

Daisuke Takano [a], Yuki Fukunaga [a], Matsumi Doe [a],
Kazuo Yoshihara [b] and Takamasa Kinoshita* [a]

[a] Department of Chemistry, Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

[b] Suntory Institute for Bioorganic Research, Shimamoto-cho, Osaka 618, Japan

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The title compound was efficiently synthesized from 3-furoic acid and 3-bromoanisole *via* the Birch reduction.

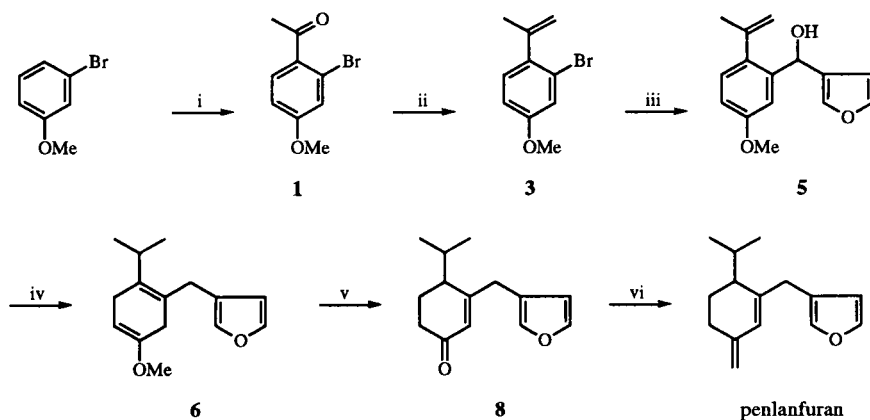
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Penlanfuran is a furanoid sesquiterpene with a novel skeleton isolated from the marine sponge *Dysidea fragilis* of North-Brittany waters [1]. A synthesis of the unnatural enantiomer (+)-penlanfuran was accomplished by Pietra *et. al.* [2], however, the overall yield was 0.7% (7 steps) from (+)-cryptose. In this paper we describe an efficient synthesis of (±)-penlanfuran as an application of the Birch reduction of 3-acylfurans [3].

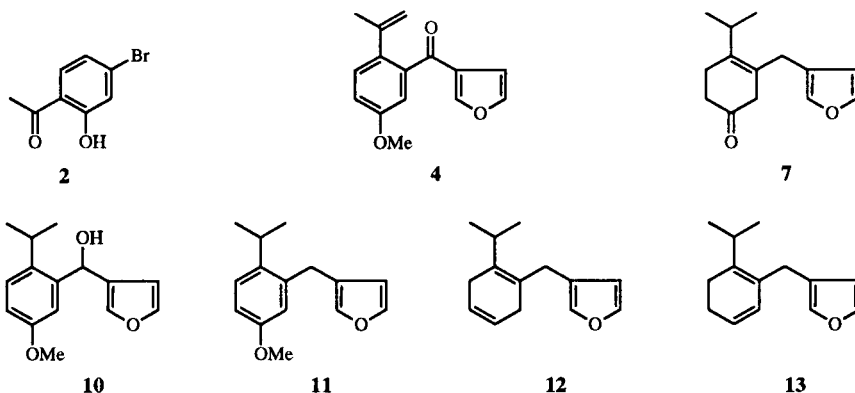
The Friedel-Crafts reaction of 3-bromoanisole with acetyl chloride in carbon disulfide gave 2-bromo-4-methoxyacetophenone **1** (73%) and 4-bromo-2-hydroxyacetophenone **2** (25%), respectively (Scheme 1). The structure assigned to **1**

was confirmed by nmr and a derivation by reductive-debromination [4] to the known 4-methoxy- α -phenethylalcohol [5]. Undesirable *ortho* demethylation occurred in the ring acylation to afford hydroxyacetophenone **2** [6]. The bromoisopropenyl derivative **3** was obtained by the Wittig olefination of **1** with the ylide generated from methyltriphenylphosphonium bromide and *n*-butyllithium. Although treatment of the Grignard reagent derived from **3** with *N*-methoxy-*N*-methyl-3-furamide gave 3-arylfuran **4** in low yield (32%), the coupling reaction of 3-lithio-4-isopropenylanisole prepared from **3** and *n*-butyllithium in tetrahydrofuran with furan-3-carbaldehyde produced **5** in 93% yield.

Scheme 1

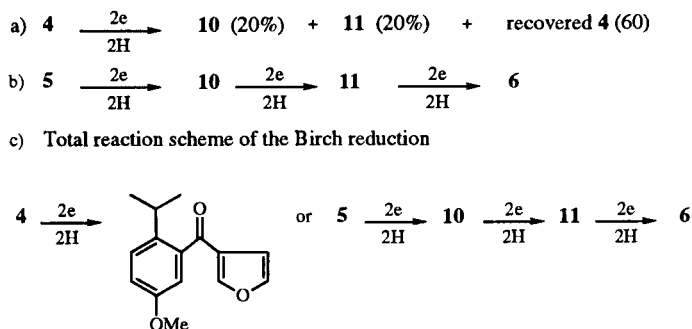


i) CH_3COCl , AlCl_3 , CS_2 rt, 12 hours, 73% ii) $\text{Ph}_3\text{PCH}_2\text{Br}$, *n*-BuLi, ether, reflux, 3 hours, 74% iii) a) *n*-BuLi, THF, -78°
b) furan-3-carbaldehyde, 1 hour, 93% iv) 6 Li, NH_3 , EtOH, -33° , 89% v) HCl-MeOH, rt, 12 hours vi) ref. [6]

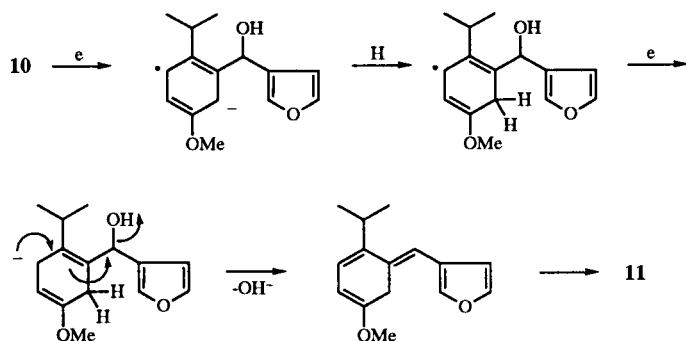


The Birch reduction of **4** with 8 equivalents of lithium and **5** with 6 equivalents of lithium provided the desired intermediate **6** for the synthesis of penlanfuran, in high yield (91% from **4**, 89% from **5**) along with the demethoxy products **12** and **13** (3~6%), respectively. As shown in Scheme 2, reduction of **4** with 2 equivalents of lithium

Scheme 2

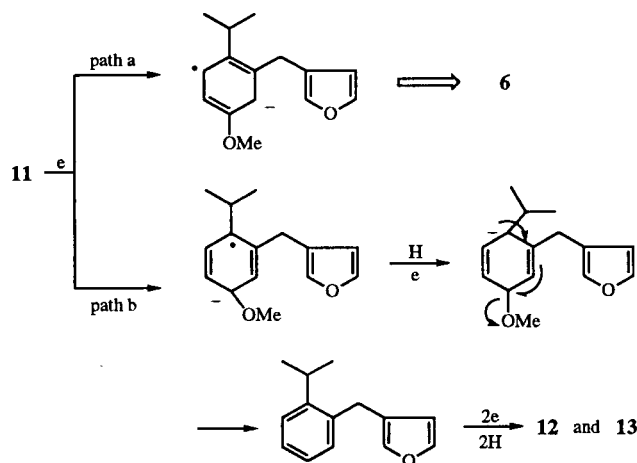


gave a mixture of **10** (20%), **11** (20%) and recovered starting material (60%). On the other hand, reduction of **5** with 2 equivalents of lithium gave a sole product **10**, which was reduced with 2 equivalents of lithium to a single product **11**, and **6** was obtained from **11** by reduction with 2 equivalents of lithium. From these results mentioned above, the total reaction scheme of the Birch reduction is shown as c) in Scheme 2. Reductive demethoxylation and elimination of the hydroxyl group are involved in the Birch reduction of $5 \rightarrow 6$. Each mechanism of these eliminations is shown in Schemes 3 and 4 [3]. Acid hydrolysis of **6** proceeded slowly at room temperature to provide a mixture of ketones. The α,β -enone **8** and its isomeric $\beta\gamma$ -enone **7** were cleanly separated by chromatography in 56% and 36% yields, respectively. On treatment with *p*-toluenesulfonic acid in dichloromethane, the $\beta\gamma$ -enone **7** isomerized to the conjugated α,β -enone **8**.

Scheme 3
Mechanism of deoxygenation

The conversion of the enone **8** by Wittig olefination to penlanfuran was carried out according to the procedure reported by Pietra [7]. A colorless oil was obtained after

separation and purification by column chromatography on silica gel of the residue of the reaction mixture. The resulting compound was identical by comparing its ^1H and ^{13}C nmr spectra with those reported [1]. The overall yield in our synthesis was 28% (6 steps) from 3-bromoanisole.

Scheme 4
Mechanism of demethoxylation

EXPERIMENTAL

Column chromatography was performed with silica gel (Merck NO. 7734; 63-200 μm), and thin layer chromatography was performed with Kieselgel 60 GF₂₅₄ (Merck), detecting by uv light. The ir spectra were measured on a JASCO A-102 IR spectrophotometer. The ^1H and ^{13}C nmr (deuteriochloroform), and mass spectra were recorded on JEOL LA-300 (300 MHz) and JEOL AX-500 spectrometers, respectively. Freshly dried and distilled tetrahydrofuran was used.

2-Bromo-4-methoxyacetophenone (**1**).

A solution of 3-bromoanisole (18.7 g, 0.1 mole) in carbon disulfide (30 ml) was added dropwise at room temperature to the mixture prepared from acetyl chloride (7.9 g, 0.1 mole) and aluminium trichloride (13.4 g, 0.1 mole) in carbon disulfide (180 ml). The mixture was stirred overnight at room temperature, then poured into ice-water and extracted with dichloromethane. After washing twice with 1*N* sodium hydroxide (50 ml) the organic layer was distilled to afford **1** (16.1 g, 73%), bp 106-109°/mm Hg; ir (neat): 1685, 1595, 1250, 1230, 1025 cm^{-1} ; ^1H nmr: δ 2.59 (s, 3H), 3.81 (s, 3H), 6.85 (dd, 1H, $J = 2.5$ Hz, $J = 9.0$ Hz, H-5), 7.12 (d, 1H, $J = 2.5$ Hz, H-3), 7.56 (d, 1H, $J = 9.0$ Hz, H-6); ^{13}C nmr: δ 29.9 (q), 55.7 (q), 113.1 (d, C-5), 119.5 (d, C-3), 121.2 (s, C-2), 131.6 (d, C-6), 132.7 (s, C-1), 161.9 (s, C-4), 198.9 (s, C=O).

Anal. Calcd. for $\text{C}_9\text{H}_9\text{BrO}_2$: C, 47.19; H, 3.96. Found: C, 47.24; H, 4.01.

The alkaline solution was acidified with concentrated hydrochloric acid, and extracted with dichloromethane and distilled to afford 4-bromo-2-hydroxyacetophenone **2** (5.2 g, 25%), bp 81-83°/7 mm Hg, mp 41° (from *n*-hexane); ir (nujol): 1630,

1610, 1210 cm^{-1} ; ^1H nmr: δ 2.61 (s, 3H), 7.03 (dd, 1H, J = 2.0 Hz, J = 8.3 Hz, H-5), 7.17 (d, 1H, J = 2.0 Hz, H-3), 7.57 (d, 1H, J = 8.3 Hz, H-6), 12.45 (s, 1H, OH); ^{13}C nmr: δ 26.4 (q), 118.3 (s, C-4), 121.2 (d, C-3), 122.2 (d, C-5), 130.5 (s, C-1), 131.4 (d, C-6), 162.5 (s, C-2), 203.8 (s, C=O).

Anal. Calcd. for $\text{C}_8\text{H}_7\text{BrO}_2$: C, 44.68; H, 3.28. Found: C, 44.75; H, 3.22.

To a stirred suspension of lithium aluminium hydride (1.90 g) in tetrahydrofuran (50 ml) was added **1** (2.29 g, 10 mmoles) in tetrahydrofuran (20 ml). After reflux for 6 hours, usual work-up gave 4-methoxy- α -phenetylalcohol (1.14 g, 75%), bp 103–105°/10 mm Hg, [lit [5] bp 110°/13 mm Hg]; ^1H nmr: δ 1.66 (d, 3H, J = 6.4 Hz), 2.10 (d, 1H, J = 3.3 Hz, OH), 3.78 (s, 3H), 4.82 (dq, 1H, J = 3.3 Hz, J = 6.4 Hz), 6.86 (d, 2H, J = 8.8 Hz), 7.27 (d, 2H, J = 8.8 Hz); ^{13}C nmr: δ 25.1 (q), 55.2 (q), 69.6 (d), 113.7 (d), 126.6 (d), 138.1 (s), 158.7 (s).

3-Bromo-4-isopropenylanisole (**3**).

To a stirred solution prepared at room temperature for one hour from methyltriphenylphosphonium iodide (8.08 g, 20 mmoles) in ether (100 ml) and the equivalent of *n*-butyllithium (1.6N in hexane, 12.5 ml) was added **1** (4.58 g, 20 mmoles) in ether (40 ml) under nitrogen atmosphere at room temperature. The mixture was boiled for 3 hours with stirring, filtered and evaporated. The residue was distilled to give **3** (3.36 g, 74%) as a colorless oil, bp 66–69°/2 mmHg, ^1H nmr: δ 2.08 (s, 3H), 3.79 (s, 3H), 4.93 (s, 1H), 5.21 (s, 1H), 6.82 (dd, 1H, J = 2.5 Hz, J = 8.5 Hz, H-6), 7.11 (d, 1H, J = 2.5 Hz, H-2), 7.11 (d, 1H, J = 8.5 Hz, H-5); ^{13}C nmr: δ 23.8 (q), 55.5 (q), 113.3 (d, C-6), 116.1 (t), 118.0 (d, C-2), 121.8 (s, C-3), 130.1 (d, C-5), 137.2 (s, C-4), 145.4 (s), 159.0 (s, C-1).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{BrO}$: C, 52.89; H, 4.88. Found: C, 53.14; H, 4.94.

3-[(2-Isopropenyl-5-methoxy)benzoyl]furan (**4**).

To a stirred solution of *N*-methoxy-*N*-methyl-3-furamide [8] (3.10 g, 20 mmoles) in dry benzene (60 ml) was added the Grignard reagent prepared from **3** (4.51 g, 20 mmoles) and magnesium (485 mg) in tetrahydrofuran (50 ml) at 0°. After stirring for 3 hours at room temperature, the mixture was quenched by addition of water and acidified with dilute hydrochloric acid. The extract with ether was chromatographed with benzene to give **4** (1.54 g, 32%); ir (neat): 1655, 1600, 1560, 1230, 1150, 820 cm^{-1} ; ^1H nmr: δ 1.88 (s, 3H), 3.80 (s, 3H), 4.77 (s, 1H), 4.90 (s, 1H), 6.71 (d, 1H, J = 1.8 Hz), 6.83 (d, 1H, J = 2.5 Hz), 6.88 (dd, 1H, J = 2.5 Hz, J = 8.5 Hz), 7.18 (d, 1H, J = 8.5 Hz), 7.34 (d, 1H, J = 1.8 Hz), 7.56 (s, 1H); ^{13}C nmr: δ 23.9 (q), 55.5 (q), 109.3 (d), 112.9 (d), 115.9 (d), 116.4 (t), 128.2 (s), 129.6 (d), 134.7 (s), 140.0 (s), 143.5 (s), 144.2 (d), 149.3 (d), 158.4 (s), 191.9 (s); hrms: Calcd. for $\text{C}_{15}\text{H}_{14}\text{O}_3$: (M^+) 242.0943. Found: m/z 242.0955.

(Furan-3-yl)[(2-isopropenyl-5-methoxy)phenyl]methanol (**5**).

To a stirred solution of phenyllithium derivative prepared from **3** (1.00 g, 4.40 mmoles) and *n*-butyllithium (1.6N in hexane, 2.76 ml) in tetrahydrofuran (30 ml) was added dropwise during 15 minutes the solution of furan-3-carbaldehyde (470 mg, 4.41 mmoles; prepared from 3-furoic acid) in tetrahydrofuran (5 ml) at -78°. After stirring for 15 minutes at -78° and additional 45 minutes at room temperature, the reaction mixture was quenched by addition of saturated ammonium chloride and

extracted with ether. The extract was chromatographed to give **5** (671 mg, 63%; 93% based on the consumed **3**) and recovered **3** (332 mg); ir (neat): 3450, 1620, 1510, 1240, 1030 cm^{-1} ; ^1H nmr: δ 2.00 (dd, 3H J = 0.9 Hz, J = 1.5 Hz), 2.10 (d, 1H, J = 2.8 Hz, OH), 3.80 (s, 3H), 4.80 (dd, 1H, J = 0.9 Hz, J = 2.2 Hz, =CH₂), 5.19 (quint, 1H, J = 1.5 Hz, J = 2.2 Hz, =CH₂), 5.99 (d, 1H, J = 2.8 Hz), 6.33 (bs, 1H), 6.82 (dd, 1H, J = 2.6 Hz, J = 8.6 Hz), 7.07 (d, 1H, J = 8.5 Hz), 7.09 (d, 1H, J = 2.6 Hz), 7.24 (bs, 1H), 7.36 (bs, 1H); ^{13}C nmr: δ 25.6 (q), 55.8 (q), 66.2 (d), 109.5 (d), 111.7 (d), 113.5 (d), 115.8 (t), 129.1 (d), 134.9 (s), 140.1 (d), 141.0 (s), 143.2 (s), 143.2 (d), 144.1 (s), 158.8 (s); hrms: Calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_3$: (M^+) 244.1099. Found: m/z 244.1114.

5-[(Furan-3-yl)methyl]-4-isopropyl-1-methoxy-1,4-cyclohexadiene (**6**).

The Birch Reduction of **4** and **5**.

a) Lithium metal (189 mg, 9 equivalents) was added in pieces to a stirred solution of **4** (726 mg, 3 mmoles) in liquid ammonia (50 ml) and tetrahydrofuran (5 ml) in the presence of ethanol (1.38 g) at -33°. The mixture was then stirred for 30 minutes and the ammonia was removed by evaporation at room temperature. The residue was extracted with ether and chromatographed to give **6** (633 mg, 91%) and a mixture of demethoxy dihydro derivatives **12** and **13** (3–4%).

b) Lithium metal (245 mg, 7 equivalents) was added to a solution of **5** (1.22 g, 5 mmoles) in ammonia-tetrahydrofuran-ethanol. The usual work-up as above gave oily compound **6** (1.03 g, 89%), **12** and **13** (5–6%); ^1H nmr: δ 1.01 (d, 6H, J = 6.8 Hz), 2.66 (d, 2H, J = 6.8 Hz), 2.77 (dd, 2H, J = 3.3 Hz, J = 6.8 Hz), 3.04 (sep, 1H, J = 6.8 Hz), 3.19 (s, 2H), 3.53 (s, 3H), 4.63 (t, 1H, J = 3.3 Hz), 6.22 (bs, 1H), 7.20 (bs, 1H), 7.33 (t, 1H, J = 1.7 Hz); ^{13}C nmr: δ 21.0 (q), 24.6 (t), 27.6 (t), 28.9 (d), 33.1 (t), 53.8 (q), 90.1 (d), 111.1 (d), 123.1 (s), 123.7 (s), 134.1 (s), 139.4 (d), 142.8 (d), 152.7 (s).

Compounds **12** and **13** were obtained as an inseparable oily mixture. No signals for the methoxyl group were observed in ^1H nmr and ^{13}C nmr.

(Furan-3-yl)[(2-isopropyl-5-methoxy)phenyl]methanol (**10**).

This compound was obtained as an oil by the Birch reduction of **5** with 2 equivalents of lithium; ^1H nmr: δ 1.10 (d, 3H, J = 7.0 Hz), 1.21 (d, 3H, J = 7.0 Hz), 2.04 (bs, 1H), 3.13 (sep, 1H, J = 7.0 Hz), 3.79 (s, 3H), 6.06 (d, 1H, J = 3.3 Hz), 6.33 (s, 1H), 6.85 (dd, 1H, J = 2.8 Hz, J = 8.4 Hz), 7.09 (d, 1H, J = 2.8 Hz), 7.21 (s, 1H), 7.23 (d, 1H, J = 8.4 Hz), 7.37 (bt, 1H).

3-[(Furan-3-yl)methyl]-4-isopropylanisol (**11**).

This compound was obtained as an oil by Birch reduction of **10** with 2 equivalents of lithium; ^1H nmr: δ 1.17 (d, 6H, J = 7.3 Hz), 3.11 (sep, 1H, J = 7.3 Hz), 3.77 (bs, 2H), 3.75 (s, 3H), 6.23 (bs, 1H), 6.70 (d, 1H, J = 2.7 Hz), 6.77 (dd, 1H, J = 2.7 Hz, J = 8.4 Hz), 7.09 (bs, 1H), 7.20 (d, 1H, J = 8.4 Hz), 7.34 (t, 1H, J = 1.8 Hz); ^{13}C nmr: δ 23.9 (q), 28.2 (d), 28.5 (t), 55.1 (q), 111.1 (d), 111.9 (d), 115.2 (d), 124.3 (s), 126.3 (d), 138.1 (s), 139.0 (s), 139.6 (d), 142.9 (d), 157.4 (s).

3-[(Furan-3-yl)methyl]-4-isopropylcyclohex-2-enone (**8**) and its Isomeric 3-Enone (**7**).

To a stirred solution of **6** (380 mg, 1.6 mmoles) in methanol (5 ml) a catalytic amount of concentrated hydrochloric acid was added at room temperature. After stirring for 12 hours, the mixture was neutralized with sodium bicarbonate and extracted with

ether. The residue was chromatographed (hexane-ethyl acetate, 10:1) to give **8** (R_f 0.12) (200 mg, 56%) and **7** (R_f 0.25) (127 mg, 36%). Compound **7** was isomerized into **8** in dichloromethane in the presence of *p*-toluenesulfonic acid.

Compound **8** was obtained as an oil; ^1H nmr: δ 0.90 (d, 3H, $J = 6.6$ Hz), 1.05 (d, 3H, $J = 6.6$ Hz), 1.94 (m, 2H), 2.23 (m, 2H), 2.45 (m, 2H), 3.37 (bs, 2H), 5.91 (d, 1H, $J = 0.9$ Hz), 6.22 (bs, 1H), 6.27 (bs, 1H), 7.34 (bs, 1H); ^{13}C nmr: δ 18.5 (q), 21.5 (q), 22.7 (t), 29.0 (d), 32.0 (t), 35.4 (t), 43.4 (d), 111.1 (d), 120.5 (s), 127.8 (d), 140.1 (d), 143.3 (d), 166.5 (s), 199.4 (s); hrms: Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2$: (M^+) 218.1306. Found: m/z 218.1306.

Compound **7** was obtained as an oil; ^1H nmr (500 MHz; Varian U-500): δ 1.04 (d, 6H, $J = 6.9$ Hz), 2.40 (bd, 2H, $J = 2.7$ Hz), 2.41 (bd, 2H, $J = 2.7$ Hz), 2.80 (s, 2H), 3.07 (sep, 1H, $J = 6.9$ Hz), 3.20 (s, 2H), 6.19 (d, 1H, $J = 1.0$ Hz), 7.18 (dd, 1H, $J = 0.9$ Hz, $J = 1.5$ Hz), 7.35 (dd, 1H, $J = 0.8$ Hz, $J = 1.7$ Hz); ^{13}C nmr: δ 20.6 (q), 23.2 (t), 27.5 (t), 29.1 (d), 39.0 (t), 43.8 (t), 110.8 (d), 122.5 (s), 124.7 (s), 138.0 (s), 139.3 (d), 143.1 (d), 211.7 (s); hrms: Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2$: (M^+) 218.1306. Found: m/z 218.1343.

Penlanfuran.

($\pm$)-Penlanfuran was synthesized in 70% yield from **8** according to the procedure reported by Pietra *et al.* [7]; ^1H nmr (300 MHz): δ 0.81 (d, 3H, $J = 6.6$ Hz), 0.96 (d, 3H, $J = 6.6$ Hz), 1.64 (m, 2H), 2.05 (m, 2H), 2.21 (m, 1H), 2.40 (m, 1H), 3.15 and 3.26 (q, 2H,

$J_{AB} = 15.8$ Hz), 4.69 (s, 1H), 4.71 (s, 1H), 6.04 (s, 1H), 6.24 (s, 1H), 7.23 (bs, 1H), 7.35 (dd, 1H, $J = 1.5$ Hz, $J = 1.8$ Hz); ^{13}C nmr: δ 17.8 (q), 21.4 (q), 22.9 (t), 28.7 (t), 28.8 (d), 31.3 (t), 42.3 (d), 109.1 (t), 111.4 (d), 122.8 (s), 127.7 (d), 139.7 (d), 142.7 (d), 143.5 (s), 143.8 (d).

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REFERENCES AND NOTES

- [1] G. Guella, A. Guerriero, P. Traldi, and F. Pietra, *Tetrahedron Letters*, **24**, 3897 (1983).
- [2] I. Mancini, G. Guella, M. Cavazza, and F. Pietra, *Helv. Chim. Acta*, **73**, 652 (1990).
- [3] To be published.
- [4] G. J. Karabatsos and R. L. Shone, *J. Org. Chem.*, **33**, 619 (1968).
- [5] S. Stedman, *J. Chem. Soc.*, 611 (1929).
- [6] G. P. Rizzi, *Synth. Commun.*, **13**, 1173 (1983).
- [7] G. Guella, A. Guerriero, and F. Pietra, *Helv. Chim. Acta*, **68**, 39 (1985).
- [8] T. Kinoshita, D. Ichinari, and J. Sinya, *J. Heterocyclic Chem.*, **33**, 1313 (1996).