Total Synthesis of (±)-Nudenoic Acid

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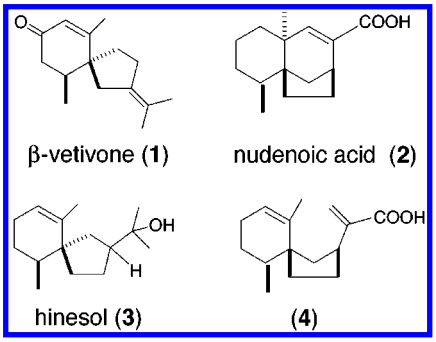
In 1968, Marshall and Johnson settled a long-standing structural problem with β-vetivone, firmly establishing it as **1** by synthesis.[1] Previously, β-vetivone was considered to be a bicyclic α,β-unsaturated ketone possessing a hydrazulene framework, interpretive of its dehydrogenation to give vetivazulene. The interpretive error arose from the assumption that the dehydrogenation occurred without skeletal rearrangement. It is interesting that after 28 years sesquiterpenes having a skeleton which is directly descendant of the spirovetivanes were isolated.

A member of the new tricyclic sesquiterpenes, nudenoic acid (**2**), is elaborated by the liverwort *Mylia nuda*, which is indigenous to Taiwan.[2] On examination of the molecular constitution (absolute configuration unknown) one can readily surmise a close relationship of nudenoic acid with the spirovetivanes, particularly hinesol **3**. Thus, it is conceivable that acid **4**, an oxidized derivative of hinesol, undergoes cyclization in vivo to generate **2**. The occurrence of spirovetivanes in several liverworts[3−5] lends support to this speculation.



We were interested in a synthesis of nudenoic acid because it is an indigenous natural product with a new skeleton. Furthermore, when we selected 2,6-dimethylcyclohexanone as our starting material the work would subjoin our desire in devising syntheses based on symmetry considerations.[6]

According to the procedure of Duhamel et al.,[7] the trimethylsilyl enol ether of 2,6-dimethylcyclohexanone was treated with 3-methoxy-2-buten-1-ol in the presence of BF_3-etherate, and the diketone product was cyclized on base treatment. The dimethyloctalone **5** thus acquired was reduced, with the intention of transforming it into alcohol **7**. However, after numerous trials to determine useful systems for producing the desired stereochemical outcome, reduction using diisobutylaluminum hydride in an equivolume mixture of THF and DME at −78 °C emerged as the method of choice.[8] This reagent engendered major alcohol **6** (ratio 93:7) which was the result of axial delivery of hydride. Both the use of L-selectride and lithium tri-*tert*-butoxyaluminum hydride in THF led to a 75:25 mixture enriched in **6**. The conversion of **6** to the axial alcohol **7** via a Mitsunobu reaction proceeded in 75% yield (Scheme 1).

Our plan called for the stereoselective introduction of a two-carbon unit to the angular position employing a Claisen rearrangement.[9] After experimenting with several variants of this rearrangement, we concluded that the best result was obtained with the Johnson orthoacetate protocol using pivalic acid as catalyst. Some homonuclear diene (dehydration product) and the acetate of **6** were produced along with the desired ester **8**. To facilitate isolation of the homologated compound, the rearrangement reaction mixture was saponified with KOH in aqueous methanol to afford the acid **9**. The stage was now set for the elaboration of the bicyclo[3.2.1]octane unit. Accordingly, **9** was reduced with $LiAlH_4$ to alcohol **10**; subsequent tosylation furnished **11**. Next, the double bond of the octalin system served the role of directing an allylic oxidation, the site of which is coincident with the base of the carboxyl group of our target molecule. To this end we applied the method of Salvador and Melo,[10] which involved a CuI-catalyzed reaction with *t*-BuOOH. We found that the resulting enone tosylate **12** slowly decomposed during purification so column chromatography of this material had to be conducted at about ice-temperature. We also experienced some difficulties in the hydrogenation of **12** with Pd/C catalysts, but carrying out the reduction in the presence of Raney nickel gave rise to three products: the saturated keto tosylate **13**, the tricyclic ketone **14**, and the corresponding alcohol **15**. We have been unable to produce only one of these products by varying the solvent system; only different ratios of the three were observed. Although inconvenient, the mixture was separable into its components, and both **13** and **15** could be converted to **14** by treatment with LDA and PCC, respectively. The final steps of our synthesis consisted of reacting the ketone **14** with trimethylsilyl cyanide, exposure of the adduct to phosphorus oxychloride in pyridine under reflux, and acid hydrolysis of the unsaturated nitrile. (±)-Nudenoic acid thus obtained exhibits spectral characteristics in total agreement with those of the natural product. Our work represents the first total synthesis of the novel sesquiterpene.

Experimental Section

General Methods. NMR spectra were recorded with $CDCl_3$ as solvent, at 300 and 75 MHz, respectively for ^1H and ^{13}C

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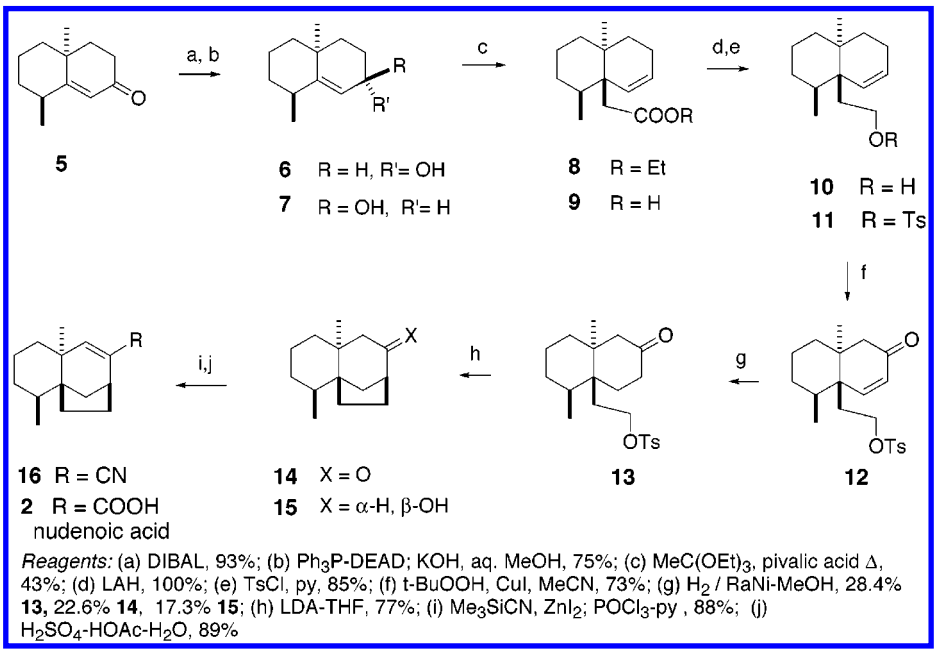
Scheme 1



Reagents: (a) DIBAL, 93%; (b) Ph_3P-DEAD; KOH, aq. MeOH, 75%; (c) $MeC(OEt)_3$, pivalic acid Δ, 43%; (d) LAH, 100%; (e) TsCl, py, 85%; (f) t-BuOOH, CuI, MeCN, 73%; (g) H_2 / RaNi-MeOH, 28.4% **13,** 22.6% **14**, 17.3% **15**; (h) LDA-THF, 77%; (i) Me_3SiCN, ZnI_2; $POCl_3$-py , 88%; (j) H_2SO_4-HOAc-H_2O, 89%

absorptions. Chemical shifts are reported in ppm relative to 0 for TMS. Electron impact mass spectra were measured at 70 eV. Drying of organic solutions used anhydrous Na_2SO_4. Silica gel (70−230 mesh) used for chromatography was an E. Merck product. Melting points, determined with a Laboratory Devices apparatus, were uncorrected.

***rel*-(2*S*,4a*R*,8*R*)-4a,8-Dimethyl-2,3,4,4a,5,6,7,8-octahydro-2-naphthalenol (7).** A solution of **6** (7.38 g, 41 mmol), triphenylphosphine (15.06 g, 57.4 mmol), and benzoic acid (7.01 g, 57.4 mmol) in dry THF (200 mL) was added to diethyl azodicarboxylate (10.0 g, 57.4 mmol) in THF (60 mL) with stirring at room temperature. After 1 h, the solvent was evaporated and the residue was taken up in ether (250 mL). After removal of the precipitate by filtration, the solution was washed with saturated $NaHCO_3$ solution, dried, and concentrated. The product was saponified on refluxing with a solution of KOH (16.07 g) in aqeous methanol (1:10, 220 mL) for 8 h. The cooled solution was concentrated, diluted with ether, decanted from some residue and again washed with saturated $NaHCO_3$ solution. Drying and evaporation of solvent followed by chromatography over silica gel (eluent: hexanes−ethyl acetate, 6:1) furnished **7** (mp 72.5−73.0 °C, 5.54 g, 75%): IR 3384 cm^{-1}; ^1H NMR δ 0.87−1.07 (3H, m), 0.95 (3H, d, J = 6.4 Hz), 1.01 (3H, s), 1.20−1.83 (7H, m), 2.18 (1H, m), 4.12 (1H, m), 5.38 (1H, d, J = 3.9 Hz); ^{13}C NMR δ 18.6 (q), 22.1 (t), 24.1 (q), 27.9 (t), 32.8 (d), 35.1 (t), 35.4 (s), 37.0 (t), 41.6 (t), 65.5 (d), 118.9 (d), 152.0 (s); HRMS (EI) 180.1519 (180.1515 calcd for $C_{12}H_{20}O$); Anal. Calcd for $C_{12}H_{20}O$: C 79.94, H 11.18. Found: C 79.86, H 11.25.

Ethyl 2-[*rel*-(4a*R*,*8R*,8a*R*)-4,8a-Dimethyl-1,2,3,4,4a,7,8,-8a)-octahydro-4a-naphthyl)acetate (8). A mixture of **7** (5.54 g, 30.7 mmol), triethyl orthoacetate (34.86 g, 215 mmol), and a catalytic amount of pivalic acid (0.16 g) was heated at 160−170 °C for 48 h under nitrogen. The reaction mixture was distilled to recover the unreacted ortho ester, and the residue was diluted with ether (150 mL). The organic solution was washed successively with 0.5 N HCl and saturated $NaHCO_3$ solution and dried. Evaporation and chromatography (silica gel, hexanes−ethyl acetate, 20:1) provided a mixture of a small amount of the acetate of **7** and the oily ester **8** (5.24 g): IR 1730 cm^{-1}; ^1H NMR δ 0.89 (3H, d, J = 6.9 Hz), 0.96 (3H, s), 1.00−1.23 (4H, m), 1.19 (3H, t, J = 6.8 Hz), 1.60−1.98 (5H, m), 1.98−2.06 (2H, m), 3.95 (1H, d, J = 13.2 Hz), 3.97 (2H, q, J = 6.8 Hz), 4.00 (1H, d, J = 13.2 Hz), 5.534 (1H, dt, J = 1.2, 3.4 Hz), 5.73 (1H, d, J = 10.2 Hz); ^{13}C NMR δ 14.2 (q), 16.0 (q), 19.8 (q), 20.4 (t), 23.1 (t), 30.1 (t), 32.2 (t), 32.7 (d), 33.2 (t), 36.5 (s), 37.8 (t), 43.1 (s), 59.8 (t), 126.8 (d), 130.6 (d), 173.3 (s); HRMS (EI) 250.1927 (250.1934 calcd for $C_{16}H_{26}O_2$).

2-[*rel*-(4a*R*,8*R*,8a*R*)-4,8a-Dimethyl-1,2,3,4,4a,7,8,8a)-octahydro-4-naphthyl)acetic Acid (9). The ethyl ester **8** (7.30 g, 29 mmol) and KOH (8.6 g) were refluxed in aqueous MeOH (1:10, 110 mL) for 8 h. The cooled reaction mixture was evaporated, diluted with water, and washed with ether. The alkaline solution was acidified with 3 N HCl and extracted with ether, and the extracts were dried and concentrated. The residue was recrystallized from chloroform−hexane to give acid **9** (2.80 g, 43%): Mp 110−110.5 °C; IR 3400−2400, 1699 cm^{-1}; ^1H NMR δ 0.90 (3H, d, J = 6.7 Hz), 0.97 (3H, s), 1.04−1.25 (4H, m), 1.32−1.50 (2H, m), 1.61−1.75 (2H, m), 1.77−1.87 (1H, m), 2.00−2.14 (2H, m), 2.34 (1H, d, J = 13.0 Hz), 2.47 (1H, d, J = 13.0 Hz), 5.59 (1H, dt, J = 10.1, 3.4 Hz), 5.80 (1H, d, J = 10.1 Hz), 9.92 (1H, br.s); ^{13}C NMR δ 15.9 (q), 19.8 (q), 20.3 (t), 23.0 (t), 30.0 (t), 32.1 (t), 32.7 (d), 33.2 (t), 36.4 (s), 37.8 (t), 43.4 (s), 127.3 (d), 130.2 (d), 180.6 (s); HRMS (EI) 222.1624 (222.1620 calcd for $C_{14}H_{22}O_2$). Anal. Calcd for $C_{14}H_{22}O_2$: C 75.62, H 9.97. Found: C 75.76, H 9.94.

2-[*rel*-(4a*R*,8*R*,8a*R*)-4,8a-Dimethyl-1,2,3,4,4a,7,8,8a)-octahydro-4-naphthyl)ethanol (10). To an ice-cooled, magnetically stirred suspension of lithium aluminum hydride (0.71 g, 18.57 mmol) in diethyl ether (10 mL) was added dropwise a solution of acid **9** (2.75 g, 12.38 mmol) in ether (40 mL). After the addition, the ice bath was removed and the reaction was allowed to proceed for 10 min more. On quenching with saturated Na_2SO_4 the precipitate was separated by filtration. The fitrate was dried and evaporated and the residue recrystallized from ethyl acetate−hexane to afford alcohol **10** (2.58 g, 100%): IR 3328 (br) cm^{-1}; ^1H NMR δ 0.82 (3H, d, J = 6.7 Hz), 0.90 (3H, s), 0.97−1.10 (2H, m), 1.27−1.49 (4H, m), 1.59−1.79 (5H, m), 1.89−2.17 (3H, m), 3.52 (2H, d, J = 7.4 Hz), 5.62 (1H, dt, J = 10.1, 3.1 Hz), 5.71 (1H, d, J = 10.1 Hz); ^{13}C NMR δ 16.5 (q), 19.8 (q), 20.8 (t), 23.5 (t), 30.1 (t), 32.5 (t), 32.9 (d), 33.2 (t), 34.5 (t), 36.7 (s), 41.7 (s), 63.0 (t), 127.6 (d), 131.5 (d); HRMS (EI) 208.1829 (208.1828 calcd for $C_{14}H_{24}O$).

2-[*rel*-(4a*R*,8*R*,8a*R*)-4,8a-Dimethyl-1,2,3,4,4a,7,8,8a)-octahydro-4-naphthyl)ethyl Tosylate (11). A solution of tosyl chloride (1.95 g, 10.23 mmol) in dichloromethane (5.0 mL) was added slowly to an ice-cooled solution of **10** (1.42 g, 6.82 mmol) and pyridine (1.10 mL, 13.64 mmol) in dichloromethane (5.0 mL) with stirring. After 30 min, the reaction mixture was warmed to room temperature, kept for 8 h, and poured into ice−water. Layers were separated, and the aqueous phase was extracted further with dichloromethane. The combined organic solutions were washed with dilute HCl and $NaHCO_3$ solution, concentrated, and chromatographed using ethyl acetate−hexane (1:10) as eluent to provide the tosylate **11** (2.10 g, 85%): Mp 59 °C (hexane); IR 1598 cm^{-1}; ^1H NMR δ 0.71 (3H, d, J = 6.8 Hz), 0.87 (3H, s), 0.91−1.11 (2H, m), 1.12−1.28 (2H, m), 1.28−1.53 (2H, m), 1.54−1.90 (5H, m), 1.97−2.12 (2H, m), 2.42 (3H, s), 3.91 (2H, t, J = 9.3 Hz), 5.46 (1H, d, J = 10.3 Hz), 5.52 (1H, dt, J =

10.3, 2.9 Hz), 7.31 (2H, d, J = 7.8 Hz), 7.75 (2H, d, J = 7.8 Hz); ^{13}C NMR δ 15.9 (q), 19.4 (q), 20.2 (t), 21.6 (q), 22.8 (t), 29.55 (t), 29.58 (t), 32.0 (t), 32.4 (d), 32.8 (t), 36.3 (s), 41.2 (s), 71.2 (t), 127.7 (d), 127.8 (d), 129.2 (d), 129.7 (d), 133.5 (s), 144.5 (s); HRMS (EI) 362.1922 (362.1917 calcd for $C_{21}H_{30}O_3S$). Anal. Calcd for $C_{21}H_{30}O_3S$: C 69.58, H 8.35. Found: C 69.36, H 8.46.

2-[*rel*-(4a*R*,8*R*,8a*R*)-4,8a-Dimethyl-7-oxo-1,2,3,4,4a,7,8,-8a)-octahydro-4-naphthyl)ethyl Tosylate (12). A solution of **11** (0.35 g, 0.97 mmol), copper(I) iodide (2 mg, 0.01 mmol), and 70% *tert*-butyl hydroperoxide (1.0 mL, 7.0 mmol) in acetonitrile (6.0 mL) was stirred and heated at 50 °C for 20 h. On cooling to room temperature the reaction mixture was treated with 10% sodium sulfite and extracted with ether. The ethereal extracts were combined, washed with $NaHCO_3$ solution and water, and dried. Evaporation and chromatography of the residue at 5 °C (double-walled column with ice−water circulation) gave the enone **12** (0.266 g, 73%): Mp. 111 °C (CH_2Cl_2−hexane); IR 1675, 1598 cm^{-1}; ^{1}H NMR δ 0.87 (3H, d, J = 6.7 Hz), 0.92−1.12 (2H, m), 1.02 (3H, s), 1.13−1.39 (2H, m), 1.41−1.71 (2H, m), 1.83−1.93 (1H, m), 1.93−2.36 (4H, m), 2.42 (3H, s), 3.75−3.95 (2H, m), 5.84 (1H, d, J = 10.2 Hz), 6.70 (1H, d, J = 10.2 Hz), 7.31 (2H, d, J = 8.3 Hz), 7.70 (2H, d, J = 8.3 Hz); ^{13}C NMR δ 16.3 (q), 19.8 (t), 21.3 (q), 21.6 (q), 28.1 (t), 29.5 (t), 32.0 (d), 32.4 (t), 41.1 (s), 43.3 (s), 49.1 (t), 69.1 (t), 127.76 (d), 127.79 (d), 129.9 (d), 132.9 (s), 145.0 (s), 151.6 (d), 199.0 (s); HRMS (EI) 376.1703 (376.1709 calcd for $C_{21}H_{28}O_4S$). Anal. Calcd for $C_{21}H_{28}O_4S$: C 66.99, H 7.50. Found: C 67.20, H 7.62.

2-[*rel*-(4a*S*,5*R*,8a*S*)-5,8a-Dimethyl-2-oxo-perhydro-4a-naphthyl)ethyl Tosylate (13). A solution of **12** (0.52 g, 1.38 mmol) in methanol (30 mL) was mixed with Raney nickel (ca. 2 mL) and hydrogenated for 20 h. The catalyst was removed by filtration with the aid of Celite, and the filtrate was concentrated. The product was chromatographed (eluent: hexanes−ethyl acetate 5:1) to furnish **13** (0.148 g, 28.4%), **14** (0.065 g, 22.6%), and **15** (0.05 g, 17.3%).

Keto tosylate **13**: mp 86−87 °C (EtOAc−hexane); IR 1716 cm^{-1}; ^{1}H NMR δ 0.73 (3H, d, J = 7.0 Hz), 0.75−1.02 (2H, m), 0.92 (3H, s), 1.20−1.30 (2H, m), 1.41−1.86 (4H, m), 1.87−2.37 (7H, m), 2.43 (3H, s), 4.10 (1H, m), 4.32 (1H, m), 7.34 (2H, d, J = 8.3 Hz), 7.78 (2H, d, J = 8.3 Hz); ^{13}C NMR δ 17.6 (q), 20.6 (t), 21.2 (q), 21.6 (q), 26.6 (t), 28.2 (t), 30.0 (t), 33.7 (t), 35.2 (d), 38.2 (t), 39.7 (s), 41.2 (s), 51.7 (t), 68.9 (t), 127.8 (d), 129.9 (d), 133.1 (s), 145.0 (s), 210.9 (s); HRMS (EI) 378.1857 (378.1866 calcd for $C_{21}H_{30}O_4S$).

Tricyclic ketone **14**: mp 74−75 °C (hexane); IR 1711 cm^{-1}; ^{1}H NMR δ 0.85 (3H, d, J = 6.7 Hz), 0.96−1.11 (2H, m), 0.96 (3H, s), 1.15−1.24 (2H, m), 1.43−1.86 (10H, m), 2.22 (1H, d, J = 14.8 Hz), 2.64 (1H, br. s); ^{13}C NMR δ 16.0 (q), 20.6 (q), 21.9 (t), 23.3 (t), 28.6 (t), 31.7 (d), 32.9 (t), 36.6 (t), 37.1 (t), 41.0 (s), 49.3 (s), 51.4 (t), 51.8 (d), 214.8 (s); HRMS (EI) 206.1663 (206.1671 calcd for $C_{14}H_{22}O$).

Tricyclic alcohol **15**: mp 97 °C (hexane); IR 3358 (br) cm^{-1}; ^{1}H NMR δ 0.75 (3H, d, J = 6.8 Hz), 0.92−1.07 (2H, m), 1.19 (3H, s), 1.13−1.27 (2H, m), 1.27−1.43 (4H, m), 1.43−1.65 (5H, m), 1.70−1.87 (3H, m), 2.16 (1H, m), 3.77 (1H, t, J = 3.9 Hz); ^{13}C NMR δ 15.7 (q), 21.2 (t), 21.5 (q), 22.3 (t), 27.4 (t), 29.8 (t), 31.7 (d), 33.0 (t), 36.9 (t), 37.0 (s), 42.4 (t), 42.8 (d), 49.3 (s), 72.9 (d); HRMS (EI) 208.1821 (208.1828 calcd for $C_{14}H_{24}O$).

2,6-Dimethyltricyclo[7.2.1.0^{1,6}]dodecan-8-one (14). (a) To a solution of the keto tosylate **13** (0.094 g, 0.24 mmol) in THF (4 mL) at −78 °C was added LDA (2M in THF/hexane, 0.24 mL, 0.48 mmol). After stirring for 30 min the reaction mixture was warmed to 0 °C, quenched with saturated NH_4Cl, and extracted with ether. The dried extracts were concentrated and the product was purified by chromatography to afford **14** (0.040 g, 77%).

(b) A solution of alcohol **15** (0.050 g, 0.24 mmol) in dichloromethane (10 mL) was stirred with PCC (0.121 g, 0.56 mmol) and Celite (0.121 g) for 1 h. Filtration followed by evaporation afforded a crude product which was chromatographed (eluent: hexanes−ethyl acetate 10:1) to give **14** (0.048 g, 99%).

8-Cyano-2,6-dimethyltricyclo[7.2.1.0^{1,6}]dodec-7-ene (16). A mixture of ketone **14** (0.040 g, 0.19 mmol), zinc iodide (0.002 g), and trimethylsilyl cyanide (0.05 mL, 0.38 mmol) in dry dichloromethane (2 mL) was stirred at room temperature for 3 h and then the starting material disappeared (TLC monitor). The reaction mixture was concentrated and then treated with phosphorus oxychloride (0.04 mL, 0.42 mmol) and pyridine (2.0 mL) under reflux for 20 h. The solution was cooled, poured into ice-cold 10% HCl (5 mL), and extracted with ether. The extracts were combined, dried, and evaporated. The product was chromatographed (silica gel, eluent: hexanes−ethyl acetate 20:1) to give nitrile **16** (0.036 g, 88%) as a colorless oil: IR 2230 cm^{-1}; ^{1}H NMR δ 0.78 (3H, d, J = 7 Hz), 0.71−0.88 (4H, m), 1.08 (3H, br.s), 1.41−1.90 (9H, m), 2.62 (1H, br.s), 6.01 (1H, s); ^{13}C NMR δ 15.2 (q), 20.3 (t), 21.7 (q), 24.2 (t), 30.7 (t), 31.1 (d), 31.9 (t), 32.7 (t), 34.0 (t), 40.5 (d), 43.8 (s), 48.0 (s), 114.1 (s), 119.2 (s), 152.6 (d); HRMS (EI) 215.1668 (215.1675 calcd for $C_{15}H_{21}N$).

Nudenoic Acid (2). A mixture of the nitrile **16** (0.020 g, 0.09 mmol), concentrated H_2SO_4 (0.1 mL), water (0.2 mL), and HOAc (1 mL) was refluxed for 3.5 h and concentrated. The residue was diluted with water and extracted with ethyl acetate. The organic solution was dried, evaporated, and chromatographed (silica gel, eluent: hexanes−ethyl acetate 5:1) to give **2** as a white solid (0.019 g, 89%): mp 204 °C (EtOAc−hexane); IR 3400−2400, 1676 cm^{-1}; ^{1}H NMR δ 0.80 (3H, d, J = 6.7 Hz), 1.00−1.23 (2H, m), 1.09 (3H, s), 1.41−1.75 (8H, m), 1.76−1.87 (3H, m), 2.97 (1H, br.s), 6.50 (1H, s); ^{13}C NMR δ 15.5 (q), 20.6 (t), 21.9 (q), 24.6 (t), 31.1 (t), 31.4 (d), 32.2 (t), 33.0 (t), 34.6 (t), 37.0 (d), 43.3 (s), 48.4 (s), 131.5 (s), 150.1 (d), 172.6 (s); HRMS (EI) 234.1613 (232.1620 calcd for $C_{15}H_{22}O_2$).

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Supporting Information Available: Copies of ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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