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A New Synthesis of (*E,E*)-Tricyclohexaprenol

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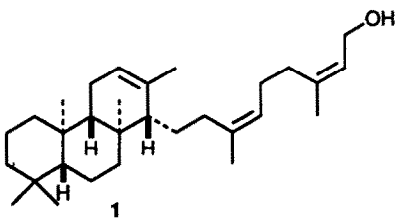
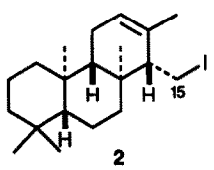
Abstract: (*E,E*)-Tricyclohexaprenol has been synthesized by addition of the isocopal-12-en-15-yl radical to a 3-hydroxy-2-methylene alkenenitrile, stereoselective elimination of acetic acid from the acetylated adducts, and reduction of the cyano group into a methyl *via* the corresponding amine.

In a recent letter, we have described the radical-based synthesis of (*Z,Z*)-tricyclohexaprenol **1** — a possible precursor of a family of tricyclic geoterpanes — starting from isocopalenyl iodide **2** and the substituted acrylate **3**.[1] We now report that this strategy also allows the selective obtention of (*E,E*)-tricyclohexaprenol **4** — another possible precursor of the same geoterpanes — provided that the isocopalenyl radical is added to the acrylonitrile **5** [2,4] (Scheme). When the so obtained diastereomeric adducts **6** are acetylated and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a 8:2 mixture[5] of *Z*/*E* α,β-unsaturated nitriles **7** [4] is formed in 62% yield.



1



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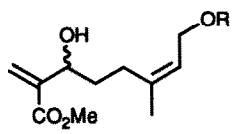
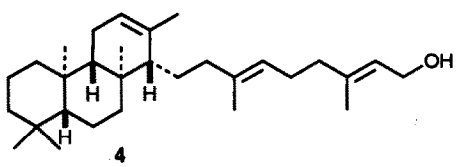


3 R = $SiPh_2t$-Bu



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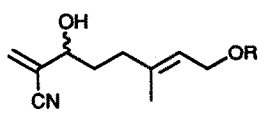
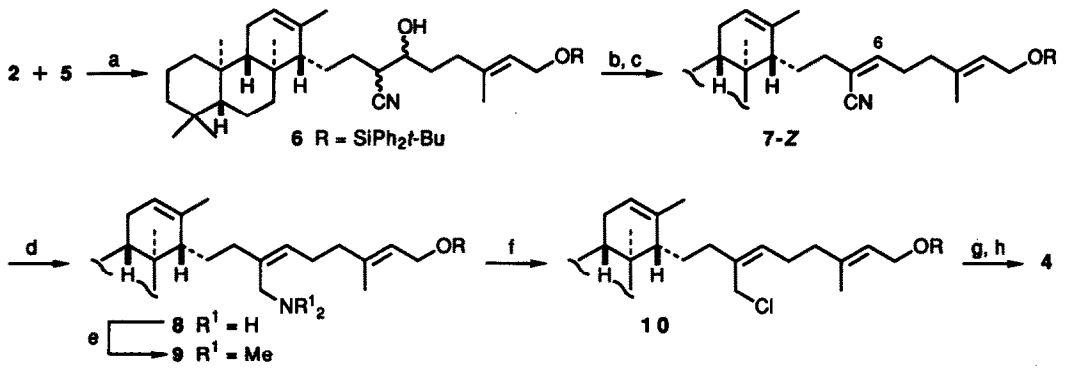


5 R = $SiPh_2t$-Bu

After chromatographic separation of the nitriles **7**, the cyano group of **7-*Z*** had to be reduced into a methyl to give (*E,E*)-tricyclohexaprenol **4**. For this purpose, we first transformed **7-*Z*** into the corresponding aldehyde [i) diisobutylaluminium hydride, tetrahydrofuran (THF), –40 °C; ii) aqueous *p*-toluenesulfonic acid, 0 °C] but, not quite unexpectedly, variable amounts of the *E* α,β-unsaturated aldehyde were also obtained. This outcome led us to carry out the desired conversion by an alternative sequence: after reduction of the nitrile **7-*Z*** into

the amine **8**, the latter was transformed into the corresponding dimethylamine **9** according to the procedure of Charles[6] and then into the allylic chloride **10** by a modified von Braun reaction;[7] finally reduction of the chloride **10** with lithium triethylborohydride and deprotection of the hydroxy group gave (*E,E*)-tricyclohexaprenol **4** [8] (Scheme).



Scheme. a) **2** (0.13 mmol), **5** (0.88 mmol), *n*-Bu_3SnH (0.29 mmol), ether (12.5 ml), hv (300 W tungsten lamp), reflux, 8.5 h (40% yield); b) acetic anhydride, 4-(dimethylamino)pyridine, toluene; c) DBU, toluene, reflux, 5 days (b + c: 62%; **7-Z**/**7-E** = 8:2; 23% of starting **6** are recovered); d) AlH_3, ether, 0 °C → r.t., 2 h; e) $(CH_2O)_n$, MeOH, reflux, 1.5 h; then $NaBH_3CN$, r. t., 1 h; f) $ClCO_2Et$, K_2CO_3, toluene, 0 °C, 1 h; then r. t., 1 day; g) $LiBHEt_3$, THF, r. t., 0.25 h (d - g: 43%); h) *n*-Bu_4NF, THF, r. t., 8 h (81%).

References and notes

1. Heissler, D.; Jenn, T.; Nagano, H. *Tetrahedron Lett.* **1991**, *32*, 7587-7590.
2. The α,β-unsaturated nitrile **5** was prepared in three steps from geraniol: i) *t*-$BuPh_2SiCl$, imidazole, dimethylformamide; ii) O_3, pyridine, CH_2Cl_2, –78 °C; then Me_2S, r. t.; iii) acrylonitrile, 1,4-diazabicyclo[2.2.2]octane, r. t.[3]
3. Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653-4670.
4. ^{1}H-NMR data (200 MHz, $CDCl_3$) for:
   Nitrile **5**: δ 1.04 (s, 9 H), 1.46 (s, 3 H), 1.65 - 2.18 (m, 4 H), 4.18 and 4.22 (m and d, *J* 6.2 Hz, 3 H), 5.41 (t, *J* 6.2 Hz, 1 H), 5.98 (d, *J* 1.2 Hz, 2 H), 7.30 - 7.50 (m, 6 H), 7.60 - 7.75 (m, 4 H).
   Nitrile **7-Z**: δ 0.72 (s, 3 H), 0.81 (s, 3 H), 0.85 (s, 3 H), 0.87 (s, 3 H), 1.04 (s, 9 H), 1.46 (s, 3 H) 1.67 (br s, 3 H), 2.43 (m, 3 H), 4.21 (d, *J* 6.4 Hz, 2 H), 5.39 (m, 2 H), 6.09 (t, *J* 7.5 Hz, 1 H), 7.30 - 7.50 (m, 6 H), 7.60 - 7.75 (m, 4 H).
5. Determined by 200 MHz ^{1}H-NMR: the side-chain H-6 triplet was at δ 6.09 for **7-Z** and at δ 6.29 for **7-E**.
6. Kapnang, H.; Charles, G.; Sondengam, B. L.; Hentchoya Hemo, J. *Tetrahedron Lett.* **1977**, 3469-3472; see also: Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673-1674.
7. Mornet, R.; Gouin, L. *Synthesis* **1977**, 786-787; Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233-3236; for a review, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1-7.
8. Compound **4** has been identified (GC, IR, 200 MHz ^{1}H-NMR) with (*E,E*)-tricyclohexaprenol obtained earlier: Heissler, D.; Ladenburger, C. *Tetrahedron* **1988**, *44*, 2513-2521.

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