For the latter species, the results of HMO calculations[15] show decreasing π-electron densities in the same order.

Inasmuch as the theory[4,12] invokes a critical dependence of k_{nr} on π-electron densities and relative atom displacements of particular vibrational modes, more meaningful interpretation of such data will require reliable normal mode formulations. Thus, an extension of this approach will involve a determination of the lifetime of a large number of specifically deuterated analogues and an intensive effort to obtain a realistic force field via normal coordinate calculations based on extensive vibrational spectroscopic data. Such studies and efforts are currently under way in our laboratory.

(14) (a) Kramer, F. A.; West, R. *J. Phys. Chem.* **1965**, *69*, 673. (b) Castellano, S.; Gunther, H.; Ebersole, S. *J. Phys. Chem.* **1965**, *69*, 4166. (c) Gil, V. M. S. *Mol. Phys.* **1965**, *9*, 97.
(15) Sinha, S. P. *Rev. Roum. Chim.* **1973**, *18*, 777.

Enantiospecific Total Synthesis and Absolute Configurational Assignment of (−)-Punctatin A (Antibiotic M95464)

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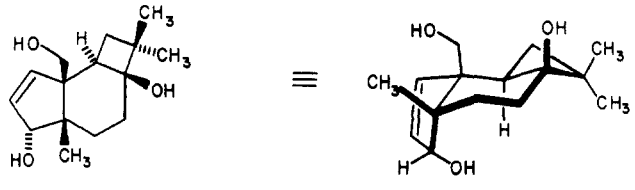
In 1984, Anderson and his associates[1] reported the isolation from the dung fungus *Poronia punctata* (Linnaeus ex Fries) of a trishydroxylated sesquiterpene possessing a previously unknown caryophyllene-related tricyclic framework. The crystalline levorotatory substance, originally known as antibiotic M95464, was assigned the trivial name punctatin A.[2,3] The biological activity of **1** and particularly the presence within its structure of a

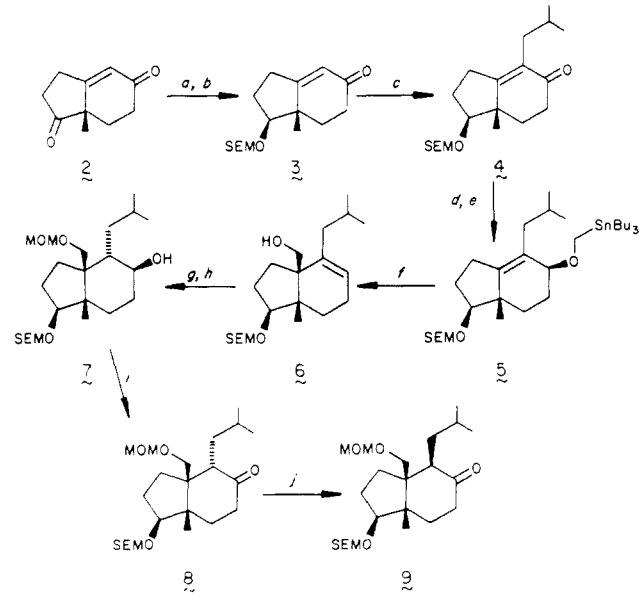


1

trans-fused tertiary cyclobutanol aroused our interest in its laboratory preparation. We herein describe an enantiospecific route to (−)-**1** that permits the assignment of absolute configuration and showcases several interesting synthetic facets including (a) utilization of the Still rearrangement[4] as a viable means for elaborating an angular hydroxymethylated *cis*-perhydroindane system and (b) construction of the completely functionalized four-membered ring in proper stereochemical disposition by application of Norrish Type II photochemistry.[5]

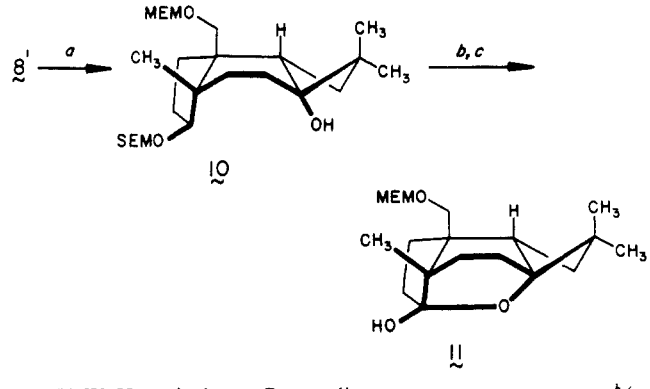
(1) Anderson, J. R.; Briant, C. E.; Edwards, R. L.; Mabelis, R. P.; Poyser, J. P.; Spencer, H.; Whalley, A. J. S. *J. Chem. Soc., Chem. Commun.* **1984**, 405.
(2) Care should be exercised not to confuse punctatin A with punctatin, a germacradienolide obtained from *Liatris punctata* Hook (Herz, W.; Wahlberg, I. *Phytochemistry* **1973**, *12*, 1421). This substance was later renamed punctaliatrin (Herz, W.; Wahlberg, I. *Phytochemistry* **1974**, *13*, 315). An even earlier use of the name for a group of homoisoflavones has turned up (Heller, W.; Tamm, C. *Prog. Chem. Org. Nat. Prods.* **1981**, *40*, 105).
(3) Two additional metabolites that are coproduced with **1** and assigned the names punctatin B and C have more recently been structurally characterized (Anderson, J. R.; Edwards, R. L.; Freer, A. A.; Mabelis, R. P.; Poyser, J. P.; Spencer, H.; Whalley, A. J. S. *J. Chem. Soc., Chem. Commun.* **1984**, 917.
(4) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1480. (b) Still, W. C.; Mitra, A. *Ibid.* **1978**, *100*, 1927.

Scheme I



[a] $LiAlH(O\text{-}t\text{-}Bu)_3$, ether. [b] $Me_3SiCH_2CH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$. [c] $CH_3SOCH_2^-Na^+$, $(CH_3)_2CHCH_2I$, Me_2SO. [d] $LiAlH_4$, ether. [e] KH, ICH_2SnBu_3, THF. [f] *n*-BuLi, hexane, −78 → 0 °C. [g] CH_3OCH_2Cl, $(i\text{-}Pr)_2NEt$. [h] BH_3·THF, diglyme; H_2O_2, NaOH, H_2O. [i] PCC, CH_2Cl_2. [j] $NaOCH_3$, CH_3OH.

Scheme II



[a] 450-W Hanovia lamp, Pyrex, dioxane, room temperature. [b] $(n\text{-}Bu)_4N^+F^-$, 60 °C, 2 mmHg. [c] PCC, CH_2Cl_2.

(+)-Diketone **2**, readily available in an enantiomeric purity of 99.6%,[6] underwent regio- and stereocontrolled hydride reduction[7] together with conversion[8] to SEM ether **3** in 88% yield (Scheme I). Alkylation of the thermodynamic enolate of **3**[9] with 1-iodo-2-methylpropane provided **4** (54%) with the intention that the alkyl side chain ultimately become the carbocyclic backbone of the four-membered ring. As expected,[10] **4** was reduced by $LiAlH_4$ exclusively to the β-alcohol (97%). Deprotonation and alkylation of this intermediate with (iodomethyl)tributyltin afforded the allyl stannylmethyl ether **5** which was treated with excess *n*-butyllithium in hexane. Smooth [2,3]-sigmatropic rearrangement ensued to deliver homoallylic alcohol **6** ($[\alpha]^{22}$ +59.3° (*c* 4.0, C_6H_6)) with complete transfer of chirality[11] (34% overall).

Careful conformational analysis of the MOM ether of **6** revealed that its hydroboration should be less encumbered from the

(5) (a) Fleming, I.; Kemp-Jones, A. V.; Long, W. E.; Thomas, E. J. *J. Chem. Soc., Perkin Trans 2* **1976**, 7. (b) Fleming, I.; Long, W. E. *Ibid.* **1976**, 14 and relevant references cited in these papers.
(6) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1984**, *63*, 26.
(7) Hajos, Z. G.; Parrish, D. R.; Oliveto, E. P. *Tetrahedron* **1968**, *24*, 2039.
(8) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, 3343.
(9) Hajos, Z. G.; Micheli, R. A.; Parrish, D. R.; Oliveto, E. P. *J. Org. Chem.* **1967**, *32*, 3008.
(10) Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312.
(11) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, 5013 and relevant references cited therein.

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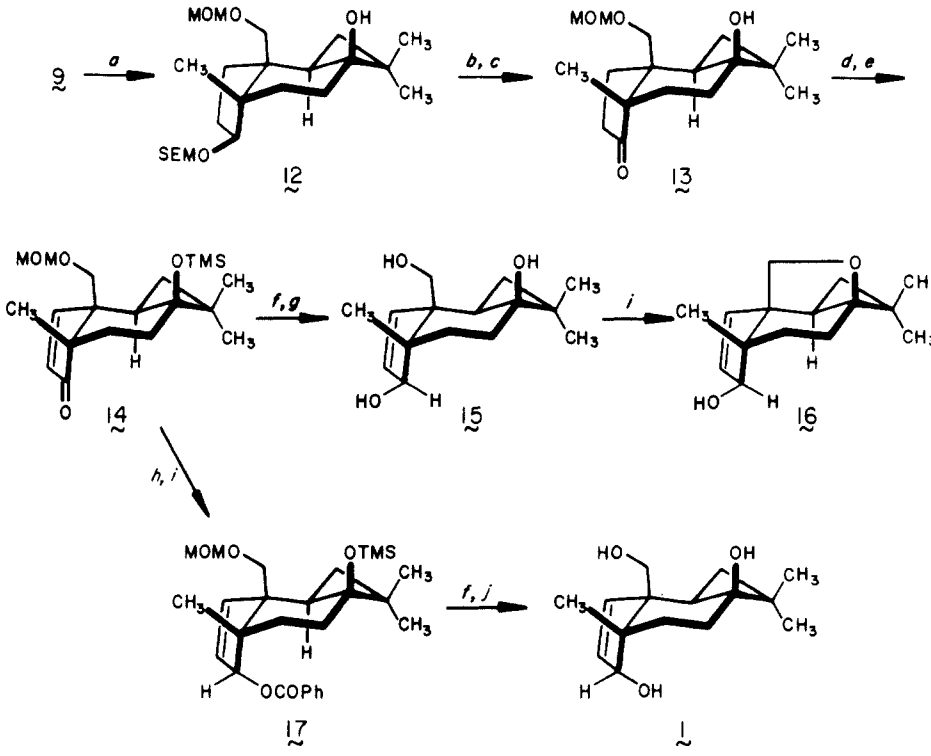
Scheme III



[a] $h\nu$, 253.7 nm, C_6H_6, room temeprature. [b] $(n\text{-Bu})_4N^+F^-$, 55 °C, 2 mmHg. [c] PCC, CH_2Cl_2. [d] $Me_3SiCH_2COOCH_3$, $(n\text{-Bu})_4N^+F^-$, THF. [e] $Pd(OAc)_2$, CH_3CN. [f] $HClO_4$, $THF-H_2O$, room temperature. [g] Dibal, THF, 0 °C. [h] $NaBH_4$, $CeCl_3$, CH_3OH, 0 °C. [i] $(=NCOOC_2H_5)_2$, Ph_3P, C_6H_5COOH, room temperature. [j] KOH, C_2H_5OH, 50 °C, 3 h.

β face. For this reason, the derived ketone was formulated as **8** having the large alkyl sidechain in an alpha disposition.

Support for these stereochemical assignments came first from the demonstration that base-promoted equilibration of **8** to **9** occurs readily. Furthermore, irradiation of dioxane solutions of **8'**, the MEM ether analogue of **8**, through Pyrex with a 450-W Hanovia lamp produced **10** as the only cyclobutane product in 62% yield (Scheme II). The low level of β-cleavage[12] associated with this cyclization was considered to be a harbinger of success in the stereoisomeric series required for arrival at **1**. Recognizing that the hydroxyl group in **10** is rigidly oriented axially if the cyclobutanol is trans-fused, we removed the SEM group and effected oxidation to the ketone. The efficient production of hemiketal **11** reflects not only the close proximity of the two oxygen functionalities but also the existing conformational bias.[13]

When **9** was irradiated with 253.7-nm light (Rayonet reactor), conversion to **12** was observed in 49% yield (Scheme III). Following uneventful conversion to keto alcohol **13**, the A-ring double bond was introduced by sequential O-silylation with methyl (trimethylsilyl)acetate–tetra-*n*-butylammonium fluoride[14] and oxidation with 1.5 equiv of palladium acetate in acetonitrile[15] (65% for the sequence). If the stereochemical outcome of the photocyclization of **9** is as indicated, the tertiary hydroxyl group in **12** is necessarily cis-oriented to the MOM ether functionality. Specific confirmation of this relative stereochemical relationship was sought by conversion of **14** to **15** and exposure of this triol for a brief period of time to the conditions of the Mitsunobu reaction.[16] Rapid conversion to tetrahydrofuran **16** occurred, in complete accord with expectations for the structures shown.

Armed with this information, we subjected **14** to reduction with numerous hydridic reagents. The outcome varied from 1,4-reduction and formation of the dihydro ketone (e.g., $LiAlH_4$, Red-Al, $NaBH_4$–$CeCl_3$) to exclusive production of the β-allylic alcohol (e.g., $(i\text{-Bu})_2AlH$) (see Note Added in Proof). Consequently, to arrive at the desired α-hydroxyl stereoisomer, the latter clean reduction process was exploited and followed in turn by implementation of Mitsunobu technology (62%).[16] Following hydrolytic removal of the three blocking groups, a colorless crystalline solid was obtained whose IR and 300-MHz ^1H NMR spectra proved identical with that of authentic punctatin A.[17] That indeed the correct enantiomer of natural **1** had been synthesized was recognized from the optical rotation, $[\alpha]^{22}$ −27° (*c* 0.4, CH_3OH) (lit.[1] $[\alpha]^{20}$ −26° (*c* 1.0, CH_3OH)).

In summary, the first total synthesis of (−)-punctatin A has been achieved. The serial sequence proceeded in 19 steps from **2**, afforded (−)-**1** in enantiomerically pure condition, and made evident the absolute configuration of the antibiotic.

Acknowledgment. This investigation was made possible by grants from the National Institutes of Health (GM 30827) and Eli Lilly Co.

Note Added in Proof. Following completion of the present work and submission of this paper, the β-alcohol was reported as also being produced by the same fungus. It has been called punctatin D (antibiotic M167906) (Poyser, J. P.; Edwards, R. L.; Anderson, J. R.; Hursthouse, M. B.; Walker, N. P. C.; Sheldrick, G. M.; Whalley, A. J. S. *J. Antibiot.* **1986**, *39*, 167).

(12) See, for example: (a) Yang, N. C.; Thap, D.-M. *Tetrahedron Lett.* **1966**, 3671. (b) Lewis, F. D.; Hilliard, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 3852.

(13) All new compounds were characterized satisfactorily by IR, ^1H NMR, ^{13}C NMR, and optical rotation, as well as by accurate high-resolution mass spectra or combustion data.

(14) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346.

(15) Under these conditions, no benzoquinone or other oxidant proved necessary to effect the conversion to enone. Compare: Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(16) Mitsunobu, O. *Synthesis* **1981**, 1.

(17) We thank Dr. R. L. Edwards (University of Bradford) for generously making available to us a sample of the natural product and copies of its spectra.