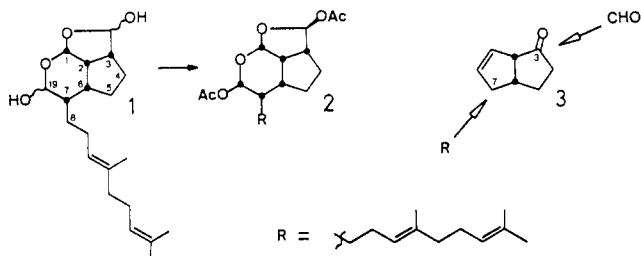


Total Synthesis of (±)-Udoteatrial

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

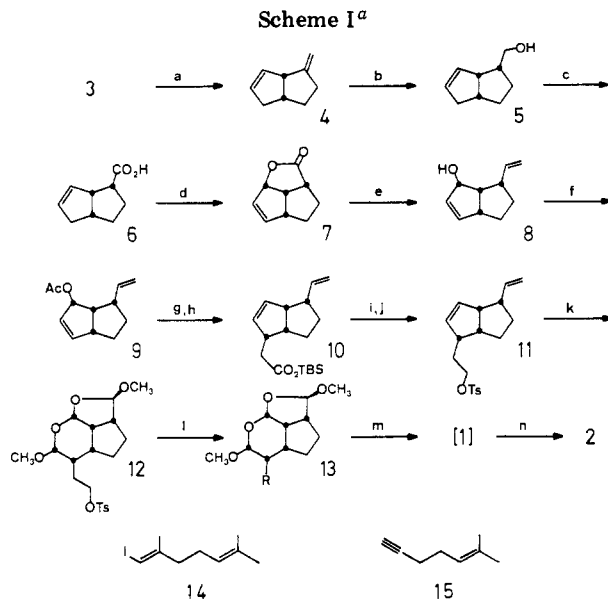
Sir: In 1981 Faulkner¹ reported the isolation of the antimicrobial diterpene udoteatrial from the alga *Udotea flabellum*. Assignment of structure 1 for this natural product was based on spectral analysis of the derivative diacetate 2 and its degradation products since, as would be expected, 1 was found to be a readily interconverted mixture of stereoisomers. Our current interest in the synthesis of a number of mono- and sesquiterpenes such as xylomollin² and allamandin³ 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-3⁴ 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 disiamylborane⁵ proceeded stereo- and regioselectively to give exclusively the endo alcohol 5.⁶ Of many methods tried, only the use of a large excess of PDC⁷ 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 procedure⁸ to form the unsaturated lactone 7 in 94% overall yield. Reduction of the lactone with diisobutylaluminum hydride in toluene at -78 °C followed immediately⁹ by Wittig methylenation¹⁰ 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 acetate¹¹ 9 as the *tert*-butyldimethylsilyl ketene acetal¹² afforded the silyl ester 10,



^a All reactions were carried out under argon. (a) (i) NaH (1.2 equiv), Me₂SO, 50 °C, 4 h; (ii) Ph₃PCH₂I (1.25 equiv), 1 h, (iii) 3, 50 °C, 4 h (100%). (b) (i) 2-Methyl-2-butene (2.65 equiv), BH₃ (1.3 equiv), THF, 0-25 °C, 2 h; (ii) 4, 25 °C, 4 h, (iii) H₂O₂, NaOH, H₂O (96%). (c) Pyridinium dichromate (8 equiv), DMF, 12 h (78%). (d) (i) PhSeBr (1.1 equiv), CH₂Cl₂, -78 to 25 °C, 8 h; (ii) mCPBA (5 equiv), 1 h (94%). (e) (i) DIBALH (1.5 equiv), toluene, -78 °C, 2 h; (ii) (a) *t*-BuOK (8 equiv), toluene, Ph₃PCH₂I (8.1 equiv), 90 °C, 2 h, (b) rapid cannula transfer of DIBALH reaction mixture, 8 h (76%). (f) 4-Pyrrolidinopyridine (0.05 equiv), TEA (2 equiv), Ac₂O (2 equiv), 0 °C, 5 min (94%). (g) (i) *i*-Pr₂NH (1.39 equiv), THF, *n*-BuLi (1.26 equiv), H₂H, 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) LiAlH₄ (8 equiv), Et₂O, 0 °C, 1 h, (ii) minimal saturated aqueous NH₄Cl. (j) TsCl (2 equiv), pyridine, 4 °C, 8 h (85% from 9). (k) (i) O₃ (excess), MeOH, -78 °C. (ii) Me₂S (5 equiv), -78 to 25 °C, 8 h (48%). (l) (i) Cl₂ZrCp₂ (5 equiv), ClCH₂CH₂Cl, Me₃Al (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 H₂H and filtration, (v) *n*-BuLi (4.9 equiv), H₂H, THF, (vi) 12, 50 °C, 48 h, (vii) aqueous HCl (56%). (m) *p*-TsOH (0.1 M), 4:2:1 THF/H₂O/acetone, 50 °C, 12 h. (n) 4-Pyrrolidinopyridine (0.05 equiv), TEA (2 equiv), Ac₂O (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 14¹³ resulted only in the displacement of the tosylate group by iodide. Alternatively, zirconium-catalyzed carboalumination of acetylene 15¹⁴ followed by reaction with *n*-butyllithium provided an ate complex that coupled with the tosylate in a stereo- and

(1) Nakatsu, T.; Ravi, B. N.; Faulkner, D. J. *J. Org. Chem.* 1981, 46, 2435-2438.

(2) Nakane, M.; Hutchinson, C. R.; VanEngen, D.; Clardy, J. *J. Am. Chem. Soc.* 1978, 100, 7079.

(3) Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* 1974, 39, 2477.

(4) For consistency the numbering system used is that corresponding to the natural system.

(5) Brown, H. C.; Zweifel, F. *J. Am. Chem. Soc.* 1961, 83, 1241-1246.

(6) Spectral data consistent with the proposed structures were obtained for all new compounds.

(7) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* 1979, 399-402.

(8) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* 1979, 101, 3884-3893.

(9) Boland, W.; Ney, P.; Jaenicke, L. *Synthesis* 1980, 1015-1017.

(10) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* 1979, 44, 3760-3765.

(11) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* 1978, 34, 2069-2076.

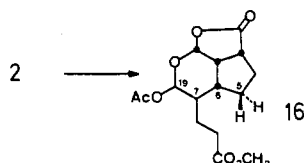
(12) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* 1980, 45, 48-61. The endo ketene acetal was unusually stable, exhibiting virtually no rearrangement at ambient temperature and having a reaction half-life of 33 min at 100 °C.

(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).

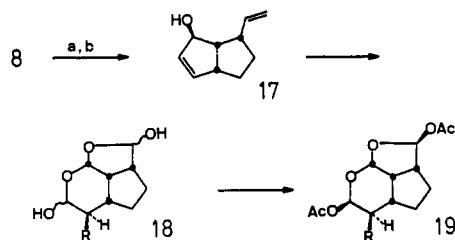
regioselective manner to produce 13.¹⁵ Hydrolysis of the acetals followed by acetylation afforded a major diacetate, which was not identical by ¹H and ¹³C NMR with that derived from the natural product.¹⁶

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 enhancement¹⁷ 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,



(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).

triphenylphosphine, and benzoic acid,¹⁸ followed by LAH reduction, cleanly affording the exo alcohol 17.

The sequence of reactions described above was now 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.

Acknowledgment is gratefully made to the National Institutes of Health (No. GM-29195) for financial support of this research.

(15) Okukado, N.; Negishi, E. I. *Tetrahedron Lett.* 1978, 2357-2360.

(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.

(17) Hall, L. D.; Saunders, J. K. M. *J. Am. Chem. Soc.* 1980, 102, 5703-5711.

(18) (a) Grynkiewicz, G.; Burzynska, H. *Tetrahedron* 1976, 32, 2109-2111. (b) Mitsunobu, O. *Synthesis* 1981, 1-28.

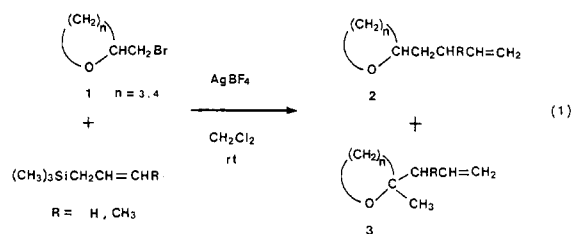
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Silver-Induced Allylation of β -Bromo Ethers with Allylsilanes

Summary: Cyclic β -bromo ethers can be allylated with allyltrimethylsilanes in the presence of silver tetrafluoroborate via the corresponding carbocations. Direct substitution of the bromine atom in the cyclic ethers by an allyl group was observed, but in the case of tetrahydropyranyl derivatives the allylation occurred exclusively via the carboxonium ions which were generated by debromination and subsequent hydrogen shift.

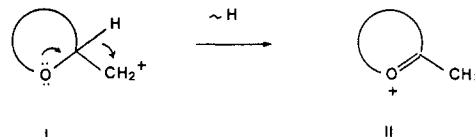
Sir: Effective alkylation of β -halo ethers has not been generally achieved yet, since substitution of the halogen atom with nucleophilic reagents is inherently in difficulty due to competition in facile undesirable elimination. Keck and Yates recently succeeded in allylation of several organic halides, including β -bromo ethers by the use of allyltrialkylstannanes in a free radical process.¹ During the course of our studies on the synthetic utility of allylsilanes,² we have attempted the regiospecific allylation of β -bromo ethers with allylsilanes in a cationic process. We describe here a new allylation reaction of β -bromo ethers, including cyclic ethers, with allylsilanes in the presence of silver tetrafluoroborate.

To a solution of 1³ and allylsilane (2.5 equiv/equiv of 1) in anhydrous dichloromethane (5 mL/mmol of 1) was added well-dried silver tetrafluoroborate (2.0 equiv/equiv of 1)⁴ under an argon atmosphere (eq 1). The mixture was



stirred at ambient temperature in the dark, and the reaction was monitored by TLC. The reaction mixture was diluted with ether (ca. 20 mL), filtered, and treated with aqueous sodium bicarbonate. The extract was concentrated, and the residual oil was purified by silica gel column chromatography to give a mixture of the corresponding isomeric ethers 2 and 3 in good yield (Table I).

2-(Bromomethyl)tetrahydrofurans 1a and 1b gave predominantly the ethers 2a, 2b, 2c, and 2d, respectively, by way of electrophilic attack of the silver-induced primary carbonium ions I on the allylsilanes. On the other hand,



(1) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* 1982, 104, 5829.

(2) (a) Nishiyama, H.; Itagaki, K.; Sakuta, K.; Itoh, K. *Tetrahedron Lett.* 1981, 5285. (b) Nishiyama, H.; Narimatsu, S.; Itoh, K. *Ibid.* 1981, 5289. (c) Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Ibid.* 1982, 1267. (d) Nishiyama, H.; Narimatsu, S.; Sakuta, K.; Itoh, K. *J. Chem. Soc., Chem. Commun.* 1982, 459. (e) Nishiyama, H.; Itoh, K. *J. Org. Chem.* 1982, 47, 2496.

(3) Starting cyclic β -bromo ethers 1 were prepared by treatment of the corresponding ω -hydroxyolefins with *N*-bromosuccinimide in CH_2Cl_2 ; see supplementary material for preparation and structural characterization.

(4) A 0.25 molar equiv of AgBF_4 did not cause a reaction even after 6 days. Equimolar amount of AgBF_4 gave ca. 50% conversion of 1a for 1 day.