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Synthesis of (±)-(E)-2,6-Dimethyl-6-hydroxyocta-2,7-dienoic Acid and the Corresponding Amide ("Acacialactam")

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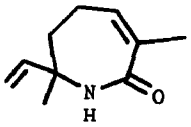
Abstract: The total synthesis of the title compounds in racemic form is described. Linalool was used as the starting material and transformed into the target molecules in 6 steps. The synthetic amide displays spectral properties identical to those reported for the natural compound acacialactam, indicating that the structure proposed for the latter compound is not correct.

Acacialactam is a product isolated in optically active form from the seeds of *Acacia concinna* DC. (Leguminosae). The seeds of this plant are used in folk medicine of several tropical countries for treating some skin diseases. The compound was assigned structure **1** by Sekine *et al.* on the basis of its physical and spectral properties.[1] Three years later, a compound with structure **1** was synthesized in an unambiguous way and found to have spectral properties different from those reported for acacialactam.[2] The latter authors then proposed that the natural compound might possibly be the acyclic amide **3**. The corresponding acid **2** has been isolated earlier in glycosidic form from fruits of *Gymnocladus chinensis*[3]



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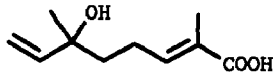

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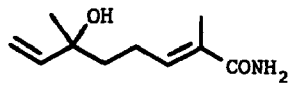
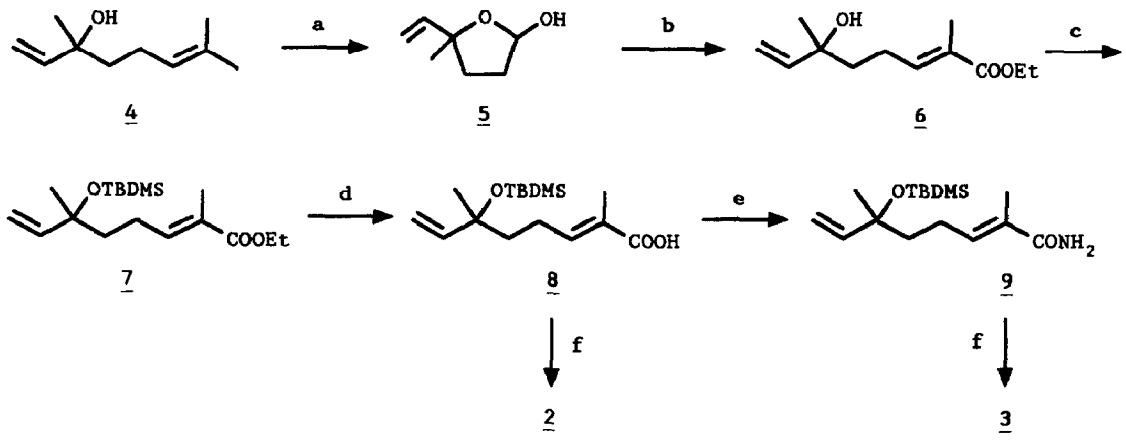


3

and, very recently, in the free form from *Artemisia sieberi*.[4] We now wish to report a short synthesis of both **2** and **3** in racemic form, using commercially available linalool (±)-**4** as the starting compound.

Selective ozonolysis of the trisubstituted double bond in **4** was achieved at low temperature in the presence of pyridine.[5,6] The obtained lactol **5** was then transformed into the conjugated ester **6** by Wittig reaction with the corresponding phosphorane.[7] Attempts at saponification of **6** to **2** only produced extensive decomposition of the ester. Temporary protection of the tertiary hydroxyl group as its *t*-butyldimethylsilyl derivative (TBDMS) permitted us to circumvent this problem. The silylated ester **7** could be uneventfully hydrolyzed to **8** in 83% yield. Desilylation of **8** gave an acid identical with the natural product[4] in its spectral and chromatographic behaviour. Furthermore, acid **8** could be converted



a: O_3, pyridine (1 eq), CH_2Cl_2, −78 °C, 45 min, 88%. **b**. $Ph_3P=C(Me)COOEt$, benzoic acid (cat. am.), C_6H_6, reflux, 2 h, 57%. **c**: TBDMSIOTf, 2,6-lutidine, CH_2Cl_2, room temp., 24 h, 92%. **d**: aq NaOH/EtOH, reflux, 24 h, 83%. **e**: 1) EtOCOCl (1 eq), Et_3N, THF, −78 °C, 15 min. 2) aq NH_3 (3 eq), room temp., 3 h, 60% overall. **f**: TBAF (4 eq), THF, 60 °C, 3 h, 95%.

into the primary amide **9** in 60% overall yield via the mixed anhydride.[8] Desilylation of **9** furnished a primary amide **3** identical in its spectral properties to the product described as acacialactam in the bibliography.[1,2,9] The latter compound therefore is not a lactam but has, in fact, acyclic structure **3**.[2]

The synthesis of compounds **2** and **3** in optically active form is presently underway.

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7. Bestmann, H.-J. and Hartung, H., *Chem.Ber.* **1966**, *99*, 1198. Compound **6** was obtained as an inseparable 87:13 E/Z mixture. After silylation, the minor isomer was eliminated during the chromatographic purification. The configuration of the C_2-C_3 double bond was substantiated by NOE measurements.
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9. All products gave satisfactory spectral and microanalytical data. Spectral data of synthetic **3**: IR $\bar{\nu}_{max}$ (film): 3350, 3190, 1670, 1640sh, 1582, 1402 cm^{-1}. UV λ_{max} (MeOH): 225 nm (ε_{max} 4500). EIMS, m/z (% rel.int.): 168 [M^+ − Me] (4), 165 [$M^+ - H_2O$] (5), 150 [$M^+ - Me - H_2O$] (5), 138 (11), 123 (10), 121 (15), 112 (23), 110 (25), 102 (40), 95 (34), 71 (100), 67 (73), 55 (96). ^1H NMR (δ ppm, $CDCl_3$, 400 MHz): 6.40 (1H, tq, J = 7.5 and 1.3 Hz), 5.95 (2H, br s), 5.86 (1H, dd, J = 17.4 and 10.8 Hz), 5.20 (1H, dd, J = 17.4 and 1 Hz), 5.05 (1H, dd, J = 10.8 and 1 Hz), 2.18 (2H, m), 1.80 (3H, dt, J = 1.3 and 1 Hz), 1.60 (2H, m), 1.27 (3H, s). ^{13}C NMR (δ ppm, $CDCl_3$, 75 MHz): 171.6 (C), 144.5 (CH), 137.7 (CH), 129.8 (C), 112.1 (CH_2), 73.0 (C), 40.7 (CH_2), 27.9 (CH_3), 23.2 (CH_2), 12.6 (CH_3). The spectra of the synthetic product were practically superimposable with those of the natural product (see acknowledgements).

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