.3.1]nonene derivative **4** [1] *(Scheme 1)*. In this communication, we wish to report that **3** is also a convenient starting material for the synthesis of **1**.

Scheme 1

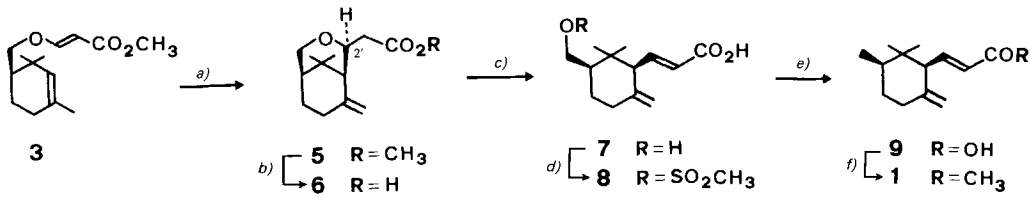


3 **4**

a) MsOH, CH_2Cl_2, −5°. b) 5 steps.

[1]) A synthesis leading to a 9:1 mixture of *trans*- and *cis*-γ-irone had already been described earlier [6]. This mixture of isomers, however, is difficult to separate on a preparative scale.

Scheme 2



a) Toluene, 300°. b) NaOH, H_2O, MeOH, 25°. c) 2 equiv. LDA, THF, −70°→5°, then H_3O^+. d) MsCl, pyridine, CH_2Cl_2, 0°. e) Zn, NaI, DME, reflux. f) MeLi, Et_2O, reflux.

Results and Discussion. – Since the acid-catalyzed cyclization of **3** afforded only trace amounts (< 1%) of the corresponding exocyclic double bond isomer **5** [1], which would give access to **1**, we turned our attention to the thermal cyclization of **3**. By inspection of molecular models, we anticipated that an intramolecular ene reaction [11] of **3** might preferentially lead to **5**. Indeed, heating a solution of **3** in toluene in a sealed tube at 300° for 9 h afforded the desired **5** in 25% yield as the only cyclization product *(Scheme 2)*.

In addition, two major side products were formed by competitive fragmentation reactions of **3**: *ca.* 40% of 1,3,3-trimethyl-4-methylidene-1-cyclohexene (*retro*-en reaction [12]) and *ca.* 10% of (2,2,4-trimethyl-3-cyclohexen-1-yl)methanol (for the reverse of this reaction, see [13]). Various attempts to induce the ene reaction **3**→**5** by *Lewis*-acid catalysis [14] were unsuccessfull.

The exocyclic nature of the double bond was evident from the ^{1}H-NMR spectrum of **5**, which revealed 2 *t* at 4.83 and 4.53 ppm with J = 2.5 Hz. The presence of a methylidene group was supported by an in IR absorption at 885 cm^{-1}. The *endo*-configuration at C(2') in the cyclization product **5** was deduced by NOE-difference spectroscopy: irradiation of the Me signal at 1.22 ppm resulted in 7% enhancement of the signal at 4.42 ppm (CH(2')).

The transformation of **5** to *cis*-γ-irone (**1**) was carried out in analogy to our earlier work [1] and proceeded in an overall yield of 57% *(Scheme 2)*. Hydrolysis of **5** with aqueous NaOH solution at r.t. afforded the crystalline acid **6**. Cleavage of the tetrahydropyran moiety of **6** was effected through the corresponding dianion, which was generated with 2 equiv. of LDA in THF, to give hydroxy acid **7** in almost quantitative yield[2]). Treatment of **7** with an excess of MsCl in CH_2Cl_2/pyridine afforded the corresponding mesylate **8**, which was then reduced with Zn/NaI in refluxing 1,2-dimethoxyethane (DME) [16] to the crystalline acid **9**. Reductive removal of the MsO group of **8** could also be effected with $NaBH_4$ in DMPU (= 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone), at 80°, although the yields of **9** were somewhat lower. Finally, reaction of **9** with 2.5 equiv. of MeLi in Et_2O furnished isomerically pure[3]) (±)-*cis*-γ-irone (**1**).

The exclusive formation[4]) of only one double-bond- and stereoisomer *(endo vs. exo)*[5]), respectively, in the thermal ene reaction of **3** can be understood by inspecting molecular models of the different possible transition states.

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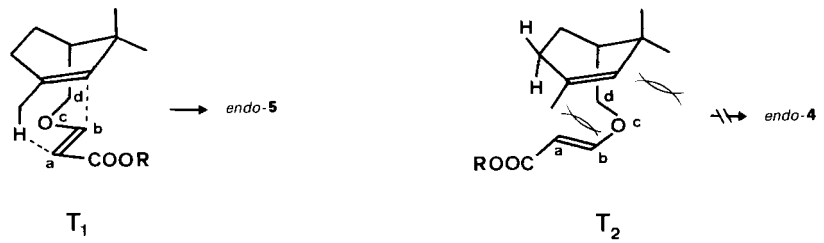
[2]) For a similar case, see *Seebach* and *Pohmakotr* [15].

[3]) Our synthetic sample has been compared (capillary GC and 400-MHz ^{1}H-NMR) with *Irone alpha® (Givaudan)* which contains *ca.* 43% of *cis*-α-, 51% of *trans*-α-, and 4% of β-irone, and also with a mixture of *cis*- and *trans*-γ-irone, provided by the late Professor *F. Leyendecker* (Strasbourg), see also [2].

[4]) It has been shown that **5** as well as **4** [1] are stable under the reaction conditions. Thus, the ene reaction **3**→**5** is not reversible, and **5** corresponds to the kinetic product of the reaction. However, treatment of **5** with MsOH in CH_2Cl_2 (under conditions which effected the cyclization **3**→**4** [1]) afforded **4**/**5** in a ratio of 7:1.

[5]) In the following, the prefixes *endo* and *exo* refer to the configuration at C(2') of **4** and **5**.

Scheme 3



The transition-state geometries are defined by rotation around the bonds C(d)–O and C(b)–O *(Scheme 3)*. In the transition state T_1 (C(b)–O s-*trans*) which leads to the observed product *endo*-**5**, the conformation of the tetrahydropyran ring to be formed is chair-like, and the stereoelectronic requirements for the ene reaction are ideally fulfilled. A distorted form of T_1 which could eventually yield *endo*-**4** is geometrically not feasible. The transition state corresponding to T_1 with a s-*cis* conformation of the C(b)–O bond is not capable to undergo an ene reaction to either **4** or **5** because of spatial reasons.

In the transition state T_2 (C(b)–O s-*cis*), the geometry for an ene reaction furnishing *endo*-**4** is favorable, but severe steric interaction between H–C(a) and H–C(d) and a 1,4-interaction of the O-atom and the geminal dimethyl group in the boat-like tetrahydropyran moiety to be formed make this transition state energetically disadvantageous. A distorted form of T_2 which could yield *endo*-**5** has, in addition, an unsuitable geometry for the ene reaction. The transition state corresponding to T_2 with a s-*trans* configuration of the C(b)–O bond is, again for spatial reasons, unrealistic for an ene reaction to either **4** or **5**.

In conclusion, it is clear that the only feasible transition state is T_1 leading to *endo*-**5**.

In summary, we have demonstrated that the thermal as well as the acid-catalyzed [1] [17] cyclization of *β*-(alkenyloxy)acrylates gives access to substituted, synthetically useful tetrahydropyran derivatives.

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Experimental Part

General. See [1] [17]. GC: *Carlo Erba GC 6000 Vega Series* instrument equipped with a *SE-30* glass capillary column (26 m × 0.3 mm), He as carrier gas (40 kPa); temp. programming: samples were injected at 90°; after 2 min, 6°/min → 250°.

(±)-Methyl (9',9'-Dimethyl-8'-methylidene-3'-oxabicyclo[3.3.1]non-2'-endo-*yl)acetate* (**5**). A soln. of 5.44 g (22.8 mmol) of *β*-(alkenyloxy)acrylate **3** [1] in 10 ml of toluene was heated in a sealed glass tube (washed successively with dil. aq. K_2CO_3 soln. and H_2O and then dried) at 300 ± 5° for 9 h. After cooling[6]), the yellow soln.

[6]) Capillary GC analysis of the freshly opened tube revealed 4 major peaks with t_R 4.6, 9.0, 18.0, and 20.2 min in a ratio of 6:2:6:3. These peaks correspond to 1,3,3-trimethyl-4-methylidene-1-cyclohexene and (2,2,4-trimethyl-3-cyclohexen-1-yl)methanol [1], **5** and **3**, respectively. No signal attributable to **4** [1] (t_R 18.3 min) could be detected.

was evaporated and chromatographed on silica gel (80 g). Elution with pentane/Et_2O 20:1 afforded 805 mg (15%) of **3**. Further elution with pentane/Et_2O 15:1, followed by bulb-to-bulb distillation (120°/0.2 Torr), yielded 1.37 g (25%) of **5** as a colorless oil (> 90% pure by capillary GC). IR (film): 3065*w*, 1740*s*, 1645*w*, 1435*m*, 1390*w*, 1380*w*, 1365*w*, 1310*m*, 1245*m*, 1168*m*, 1100*m*, 1035*m*, 885*m*, 730*m*. ^{1}H-NMR ($CDCl_3$): 0.95 (*s*, CH_3); 1.22 (*s*, CH_3), overlapped by *m* (1 H); 1.60–1.68 (*m*, 1 H); 1.74 (*m*, 1 H); 1.92–2.04 (*m*, 1 H); 2.17–2.25 (*m*, 1 H); 2.27 (*dd*, *J* = 5, 15.5, 1 H, CH_2COO); 2.42 (*dd*, *J* = 8.5, 15.5, 1 H, CH_2COO); 2.65–2.77 (*m*, 1 H); 3.68 (*s*, CH_3O); 3.74 (*dd*, *J* = 1.5, 11.5, 1 H); 4.19 (*dt*, *J* = 11.5, 2.5, 1 H); 4.42 (*ddd*, *J* = 2, 5, 8.5, H–C(2')); 4.53 (*t*, *J* = 2.5, 1 H); 4.83 (*t*, *J* = 2.5, 1 H). ^{13}C-NMR ($CDCl_3$): 25.35 (*q*); 27.37 (*t*); 28.43 (*q*); 30.53 (*t*); 32.98 (*s*); 38.17 (*d*); 39.79 (*t*); 51.57 (*q*); 53.51 (*d*); 69.89 (*t*); 70.74 (*d*); 111.22 (*t*); 147.31 (*s*); 172.38 (*s*). MS: 238 (11, $M^{+\cdot}$), 206 (7), 134 (26), 121 (100), 93 (90). Anal. calc. for $C_{14}H_{22}O_3$ (238.33): C 70.56, H 9.30; found: C 70.19, H 8.94.

Continued elution of the column with pentane/Et_2O 1:1 gave 350 mg (10%) of (2,2,4-trimethyl-3-cyclohexen-1-yl)methanol [1].

In another experiment, the crude thermolysis mixture was carefully evaporated and then filtrated through a pad of silica gel with pentane to give 1,3,3-trimethyl-4-methylidene-1-cyclohexene as a colorless oil. ^{1}H-NMR ($CDCl_3$): 1.12 (*s*, 2 CH_3); 1.64 (*q*, *J* = 1.5, CH_3); 2.02 (br. *t*, *J* ≈ 6.5, 2 H); 2.36 (*td*, *J* = 6.5, 1, 2 H); 4.73 (*m*, 1 H); 5.08 (*m*, 1 H). MS: 136 (28, $M^{+\cdot}$), 121 (100), 105 (21), 93 (53), 79 (27).

*(±)-(9',9'-Dimethyl-8'-methylidene-3'-oxabicyclo[3.3.1]non-2'-*endo*-yl)acetic Acid* (**6**). To a soln. of 1.40 g (5.9 mmol) of **5** in 3 ml of MeOH were added 14 ml of 2.5M aq. NaOH (35 mmol). The resulting mixture was stirred at r.t. for 24 h, then poured into ice/H_2O, and acidified with 4N H_3PO_4 to pH 3. The aq. phase was extracted with CH_2Cl_2 (3 × 100 ml) and the combined org. extract dried ($MgSO_4$) and evaporated. Crystallization from AcOEt/hexane afforded 1.066 g (81%) of **6** as white needles. M.p. 166–167°. IR ($CHCl_3$): 3500–2500*m*, 1740*m*, 1712*s*, 1642*w*, 1175*m*, 1100*m*, 1030*m*, 890*m*. ^{1}H-NMR (CD_3OD): 0.96 (*s*, CH_3); 1.24 (*s*, CH_3), overlapped by *m* (1 H); 1.62–1.70 (*m*, 1 H); 1.81 (*m*, 1 H); 1.96–2.08 (*m*, 1 H); 2.18–2.26 (*m*, 1 H); 2.27 (*dd*, *J* = 6, 16, 1 H, CH_2COO); 2.32 (*dd*, *J* = 8, 16, 1 H, CH_2COO); 2.64–2.77 (*m*, 1 H); 3.71 (*dd*, *J* = 1.5, 12, 1 H); 4.20 (*dt*, *J* = 12, 2.5, 1 H); 4.41 (*ddd*, *J* = 2, 6, 8, H–C(2')); 4.57 (*t*, *J* = 2.5, 1 H); 4.85 (*t*, *J* = 2.5, 1 H). ^{13}C-NMR (CD_3OD): 25.68 (*q*); 28.45 (*t*); 28.96 (*q*); 31.59 (*t*); 33.85 (*s*); 39.48 (*d*); 40.62 (*t*); 54.62 (*d*); 70.77 (*t*); 71.96 (*d*); 111.86 (*t*); 148.82 (*s*); 175.40 (*s*). MS: 224 (8, $M^{+\cdot}$), 206 (22, $M^{+\cdot} - H_2O$), 134 (15), 121 (100), 93 (81). Anal. calc. for $C_{13}H_{20}O_3$ (224.30): C 69.61, H 8.99; found: C 69.76, H 9.09.

*(±)-(2E)-3-[*cis*-2',2'-Dimethyl-6'-methylidene-3'-(hydroxymethyl)cyclohex-1'-yl]-2-propenoic Acid* (**7**). To a soln. of 1.56 ml (11 mmol) of $(i\text{-}Pr)_2NH$ in 30 ml of dry THF were added, at 0° under N_2, 6.9 ml of 1.23M BuLi (8.5 mmol) in hexane within 5 min. The mixture was stirred at 0° for 12 min and then cooled to −70°. A soln. of 950 mg (4.24 mmol) of **6** in 10 ml of dry THF was added with a syringe over 5 min and the resulting colloidal mixture warmed up to +5° during 2 h. After addition of 4N aq. H_3PO_4 (*ca.* 20 ml), the mixture was extracted with Et_2O (2 × 150 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated. Crystallization from AcOEt/hexane gave 927 mg (98%) of pure **7** as white crystals. M.p. 145–146°. IR (nujol): 3500–2300*m*, 1680*s*, 1640*m*, 1313*m*, 1276*m*, 1246*m*, 892*m*. ^{1}H-NMR (CD_3OD): 0.75 (*s*, CH_3); 0.99 (*s*, CH_3); 1.25–1.37 (*m*, 1 H); 1.43–1.52 (*m*, 1 H); 1.95–2.17 (*m*, 2 H); 2.39–2.46 (*m*, 1 H); 2.67 (br. *d*, *J* ≈ 10.5, H–C(1')); 3.26 (*dd*, *J* = 8.5, 11, 1 H); 3.82 (*dd*, *J* = 4, 11, 1 H); 4.45 (*m*, 1 H); 4.83 (*m*, 1 H); 5.82 (*d*, *J* = 16, H–C(2)); 7.06 (*dd*, *J* = 10.5, 16, H–C(3)). ^{13}C-NMR (CD_3OD): 16.16 (*q*); 28.04 (*t*); 28.04 (*q*); 36.73 (*t*); 38.64 (*s*); 51.00 (*d*); 58.54 (*d*); 63.73 (*t*); 109.26 (*t*); 125.39 (*d*); 149.25 (*d*); 149.90 (*s*); 169.47 (*s*). MS: 224 (2, $M^{+\cdot}$), 206 (5, $M^{+\cdot} - H_2O$), 191 (10), 145 (24), 121 (26), 105 (36), 93 (51), 81 (63), 69 (79), 43 (70), 41 (100). Anal. calc. for $C_{13}H_{20}O_3$ (224.30): C 69.61, H 8.99; found: C 69.69, H 9.22.

(±)-(2E)-3-{cis-*2',2'-Dimethyl-6'-methylidene-3'-[(methanesulfonyl)oxy]cyclohex-1'-yl*}*-2-propenoic Acid* (**8**). To a suspension of 586 mg (2.61 mmol) of **7** in 25 ml of dry CH_2Cl_2 were added 4 ml of pyridine. The resulting soln. was cooled to 0°, and 1.25 ml (16.1 mmol) of MsCl were added dropwise. This mixture was stirred at 0° under N_2 for 3 h, and then 3 ml of H_2O/pyridine 1:1 (*v/v*) were added. The soln. was stirred at r.t. for another 90 min, then acidified with 4N H_3PO_4, and extracted with CH_2Cl_2 (3 × 80 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated. Crystallization of the residue from CH_2Cl_2/hexane afforded 706 mg (89%) of **8** as white plates. M.p. 133–134°. IR ($CHCl_3$): 3500–2500*m*, 1698*s*, 1652*m*, 1358*m*, 1340*m*, 1280*m*, 1173*s*, 970*m*, 948*s*, 900*m*. ^{1}H-NMR ($CDCl_3$): 0.81 (*s*, CH_3); 1.02 (*s*, CH_3); 1.36–1.48 (*m*, 1 H); 1.72–1.81 (*m*, 1 H); 1.90–1.98 (*m*, 1 H); 2.06–2.16 (*m*, 1 H); 2.41–2.48 (*m*, 1 H); 2.65 (br. *d*, *J* ≈ 10.5, H–C(1')); 3.02 (*s*, CH_3SO_2); 3.98 (*dd*, *J* = 8.5, 10, 1 H); 4.43 (*dd*, *J* = 4, 10, 1 H); 4.52 (*m*, 1 H); 4.88 (*m*, 1 H); 5.89 (*d*, *J* = 15.5, H–C(2)); 7.16 (*dd*, *J* = 10.5, 15.5, H–C(3)). ^{13}C-NMR ($CDCl_3$): 15.89 (*q*); 26.53 (*t*); 27.56 (*q*); 35.21 (*t*); 37.42 (*q*, CH_3SO_2); 37.82 (*s*); 46.87 (*d*); 57.15 (*d*); 70.86 (*t*); 110.13 (*t*); 124.14 (*d*); 146.82 (*s*); 149.48 (*d*); 171.23 (*s*). MS: 284 (4), 206 (12), 191 (21), 173 (33), 145 (48), 121 (53), 105 (74), 93 (58), 81 (72), 79 (95), 69 (64), 43 (62), 41 (100). Anal. calc. for $C_{14}H_{22}O_5S$ (302.39): C 55.61, H 7.33, S 10.60; found: C 55.56, H 7.06, S 10.35.

*(±)-(2E)-3-(*cis*-2',2',3'-Trimethyl-6'-methylidenecyclohex-1'-yl)-2-propenoic Acid* (**9**). A mixture of 514 mg (1.70 mmol) of **8**, 1.08 g (7.2 mmol) of NaI, 915 mg (14 mmol) of Zn powder, and 12 ml of DME was heated in an oil bath at 90° for 5 h. After cooling, the mixture was filtered through *Celite* and the flask rinsed with Et_2O and H_2O. The combined filtrates were acidified with 2N H_3PO_4 to pH 3 and extracted with Et_2O (3 × 100 ml). The org. extracts were dried ($MgSO_4$) and evaporated. Filtration through a pad of silica gel (6 g) with pentane/Et_2O 1:1 afforded 317 mg (90%) of crystalline **9**. M.p. 111–118° (> 95% pure by 400-MHz ^{1}H-NMR). An anal. sample was prepared by recrystallization from pentane at −30°. M.p. 125–126°. IR ($CHCl_3$): 3500–2500*m*, 1696*s*, 1650*m*, 1418*m*, 1280*m*, 895*m*. ^{1}H-NMR ($CDCl_3$): 0.73 (*s*, CH_3); 0.87 (*d*, *J* = 6.5, CH_3); 0.89 (*s*, CH_3); 1.26–1.59 (*m*, 3 H); 2.05–2.15 (*m*, 1 H); 2.34 (*ddd*, *J* = 2, 4.5, 13.5, 1 H); 2.59 (br. *d*, *J* ≈ 10.5, H–C(1')); 4.46 (*m*, 1 H); 4.80 (*m*, 1 H); 5.85 (*d*, *J* = 15.5, H–C(2)); 7.23 (*dd*, *J* = 10.5, 15.5, H–C(3)). ^{13}C-NMR ($CDCl_3$): 14.26 (*q*); 15.84 (*q*); 27.67 (*q*); 31.92 (*t*); 36.28 (*t*); 38.80 (*s*); 41.99 (*d*); 57.69 (*d*); 108.95 (*t*); 123.24 (*d*); 148.47 (*s*); 151.38 (*d*); 171.84 (*s*). MS: 208 (12, $M^{+\cdot}$), 193 (15), 165 (14), 147 (14), 123 (28), 83 (100), 55 (60), 43 (30), 41 (41). Anal. calc. for $C_{13}H_{20}O_2$ (208.30): C 74.96, H 9.68; found: C 75.19, H 9.93.

*(±)-(3E)-4-(*cis*-2',2',3'-Trimethyl-6'-methylidenecyclohex-1'-yl)but-3-en-2-one* (= cis-γ-*Irone*, **1**). A soln. of 86 mg (0.41 mmol) of **9** (m.p. 111–118°) in 5 ml of dry Et_2O under N_2 was cooled to −55°, and 0.85 ml (1.02 mmol) of 1.2M MeLi in Et_2O was added with vigorous stirring over 1 min. The homogeneous soln. was stirred 5 min at −55°, warmed up to 0° during 20 min, and then refluxed for 90 min. The heterogeneous mixture was cooled and then transferred with a dry syringe to 25 ml of cold 0.1N HCl which was vigorously stirred. (The flask was rinsed with Et_2O (2 × 3 ml) under N_2 with a dry syringe). After 5 min, the mixture was extracted with Et_2O (3 × 100 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on silica gel (4 g) with pentane/Et_2O 11:1 to give 76 mg (89%) of **1** as colorless oil. Capillary GC: 97% purity (t_R 16.4 min); 2 impurities at 15.0 (2%) and 15.4 min (1%), which didn't correspond, however, to other irone isomers[3]). IR (film): 3080*w*, 1697*m*, 1678*s*, 1644*m*, 1627*m*, 1390*m*, 1362*m*, 1252*m*, 992*m*, 890*m*. ^{1}H-NMR ($CDCl_3$): 0.73 (*s*, CH_3); 0.87 (*d*, *J* = 6.5, CH_3); 0.88 (*s*, CH_3); 1.26–1.60 (*m*, 3 H); 2.04–2.16 (*m*, 1 H); 2.29 (*s*, CH_3(1)); 2.35 (*ddd*, *J* = 2, 4.5, 14, 1 H); 2.56 (br. *d*, *J* ≈ 10.5, H–C(1')); 4.44 (*m*, 1 H); 4.80 (*m*, 1 H); 6.09 (*d*, *J* = 15.5, H–C(3)); 6.94 (*dd*, *J* = 10.5, 15.5, H–C(4)). ^{13}C-NMR ($CDCl_3$): 14.36 (*q*); 15.86 (*q*); 27.25 (*q*); 27.70 (*q*); 31.88 (*t*); 36.27 (*t*); 38.80 (*s*); 41.96 (*d*); 57.81 (*d*); 108.70 (*t*); 133.61 (*d*); 147.11 (*d*); 148.82 (*s*); 198.10 (*s*). MS: 206 (3, $M^{+\cdot}$), 191 (4), 163 (18), 121 (58), 43 (100).

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