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.

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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.

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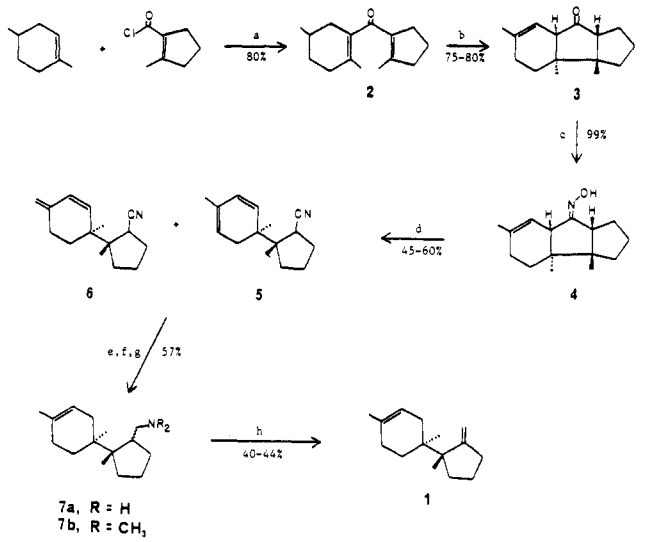
A Highly Stereoselective, Convergent Synthesis of (±)-Trichodiene

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.

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(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.
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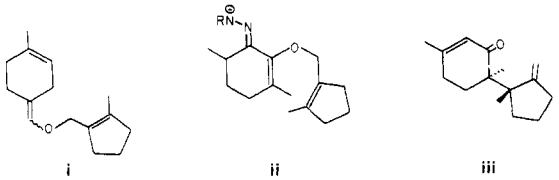
(5) Gilbert, J. C.; Wiechman, B.; Senaratne, K. P. A. "Abstracts of Papers" 186th National Meeting of the American Chemical Society, Washington, DC, 1983, American Chemical Society: Washington, DC.; ORGN 203.
(6) (a) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442. (b) Preliminary studies 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.

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transformation to trichodiene.

The dienone **2** was prepared in 80% yield by the stannic chloride catalyzed acylation[9] of 1,4-dimethylcyclohexene[10] with the acid chloride of 2-methyl-1-cyclopentene carboxylic acid.[11] High yields were possible only when this reaction was performed by slow addition of 3 equiv of stannic chloride to a rapidly stirred solution of the acid chloride (generated in situ by treatment of the acid with oxalyl chloride) and 4 equiv of the cyclohexene in methylene chloride at −78 °C. The crude product was treated with sodium methoxide in methanol to dehydrohalogenate any β-chloro ketone material formed in the reaction. The cyclization of dienone **2** required more vigorous conditions than model compounds lacking the 2° methyl group on the cyclohexene ring.[8b,12] Thus, while cyclization of the model system proceeded readily in high yield upon treatment with trifluoroacetic acid,[8b] dienone **2** could not be cyclized to any significant extent with trifluoroacetic acid or mixtures of trifluoroacetic acid and trifluoroacetic anhydride. Reactions using Lewis acid catalysis[13] proved more fruitful. Reaction with 8 equiv of boron trifluoride etherate in refluxing chloroform for 5 days led to cyclization in 75–80% yield. The product was shown to be a diastereomeric mixture (ca. 2.4:1) of the cis-anti-cis and cis-anti-trans isomers of ketone **3**. Since the stereocenters other than at the quaternary carbons are immaterial to the synthesis, the mixture was used in further transformations.

Numerous reaction sequences were investigated[14] to find conditions to cleave the central five-membered ring, and the only useful reaction was found to be the Beckmann fragmentation reaction[15] of the oxime derived from ketone **3**. Reaction of ketone **3** with hydroxylamine gave oxime **4**, containing about 10% of the α,β-unsaturated isomer, in quantitative yield. Treatment of the oxime with trifluoroacetic anhydride followed by triethylamine gave the cyano dienes **5** and **6** (ratio varied from 3:1 to 6:1) in yields ranging from 45% to 60%. After an attempt to reduce both the diene system and the nitrile with lithium in ammonia failed,[16] the nitrile was reduced with lithium aluminum hydride to give the corresponding amino diene, which was reduced with lithium in ammonia to give amine **7a** in 80% yield. This amine was converted to the corresponding dimethyl derivative **7b** in 72% yield by reaction with formaldehyde and sodium cyanoborohydride followed by evaporative distillation.[17] Oxidation with *m*-chloroperoxybenzoic acid gave the amine oxide, which was heated at 150 °C under vacuum. The distillate was chromatographed on silica gel to give racemic trichodiene (**1**) in 40–44% overall yield from amine **7a**.[18] Examination of the product by ^{13}C and ^{1}H NMR spectroscopy showed no detectable signals attributable to the diastereomer, bazzanene.[19]

Thus, racemic trichodiene was synthesized in nine steps from 2-methyl-1-cyclopentenecarboxylic acid chloride. The possibility that this synthetic approach could also serve as a method for stereoselective synthesis of bazzanene through selective 1,2-reduction of diene **5** is currently under investigation.

Acknowledgment. We thank the Robert A. Welch Foundation (Grant A-442) for support of this research. The NMR spectrometers used in this research were purchased with the aid of National Science Foundation Grants to Texas A&M University.

Registry No. (±)-**1**, 61505-17-7; (±)-**2**, 91861-30-2; (±)-**3** (isomer 1), 91861-31-3; (±)-**3** (isomer 2), 91926-35-1; **4**, 91861-32-4; **5**, 91861-33-5; **6**, 91861-34-6; **7a**, 91861-35-7; **7b**, 91861-36-8; (±)-1,4-dimethylcyclohexene, 91926-34-0; 2-methyl-1-cyclopentenecarbonyl chloride, 59253-86-0.

Supplementary Material Available: Analytical and spectral data for structures **1–7b** (4 pages). Ordering information is given on any current masthead page.

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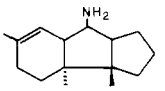
(16) The product of this reaction was determined to be tricyclic amine iv resulting from ring closure during the reduction:



iv

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(18) One side product of the elimination reaction was the dimethylamine precursor **7b**, which was easily removed in the chromatography. See: Cope, A. C.; Trumball, E. R. In "Organic Reactions"; Cope, A. C., Ed.; Wiley: New York, 1957; Vol. 11, Chapter 5, pp 317–493.

(19) We thank Prof. J. C. Gilbert at the University of Texas for providing copies of spectra of trichodiene and bazzanene.

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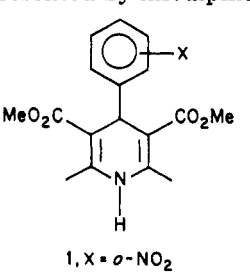
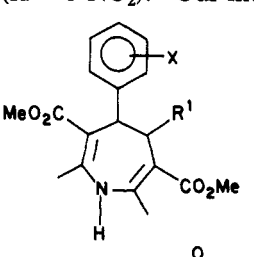
Synthesis of 4,5-Dihydroazepine-3,6-dicarboxylate Derivatives by Stereoselective Ring Expansion–Nucleophilic Addition to 4-(α-Chloroalkyl)-1,4-dihydropyridine-3,5-dicarboxylates

Summary: The synthesis of highly substituted 4,5-dihydroazepines by ring expansion of 1,4-dihydropyridines is described.

Sir: Among the various agents which block the transmembrane flux of calcium[1-3] are 1,4-dihydropyridine derivatives[4] originally prepared by Hantzsch[5] in 1882 and represented by nifedipine **1** (X = *o*-NO_2). Our interest



1, X = *o*-NO_2



2, R^1 = H, Me, Ph, $CH_2OC(=O)$-*t*-Bu

in the structural requirements of the dihydropyridine binding sites, proposed by Snyder[6] and others,[7] led us into

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