Total synthesis of cadalen-15-oic acid

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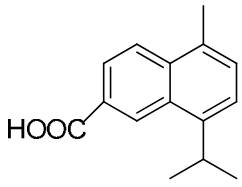
Abstract
Two routes for the total synthesis of cadalen-15-oic acid **1** are described. Route A which involves 10 steps deals with the conversion of 5-methoxy-α-tetralone **3** into the cadalen-15-oic acid **1**. The transformation of 6-methoxy-α-tetralone **5** into the cadalen-15-oic acid **1** in 9 steps is described in route B. The deoxygenation of the compound **6** with Pd/C, Mg metal and ammonium acetate and the nickel catalyzed cyanation of triflate **14** are the key steps in route A and route B respectively.

Keywords: Cadalen-15-oic acid, 5-methoxy-α-tetralone, 6-methoxy-α-tetralone, deoxygenation, cyanation.

Introduction

Cadalen-15-oic acid **1** is a sesquiterpene isolated from the aerial parts of *Heterotheca inuloides* (Mexican arnica)[1] and the bark of *Scorodocarpus borneensis*[2]. Its structure was proposed by Delgado G. *et al.*[1] and Wiart M. *et al.*[2] on the basis of spectral data. To date only one synthesis of **1** has been reported.[3]



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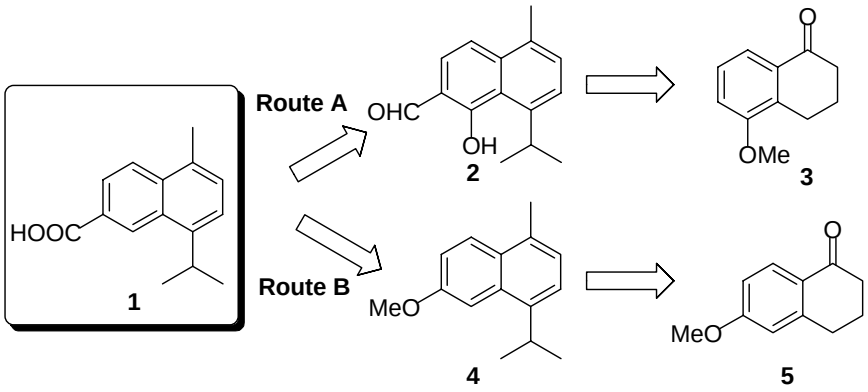
Substituted 1-tetralones have played an important role in organic synthesis as a result of their high reactivity and suitability as starting materials for a wide range of natural products and synthetic compounds with biological activities and other useful properties.[4-8] As a part of a study aimed at expanding the synthetic utility of 1-tetralone[8-12] we tried to devise an alternative synthesis for the acid **1** which has attracted our attention due to its anti-inflammatory and analgesic activity. Two different routes were developed to achieve the synthesis of the target molecule **1**.

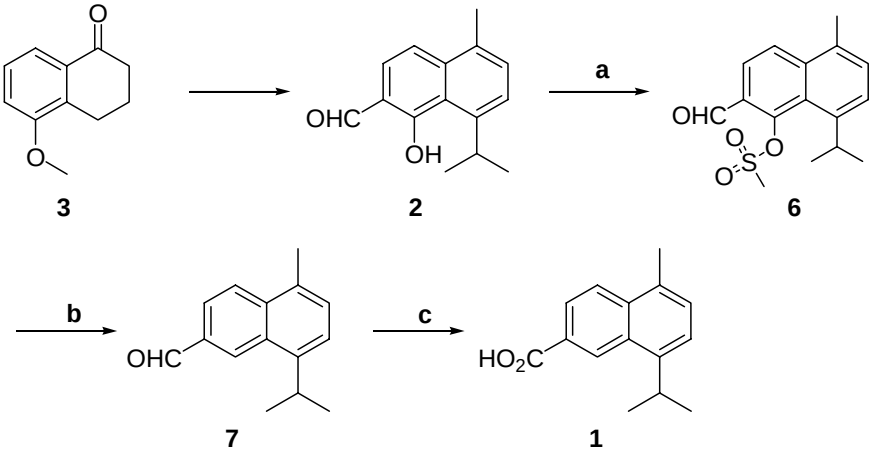
Results and Discussion

Two retrosynthetic routes envisaged for the desired cadalen-15-oic acid **1** as depicted in Scheme 1 led us to select the methoxy-α-tetralones **3** and **5** as starting material for its synthesis. In this paper we disclose the strategy designed to achieve the synthesis of the acid **1** from the tetralones **3** and **5**.



Scheme 1

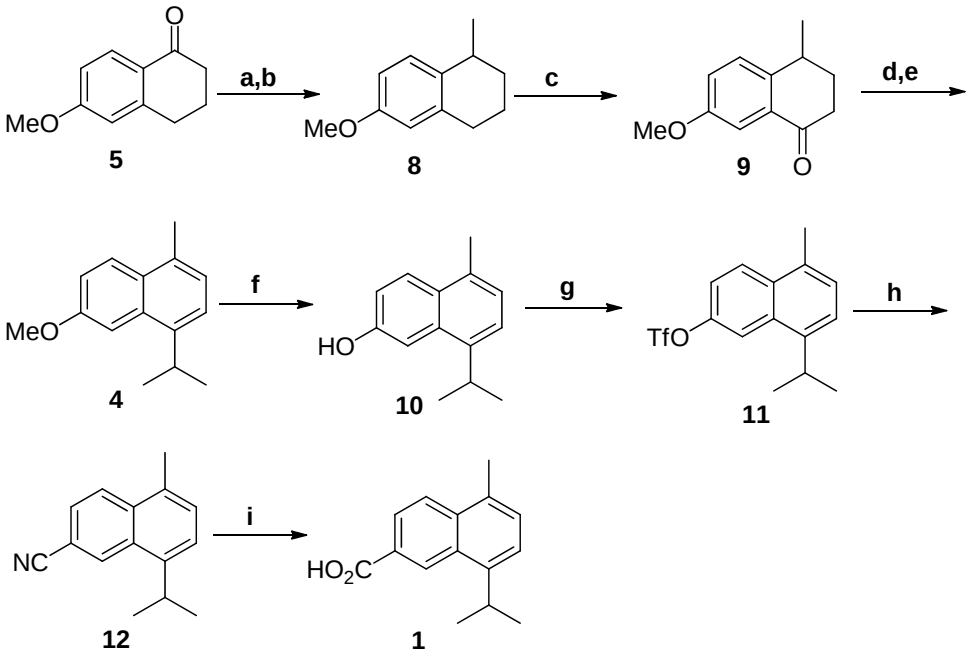
As outlined in Scheme 2 (route A) the hydroxy aldehyde **2**, prepared from tetralone **3** by the published procedure[12] was treated with mesyl chloride to produce the corresponding aryl mesylate **6** in 91% yield, which on treatment with 10% palladium-charcoal, magnesium metal and ammonium acetate[13] afforded the compound **7** in 35% yield. Other methods for reductive hydrogenolysis[14,15] were tried in order to improve the low yield, but poor conversions and hydrolysis of sulfonate to naphthol were observed and this is definitively due to the presence of the electron-withdrawing group at the *ortho* position of aryl mesylate. Finally, the cadalen-15-oic acid **1** was prepared by oxidation of the resulting aldehyde **7** with sodium biphosphate, sodium chlorite and sulfamic acid.[16]



Scheme 2 (route A). *Reagents and conditions:* a: CH_3SO_2Cl, Et_3N. b: 10%Pd/C, Mg, MeOH, NH_4OAc. c: NaH_2PO_4, $NaClO_2$, H_2NSO_3H.

Although the above synthetic strategy allowed us to obtain the cadalen-15-oic acid **1**, the approach proved to be somewhat complicated owing to the difficulty in the hydrodeoxygenolysis of aryl mesylate **6**. Therefore, an alternative route B depicted in Scheme 3 was investigated. Treatment of the commercially available 6-methoxy-1-tetralone **5** with methylmagnesium bromide followed by dehydration afforded an olefin, which was easily transformed into the tetralin **8** by catalytic hydrogenation with 5% Pd/C. Oxidation of **8** with 10% chromic acid in acetic acid at 0°C yielded the tetralone **9** in 62%. Alternative approaches for the syntheses of tetralone **9** have been reported by a lengthy procedure.[17,18]

Treatment of **9** with *i*-$Pr_3ZnMgCl$ complex, generated *via* iPr_2Zn from inexpensive zinc (II) chloride[19]and iPrMgCl, produced a tertiary alcohol which subsequent dehydration with acid and dehydrogenation with 1.2 equiv of 2,3-dichloro-5,6-dicyanoquinone (DDQ) provided naphthalene **4**. The Grignard reaction can also be achieved in presence of cerium chloride[20,21] but as the cerium chloride is expensive zinc chloride was chosen for this experiment. In absence of zinc chloride[19] or cerium chloride,[20,21] the Grignard reaction yields undesired products that result from reduction and aldol reactions. Demethylation of aromatic ether **4** with 48% aqueous hydrobromic acid furnished naphthol **10** in 87% yields whose conversion to trifluoromethanesulfonate ester **11** was performed by mixing **10** with trifluoromethanesulfonic anhydride in the presence of triethylamine. The introduction of triflate group was found essential for its facile transformation to nitrile and subsequently to carboxylic acid. Treatment of trifluoromethanesulphonate ester **11** with potassium cyanide in the presence of tetrakistriphenylphosphinenickel(0) generated *in situ* from bistriphenylphosphinenickel(II) chloride,[22,23] zinc and phosphine, afforded carbonitrile **12** in 81% yield which was hydrolyzed with ethanolic potassium hydroxide to obtain cadalen-15-oic acid **1** in 65% yield. Its m.p. and spectroscopic data (NMR ^1H and ^{13}C) were identical with those reported.[2,3]



Scheme 3. Route B. *Reagents and conditions:* a) i:MeMgBr, ii: HCl 6N; b)H_2, Pd/C 10%, c)10% CrO_3-CH_3CO_2H; d) i: iPrMgCl, $ZnCl_2$, ii: HCl; e)DDQ; f) HBr 48%; g)$(CF_3SO_2)_2O$, Et_3N; h) KCN, $Ni(PPh_3)_2Cl_2$, Zn, PPh_3; j) H_2O, CH_3CH_2OH, KOH

Conclusion

In summary two distinct approaches for the synthesis of cadalen-15-oic acid **1** have been described. The key step in the first approach was the hydrogenolysis of the hydroxyl group which provided the acid **1** in moderate yield. In the second approach, the key step was the transformation of hydroxyl group (via triflate and nitrile) to acid group to obtain acid **1** in good yield.
The present synthesis proceeds via intermediates which may prove useful in the synthesis of other sesquiterpenoids.

Experimental Section

General. Unless otherwise stated, IR spectra were taken on Nicolet FT instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker AM 300 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra of compounds **7**, **8**, **9**, **10**, **11**, **12** and **1**, were run on (GC/MS) gas chromatography Hewlett Packard 5890 Quadrupolar 5972 Serie S. Mass spectra of compound **6** was recorded on a Thermo Finnigan TSQ Quantum ultra AM (Electron spray ionization) mass spectrometer. Column chromatography was performed on silica gel (Merck grade 60, 70-230 mesh). The spectral and analytical data of all new compounds have been reported in the Experimental Section. Microanalyses were carried out at the Chemistry Department, IVIC, Caracas.

2-formyl-8-isopropyl-5-methyl-1-naphthylmethane sulfonate 6. To a solution of the aldehyde **2** (210 mg, 0.91 mmol) and triethylamine (0.15 mL, 1.10 mmol) in dichloromethane (5 mL) was added dropwise methanesulfonyl chloride (0.1 mL, 1.29 mmol) and the mixture was stirred at ambient temperature for 2 hours. The resulting solution was diluted with water and extracted with dichloromethane. The organic extract was washed, dried over anhydrous magnesium sulfate, concentrated under reduced pressure and purified by column chromatography (eluent hexane/ether 7:3) on silica gel. The desired product **6** (253 mg) was obtained as pink solid in 91% yield, mp. 86-88 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.32 (d, 6H, C12-2CH_3, *J*=6.90 Hz), 2.58 (s, 3H, C5-CH_3), 3.16 (sept., 1H, C12-H, *J*=6.80 Hz), 3.44 (s, 3H, OSO_2CH_3), 7.24 (d, 1H, ArH, *J*=7.0Hz), 7.41 (d, 1H, ArH, *J*=7.0Hz), 7.89 (d, 1H, ArH, *J*=8.3Hz), 7.99 (d, 1H, ArH, *J*=8.3Hz), 10.43 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.98, 23.85, 30.56, 38.05 (OSO_2CH_3), 112.51, 119.11, 119.47, 120.65, 125.31, 126.85, 139.08, 139.73, 153.76, 191.90 ppm; m/z: 307 (M^++1), 263 (M^+-C_3H_7), 228 (M^+-CH_3O_2S); Anal. Calc. for $C_{16}H_{18}O_4S$ requires C, 62.72; H, 5.92; S, 10.47 (Found: C, 62.90; H, 6.07; S, 10.32).
8-isopropyl-5-methyl-2-naphthaldehyde 7. To a solution of aryl mesylate **6** (563 mg, 1.84 mmol) in dry methanol (30 mL) was added palladium-charcoal 10% (0.41 mg), magnesium metal (108 mg, 4.43 mmol), ammonium acetate (2.13 g, 27.74 mmol), and the mixture was stirred at room temperature for 24 hours. The resulting mixture was filtered and the filtrate was extracted with ether, washed, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue on chromatographic purification (hexane/ether 7:3) yielded the aldehyde **7** (136 mg, 35 %) as a pale yellow oil; ν_{max} (KBr) 1645 cm^{-1} (CO); ^{1}H NMR (300

MHz, $CDCl_3$) δ: 1.39 (d, 6H, C12-2CH_3, *J*=6.78 Hz), 2.68 (s, 3H, C5-CH_3), 3.69 (sept., 1H, C12-H, *J*=6.80 Hz), 7.15 (d, 1H, ArH, *J*=8.3Hz), 7.25 (d, 1H, ArH, *J*=8.3Hz), 7.95-8.21 (m, 2H, Ar-2H), 8.64 (bs, 1H, ArH), 10.15 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.50, 23.58, 28.65, 120.82, 122.05, 123.96, 125.97, 130.26, 130.65, 131.82, 132.40, 134.69, 139.88, 192.02 ppm; m/z: 212 (M^+), 197 (M^+-CH_3), 183 (M^+-CHO), 182 (M^+-2CH_3); Anal. Calc. for $C_{15}H_{16}O$ requires C, 84.87; H, 7.60 (Found: C, 85.15; H, 7.77).

6-methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene 8. To a solution of commercially available 6-methoxy-1-tetralone **5** (3.20 g, 18.18 mmol) in dry ether was slowly added a solution of 3M methyl magnesium bromide in ether (7 mL, 21 mmol) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 4h, and then the hydrochloric acid was added at 0^{o}C until pH = 2 was reached. The mixture was stirred for 2 h and extracted with ether. The organic extract was washed with water, dried and evaporated under reduced pressure. The resulting compound on flash chromatography (eluent hexane/ether 9:1) yielded the olefin (2.75 g) as a colorless oil in 87% yield which was hydrogenated with 5% palladium-charcoal (220 mg) and ethanol (20 mL) for 6 h at 300 psi to give the compound **8** (2.64 g, 95%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, 3H, CH_3, *J*=7.0 Hz), 1.40-1.74 (m, 2H, C2-2H), 1.76-1.90 (m, 2H, C3-2H), 2.71-2.78 (m, 2H, C4-2H), 2.80-2.88 (m, 1H, C1-1H), 3.77 (s, 3H, OCH_3), 6.61 (s, 1H, C5-1H), 6.71 (d, 1H, C7-1H, *J*= 8.49 Hz), 7.12 (d, 1H, C8-1H, *J*=8.49Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.58, 23.00, 30.40, 31.80, 31.83, 55.15, 111.98, 113.47, 129.01, 134.41, 138.02, 157.31 ppm; m/z: 176 (M^+), 161 (M^+-CH_3), 146 (M^+-CH_2O); Anal. Calc. for $C_{12}H_{16}O$ requires C, 81.77; H, 9.15 (Found: C, 81.43; H, 9.29).

7-methoxy-4-methyl-3,4-dihydronaphthalen-1(2*H*)-one 9. To a stirred solution of compound **8** (100 mg, 0.56 mmol) in CH_3CN/H_2O (3:1, v/v) (8 mL) was added *tert*-butyl hydroperoxide (0.4 ml/2.80 mmol, 70% aqueous solution) and sodium chlorite (76 mg, 0.67 mmol). The reaction mixture was heated at 50 ^{o}C for 12 hours, then diluted with sodium sulfite solution (10%) and extracted with dichloromethane. The organic extracts were washed with water and saturated aqueous $NaHCO_3$, dried and chromatographed (hexane/ether 1:1) to obtain the tetralone **9** (63 mg, 60%) as a colorless liquid; ν_{max} (KBr) 1675 cm^{-1} (CO); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (d, 3H, C4-CH_3, *J*=7.0 Hz), 1.79-1.91 (m, 1H, C3-1Ha), 2.15-2.26 (m, 1H, C3-1He), 2.51-2.61 (m, 1H, C2-1Ha), 2.71-2.81 (m, 1H, C2-1He), 2.99-3.05 (m, 1H, C4-1He), 3.81 (s, 3H, OCH_3), 7.07 (dd, 1H, C6-1H, *J*= 8.6Hz, *J*= 2.9Hz), 7.24 (s, 1H, C5-1H), 7.50 (d, 1H, C8-1H, *J*=2.9Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.72, 30.77, 32.09, 36.33, 55.42, 109.13, 121.80, 128.63, 132.64, 141.58, 158.11, 198.31 ppm; m/z: 190 (M^+), 175 (M^+-CH_3), 147 (M^+-CH_3CO); Anal. Calc. for $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42 (Found: C, 76.05; H, 7.58).

4-isopropyl-6-methoxy-1-methylnaphthalene 4. To a solution of isopropylmagnesium chloride (2M, 6.5 mL, 12.60 mmol) in dry tetrhydrofuran (5 mL) was added zinc chloride (11 mg, 0.84 mmol) under a nitrogen atmosphere and stirred at room temperature for 1 h. Tetralone **9** (1.60 g, 8.42 mmol) was added dropwise at 0^{o}C and stirred at room temperature for 6 h. The reaction mixture was quenched by saturated aqueous ammonium chloride and extracted with diethyl ether. To the resulting organic extract was added hydrochloric acid (6N, 8 mL) and stirred for 3 h at room temperature. The aqueous phase was extracted with ether and the combined extracts were dried and concentrated. The residue on chromatographic purification (hexane/ether 9:1) yielded the olefin (1.54 g, 85%) as a light yellow liquid.

To a solution of the corresponding olefin (240 mg, 1.11 mmol) in dichloromethane (6 mL) at 0-5 ^{o}C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (300 mg, 1.33 mmol). The mixture was stirred at room temperature for 1 h, concentrated, chromatographed (hexane) to provide the oily naphthalene **4** (214 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (d, 6H, C13-2CH_3, *J*=6.81 Hz), 2.65(s, 3H, C1-CH_3), 3.63 (sept., 1H, C13-H, *J*=6.80 Hz), 3.97(s, 3H, OCH_3), 7.18-7.24 (m, 2H, C2-1H, C3-1H), 7.30 (d, 1H, C7-1H, *J*= 7.3Hz),7.45 (d, 1H, C5-1H, *J*=2.6 Hz), 7.97 (d, 1H, C8-1H, *J*=8.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.45, 23.37, 28.57, 55.24, 103.01, 116.91, 121.99, 124.33, 126.51, 128.30, 132.02, 132.56, 141.45, 157.22 ppm; m/z: 214 (M^+), 199 (M^+-CH_3), 184 (M^+-2CH_3); Anal. Calc. for $C_{15}H_{18}O$ requires C, 84.07; H, 8.47 (Found: C, 84.31; H, 8.63).

8-isopropyl-5-methyl-2-naphthol 10. A solution of hydrobromic acid 48% (11 mL) was added slowly to a stirred solution of naphthalene **4** (130 mg, 0.61 mmol) in acetic acid (2 mL) at room temperature and then refluxed for 1 h. The reaction mixture was diluted with water, extracted with ether. The extracts were washed with water, $NaHCO_3$ (5%), dried over magnesium sulfate, evaporated and chromatograhed (hexane) to yield **10** (110 mg, 91%) as colorless oil; ν_{max} (KBr) 3220 cm^{-1} (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34 (d, 6H, C12-2CH_3, *J*=6.81 Hz), 2.62(s, 3H, C5-CH_3), 3.54 (sept., 1H, C12-H, *J*=6.80 Hz), 5.09(s, 1H, OH), 7.10 (dd, 1H, C3-1H, *J*=8.0Hz, *J*=2.6Hz), 7.13 (s, 1H, C6-1H), 7.25 (s, 1H, C7-1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.45, 23.38, 28.45, 106.34, 116.43, 122.07, 124.29, 126.91, 128.29, 132.06, 132.73, 141.26, 153.00 ppm; m/z: 200 (M^+), 185 (M^+-CH_3), 170 (M^+-2CH_3), 157 (M^+-C_3H_7); Anal. Calc. for $C_{14}H_{16}O$ requires C, 83.96; H, 8.05 (Found: C, 84.18; H, 8.21).

8-isopropyl-5-methyl-2-naphthyl trifluoromethanesulfonate 11. To a solution of **10** (84 mg, 0.42 mmol) in dichloromethane at 0^{o}C was added dropwise under an argon atmosphere, triethylamine (0.07 mL, 0.51 mmol), trifluoromethanesulfonic anhydride (0.1 mL, 0.51 mmol). The mixture was stirred at room temperature for 3 h, poured into water and extracted with dichloromethane. The organic phase was washed with hydrochloric acid 1 N, washed with water, dried over magnesium sulfate and evaporated. The resulting material was purified by flash chromatography (hexane-ethyl ether) to afford yellow oil **11** (118 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (d, 6H, C10-2CH_3, *J*=6.84 Hz), 2.70(s, 3H, C5-CH_3), 3.61 (sept., 1H, C10-1H, *J*=6.84 Hz), 7.33-7.47 (m, 3H, C6-1H, C7-1H, C3-1H), 8.05 (d, 1H, C1-1H, *J*=2.52 Hz), 8.11 (d, 1H, C4-1H, *J*=9.24Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.35, 23.34, 28.69, 115.72, 118.44, 119.13 (CF_3), 123.26, 127.46, 127.83, 132.35, 143.06, 147.22 ppm; m/z: 332 (M^+), 302 (M^+-2CH_3), 168 (M^+-CH_3-SO_2CF_3); Anal. Calc. for $C_{15}H_{15}F_3O_3S$ requires C, 54.21; H, 4.55; F, 17.15; S, 9.65 (Found: C, 54.52; H, 4.70; F, 17.30; S, 9.72).

8-isopropyl-5-methylnaphthalen-2-carbonitrile 12. A suspension of triflate **11** (1.46 g, 4.42 mmol), triphenylphosphine (120 mg, 0.45 mmol), bistriphenyphosphinenickel(II) chloride (145 mg, 0.22 mmol), zinc powder (0.94 mg, 1.46 mmol), potassium cyanide (324 mg, 4.93 mmol) in acetonitrile (20 mL) was stirred at 60^{o}C under an argon atmosphere for 6 h. After cooling, the mixture was poured into water and extracted with ether. The organic phase was filtered through celite, dried over anhydrous magnesium sulfate, evaporated and the residue was purified by chromatography (hexane-ethyl ether) to afford **12** (749 mg) as yellow oil in 81% yield; ν_{max} (KBr) 2250 cm^{-1} (CN); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (d, 6H, C12-2CH_3, *J*=6.90 Hz), 2.70 (s, 3H, C5-CH_3), 3.51 (sept., 1H, C12-H, *J*=6.90 Hz), 7.21 (d, 1H, ArH, *J*=8.3Hz), 7.38 (d, 1H, ArH, *J*=8.3Hz), 7.95 (d, 1H, ArH, *J*=8.35Hz), 8.09 (d, 1H, ArH, *J*=8.45Hz), 8.73 (s, 1H, ArH)

ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.38, 23.84, 28.93, 108.97, 119.79, 123.77, 124.58, 126.29, 126.38, 129.13, 131.16, 132.86, 135.67 ppm; m/z: 210 (M^++1), 209 (M^+), 194 (M^+-CH_3), 179 (M^+-2CH_3), 182(M^+-CH_2N); 167 (M^+-C_2H_4N); Anal. Calc. for $C_{15}H_{15}N$ requires C, 86.08; H, 7.22; N, 6.69 (Found: C, 86.21; H, 7.38; N, 6.72).

4-Isopropyl-1-methylnaphthalene-15-oic acid (cadalen-15-oic acid) 1. *First Approach:* To a solution of aldehyde **7** (275 mg, 1.30 mmol) in dioxane (15 mL) were added NaH_2PO_4 (800 mg, 5.10 mmol) in water (5 mL) and sulfamic acid (186 mg, 1.92 mmol). To the mixture cooled at 5°C was added slowly sodium chlorite (186 mg, 1.70 mmol) in water (1 mL) below 10°C followed by the addition of sodium sulfite (195 mg, 1.50 mmol). The mixture was stirred for 15 min and acidifided to pH=2 with hydrochloric acid and extracted with ether. The organic extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated in *vacuo*. The resulting material on cooling afforded the compound **1** (222 mg, 75%); mp 188-190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (d, 6H, C12-2CH_3, *J*=6.85 Hz), 2.68 (s, 3H, C1-CH_3), 3.81 (sept., 1H, C12-H, *J*=6.85 Hz), 7.39 (d, 1H, ArH, *J*=7Hz), 7.42 (d, 1H, ArH, *J*=7Hz), 8.08 (d, 1H, ArH, *J*=8.5Hz), 8.15 (dd, 1H, *J*=8.5Hz, *J*=1.5Hz), 9.01 (d,1H, ArH, *J*=1.5Hz), 11.19 (bs, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.45, 23.68, 28.60, 122.43, 124.55, 125.37, 125.87, 127.98, 129.36, 130.65, 132.40, 135.64, 144.80, 172.75 ppm. MS m/z: 228 (M^+), 213 (M^+-CH_3), 198 (M^+-2CH_3), 183 (M^+-CHO_2); Anal. Calc. for $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06 (Found: C, 78.99; H, 7.14).

Second Approach: A mixture of nitrile **12** (241 mg, 1.15 mmol) in aqueous potassium hydroxide (20 mL, 1.8 N, 36 mmol) and ethanol (25 mL) was stirred at 75°C for 24 h. After removing ethanol in vacuo, the aqueous layer was acidified to pH 3 and extracted with ether. The organic extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated at reduced pressure to obtain **1** as white solid (170 mg, 65%) whose m.p. and spectroscopic data were identical with that of obtained by first approach.

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References

1. Delgado, G.; Olivares, M.; Chavez, M. I.; Ramirez-Apan, T.; Linares, E.; Bye, R.; Espinosa-Garcia, F. J. *J. Nat. Prod*. **2001**, *64*, 861.
2. Wiart, C.; Martin, M.-T.; Awang, K.; Hue, N.; Serani, L.; Laprevote, O.; Pais, M.; Rhamani, M. *Phytochemistry* **2001**, *58*, 653.
3. Reddy, M. Parameswara; Rao, G. S. Krishna. *Indian J. Chem. B Org.* **1982**, *21B*, 885.
4. Carreño, M. C.; Gonzalez-Lopez, M.; Latorre, A.; Urbano, A. *J. Org. Chem.* **2006**, *71*, 4956.
5. Alcock, L. J.; Mann, I.; Peach, P.; Willis, M. *Tetrahedron: Asymm*etry **2002**, *13*, 2485.
6. Suh, Y.; Kim, S. N.; Shin, D.; Hyun, S.; Lee, D.; Min, K.; Han, S.; Li, F.; Choi, E.; Choi, S. *Bioorg Med. Chem. Lett.* **2006**, *16*, 142.

7. Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Synlett* **2003**, 558.
8. Poon P. S.; Banerjee, A.K.; Vera, W. J.; Mora, H.; Laya, M. S.; Bedoya, L.; Cabrera, E.V.; Melean, C.E. *J. Chem. Res. (S)* **2008**, *11*, 181.
9. Poon, P. S.; Banerjee, A. K. *Nat. Prod. Res*. **2006**, *20*, 629.
10. Vera, W.; Banerjee, A. K. *J. Chem. Res.* **2006**, 707.
11. Poon, P. S.; Banerjee, A. K. *Org. Chem.: An Indian J.* **2007**, *3,* 10.
12. Poon, P. S.; Banerjee, A. K. *Synth. Commun*. **2008**, *38*, 2261.
13. Sajiki, H.; Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Hirota, K. *Org. Lett.* **2006**, *8*, 987.
14. Wang, F.; Chiba, K.; Tada, M. *J. Chem. Soc., Perkin Trans. I* **1992**, 1897.
15. Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2007**, *63,* 1270.
16. Weidner-Wells, M.A.; Fraga-Spano, S.A. *Synth. Commun*. **1996**, *26*, 2775.
17. Tanaka, J.; Miyake, T.; Iwasaki, N.; Adachi, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2851.
18. Rao, G. S.; Dev, S. *J. Indian Chem. Soc.,* **1957**, *34*, 255.
19. Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc*. **2006***, 128,* 9998.
20. Vera, W.; Banerjee, A.K. *J. Chem. Res.* **2006**, 707.
21. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatayima, T.; Kamiya, Y. *J. Am. Chem. Soc*. **1989**, 4392.
22. Chambers, M. R.; Widdowson, D. *J. Chem. Soc., Perkin Trans. I* **1989**, 1365.
23. Almansa, C.; Carceller, E.; Bartroli, J.; Forn, J. *Synth. Commun.* **1993**, 23, 2965.