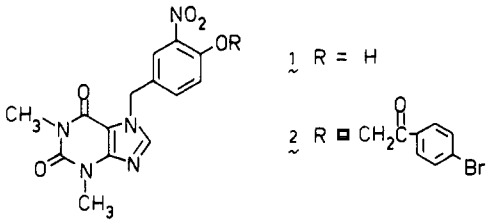
Phidolopin, a New Purine Derivative from the Bryozoan *Phidolopora pacifica*

Summary: The structure of phidolopin (1), a purine derivative isolated from the bryozoan *Phidolopora pacifica*, was solved by X-ray diffraction analysis.

Sir: A number of interesting nitrogenous metabolites containing the physostigmine,[1] indole,[2] quinoline,[3] and bipyrrole[4] ring systems have recently been reported from bryozoans. As part of an ongoing search for biologically active metabolites from British Columbia marine organisms, we have examined extracts of the bryozoan *Phidolopora pacifica*, commonly referred to as the "lacey bryozoan" because of its highly intricate calcium carbonate skeleton. Our attention was drawn to *P. pacifica* by the total absence of fouling organisms on its skeleton and by the strong in vitro antifungal and antialgal activity of its extracts. Herein, we report the structure of phidolopin (1), an unusual purine derivative, which is largely responsible for the biological activity of the crude extracts.[5]



P. pacifica was collected by hand using SCUBA (-3 to -15 m) on several rocky reefs in Barkley Sound, British Columbia. Freshly collected specimens were homogenized in methanol. The ethyl acetate soluble portion of the concentrated methanol extract was fractionated via flash chromatography and preparative TLC to give pure phidolopin (1) (4 mg): mp 226-227 °C (methanol); TLC (silica gel) R_f 0.16 (ethyl acetate); HRMS EI, m/z (relative intensity) M^+ 331.0917 (calcd for $C_{14}H_{13}N_5O_5$ 331.0917), 180 ($C_7H_8N_4O_2$, 75), 152 ($C_7H_6NO_3$, 100); UV ($CH_3C{\equiv}N$) λ max 353 (ϵ 3300), 275 (ϵ 16,800) nm; IR ($CHCl_3$) 3300, 1697, 1626, 1532 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.39 (s, 3 H), 3.59 (s, 3 H), 5.46 (s, 2 H), 7.16 (d, J = 8.6 Hz, 1 H), 7.61 (dd, J = 2.2, 8.6 Hz, 1 H), 7.63 (s, 1 H), 8.08 (d, J = 2.2 Hz, 1 H), 10.56 (s, 1 H, exchanges with D_2O).

We were able to assign the ^1H NMR resonances at δ 5.46, 7.16, 7.61, 8.08, and 10.56 to a 4-hydroxy-3-nitrobenzyl residue by comparing the chemical shifts of the aromatic protons to the literature values for 4-hydroxy-3-nitrotoluene.[6] A benzylic cleavage in the mass spectrum of phidolopin (1), which results in the nitrophenol residue giving rise to the observed base peak at m/z 152 ($C_7H_6NO_3$), supported our assignment. The remainder of phidolopin had to consist of a $C_7H_7N_4O_2$ fragment which contained six sites of unsaturation. ^1H NMR resonances at δ 3.39 (s, 3 H) and 3.59 (s, 3 H) indicated two methyl groups attached to either oxygen or nitrogen atoms and the IR spectrum suggested the presence of at least one amide carbonyl. A purine nucleus containing oxygen, methyl, and 4-hydroxy-3-nitrobenzyl substituents could account for all the structural requirements of phidolopin. We were, however, unable to unambiguously establish the substitution pattern on the purine nucleus by spectral correlations. The structure of phidolopin (1) was therefore solved via a single-crystal X-ray diffraction analysis on its *p*-bromophenacyl derivative 2.[7]

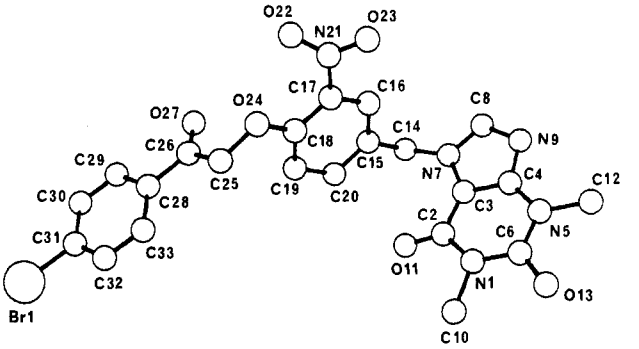


Figure 1. A computer-generated perspective drawing of the final X-ray model of *p*-bromophenacylphidolopin. Hydrogens are omitted for clarity.

A crystal of 2 which was suitable for X-ray diffraction was grown by slow evaporation of an acetone-methanol-acetonitrile solution. Preliminary X-ray photographs showed triclinic symmetry, and accurate lattice constants of a = 9.549 (3) Å, b = 9.514 (1) Å, c = 15.212 (3) Å, α = 72.69 (1)°, β = 82.96 (2)°, and γ = 81.87 (2)° were determined by a least-squares fit of 15 diffractometer measured 2θ values. An estimated density was consistent with two units of composition $C_{22}H_{18}O_6N_5Br{\cdot}C_3H_6O$ forming the unit cell. All unique diffraction maxima $2\theta \leq 114°$ were recorded on a computer-controlled four-circle diffractometer using a variable speed 1° ω scan and graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.54178 Å). After correction for Lorentz, polarization, and background effects, only 1255 (36%) were judged observed ($|F_0| \geq 3\sigma(F_0)$). A phasing model was obtained by standard heavy atom methods.[8] Space group *P1* was assumed, and this choice was verified by the successful completion and refinement of the structure. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a standard crystallographic residual of 0.0939 for the observed reflections. Additional crystallographic material is described in the paragraph on supplementary material at the end of the paper.

Figure 1 is a computer generated perspective drawing of the final X-ray model of the *p*-bromophenacyl derivative of phidolopin less hydrogens. Bond distances and angles generally agree well with anticipated values.

(1) (a) Carle, J. S.; Christophersen, C. *J. Am. Chem. Soc.* **1980**, *45*, 1586. (b) Carle, J. S.; Christophersen, C. *J. Org. Chem.* **1981**, *46*, 3440.

(2) (a) Wulff, P.; Carle, J. S.; Christophersen, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2895. (b) Sato, A.; Fenical, W. *Tetrahedron Lett.* **1983**, *24*, 481.

(3) Wulff, P.; Carle, J. S.; Christophersen, C. *Comp. Biochem. Physiol. B* **1982**, *71B*, 525.

(4) Cartê, B.; Faulkner, D. J. *J. Org. Chem.*, **1983**, *48*, 2314.

(5) Phidolopin (1) shows in vitro antifungal activity against *Pythiam ultimum*, *Rhizoctonia solani*, and *Helminthosporium satium* (minimum inhibitory concentration = 70 $\mu g/^1/_4$-in. disk, for all three species). It also shows antialgal activity against the pennate diatom *Cylindrotheca fusiformis*. (See: Chan, A. T.; Andersen, R. J.; LeBlanc, M. J.; Harrison, P. J. *Marine Biology* **1980**, *59*, 7.)

(6) Sadtler Standard NMR Spectra No. 18051.

(7) Bromo derivative 2 shows: mp 197 °C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3 H), 3.57 (s, 3 H), 5.38 (s, 2 H), 5.45 (s, 2 H), 6.91 (d, J = 8.4 Hz, 1 H), 7.49 (dd, J = 2.3, 8.4 Hz, 1 H), 7.59 (d, J = 8 Hz, 2 H), 7.68 (s, 1 H), 7.79 (d, J = 8 Hz, 2 H), 7.80 (d, J = 2.3 Hz, 1 H).

(8) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, a system of computer programs for the automatic solution of crystal structure from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. German, J. P. Declercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University, 1978.

0022-3263/84/1949-3869$01.50/0

Phidolopin (1) represents a new addition to the very small but important group of naturally occurring purine derivatives based on the xanthine nucleus that includes caffeine, theophylline, and theobromine. It is of special interest because it is of animal rather than plant origin and because it contains a nitro functionality which is relatively rare in natural products.

Acknowledgment. The research at UBC was supported by a NSERC grant to R.J.A. and a NSERC postgraduate fellowship to S.W.A. The research at Cornell was supported by grants from NIH (CA24487) and NSF (INT8117327). We thank Mike LeBlanc and the staff of the Bamfield Marine Station for assistance with collecting *P. pacifica*.

Registry No. 1, 92014-27-2; 2, 92014-28-3.

Supplementary Material Available: Tables of fractional coordinates, equivalent isotropic thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

Stephen W. Ayer, Raymond J. Andersen*
Departments of Chemistry and Oceanography
University of British Columbia
Vancouver, B.C., Canada V6T 1W5

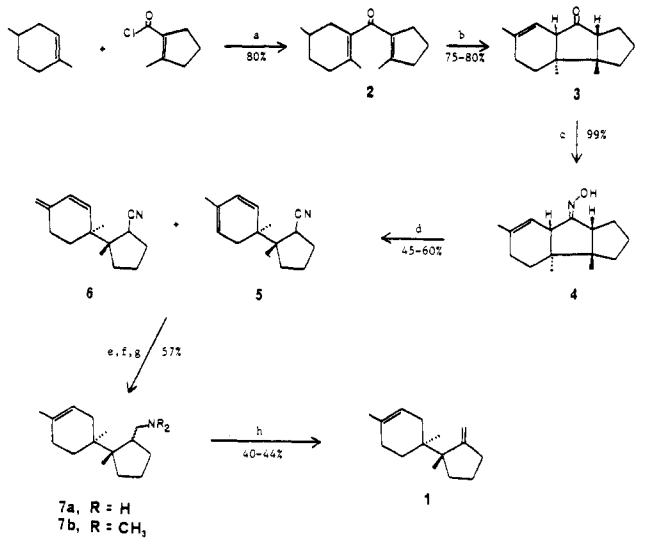
He Cun-heng, Jon Clardy*
Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, New York 14853
Received May 9, 1984

A Highly Stereoselective, Convergent Synthesis of (±)-Trichodiene

Summary: A short, highly stereoselective synthesis of (±)-trichodiene has been completed via a convergent strategy using a Nazarov cyclization for stereospecific formation of the adjacent quaternary centers.

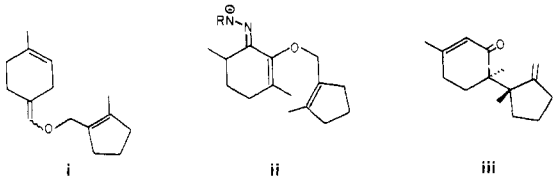
Sir: The structure of trichodiene (1),[1] the parent hydrocarbon of the trichothecane class of sesquiterpenoids,[2] presents an intriguing challenge to synthetic chemists even in the absence of complex functionality. The conceptually appealing convergent approach involving combination of a simple cyclopentane derivative and a simple cyclohexane derivative creates the quite challenging problem of forming two adjacent quaternary centers in a stereoselective manner. Previous syntheses of trichodiene have either been nonconvergent[3] (construction of one of the two rings after introduction of the adjacent quaternary centers) or have suffered from regioselectivity or stereoselectivity problems.[4] We have solved these selectivity problems through use of a Nazarov cyclization[6] in the key carbon–carbon bond-forming step. This type of convergent strategy involves an initial linking of the two rings followed by a stereospecific intramolecular reaction to form the two quaternary centers with control of stereochemistry.[7] We considered electrocyclic reactions to be ideal candidates for the key bond-forming reaction. After an initial unsuccessful investigation of the hexatriene → cyclohexadiene reaction as the key step,[8] we concentrated our efforts on the Nazarov cyclization[6] as the reaction to form the adjacent quaternary centers. The key features of this approach (Scheme I) include the synthesis of the cross-conjugated dienone **2** from simple five- and six-membered ring starting materials, stereospecific electrocyclic ring closure to form the adjacent quaternary centers, opening of the central ring to a bicyclic structure, and functional group

Scheme I



[a] $SnCl_4$, CH_2Cl_2, −78 °C; NaOMe, MeOH. [b] $BF_3 \cdot Et_2O$, $CHCl_3$, reflux, 5 days. [c] NH_2OH, EtOH. [d] $(CF_3CO)_2O$, CH_2Cl_2; Et_3N. [e] $LiAlH_4$, Et_2O. [f] $NaCNBH_3$, CH_2O, CH_3CN. [g] Li, $NH_3(l)$, Et_2O. [h] MCPBA, CH_2Cl_2; distill at 1.5 mmHg.

(1) (a) Nozoe, S.; Machida, Y. *Tetrahedron Lett.* **1970**, 2671–2674. (b) Nozoe, S.; Machida, Y. *Tetrahedron* **1972**, *28*, 5105–5111.
(2) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *15*, 388–395.
(3) (a) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077–4085. (b) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G. *Synth. Commun.* **1976**, *6*, 485–488. (c) Welch, S. C.; Rao, A. S. C. P.; Wong, R. Y. *Synth. Commun.* **1976**, *6*, 443–445. (d) Welch, S. C.; Wong, R. Y. *Tetrahedron Lett.* **1972**, 1853–1856. (e) Welch, S. C.; Wong, R. Y. *Synth. Commun.* **1972**, 291–295. (f) Schlessinger, R. H.; Schultz, J. A. *J. Org. Chem.* **1983**, *48*, 407–408.
(4) (a) Yamakawa, K.; Sakaguchi, R.; Nakamura, T.; Watanabe, K. *Chem. Lett.* **1976**, 991–992. (b) Suda, M. *Tetrahedron Lett.* **1982**, *23*, 427–428. (c) Recent results by Gilbert and Wiechman[5] indicate that the total absence of stereoselectivity in the Suda approach[4b] is a result of a lack of stereocontrol in the formation of the enol ethers used in the Claisen rearrangement.
(5) Gilbert, J. C.; Wiechman, B.; Senaratne, K. P. A. "Abstracts of Papers" 186th National Meeting of the American Chemical Society, Washington, DC, 1983, American Chemical Society: Washington, DC.; ORGN 203.
(6) (a) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442. (b) Preliminary studies on model systems were conducted by M. Wilson and C.-Y. Tseng. These results will be included in the complete paper.
(7) Synthetic approaches utilizing sigmatropic reactions involve a related strategy. (a) The approach by Suda[4b] and Gilbert[5] utilizes the Claisen rearrangement of structure i as the key step. (b) Other attempts to apply Cope, alkoxy-Cope, and Claisen rearrangement reactions to the synthesis of structures related to trichodiene have been reported to be unsuccessful: Thomas, J. A. Ph.D. Dissertation, Oregon State University, Corvallis, OR, 1979. (c) A successful synthesis of the trichodiene derivative iii with reasonable stereoselectivity has been reported recently through the Claisen rearrangement of the donor-imine derivative ii: Ponaras, A. A.; "Abstracts of Papers", 187th National Meeting of the American Chemical Society, St. Louis, MO, 1984; American Chemical Society: Washington, DC, ORGN 29. See also: Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866–3868.



(8) (a) Ligon, R.; Harding, K. E., unpublished results, Texas A&M University. (b) A related cyclization leading to only one angular methyl group has been successful: Okamura, W. H.; Condran, P., Jr. *J. Org. Chem.* **1980**, *45*, 4011–4015.

0022-3263/84/1949-3870$01.50/0