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A FACILE SYNTHESIS OF A Δ^2-CEDRENE SKELETON VIA TANDEM RADICAL CYCLIZATION

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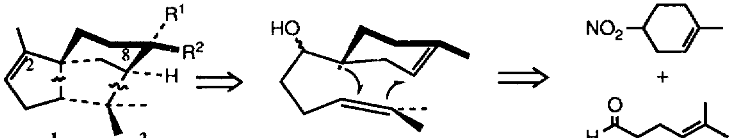
SUMMARY: A facile synthesis of a Δ^2-cedrene skeleton via tandem radical cyclization is described.

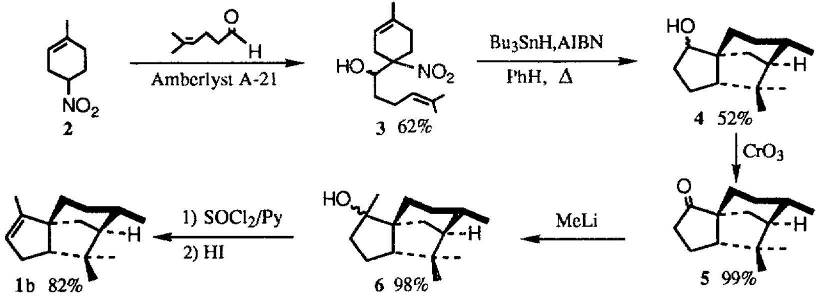
The tricyclic sesquiterpene Δ^2-cedrene **1a**, an isomer of α-cedrene, has been found in vetiver oil by Kaiser et al in 1972.[1] Previous strategies used for the construction of the tricyclo[5.3.1.0^{1,5}]undecane skeleton have included sequential cyclizations through carbonium ion intermediates,[2] intramolecular Diels-Alder reaction,[3] an intramolecular 1,3-photocycloaddition reaction,[4] sequential inter- and intra-molecular Michael reactions,[5] and Claisen cyclization.[6] We now outline a new and facile synthesis of (±)-Δ^2-8-epicedrene **1b** via tandem radical cyclization.[7]

Our retro-synthetic analysis involving a single step tandem radical cyclization strategy is outlined below.



1a $R^1=CH_3$, $R^2=H$
1b $R^1=H$, $R^2=CH_3$

From Ono's previous studies,[8] it is well known that nitro group can activate α-carbon to make C-C bonds and be removed by tin hydride by a radical process. The 1-methyl-4-nitrocyclohexene **2**, readily prepared from nitroethylene and isoprene,[9] was chosen as a starting material.



The cyclization precursor **3** is readily available in 62% yield from the addition of **2** to 5-methyl-4-hexenal catalyzed by Amberlyst A-21[10] at room temperature for 24 h. Direct tandem radical cyclization was carried out by treatment of **3** with tributyltin hydride in the presence of 10 mol% of azobisisobutyronitrile (AIBN) in benzene at 80°C for 30 h to give a mixture of secondary alcohols **4** in 52% isolated yield. Subsequent oxidation of the mixture **4** with Jones reagent at 0-5°C for 30 min gave the colorless crystals in nearly quantitative yield. The structure of crystalline product was determined by X-ray crystallography[11] and found to be the tricyclo[5.3.1.0^{1,5}]undecan-2-one **5** (Fig.1). Treatment of **5** with an excess of methyllithium in THF at -78° C for 30 min gave the tertiary alcohol **6** in 98% yield. Finally, dehydration of **6** with thionyl chloride in pyridine at 0°C for 10 min afforded an 84% yield of a mixture of hydrocarbons. The ratio of hydrocarbons was determined to be 4:1 based upon integration of the vinyl protons of 5.07 ppm and 4.78 ppm, respectively. Without further separation, the mixture was directly treated with a catalytic amount of 57% HI in benzene at room temperature for 36 h to give 98% yield of (±)-Δ^2-8-epicedrene **1b** based on ^{1}H NMR, ^{13}C NMR, IR, and HRMS data.[12]

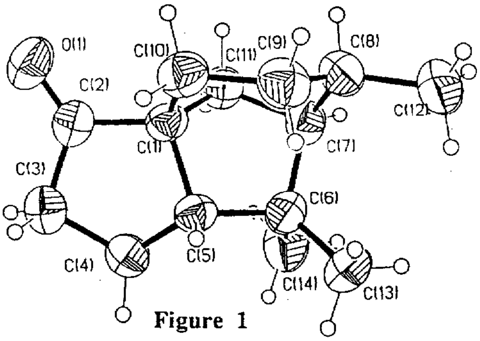


Figure 1

In conclusion, a tandem radical cyclization reaction has been utilized to construct the tricyclo[5.3.1.0^{1,5}]-undecane skeleton present in the cedrene sesquiterpenes. Further studies and applications of this methodology are under investigations in our laboratory.

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11. **5** crystalizes in the triclinic $P\bar{1}$ space group with a=6.750(2), b=7.783(2), c=11.763(3)Å, α=91.77°, β=93.93°, γ=99.35°, V=607.8(3)Å^3, and Z=2. The final coordinates were solved by direct methods and refined by full matrix least square methods with R=0.039, Rw=0.064, and GOF=1.31 for 225 variables. Final crystallographic coordinates are deposited in Cambridge Crystallographic Data Center.
12. (±)-Δ^2-8-epicedrene **1b**: IR ν_{max} (neat cm^{-1}) 3036, 2936, 1658, 1466, 1448,.1386,.1378,.1366,.1164, 1122, 1068, 1014, 998, 804; ^{1}H NMR (CDCl$_3$) δ 5.07(br.s, 1H), 2.14-2.17(m, 3H), 1.66-1.71(m, 4H), 1.55-1.58(m,2H), 1.58(s,3H), 1.24-1.30(m,2H), 1.19(s, 3H), 1.05(d, 3H, J=6.9Hz), 0.97(s,3H); ^{13}C NMR (CDCl$_3$) 144.88, 121.60, 61.37, 56.77, 55.99, 45.51, 44.13, 38.18, 35.52, 30.88, 29.76, 28.97, 27.32, 21.76, 13.40. Exact mass calcd for 204.1878, found 204.1873.

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