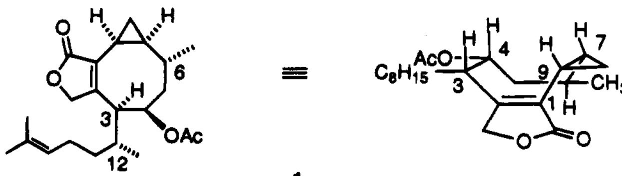
Total Synthesis of Natural (+)-Acetoxycrenulide

Leo A. Paquette,* Ting-Zhong Wang, and Emmanuel Pinard

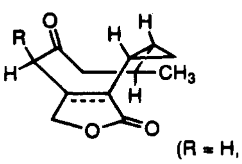
Evans Chemical Laboratories, The Ohio State University Columbus, Ohio 43210

Received October 31, 1994

Full appreciation of marine ecosystems has often been facilitated by knowledge of the dietary chain in the natural habitat.[1] For example, small brown seaweeds of the family Dictyotaceae and the sea hares that feed on them are recognized to survive very well in the most competitive of tropical environments because the algae produce unique secondary metabolites that likely function as defensive agents for both species. The most bountiful of the toxins involved would appear to be acetoxycrenulide (**1**),[2] the unprecedented structural features of which have prompted us to undertake its enantioselective synthesis.



1



(R = H, C_8H_{15})

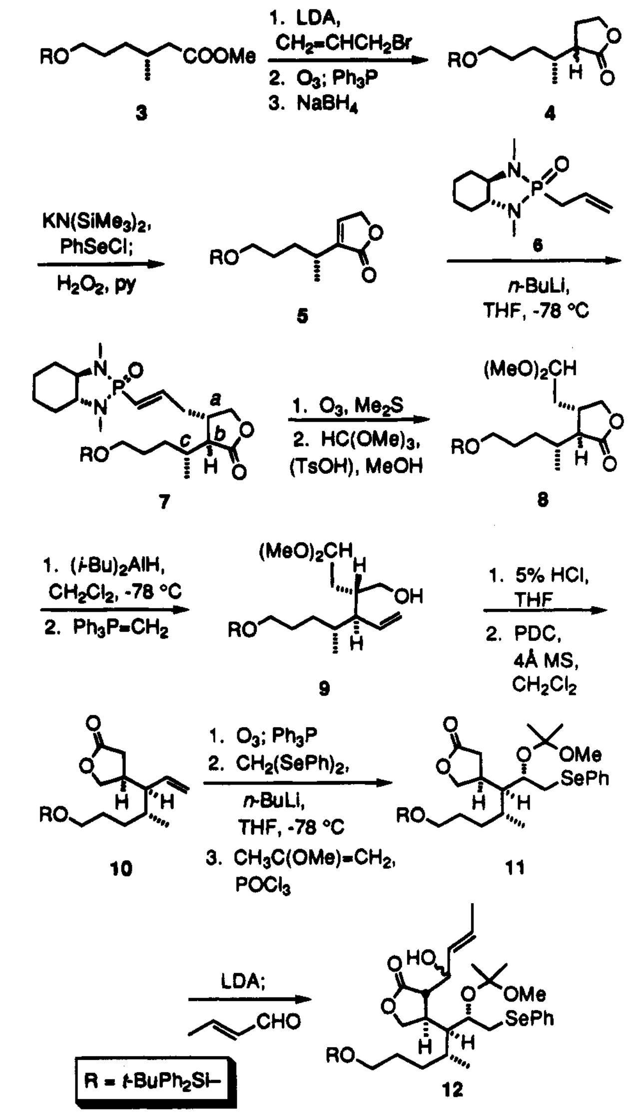
2

Our preliminary studies aimed at this diterpene[3] have provided useful guidance for proper tactical assembly of the five stereogenic centers adorning its cyclooctene core. One relevant finding is that enolization at C-3 in **2** is not easily accomplished and cannot be depended upon for either alkylation (R = H)[3a,b] or epimerization (R = C_8H_{15}).[3c] Also, the Claisen-based approach that we have adopted causes the stereogenicity resident at C-3 and C-12 to control that introduced at the remaining stereocenters (C-4, C-6, C-7, and C-9). However, this interrelationship is very effectively mismatched.[3c] Consequently, a stratagem is required that is capable of overriding this intrinsic bias that leads to a diastereomer of natural **1**. The successful realization of a conveniently workable plan is outlined here.

Ester **3**, which is readily available from (*R*)-citronellol,[4] was homologated to lactone **4** in 80% overall yield by sequential C-allylation and ozonolysis involving a reductive workup (Scheme 1). Following the conversion of **4** into butenolide **5** via organoselenium technology (87%), the asymmetric conjugate addition of enantiopure allylphosphonic diamide **6**[5] to **5** was investigated. The only isolable product **7** (81%) was assigned the indicated absolute stereochemistry on the strength of Hanessian's precedent involving simpler systems. This working assumption was ultimately corroborated by arrival at **1**. Thus, the configurations at sites *a* and *b* are fixed as a direct consequence of the inherent chirality of **6** with virtual disregard for the stereochemistry resident at site *c* (see **7**). In this way, the three contiguous stereocenters were properly set.

Ozonolysis of **7** (79%) followed directly by acetalization (90%) resulted in removal of the chiral auxiliary and formation of acetal **8**, $[\alpha]^{23}_D$ −6.4° (*c* 1.36, $CHCl_3$).[6] Exposure of **8** to Dibal-H provided the lactol (97%), which underwent ready

Scheme 1



(1) (a) McEnroe, F. J.; Robertson, K. J.; Fenical, W. In *Marine Natural Products Chemistry*; Faulkner, D. J., Fenical, W., Eds.; Plenum Press: New York, 1972; pp 179–190. (b) Fenical, W. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. II, pp 173–245.

(2) (a) Sun, H. H.; McEnroe, F. J.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 1903. (b) Midland, S. L.; Wing, R. M.; Sims, J. J. *J. Org. Chem.* **1983**, *48*, 1906. (c) Additional members of this family are known (i) Pachylactone: Ishitsuka, M.; Kusumi, T.; Kakisawa, H.; Kawakami, Y.; Nagai, Y.; Sato, T. *Tetrahedron Lett.* **1983**, *24*, 5117. (ii) Crenulacetals A–D: Kusumi, T.; Muanza-Nkongolo, D.; Goya, M.; Ishitsuka, M.; Iwashita, T.; Kakisawa, H. *J. Org. Chem.* **1986**, *51*, 384. (iii) Crenuladial: Tringali, C.; Oriente, G.; Piattelli, M.; Geraci, C.; Nicolosi, G.; Breitmaier, E. *Can. J. Chem.* **1988**, *66*, 2799. (d) Photochemical interconversions: Guella, G.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1539.

(3) (a) Ezquerra, J.; He, W.; Paquette, L. A. *Tetrahedron Lett.* **1990**, *31*, 6979. (b) Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.*, in press. (c) He, W.; Pinard, E.; Paquette, L. A. *Helv. Chim. Acta*, in press.

(4) The citronellol utilized was material of 96.3% ee. The steps involved are acetylation, ozonolysis, reduction with $BH_3{\cdot}Me_2S$, protection with TBDPSCl, saponification with K_2CO_3 in MeOH, sequential PDC and $NaClO_2$ oxidation, and esterification with CH_2N_2 (57% overall). The side chain was truncated in this manner in order to skirt around the complication introduced later by the terminal isopropenyl group, whose reactivity appreciably exceeds the reactivities present within the eight-membered ring at later stages. Consequently, this site of unsaturation is reintroduced in the final step.

(5) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudouin, S. *J. Org. Chem.* **1993**, *58*, 5032.

(6) All new compounds reported herein have been fully characterized by IR, high-field ^1H and ^{13}C NMR, high-resolution mass spectrometry, and (in many cases) combustion analysis.

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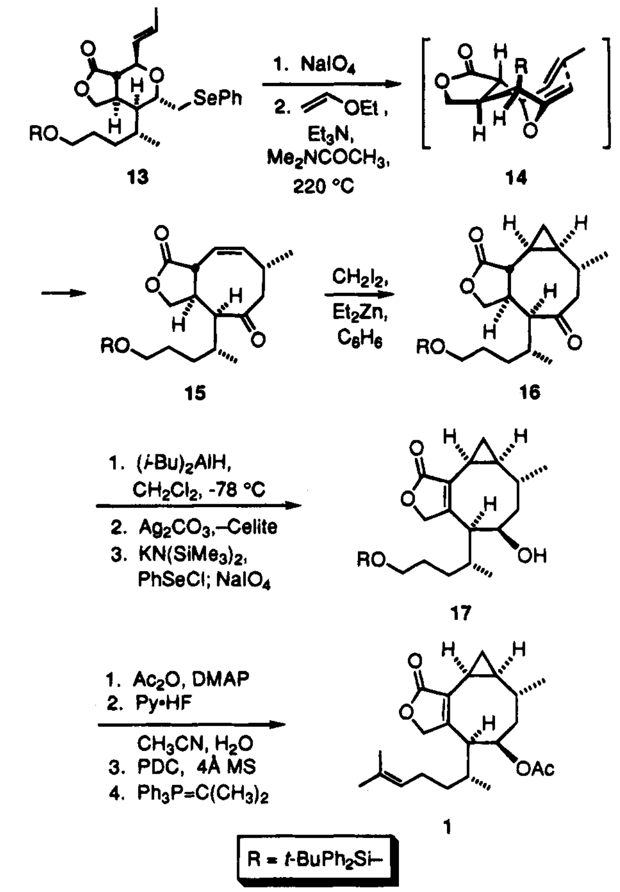
Scheme 2



condensation with methylenetriphenylphosphorane to deliver **9** as a colorless oil (80%). In preparation for suitable introduction of the remaining carbon atoms, **9** was hydrolyzed in 5% aqueous HCl and the resulting lactol (78%) was oxidized to generate **10** in 97% yield. Following ozonolysis of the lactone so formed, it proved possible to realize stereocontrolled nucleophilic addition to the aldehyde functionality with $PhSeCH_2Li$.[7] A Cram-like trajectory operates exclusively at −78 °C with formation of an alkoxide that does not enter into intramolecular attack at the lactone carbonyl at this temperature. Introduction of an acid-labile protecting group was next achieved by treatment of the alcohol with 2-methoxypropene in the presence of a catalytic amount of $POCl_3$.[8] The conversion to **11** proceeded in 77% overall yield.

The preceding tactics permitted the subsequent implementation of an aldol condensation involving **11** and crotonaldehyde. The inseparable 1:1 mixture of epimers **12** so produced was heated directly with a catalytic quantity of *p*-toluenesulfonic acid in benzene to give **13** (49% isolated).[9] The stereochemical features of this intermediate and many of the ensuing compounds were made apparent by NOE studies.[10] Oxidation of **13** to the selenoxide level set the stage for concurrent 1,2-elimination and Claisen rearrangement. Heating of this intermediate at 220 °C in *N,N*-dimethylacetamide containing triethylamine and ethyl vinyl ether to guard against unwanted interference by the PhSeOH being generated gave rise to **15** (55%). The rather elevated temperature is presumably required because the stereochemical relationships in **14** require that the alkyl side chain be projected axially as the chair-like sigmatropic transition state is approached (Scheme 2). Notwithstanding this increased energy demand, the efficiency of the two-step process is quite acceptable.

The ensuing Simmons–Smith cyclopropanation[11] of **15** is directed to the β surface as a consequence of the prevailing ground-state conformation. The isomer **16** so produced (92%, $[\alpha]^{23}_D$ +8.6° (*c* 1.86, $CHCl_3$)) underwent smooth stereocontrolled reduction with Dibal-H to a hydroxy lactol, which was chemoselectively reoxidized with the Fetizon reagent. Conversion to the butenolide as before provided **17** in 65% yield over four steps. With the structure and stereochemistry of **17** secure (NOE analysis), this intermediate was sequentially acetylated, desilylated, oxidized to the aldehyde level with PDC, and reacted with isopropylidenetriphenylphosphorane (54% overall). This protocol delivered (+)-acetoxycrenulide as determined by direct comparison of its IR and ^1H NMR spectra and optical rotation, $[\alpha]^{23}_D$ +20.1° (*c* 1.8, $CHCl_3$),[12] with data kindly provided to us by Professor James Sims.

In summary, the first total synthesis of (+)-acetoxycrenulide has been achieved in an enantioselective manner. The linear approach efficiently constructs the central eight-membered ring whose stereogenic centers are properly set in an absolute sense by exploiting the high-level capability of the anion of allylphosphonic diamide **6** for controlled elaboration of two vicinally substituted carbon atoms. The strategy should prove useful as a means for preparing other medium-ring natural products.

Acknowledgment. This work was generously supported by the National Institutes of Health (Grant GM-30827). We thank Professor James Sims (University of California, Riverside) for providing the IR and ^1H NMR spectra of acetoxycrenulide and Dr. Susumu Akutagawa (Takasago Research Institute, Tokyo) for a generous sample of (*R*)-citronellol.

Supplementary Material Available: Spectroscopic data for **7**, **11**, **13**, **15**, and **16** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA943522L

(7) Seebach, D.; Peleties, N. *Chem. Ber.* **1972**, *105*, 511.

(8) Kluge, A. F.; Untch, K. G.; Field, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

(9) At this point, chromatographic separation of **12** from its diastereomer is easily accomplished. Furthermore, the diastereomer can be converted into **12** by further heating under the same acidic conditions. These observations are precedented.[3a,b]

(10) The experiments will be detailed in the full paper.

(11) Sawada, S.; Inoue, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2669.

(12) The reported rotations for **1** are $[\alpha]^{26}_D$ +13°,[2a] +13.4°,[2b] +20.5°,[2b] and +21.5°.[2c(iii)]