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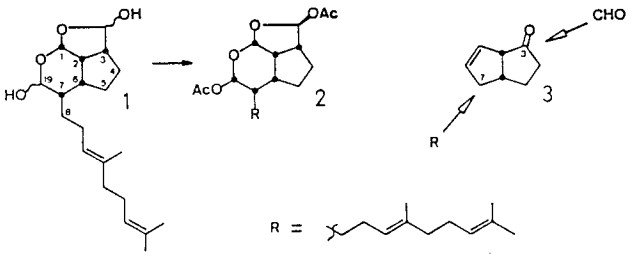
Total Synthesis of (±)-Udoteatrial

Summary: The marine natural product udoteatrial was shown by total synthesis to be **18**, epimeric at C-7 with the structure previously reported.

Sir: In 1981 Faulkner[1] reported the isolation of the antimicrobial diterpene udoteatrial from the alga *Udotea flabellum*. Assignment of structure **1** for this natural product was based on spectral analysis of the derivative diacetate **2** and its degradation products since, as would be expected, **1** was found to be a readily interconverted mixture of stereoisomers. Our current interest in the synthesis of a number of mono- and sesquiterpenes such as xylomollin[2] and allamandin[3] with similar functionality led us to investigate the total synthesis of **1**.

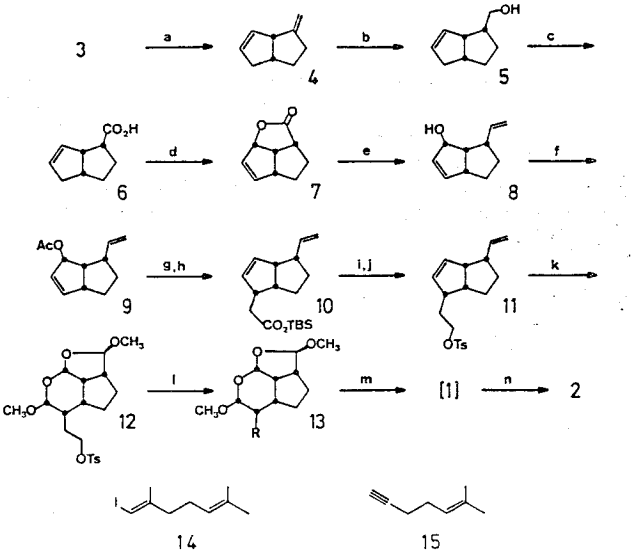


We chose to start with ketone **3**, a readily available material that we have used extensively in terpene synthesis. The general strategy would then require the endo addition of both a one-carbon aldehyde equivalent at C-3[4] and the side chain at C-7, with ozonolysis of the double bond revealing the C-1 and C-19 aldehydes.

Our scheme for the synthesis of **1** was based on the high degree of selectivity for addition of reagents from the exo face of a *cis*-bicyclo[3.3.0]octane at the positions adjacent to the bridgehead (Scheme I). Thus, hydroboration of the diolefin **4** with 1 equiv of disiamylborane[5] proceeded stereo- and regioselectively to give exclusively the endo alcohol **5**.[6] Of many methods tried, only the use of a large excess of PDC[7] was found to selectively oxidize **5** to the corresponding acid **6** without extensive epimerization. The endo substituent at C-3 was now used to stereo- and regiochemically direct oxidation in the opposite ring via Nicolaou's (phenylseleno)lactonization/elimination procedure[8] to form the unsaturated lactone **7** in 94% overall yield. Reduction of the lactone with diisobutylaluminum hydride in toluene at −78 °C followed immediately[9] by Wittig methylenation[10] in the same solvent at 90 °C afforded the olefin alcohol **8** in 76% yield. Curiously, a variety of olefination procedures performed on the isolated intermediate lactol gave inferior results.

Claisen rearrangement of acetate[11] **9** as the *tert*-butyldimethylsilyl ketene acetal[12] afforded the silyl ester **10**,

Scheme I[a]



[a] All reactions were carried out under argon. (a) (i) NaH (1.2 equiv), Me_2SO, 50 °C, 4 h; (ii) Ph_3PCH_3I (1.25 equiv), 1 h, (iii) **3**, 50 °C, 4 h (100%). (b) (i) 2-Methyl-2-butene (2.65 equiv), BH_3 (1.3 equiv), THF, 0–25 °C, 2 h; (ii) **4**, 25 °C, 4 h, (iii) H_2O_2, NaOH, H_2O (96%). (c) Pyridinium dichromate (8 equiv), DMF, 12 h (78%). (d) (i) PhSeBr (1.1 equiv), CH_2Cl_2, −78 to 25 °C, 8 h; (ii) *m*CPBA (5 equiv), 1 h (94%). (e) (i) DIBAH (1.5 equiv), toluene, −78 °C, 2 h; (ii) (a) *t*-BuOK (8 equiv), toluene, Ph_3PCH_3I (8.1 equiv), 90 °C, 2 h, (b) rapid cannula transfer of DIBAH reaction mixture, 8 h (76%). (f) 4-Pyrrolidinopyridine (0.05 equiv), TEA (2 equiv), Ac_2O (2 equiv), 0 °C, 5 min (94%). (g) (i) *i*-Pr_2NH (1.39 equiv), THF, *n*-BuLi (1.26 equiv), HxH, 25 °C, 1 h, (ii) −78 °C, **9**, 10 min, (iii) TBSCl (1.39 equiv), HMPA, 10 min. (h) Xylenes, 120 °C, 12 h. (i) (i) $LiAlH_4$ (8 equiv), Et_2O, 0 °C, 1 h, (ii) minimal saturated aqueous NH_4Cl. (j) TsCl (2 equiv), pyridine, 4 °C, 8 h (85% from **9**). (k) (i) O_3 (excess), MeOH, −78 °C. (ii) Me_2S (5 equiv), −78 to 25 °C, 8 h (48%). (l) (i) Cl_2ZrCp_2 (5 equiv), $ClCH_2CH_2Cl$, Me_3Al (15 equiv), 25 °C, 2 h, (ii) **15** (5.1 equiv), 25 °C, 8 h, (iii) removal of volatile components in vacuo (0.5 mm, 50 °C, 2 h), (iv) extraction with HxH and filtration, (v) *n*-BuLi (4.9 equiv), HxH, THF, (vi) **12**, 50 °C, 48 h, (vii) aqueous HCl (56%). (m) *p*-TsOH (0.1 M), 4:2:1 THF/H_2O/acetone, 50 °C, 12 h. (n) 4-Pyrrolidinopyridine (0.05 equiv), TEA (2 equiv), Ac_2O (2 equiv), 0 °C, 5 min (58% from **15**).

with the first two carbons of the side chain at C-7 introduced specifically endo to the [3.3.0] framework. Reduction of the ester and tosylation of the resulting alcohol gave **11** in 85% overall yield from **9**, setting the stage for the introduction of the remainder of the side chain.

Cleavage of both π-bonds in **11** with ozone in methanol released the three desired aldehyde groups, conveniently obtained directly from the ozonolysis in protected form as the cyclic mixed acetal system found in **12**. Attempted introduction of the remainder of the side chain by coupling with either the cuprate or Grignard reagent derived from the appropriate vinyl iodide **14**[13] resulted only in the displacement of the tosylate group by iodide. Alternatively, zirconium-catalyzed carboalumination of acetylene **15**[14] followed by reaction with *n*-butyllithium provided an ate complex that coupled with the tosylate in a stereo- and

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(5) Brown, H. C.; Zweifel, F. *J. Am. Chem. Soc.* **1961**, *83*, 1241–1246.
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(12) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48–61. The endo ketene acetal was unusually stable, exhibiting virtually no rearrangement at ambient temperature and having a reaction half-life of 33 min at 100 °C.
(13) Negishi, E. I.; van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, 501.
(14) Prepared from 6-methylhept-5-enal by the method of Gilbert and Weerasooriya (Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837–1845).

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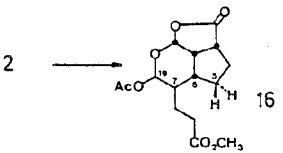
regioselective manner to produce **13**.[15] Hydrolysis of the acetals followed by acetylation afforded a major diacetate, which was not identical by ^1H and ^{13}C NMR with that derived from the natural product.[16]

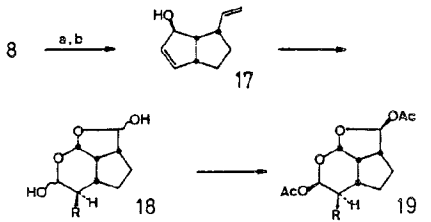
In light of our unambiguous synthesis of **2**, it appeared that the original structure assignment for this derivative of udoteatrial, and hence the natural product, was incorrect. The assignment of the hydrocarbon skeleton's stereochemistry was based on analysis of the γ-lactone **16**



(derived from **2** by ozonolysis, Jones oxidation, and methylation). The assignment of stereochemistry of C-7 was based on the observation of a nuclear Overhauser enhancement[17] of H-5 endo (δ 1.41) upon irradiation of the acetate signal at δ 2.12. However, such an NOE is unlikely with a conformationally mobile substituent such as an acetate group, and the observed enhancement was more likely the result of simultaneous irradiation of H-5 exo at δ 2.16. Indeed, the 9-Hz coupling observed in **16** between protons H-7 and H-6 is in better agreement with a revised structure in which these hydrogens have a trans relationship, with the side chain at C-7 exo.

Synthesis of the C-7 epimer **18** required introduction of the side chain from the exo face. This was accomplished by inversion of the alcohol **8** using diethylazodicarboxylate, triphenylphosphine, and benzoic acid,[18] followed by LAH reduction, cleanly affording the exo alcohol **17**.

The sequence of reactions described above was now



(a) Ph_3P (2 equiv), THF, DEAD (2 equiv), 25 °C, 1 h. (b) (i) $LiAlH_4$ (8 equiv), Et_2O, 0 °C, 1 h, (ii) minimal saturated aqueous NH_4Cl (35% from **8**).

repeated on the isomeric alcohol **17**, affording ultimately the diacetate **19**, identical by proton and carbon NMR with that derived from udoteatrial. These completely stereoselective syntheses demonstrate once again the utility of bicyclo[3.3.0]octanes in terpene synthesis.

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(16) We are grateful to Professor Faulkner for providing copies of the proton NMR spectra of the diacetates of udoteatrial and the triacetate of the LAH reduction product.
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