sodium methoxide in absolute methanol (53 mL, 105.9 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, and the filtrate was diluted with ether and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated to afford epoxide **15a** (14 g, 91.5%). An analytical sample was obtained by short-path distillation: bp 42 °C (0.7 mmHg); $[\alpha]^{25}_D$ −0.69° (*c* 4.15, EtOH).

(2*S*,3*R*)-3,4-Epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (15b). This compound was prepared in 92% yield from **14b** by using the procedure described for **15a**; $[\alpha]^{25}_D$ −10.96° (*c* 2.55, EtOH).

2-[(2*R*,3*R*)-3,4-*O*-Isopropylidene-2,3,4-trihydroxybutyl-1]-1,3-dithiane (16a). The procedure followed was identical with that described for the preparation of **5a**; $[\alpha]^{25}_D$ +24.96° (*c* 2.90, EtOH).

2-[(2*R*,3*S*)-3,4-*O*-Isopropylidene-2,3,4-trihydroxybutyl-1]-1,3-dithiane (16b). This was obtained from **15b** in 98% yield by following the method given for the synthesis of **5a**; $[\alpha]^{25}_D$ +22.62° (*c* 3.01, EtOH).

2-[(2*R*,3*R*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-2,3,4-trihydroxybutyl-1]-1,3-dithiane (17a). Benzyl ether **17a** was obtained from **16a** according to the procedure described for the preparation of **6a**: 96% yield; $[\alpha]^{25}_D$ +46.97° (*c* 2.41, EtOH).

2-[(2*R*,3*S*)-2-*O*-Benzyl-3,4-*O*-isopropylidene-2,3,4-trihydroxybutyl-1]-1,3-dithiane (17b). Alcohol **16b** was benzylated to afford **17b** by following the method described for the preparation of **6a**; $[\alpha]^{25}_D$ +33.79° (*c* 1.53, EtOH).

(3*R*,4*R*)-3-*O*-Benzyl-4,5-*O*-isopropylidene-3,4,5-trihydroxypentanal (18a). Compound **17a** was converted to the product by using the method given for **7a**; $[\alpha]^{20}_D$ +34.55° (*c* 3.19, $CHCl_3$).

(3*R*,4*S*)-3-*O*-Benzyl-4,5-*O*-isopropylidene-3,4,5-trihydroxypentanal (18b). The procedure followed was identical with that described for the preparation of **7a**; $[\alpha]^{20}_D$ −5.0° (*c* 2.74, $CHCl_3$).

Methyl 3-*O*-Benzyl-2-deoxy-D-xylofuranoside (19a). Aldehyde **18a** was cyclized to give **19a** in 90% yield by following the procedure mentioned for the preparation of **8**: ^1H NMR ($CDCl_3$) δ 1.96–2.36 (m, 2 H), 2.43–2.86 (br s, 1 H, D_2O exchangeable), 3.33 (s, 3 H), 3.23–4.75 (m, 6.5 H), 5.13 (t, *J* = 1.5 Hz, 0.5 H), 7.23 (s, 5 H).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.59; H, 7.68.

Methyl 3-*O*-Benzyl-2-deoxy-L-ribofuranoside (19b). This compound was obtained from aldehyde **18b** according to the procedure described for the preparation of **8**: ^1H NMR ($CDCl_3$) δ 1.83–2.4 (m, 3 H), 3.31 (s, 3 H) 3.48–4.63 (m, 6 H), 4.86–5.13 (m, 1 H), 7.23 (s, 5 H).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.43; H, 7.72.

Acknowledgment. We thank Drs. Leon Goodman and Raymond P. Panzica for stimulating discussions and helpful suggestions.

Stereoselective Synthesis of (±)-Trichodiene

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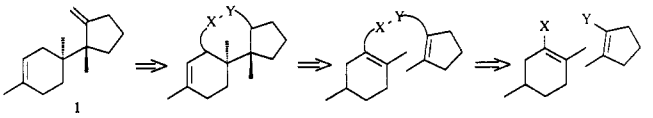
Details of a convergent stereoselective synthesis of trichodiene (1) from simple monocyclic starting materials are reported. Stereochemical control is effected by Nazarov cyclization of dienone **14** and C–C bond cleavage of the resulting tricyclic products **15** to form cyano dienes **20**.

Trichodiene (1) has attracted the attention of synthetic chemists both because it is the biogenetic precursor of the biologically active trichothecenes[1] and because it presents an interesting challenge for stereochemical control between the two adjacent quaternary carbons connected by an acyclic single bond. A variety of approaches to the synthesis of trichodiene have been reported.[2] We describe here the details of a cyclization–ring cleavage strategy, which makes use of a stereospecific electrocyclic reaction

Scheme I



to control stereochemistry.[3]

The conceptually appealing convergent approach (formation of the C–C bond between five- and six-membered rings) to the synthesis of trichodiene requires a method for synthesis of a C–C bond between two quaternary centers with control of stereochemistry. The problems of control in direct intermolecular coupling[4] led us to consider a strategy which makes the key bond-forming step an intramolecular reaction (Scheme I). We considered electrocyclic reactions[5] to be advantageous for this purpose because stereochemical control is assured by mechanistic

(1) (a) Tamm, C.; Breitenstien, W. In *The Biosynthesis of Mycotoxins*; Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 69–104. (b) Cane, D. E. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, pp 283–374. (c) Zamir, L. O.; Gauthier, M. J.; Devoe, K. A.; Nadeau, Y.; Sauriol, F. *J. Chem. Soc., Chem. Commun.* **1989**, 598–600.

(2) (a) Yamakawa, K.; Sakaguchi, R.; Nakamura, T.; Watanabe, K. *Chem. Lett.* **1976**, 991–992. (b) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077–4085. (c) Suda, M. *Tetrahedron Lett.* **1982**, *23*, 427–428. (d) Schlessinger, R. H.; Schultz, J. A. *J. Org. Chem.* **1983**, *48*, 407–408. (e) Harding, K. E.; Clement, K. S. *J. Org. Chem.* **1984**, *49*, 3870–3871. (f) Gilbert, J. C.; Wiechman, B. E. *J. Org. Chem.* **1986**, *51*, 258–260. (g) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1986**, *51*, 4485–4488. (h) Kraus, G. A.; Thomas, P. J. *J. Org. Chem.* **1986**, *51*, 503–505. (i) VanMiddlesworth, F. L. *J. Org. Chem.* **1986**, *51*, 5019–5021. (j) Pearson, A. J.; O'Brien, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1445–1447. (k) Pearson, A. J.; O'Brien, M. K. *J. Org. Chem.* **1989**, *54*, 4663–4673. (l) K. Snowden, R. L.; Brauchli, R.; Sonnay, P. *Helv. Chim. Acta* **1989**, *72*, 570–593. (m) Gilbert, J. C.; Kelly, T. A. *Tetrahedron Lett.* **1989**, *30*, 4193–4196.

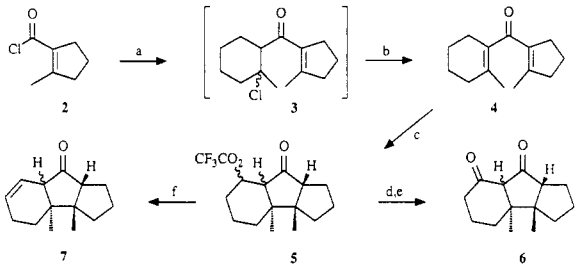
(3) Portions of these results have been published in a preliminary communication: See ref 2e.

(4) The problems of a direct intermolecular convergent synthesis have been solved recently using the reaction of tin enolates with tricarbonylcyclohexadienyliumiron cations.[2j,k] The synthetically useful stereoselectivity (5:1) obtained by this method is, however, not an obvious consequence of the reaction used.

(5) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.

0022-3263/90/1955-4403$02.50/0

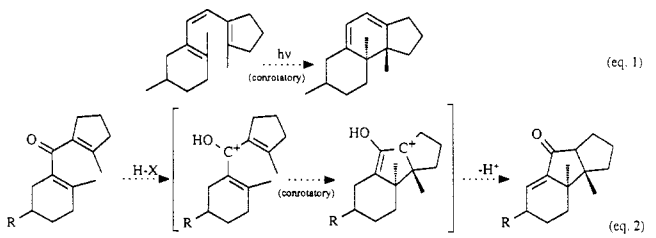
Scheme II[a]



[a] (a) $SnCl_4$, 1-methylcyclohexene, CH_2Cl_2, −78 to −10 °C; (b) KOH, EtOH; (c) CF_3CO_2H, Δ; (d) KOH, MeOH; (e) Jones' reagent; (f) NaH, THF.

constraints. The disadvantage of this strategy is the formation of an additional ring which must be cleaved to give the final product.

Electrocyclic reactions considered for the critical bond formation step include a photochemical (conrotatory) hexatriene–cyclohexadiene cyclization[6] (eq 1) and the Nazarov reaction[7] (eq 2). The 1,3,5-hexatriene system presents problems of competing photochemical reactions of trienes and cyclohexadienes, questions of equilibrium favoring the triene, and E/Z isomerization of the central double bond.[6] Mechanistic studies by Woodward, Kurland, and Lehr[5,8] had shown that the Nazarov reaction could be used to form adjacent quaternary centers with stereochemical control, but questions of yield and synthetic utility remained. Application of this reaction to the synthesis of trichodiene as shown in eq 2 also requires selectivity in deprotonation of the cyclopentenyl cation intermediate. The studies reported in this paper provide answers to the above questions and represent a novel application of the Nazarov reaction to total synthesis.[7,9]

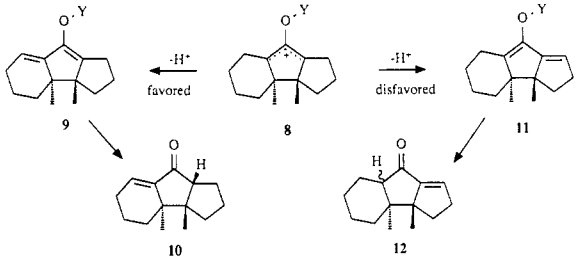


(eq. 1)

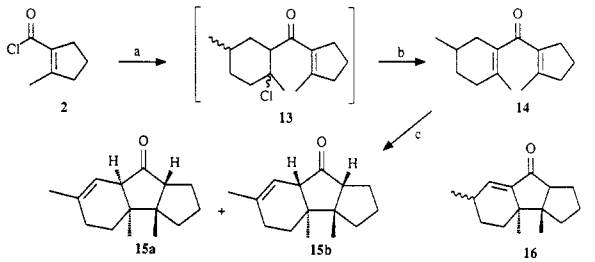
(eq. 2)

Our initial studies of the Nazarov reaction were conducted to evaluate the utility of this reaction in the synthesis of linearly fused 6,5,5 tricyclic systems. The cross-conjugated dienones used for cyclization studies were prepared by Friedel–Crafts acylation of cyclohexene derivatives.[8a,10] Efficient methods for synthesis of 2-methyl-1-cyclopentenecarboxylic acid were developed as part of this study and have been described in detail previously.[11] This acid was converted into the acid chloride **2** with oxalyl chloride, and acylation of 1-methyl-1-cyclohexene was effected using stannic chloride as catalyst (Scheme II). The crude product, which consisted primarily of β-chloro ketone **3**, was treated with sodium hydroxide in ethanol, chromatographed, and distilled to give dienone **4** in 91% yield from the carboxylic acid.

Scheme III



Scheme IV[a]



[a] (a) 1,4-Dimethylcyclohexene, $SnCl_4$, CH_2Cl_2, −78 °C; (b) NaOEt, EtOH; (c) BF_3·Et_2O, $CHCl_3$, Δ.

Although electrocyclic cyclization of dienones had been traditionally conducted with polyphosphoric acid or phosphoric acid–carboxylic acid mixtures,[7] we found that such reagents did not effect reaction with dienone **4**. However, it was found that heating dienone **4** with trifluoroacetic acid at 65 °C for 4 h produced a crystalline tricyclic ketone in 82% yield. The product was found not to be the expected α,β-unsaturated ketone, but the β-trifluoroacetoxy ketone **5**, presumably produced by acid-catalyzed conjugate addition to the intermediate enone.[12] Confirmation that the trifluoroacetoxy group was located on the six-membered ring was obtained by hydrolysis to the hydroxy ketone and oxidation to a dione assigned structure **6**. The infrared spectrum of this ketone showed two distinct carbonyl absorptions at 1710 and 1740 cm^{-1}, indicative of both cyclopentanone and cyclohexanone rings. Attempts to eliminate trifluoroacetic acid from tricyclic ketone **5** with triethylamine at reflux led to recovered starting material. However, treatment of ketone **5** with sodium hydride in tetrahydrofuran at reflux for 3 h resulted in formation of the nonconjugated enone **7**.

These studies provided evidence that the Nazarov cyclization to a 6,5,5 linear tricyclic system could be effected with good yield and resulted in regioselective deprotonation into the six-membered ring (Scheme III). The direction of deprotonation was initially assumed to be a result of differences in ring strain. However, close in-

(6) Dauben, W. G.; McInnis, E. L.; Michno, D. M. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; pp 91–129.

(7) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442. Ramaiah, M. *Synthesis* **1984**, 529–570.

(8) (a) Kurland, D., Ph.D. Dissertation, Harvard University, 1967. See *Chem. Abstr.* **1968**, *70*, 19441*m*. (b) Lehr, R., Ph.D. Dissertation, Harvard University, 1968. We thank Professor Lehr, University of Oklahoma, for providing information related to studies in this dissertation.

(9) For other recent examples of synthetic applications of the Nazarov reaction, see, inter alia: (a) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043–4060. (b) Denmark, S. E.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 195–208. (c) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168–194. (d) Wada, E.; Fujiwara, I.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 325–324. (e) Peel, M. R.; Johnson, C. R. *Tetrahedron Lett.* **1986**, *27*, 5947–5950. (f) Chenard, B. L.; Van Xyl, C. M.; Sanderson, D. R. *Tetrahedron Lett.* **1986**, *27*, 2801–2804. (g) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821–2829. (h) Sakai, T.; Miyata, K.; Takeda, A. *Chem. Lett.* **1985**, 1137–1138. (i) Kjeldsen, G.; Knudsen, J. S.; Ravn-Petersen, L. S.; Torsell, K. B. G. *Tetrahedron* **1983**, *39*, 2237–2239.

(10) (a) Groves, J. K. *Chem. Soc. Rev.* **1972**, 73–97. (b) Groves, J. K.; Jones, J. *J. Chem. Soc. C* **1969**, 608–610. (c) Groves, J. K.; Jones, J. *J. Chem. Soc. C* **1968**, 2215–2217.

(11) (a) Harding, K. E.; Clement, K. S. *J. Org. Chem.* **1984**, *49*, 2049–2050. (b) Harding, K. E.; Tseng, C.-Y. *J. Org. Chem.* **1978**, *43*, 3974–3977.

(12) Non-conjugated enones and β-addition products have been observed as major products of other Nazarov cyclizations.[7,8a]

spection reveals that, although the conjugated enones **10** and **12** differ significantly in energy because of the double bond at the bridgehead of the fused five-membered rings,[13] the deprotonation step yields dienol **9** or **11**, each of which contain such a double bond. MM calculations[14] of strain energy of the dienol intermediates show that they differ little in strain energy, and examination of models of the cyclopentenyl cation intermediate do not show significant stereoelectronic factors which would favor the observed deprotonation selectivity. At any rate, a large preference for deprotonation into the six-membered ring is observed experimentally. The isolation of enone **7** from the base treatment of **5** rather than the conjugated ketone must be a result of increased ring strain in the conjugated system.[12] No definitive evidence for the ring juncture stereochemistry was obtained for the above compounds. The cis-fusion for the fused five-membered rings is based on the known large energy difference between cis- and trans-fused five-membered rings.[15] Additional stereochemical evidence was obtained on the compounds used as intermediates in the synthesis of trichodiene, as discussed below.

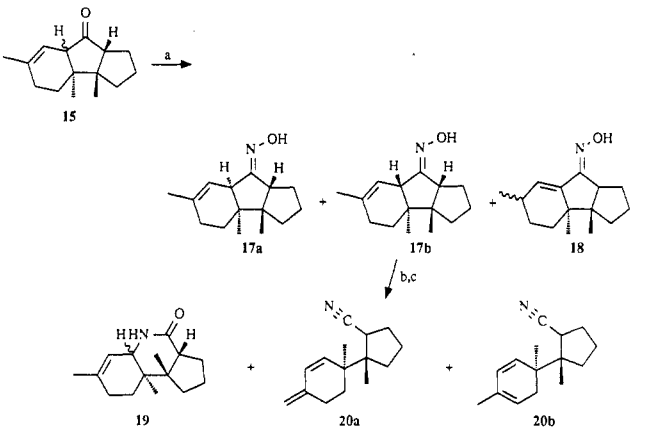
Although methods for elaboration of the tricyclic ketones **5–7** to trichodiene could be envisaged, incorporation of the additional methyl group early in the synthesis was considered advantageous. This was accomplished by acylation of 1,4-dimethyl-1-cyclohexene with acid chloride **2** (Scheme IV). High yields in this reaction required careful control of the experimental conditions. Slow addition of 3 equiv of stannic chloride to a rapidly stirred mixture of acid chloride **2** and 4 equiv of the dimethylcyclohexene in methylene chloride at −78 °C followed by dehydrohalogenation of the crude product with ethanolic sodium ethoxide gave dienone **14** in 80% yield. Dienone **14** required significantly different conditions for cyclization than those found suitable for cyclization of dienone **4**. Prolonged treatment of **14** with trifluoroacetic acid or mixtures of trifluoroacetic acid and trifluoroacetic anhydride produced only small amounts of cyclization. Lewis acid catalysis of the cyclization[7,16] proved more fruitful. Stannic chloride was not useful, but cyclization could be effected with boron trifluoride etherate in refluxing chloroform, although the reaction was slow.[17] Reaction for 3 days with 10 equiv of catalyst provided ketone **15** in 89% yield after chromatography and distillation. Although an initial product assumed to be enone **16** could be observed in the reaction at shorter reaction times or milder conditions, the slowness of the cyclization reaction resulted in essentially complete conversion to **15** under conditions which led to complete cyclization.[12]

NMR spectra of **15** indicated that it was a 2.4:1 mixture of isomers, which have been tentatively assigned the cis-anti-cis (**15a**) and trans-anti-cis (**15b**) stereochemistry, respectively. The anti relationship of the methyl groups is required by the mechanism of the Nazarov cyclization and was confirmed by completion of the synthesis of trichodiene. The assignment of cis stereochemistry to the fused five-membered ring system is firmly based on energetic grounds.[15] The ratio of the isomers of **15** was not changed upon treatment with acidic or basic catalysts and thus appears to be the equilibrium ratio. The absence of the conjugated isomer **16** as a major component of this mixture is indicated by both IR and ^{13}C NMR spectra. The assignment of ring stereochemistry at the 6-5 ring junction is based upon the signal for the vinyl proton. In addition to small long-range coupling, the signal from the major isomer shows a "large" coupling constant of 3 Hz, while no coupling of such size is observed for the signal of the minor isomer. Inspection of Dreiding models and models from MM calculations[14] shows that the trans-fused isomer, as expected, has little conformational mobility, and the dihedral angle between the vinyl proton and the adjacent bridgehead proton is about 89–90°. The cis-fused isomer has more flexibility, and the predicted dihedral angle is 73° or less. These values predict a larger vicinal coupling constant for the cis-fused isomer.[18] MM calculations also predict a slightly lower energy for the cis isomer **15a**. However, for the purposes of this synthesis, it is *only* the stereochemical relationship of the methyl groups which is critical, and both isomers of **15** can be used in further transformations.

With the ketone **15** in hand, the synthetic problem becomes the cleavage of the unwanted C–C bond to complete the carbon skeleton of trichodiene (Scheme V). The obvious approach of Baeyer–Villager oxidation to a lactone proved unsuccessful. Numerous attempts to oxidize **15** to a tricyclic lactone were thwarted by the combined presence of hindered ketone functionality, nucleophilic trisubstituted double bond, and equilibration of **15** under basic conditions with isomer **16** containing an electrophilic double bond.[19] Interestingly, reactions with base and hydrogen peroxide provided a mixture of unidentified acidic components with no vinyl protons and recovered starting material **15**, which consisted primarily of the

Scheme V

Scheme VI[a]



[a] (a) $H_2NOH{\cdot}HCl$, K_2CO_3, EtOH, Na_2SO_4; (b) $(CF_3CO)_2O$, CF_3CO_2H, CH_2Cl_2; (c) Et_3N.

(13) Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1975**, *40*, 1699–1701.
(14) MM calculations were performed with the MMX force field parameters using the program PCMODEL (Serena Software, Bloomington, Indiana).
(15) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109–3118.
(16) We thank Professor L. A. Paquette for this suggestion. Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017–3028. Paquette, L.; Schostarez, H. *Tetrahedron Lett.* **1981**, *37*, 4431–4435.
(17) Reaction in refluxing benzene[16] led to reaction of intermediates or the product with benzene, as evidenced by signals for aromatic protons in the ^1H NMR spectrum.
(18) Becker, E. D. *High Resolution NMR: Theory and Applications*; Academic Press: New York, 1980. Marchand, A. P. *Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems*; VCH Publishers: Weinheim, 1982; pp 112–145.
(19) Clement, K. S. H., Ph.D. Dissertation, Texas A&M University, 1984; *Chem. Abstr.* **1985**, *102*, 95853s.

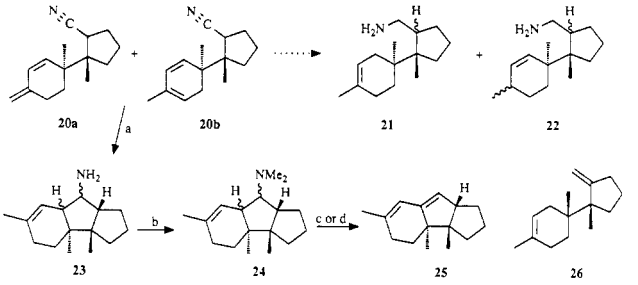
isomer **15b**. In this manner, spectral data for the minor component **15b** could be obtained. Attempts to form an enol ether derivative or to effect oxidation of the enolate anion[20] also were unsuccessful.

The one method found to cleave the desired carbon–carbon bond in good yield involved reaction under conditions to effect the Beckmann rearrangement (Scheme VI).[21] Treatment of the mixture of ketones **15a** and **15b** with hydroxylamine hydrochloride and potassium carbonate in ethanol gave an almost quantitative yield of oxime derivative. Spectral data indicated that the material was a mixture of oximes **17a** and **17b** with a small amount (~10%) of the conjugated isomer **18**. The assignment of oxime configuration is based upon the fact that the vinyl signals for the two isomers of **17** correspond almost exactly in chemical shift and coupling constant to those observed for ketone **15**. The minor isomer is assigned structure **18** based upon the observation of a methyl doublet at δ 0.85 and a vinyl signal at δ 6.0. Separation of the conjugated isomer by chromatography was difficult so the mixture was used in the rearrangement studies.

Beckmann rearrangement of the mixture of oximes could be effected under a variety of conditions, but, in addition to the expected lactam **19**, the cyano dienes **20a** and **20b** were observed as significant byproducts under most reaction conditions. Thus, the Beckmann fragmentation pathway proved to be a major pathway in the rearrangement of oxime **17**.[22] The potential difficulties in opening the lactam ring and cleaving the C–N bond of **19** led to consideration of cyano dienes **20** as key intermediates. Previous trichodiene syntheses had made use of dissolving metal reduction of cyano dienes to generate the appropriate cyclohexene ring system.[2b,d,j] Thus, efforts were directed toward maximizing the yield of cyano dienes **20a** and **20b** from the oxime derivatives.

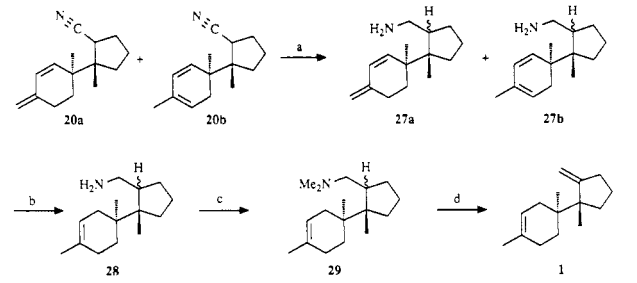
The best conditions involved the formation and rearrangement of trifluoroacetate derivatives of oxime **17**. Direct treatment of the oxime mixture with trifluoroacetic anhydride and a catalytic amount of trifluoroacetic acid in methylene chloride at room temperature for 1 h gave, after chromatography, a mixture of cyano dienes **20a** and **20b** in 52% yield.[23] The major product in these rearrangements was the more stable endocyclic cyano diene **20b**. A cleaner product mixture was obtained by treating oxime **17** with slightly more than 1 equiv of trifluoroacetic anhydride in methylene chloride for 10 min to form the trifluoroacetate and then quenching the excess trifluoroacetic acid by the addition of slightly less than 1 equiv of triethylamine. The mixture was stirred for an additional 100 min to give, after workup and chromatography, dienes **20a** and **20b** in yields up to 65%.[23] This reaction, where Beckmann fragmentation predominates over the normal Beckmann rearrangement, is an interesting example of

Scheme VII[a]



[a] (a) Li, $NH_{3(l)}$, EtOH; (b) formalin, $NaBH_3CN$, CH_3CN; (c) H_2O_2, MeOH; 170 °C (1 mm); (d) MeI; AgO; 170 °C (1 mm).

Scheme VIII[a]



[a] (a) $LiAlH_4$, Et_2O; (b) Li, $NH_{3(l)}$; (c) formalin, $NaBH_3CN$, CH_3CN; (d) MCPBA, $NaHCO_3$, CH_2Cl_2; 150 °C (1.5 mm).

fragmentation in a fused-ring system with only allylic stabilization of the secondary α-carbon of the oxime.[22]

Completion of the synthesis from cyano dienes **20** requires reduction of the diene system and conversion of the nitrile functionality to an exocyclic methylene. Two possible methods for generation of the exocyclic methylene would involve (a) reduction of the nitrile to an aldehyde followed by reduction to an alcohol and elimination of an alcohol derivative or (b) reduction of the nitrile to an amine and elimination of the amine via Cope or Hoffman elimination. Reactions of cyano diene **20** with diisobutylaluminum hydride with either acidic workup or with NaF and $CuCl_2$ gave products which showed significant destruction of the diene system.[24] Since nitriles can be reduced to amines with dissolving metals,[25] the direct reduction of the cyano diene **20** to amine **21** was attempted. Reduction with lithium in ammonia containing anhydrous ethanol gave an amine product for which IR and NMR spectra were consistent with a diastereomeric mixture of amine **21** and small amounts of other isomers such as **22** (Scheme VII).[26] Thus, this amine mixture was methylated using aqueous formaldehyde and sodium cyanoborohydride in acetonitrile.[27] Conversion of the dimethylamine mixture to a trialkylammonium hydroxide and Hoffman elimination or oxidation to the trialkylamine oxide and Cope elimination[28] produced a mixture of dienes whose

(20) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294–3297. (b) Gardner, J. N.; Popper, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. L. *J. Org. Chem.* **1968**, *33*, 3695–3699. (c) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Am. Chem. Soc.* **1978**, *43*, 188–196. (d) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999–1005. (e) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578–1591.

(21) (a) McCarty, C. G. In *The Chemistry of the Carbon–Nitrogen Double Bond*; Patai, S., Ed.; Interscience: New York, 1970; pp 408–507. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 1–420.

(22) For discussions of the Beckmann fragmentation reaction see: Conley, R. T.; Ghosh, S. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; pp 197–308, and ref 21b, pp 11–13 and 33–43.

(23) The yield for this reaction was calculated based on the 85–90% of oxime **17** in the mixture of oximes. Since oxime **18** would not undergo the Beckmann fragmentation, it was not separated from the oxime mixture prior to reaction.

(24) The proximity of the aldehyde and diene functionality might allow for facile cationic π cyclization during hydrolysis of the aldimine intermediate to the aldehyde.

(25) Doumaux, A. R., Jr. *J. Org. Chem.* **1972**, *38*, 508–510 and references cited therein.

(26) A mass spectrum would have been inconsistent with this assignment, but at that time, the departmental mass spectrometer was inoperable and remained so for some time.

(27) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673–1674.

(28) (a) Cope, A. C.; Trumball, E. R. In *Organic Reactions*; Cope, A. C., Ed.; Wiley: New York, 1957; Vol. 11, Chapter 5, pp 317–493. (b) Caserio, F. F., Jr.; Parker, S. H.; Piccolini, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1958**, *80*, 5507–5513. (c) Cope, A. C.; Bumgardner, C. L.; Schweizer, E. E. *J. Am. Chem. Soc.* **1957**, *79*, 4729–4733. (d) Cope, A. C.; Bumgardner, C. L. *J. Am. Chem. Soc.* **1957**, *79*, 960–964. (e) Cope, A. C.; Acton, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 355–359. (f) Cope, A. C.; McLean, D. C.; Nelson, N. A. *J. Am. Chem. Soc.* **1955**, *77*, 1628–1631.

NMR spectra clearly did not correspond to that of natural trichodiene (1) or the diastereomer bazzanene (26).[29] Careful examination of spectra suggested that the amine and diene products were tricyclic and corresponded to structures 23–25. Confirmation was obtained by independent synthesis of tricyclic amine 23 by reduction of oxime 17 with lithium aluminum hydride. The facile ring closure during the reduction step can be rationalized in terms of the proximity of the diene and nitrile functions resulting in capture of radical anion or dianion intermediates by the other functional group faster than by protonation.

This problem was solved by chemical reduction of the nitrile prior to use of dissolving metal (Scheme VIII). Treatment of dienes **20a** and **20b** with lithium aluminum hydride in ether provided amine **27** in greater than 90% yield. The spectra of this amine, and subsequent N-containing intermediates, were more complex than spectra of the cyano dienes **20** because of small amounts of epimerization of the nitrile prior to complete reduction. This complication is immaterial to completion of the synthesis since this stereocenter is not present in trichodiene. The synthesis was completed by reduction with lithium in liquid ammonia to give amine **28**, which was converted to the dimethyl amine **29** by reductive alkylation. Oxidation with *m*-chloroperbenzoic acid gave the amine oxide, which was heated at 150 °C under vacuum to give (±)-trichodiene (1) in 40–44% yield from amine **28**.

The trichodiene structure was confirmed by comparison of ^1H and ^{13}C NMR spectra with those of both pure trichodiene and a mixture of trichodiene and the diastereomer bazzanene (26).[2k,29] The diastereomers can be differentiated by signals in the ^1H NMR spectrum at 4.74 ppm for trichodiene and at 4.79 ppm for bazzanene. No signal for bazzanene was detectable.

The overall synthesis of racemic trichodiene proceeds through nine synthetic steps from 2-methyl-1-cyclopentene carboxylic acid and provides a single diastereomer based on the stereospecificity of the Nazarov cyclization and the high selectivity of 1,4-reduction in the conversion of amines **27** to amines **28**.[30-32]

Experimental Section

General Procedures. All compounds prepared in this section are racemic; the designation "±" is omitted. The ^1H NMR spectra were obtained in the solvent indicated on Varian Associates Model T-60, HA-100, EM-360, EM-390, or XL-200 spectrometers. The ^{13}C NMR spectra were obtained on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system, a Varian Associates Model FT-80 spectrometer operating at 20.00 MHz, or a Varian Associates Model XL-200 spectrometer operating at 50.31 MHz.

In the workup procedures, "acid" refers to aqueous 2 N hydrochloric acid, "base" refers to aqueous 10% sodium hydroxide, "bicarbonate" refers to a saturated aqueous solution of sodium bicarbonate, "brine" refers to a saturated aqueous solution of sodium chloride, and "concentration" indicates solvent removal by rotary evaporation (Büchi Rotavapor) at ca. 40 mmHg. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The temperatures cited for these distillations are the maximum temperature of the oven during distillation. Melting points were taken with a Thomas -Hoover capillary melting point apparatus. All boiling points and melting points are uncorrected.

Preparative thin-layer chromatography was performed on plates approximately 20 cm × 20 cm, prepared from 50 g of Brinkman Silica Gel 60 GF254 and 90 g of water followed by air drying overnight and activation at 120 °C for 2 h. Column chromatography was performed with Fisher silica gel (100–200 mesh).

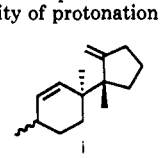
Ether, tetrahydrofuran, and hexane used in anhydrous reactions were distilled from the sodium benzophenone ketyl under nitrogen immediately before use. The methylene chloride ("anhydrous") used in the acylations was distilled from phosphorous pentoxide just prior to use. Methylene chloride ("dry") was passed through neutral alumina and stored over molecular sieves. Chloroform used in the Nazarov cyclizations was passed through netural alumina just prior to use. "Anhydrous ethanol" refers to U.S.I. pure ethyl alcohol. Triethylamine and pyridine were distilled from barium oxide and stored over molecular sieves. Anhydrous liquid ammonia was obtained by passing ammonia gas through potassium hydroxide pellets and condensing the vapor with a dry ice condenser. Boron trifluoride etherate complex was distilled from calcium hydride under aspirator pressure in an all-glass apparatus with glass wool added to prevent bumping and stored under nitrogen in the dark. "Anhydrous stannic chloride" refers to 98% stannic chloride obtained from Alfa Division.

2-Methyl-1-cyclohexenyl 2-Methyl-1-cyclopentenyl Ketone (4). 2-Methyl-1-cyclopentenecarboxylic acid (706 mg, 5.6 mmol) in 10 mL of dry benzene was converted into acid chloride **2** by treatment with 1.27 g (10 mmol) of oxalyl chloride at room temperature for 2 h. After the benzene was removed at reduced pressure, the crude acid chloride **2** was dissolved in 10 mL of anhydrous methylene chloride and treated with 3.0 g of stannic chloride at −78 °C, followed by the addition of 2.2 g of 1-methyl-1-cyclohexene. The reaction mixture was stirred at −78 °C for 1 h and another 20 min at 10 °C, and then quenched by addition of 20 mL of water. The aqueous layer was extracted twice with 50-mL portions of methylene chloride, and the combined methylene chloride solution was washed with water and brine and then dried over $MgSO_4$. After solvent was removed, 2.30 g of crude chloro ketone **3** was obtained. This ketone, without purification, was treated with 2.0 g of potassium hydroxide in 40 mL of 95% ethanol. The reaction mixture was heated at reflux for 4 h, and then the solvent was removed at reduced pressure. The residue was dissolved in 20 mL of water and extracted three times with 50-mL portions of ether. The combined ethereal solution was washed with water and brine and then dried over $MgSO_4$. The residue obtained after removal of solvent was purified through column chromatography (silica gel, 20% ether/hexane) and distillation (110 °C/0.5 mm) to give 1.05 g (91% yield) of dienone **4**: IR (film) 1660 (C=O), 1625 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 2.20–2.80 (unresolved multiplet, =CCH_2 of cyclopentene, 4 H), 1.10–2.20 ppm (unresolved multiplet, CH_2 and CH_3, 16 H); MS *m/z* (rel %) 204 (33), 190 (15), 189 (100), 175 (14), 162 (10), 161 (27), 147 (37), 109 (28), 81 (12), 79 (22), 77 (12), 55 (13), 53 (23), 41 (26), 39 (15), 27 (10); HRMS calcd for $C_{14}H_{20}O$ 204.151410, exp 204.150558.

4-(Trifluoroacetoxy)-8,9-dimethyltricyclo[7.3.0.0^{3,8}]dodecan-2-one (5). Dienone **4** (0.60 g, 2.94 mmol) in 5 mL of trifluoroacetic acid was heated at reflux (55 °C) for 4.5 h. The trifluoroacetic acid was removed at reduced pressure, and the residue was distilled at 120 °C (0.15 mm) to give 0.79 g of colorless liquid, which, upon cooling, crystallized as white crystals. The distillate turned slightly yellow when exposed to air and was recrystallized from hexane at dry ice–acetone bath temperature to give 0.77 g (82% yield) of tricyclic ketone **5** as white crystals,

(29) We thank Prof. J. C. Gilbert, University of Texas, for providing copies of NMR spectra of trichodiene and bazzanene.

(30) No evidence of 1,2-reduction to a product of the type i was observed in the reduction of **27**, although similar products have been observed in other syntheses.[2j,k] The presence of the amine functionality may be a factor in the selectivity of protonation in this reduction.



i

(31) Selective 1,2-reduction of the less substituted (but more hindered) double bond of **20b** would provide a method for synthesis of bazzanene from the same intermediates used for synthesis of trichodiene. However, exploratory studies of reactions of **20** with diimide or with H_2 over Nickel boride P-2 or P-1 were unsuccessful. Additional studies of this question are not planned.

(32) For use of this synthetic method by another research group to prepare trichodiene for use in biosynthetic studies, see: Cane, D. E.; Ha, H.-J. *J. Am. Chem. Soc.* **1988**, *110*, 6865–6870.

mp 81–83 °C: IR (CCl_4) 1720 (C=O) and 1776 cm^{-1} (C=O from trifluoroacetate); ^1H NMR (CCl_4) δ 5.50 (m, C*H*OCOCF$_3$, 1 H), 2.62 (m, F$_3$CCO$_2$CC*H*C=O, 1 H), 1.22–2.40 (m, C*H* and C*H*$_2$, 13 H), 1.18 (s, C*H*$_3$, 3 H), and 1.15 ppm (s, C*H*$_3$, 3 H); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 217.9 (C=O), 157.2 (CO_2), 116.8 (CF_3), 75.3 (*C*HC=O), 57.3 (*C*HCHO), 55.0 (*C*HC=O), 53.2 and 40.7 (quaternary C), 35.8, 33.0, 29.6, 27.0, 25.4, 19.0, 18.4 and 16.4 (methyls); MS *m/z* (rel %) 318 (11), 110 (19), 95 (19), 94 (21), 83 (11), 82 (100), 81 (12), 79 (10), 67 (35); HRMS calcd for $C_{16}H_{21}O_3F_3$ 318.144255, exp 318.143120. Anal. Calcd: C, 60.36; H, 6.65. Found: C, 60.24; H, 6.60.

4-Hydroxy-8,9-dimethyltricyclo[7.3.0.0^{3,8}]dodecan-2-one. Tricyclic ketone **5** (160 mg, 0.5 mmol), dissolved in 5 mL of methanol, was added to methanolic potassium hydroxide (100 mg of KOH in 20 mL of methanol). The reaction mixture was stirred at room temperature for 3 h. After removal of solvent, the residue was neutralized with 10% HCl, and the solution was extracted three times with 50-mL portions of ether. The combined ethereal solution was washed (water and brine) and dried over $MgSO_4$. After removal of ether, the yellow residue was distilled at 110 °C (0.15 mm) to give 1.08 mg (97% yield) of colorless liquid β-hydroxy ketone: IR (film) 3505 (—OH) and 1740 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 4.30 (m, C*H*OH, 1 H), 2.58 (br s, O*H*, 1 H), 1.40–2.50 (m, ring protons, 14 H), 1.20 (s, C*H*$_3$, 3 H), and 1.00 ppm (s, C*H*$_3$, 3 H).

4-Keto-8,9-dimethyltricyclo[7.3.0.0^{3,8}]dodecan-2-one (6). The β-hydroxy ketone prepared above (108 mg, 0.49 mmol) was dissolved in 10 mL of acetone and treated with an excess of Jones reagent. The resulting product was subjected to evaporative distillation (115 °C (0.15 mm)) to give 99 mg (93% yield) of β-diketone **6**: IR (film) 1740 (C=O from cyclopentanone) and 1710 cm^{-1} (C=O from cyclohexanone); ^1H NMR (CCl_4) δ 3.06 (s, O=CC*H*C=O, 1 H), 1.30–2.60 (m, ring protons, 13 H), and 1.12 ppm (s, 2 methyls, 6 H).

8,9-Dimethyltricyclo[7.3.0.0^{3,8}]dodec-4-en-2-one (7). A solution of 120 mg (0.377 mmol) of tricyclic ketone **5** in 4 mL of anhydrous tetrahydrofuran was added slowly to a stirred suspension of 48 mg (1.0 mmol) of 50% sodium hydride in 10 mL of anhydrous tetrahydrofuran. The mixture was heated at reflux for 3 h under nitrogen at 80 °C, and then water was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then extracted with 20 mL of ether. The aqueous layer was extracted twice with 25-mL portions of ether, and the combined ethereal solution was washed with water and brine and then dried over $MgSO_4$. The crude product obtained after removal of solvent was purified through column chromatography (silica gel, 20% ether–hexane) and distillation (120 °C (0.15 mm)) to give 74 mg of white crystals, which was further recrystallized from hexane to give 70 mg (90% yield) of tricyclic enone **7**, mp 55–56 °C: IR (CCl_4) 1735 (C=O) and 1640 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 5.71 (m, *H*C=C*H*, 2 H), 2.56 (m, *H*CC=O, 2 H), 1.20–2.40 (m, methylene ring protons, 10 H), and 1.00 ppm (s, angular methyls, 6 H); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 221.5 (C=O), 127.6 and 122.5 (*C*H=*C*H), 57.5 (*C*HC=O), 57.3 (*C*HC=O), 52.8 and 39.3 (quaternary), 35.7, 29.2, 28.1, 24.3, 22.3, 18.4, and 17.4 (methyls); MS *m/z* (rel %) 204 (9), 95 (11), 94 (100), 91 (10), 82 (10), 79 (29), 77 (12), 67 (17), 53 (10), 41 (17), 39 (16), 27 (11); HRMS calcd for $C_{14}H_{20}O$ 204.151410, exp 204.152044.

2,5-Dimethyl-1-cyclohexen-1-yl 2-Methyl-1-cyclopenten-1-yl Ketone (14). 2-Methyl-1-cyclopentenecarboxylic acid (0.97 g, 7.69 mmol) was converted to acid chloride **2** by treatment with 4 equiv of oxalyl chloride (3.9 g, 2.7 mL) in dry methylene chloride for 1 h. The mixture was then concentrated by rotary evaporation and diluted with 100 mL of freshly distilled anhydrous methylene chloride. Four equivalents of 1,4-dimethylcyclohexene[33] (3.39 g, 31 mmol) was syringed into the mixture, which was then cooled to −78 °C under nitrogen. Three equivalents of anhydrous stannic chloride was then added dropwise from a syringe to the rapidly stirring solution at a rate of ca. 1 drop every 5 s. The mixture was allowed to stir at −78 °C for an additional 2.5 h and was then quenched by pouring it into water. The aqueous layer was extracted with ether, and the combined organic extracts were then concentrated by rotary evaporation. The resulting orange oil was dissolved in ether (the use of CH_2Cl_2 led to very bad emulsions) and washed with water, bicarbonate, and brine. The ethereal solution was dried over $MgSO_4$ and concentrated to yield 1.96 g of oil, which was a mixture of β-chloro ketone **13** and a small amount of a dimerization product of the cyclohexene. This alkene dimer was removed from the chloro ketone by chromatography with hexane; the chloro ketone was removed from the column with 1:1 hexane/ether. The chloro ketone was dehydrohalogenated by treatment with 4 equiv (31 mmol) of sodium ethoxide in ethanol for 24 h. The mixture was carefully neutralized by the dropwise addition of 12 M HCl and concentrated by rotary evaporation. The residue was dissolved in ether and water and extracted three times with 50-mL portions of ether. The combined ethereal extracts were washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated to give 1.52 g (90% crude yield) of dienone **14**. The crude dienone was evaporatively distilled (95 °C, 1.0 mmHg) to give 1.4 g (6.4 mmol, 83% overall yield from carboxylic acid) of pure dienone **14**: IR (film) 1615 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.94 (d, J = 6 Hz, 3 H), 1.06–2.85 (m, 19 H); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 200.1 (C=O), 152.8, 137.1, 134.7, 132.6, 41.4, 34.9, 33.8, 31.7, 30.8, 28.5, 21.6, 21.4, 20.0, 15.8. This dienone discolored rapidly on standing and was immediately dissolved in anhydrous chloroform for the next step: HRMS calcd for $C_{25}H_{22}O$ 218.167042, found 218.166602 (2.0 ppm).

5,8,9-Trimethyltricyclo[7.3.0.0^{3,8}]dodec-4-en-2-one (15). Freshly distilled dienone **14** (1.4 g, 4.95 mmol) was dissolved in 75 mL of anhydrous chloroform, and to this was added 10 equiv of boron trifluoride etherate complex (6.5 g, 5.6 mL). The mixture was refluxed under a positive nitrogen atmosphere for 3 days and was then quenched by pouring it into 50 mL of water. The aqueous layer was extracted with methylene chloride, and the combined organic extracts were concentrated by rotary evaporation. The oily residue was dissolved in ether and washed (water, bicarbonate, and brine), dried over $MgSO_4$, and concentrated to give 1.38 g of crude **15** (98.6% crude yield). The crude ketone was chromatographed with hexane/ether (4:1) and evaporatively distilled to give 1.25 g (89% yield) of diastereomeric tricyclic ketones **15a** and **15b**: IR (film, both) 3010 (C=CH), 1730 (C=O), 1445, 1372 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.02 and 1.06 (singlets, angular methyls of **15a**), 1.08 and 1.10 (singlets, angular methyls of **15b**), 2.69 (m, 15 H), 5.29 (C=C*H*, **15b**), 5.57 (C=C*H*, **15a**); minor diastereomer **15b** (obtained by chromatography from an incomplete Baeyer–Villiger reaction) ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 223.7 (C=O), 131.0 (C=*C*H), 118.5 (C=*C*CH$_3$), 57.1, 52.7, 50.4, 38.9, 35.8, 32.8, 30.4, 26.4, 25.0, 23.1, 20.1 and 18.6 (angular methyls); mixture of both **15a*** and **15b*** ^{13}C NMR (20.00 MHz, $CDCl_3$) δ 222.2* and 220.6* (C=O), 134.9* and 131.0* (C=*C*H), 118.5* and 116.3* (C=*C*CH$_3$), 57.5*, 57.1*, 54.1*, 52.7*, 52.6*, 50.4*, 38.9**, 35.8**, 32.8*, 30.4*, 29.8*, 28.2*, 27.3*, 26.4*, 24.9*, 24.4*, 23.4*, 23.1*, 20.1*, 18.6**, 17.4*; HRMS calcd for $C_{15}H_{22}O$ 218.167042, found 218.166602 (2.0 ppm).

5,8,9-Trimethyltricyclo[7.3.0.0^{3,8}]dodec-4-en-2-one Oxime (17). Ketone **15** was converted to the oxime derivative in yields ranging from 90–99$^+$%. For example: Ketone **15** (803.8 mg, 3.68 mmol) was dissolved in 120 mL of anhydrous ethanol. Four equivalents of hydroxylamine hydrochloride (1.02 g, 14.7 mmol) and 4.1 equiv of potassium carbonate (2.09 g, 15.1 mmol) were added along with sodium sulfate (500 mg, 3.5 mmol). The mixture was stirred under nitrogen for 24 h, at which time a TLC of the mixture indicated that the reaction was complete. The mixture was evaporated to dryness on a rotary evaporator, and the residue was dissolved in water and methylene chloride. The mixture was extracted with methylene chloride and the combined extracts were dried over $MgSO_4$. Concentration gave 840.2 mg (98% yield) of oxime, which consisted of a mixture of oximes **17a** and **17b** along with 10% of the conjugated oxime **18**. The mixture of compounds was used without purification in the Beckmann rearrangements. Separation of the components by chromatography was difficult, but samples of the major isomer **17a** and a mixture of **17b** and **18** were obtained for spectral purposes: IR (film, mixture) 3280 (OH), 3010 (C=CH), 1700 (C=N), 1445 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, **17a**) δ 0.90 (s, angular C*H*$_3$), 0.93 (s, angular C*H*$_3$), 1.68 (allylic C*H*$_3$), 1.0–2.9 (m, 12 H), 5.5 (m, 1 H), 8.3 (br s, 1 H, C=NO*H*); ^{13}C NMR (20.00 MHz, $CDCl_3$, **17a**) δ 168.9 (*C*=NOH), 130.3 (C=*C*CH$_3$), 118.7 (C=*C*H), 54.2, 53.4, 48.3, 43.8, 35.8, 32.5, 31.1, 26.5, 26.0, 23.2, 20.3, 17.9; ^1H NMR (90 MHz, $CDCl_3$, mixture

(33) Wallach, A. *Annalen* **1912**, *396*, 264–284.

of 73% **17b** and 27% **18**) δ 0.93 and 0.98 (s, angular methyls of both), 0.85 (d, J = 9 Hz, CH_3 of **18**), 1.67 (allylic CH_3), 1.0–3.0 (m, 12 H), 5.2 (m, C=C*H* of **17b**), 6.0 (m, C=C*H* of **18**), 8.25 (br s, 1 H, C=NO*H*); HRMS calcd for $C_{15}H_{23}O$ 233.17784; found 233.178409 (2.4 ppm).

Lactam 19. Oxime **17** (150 mg, 0.64 mmol), containing 10–15% **18**, was treated overnight with *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) and pyridine (880 mg, 11.1 mmol) in 50 mL of dry methylene chloride. The mixture was then poured into 10 mL of acid, shaken, and separated. The organic layer was washed with acid, concentrated, and dissolved in ether. The ether solution was washed twice with bicarbonate, dried over Na_2SO_4, and concentrated to yield 190 mg of yellow oil. Proton NMR of this crude oil indicated that Beckmann rearrangement to diene **20** and amide **19** had already begun. The Beckmann rearrangement was completed by stirring the oil with potassium carbonate in a THF/water solution for 3 days. An extractive workup of this mixture followed by thin-layer chromatography gave 40 mg of a 1:1 mixture of **20a** and **20b** and 40 mg of a diastereomeric mixture of lactam **19**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.86 (s, angular CH_3), 0.96 (s, angular CH_3), 1.68 (m, allylic CH_3), 1.2–2.45 (m, 11 H), 3.47 (m, 1 H, C*H*N), 5.41 (m, 1 H, C=C*H*), 5.82 (br m, 1 H, N*H*); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 177.03 (C=O, major), 172.8 (C=O, minor), 127.8, 120.3, 138.3, 119.5, 52.7, 51.2, 50.2, 49.0, 35.4, 33.9, 32.7, 30.8, 24.5, 23.1, 23.0, 17.3.

2-Methyl-2-(4-methylene-1-methyl-2-cyclohexen-1-yl)-cyclopentanenitrile (20a) and 2-Methyl-2-(1,4-dimethyl-2,4-cyclohexadien-1-yl)cyclopentanenitrile (20b). Method A. Oxime **17** (133.8 mg, 0.57 mmol), containing 10–15% **18**, was dissolved in 30 mL of dry methylene chloride and cooled to 0 °C. Trifluoroacetic anhydride (130 mg, 0.89 mL, 0.63 mmol) and trifluoroacetic acid (3 mg, 0.002 mL, 0.03 mmol) were added, and the mixture was stirred at 0 °C for 15 min. The ice bath was removed, and the reaction was allowed to stir for an additional 55 min. The reaction was quenched by pouring the solution into 10 mL of 15% NaOH. The mixture was extracted with methylene chloride, and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to give 127.9 mg of oil. The oil was subjected to thin-layer chromatography with hexane/ether (4:1) to yield 63.6 mg of a mixture of cyano dienes **20a** and **20b** (major product) (52 % yield). The ratio of **20b** (endocyclic diene) to **20a** (exocyclic diene) under these conditions ranged from 3:1 to 6:1.

Method B. This method gave slightly higher yields with the ratio of **20b** to **20a** ranging from 2.5:1 to 6:1. Oxime **17** (10% **18**) (317.8 mg, 1.36 mmol) was dissolved in 100 mL of dry methylene chloride. Trifluoroacetic acid (3 mg, 0.002 mL) and trifluoroacetic anhydride (314 mg, 0.21 mL, 1.5 mmol) were added, and the solution was stirred under N_2 for 10 min, at which time triethylamine (124 mg, 0.17 mL, 1.23 mmol) was added and the mixture was stirred for 100 additional minutes. The solution was then poured into 50 mL of 15% NaOH and extracted with methylene chloride. The combined methylene chloride extracts were dried over $MgSO_4$, concentrated, and chromatographed to give a mixture of **20a** and **20b** (1:3.3) (172.4 mg, 0.8 mmol, 65.3% yield[23]): IR (film) 3025 (C=CH), 2240 (CN), 1450, 1380, 915, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, signals unique to **20a**) δ 1.07 (s, CH_3), 1.2 (s, CH_3), 4.75 (br s, C=CH_2), 5.92 (d, J = 10 Hz, 1 H), 6.15 (d, J = 10 Hz, 1 H); ^{1}H NMR (200 MHz, $CDCl_3$, **20b**) δ 1.05 (s, CH_3), 1.11 (s, CH_3), 1.43–2.51 (m, 9 H), 1.73 (m, J = 1.4 Hz, allylic CH_3), 5.37 (m, J = 1.4 Hz, 1 H), 5.77 (dd, J = 10 Hz, J = 1.6 Hz, 1 H), 5.85 (d, J = 10 Hz, 1 H); ^{13}C NMR (50.31 MHz, $CDCl_3$, **20b**) δ 131.9, 129.9, 127.1, 122.5 (CN), 119.1, 51.7, 39.4, 38.2, 34.9, 33.4, 33.2, 24.8, 24.1, 21.5, 21.0; ^{13}C NMR (50.31 MHz, $CDCl_3$, signals characteristic of **20a**) δ 142.0, 134.8, 129.7, 122.5 (CN), 110.9, 51.1, 40.3, 38.2, 35.0, 33.6, 30.7, 26.8, 25.3, 24.1, 21.9; HRMS calcd for $C_{15}H_{21}N$ 215.167377, found 215.167242 (0.6 ppm).

2-Amino-5,8,9-trimethyltricyclo[7.3.0.0^{3,8}]dodec-4-ene (23). Diene **20** (408.4 mg, 1.9 mmol) was dissolved in ca. 5 mL of anhydrous ethanol in a 250-mL three-necked flask fitted with a dry ice condenser and oil bubbler. Anhydrous ammonia (ca. 150 mL) was condensed into the flask, and lithium metal (0.35 g, 50 mmol) was added. The solution remained blue for approximately 1 h before it quenched itself. The ammonia was allowed to evaporate overnight, and the residue was dissolved in ether and water. The mixture was extracted with ether and then with methylene chloride. The combined extracts were washed with 10% HCl several times to remove the amine, and the remaining organic layer was dried over $MgSO_4$ and concentrated to yield 58 mg of neutral product. The acid extracts were heavily salted, made basic by the addition of KOH pellets, and then extracted with methylene chloride. The combined extracts were dried over Na_2SO_4 and concentrated to give 352 mg of amine, which was first incorrectly identified as a mixture of **21** and **22**, but was later verified to be **23** by matching the spectra to authentic **23** prepared by LAH reduction of oxime **17**. Reduction of oxime **17** with LAH produced several diastereomers of **23** in approximately equal quantities, whereas reduction of the dienes gave a mixture which appeared to be mainly two diastereomers of **23** in a 4:1 ratio: IR (film) 3275 and 3335 (NH_2), 1450, 1370 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, major peaks) δ 0.76 (s, CH_3), 0.9 (s, CH_3), 0.87, 0.84, and 0.75 (angular methyls of minor products), 1.67 (br s, allylic CH_3), 1.1–2.2 (m, ca. 11 H), 2.9 (dt, 1 H, C*H*NH_2), 5.2 and 5.5 (m, C=C*H*, ratio 4:1); ^{13}C NMR (50.31 MHz, $CDCl_3$, major diastereomer) δ 130.6, 118.6, 65.8, 55.6, 51.0, 46.8, 38.6, 37.6, 33.0, 27.7, 26.5, 26.1, 23.4, 21.4, 18.7.

***N*,*N*-Dimethyl-2-amino-5,8,9-trimethyltricyclo[7.3.0.0^{3,8}]-dodec-4-ene (24).** Tricyclic amine **23** (235.2 mg, 1 mmol) was dissolved in 20 mL of acetonitrile. Formalin (2.45 mL of 37%, 31 mmol) was added, and the mixture immediately became cloudy white and then turned clear yellow. Sodium cyanoborohydride (272.3 mg, 4.3 mmol) was added, and the solution became cloudy again. After a 15-min reaction period, the solution tested basic to Litmus paper and was neutralized by the dropwise addition of glacial acetic acid. The solution was stirred for an additional 75 min, and glacial acetic acid was added every 10–15 min to restore neutrality. The solvent was removed under reduced pressure, and 20 mL of 10% NaOH was added to the residue. The mixture was extracted with ether, and the combined extracts were washed several times with 10% HCl. The combined acid extracts were made basic by the addition of KOH pellets with cooling and extracted with ether. The combined ethereal extracts were dried over K_2CO_3 and concentrated to yield 244 mg (94% yield) of **24**, also a mixture of diastereomers: IR (film) 3010, 1450, 1370 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.8 (s, CH_3), 0.9 (s, CH_3), 0.74, 0.83, and 0.86 (s, angular methyls of minor products), 1.67 (br s, allylic CH_3), 1.1–2.2 (m, approximately 11 H), 2.23 (s, N(CH_3)$_2$), 2.31 and 2.36 (C*H*N), 5.23 and 5.5 (m, C=C*H*, ratio 4:1).

5,8,9-Trimethyltricyclo[7.3.0.0^{3,8}]dodeca-2,4-diene (25). Method A. Dimethylamine **24** (244 mg, 1.1 mmol) was oxidized with 0.1 mL of 90% H_2O_2 in methanol over 3 days. The excess peroxide was decomposed by the addition of a catalytic amount of platinum black. The solution was filtered and concentrated to give 250 mg of crude *N*-oxide: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.2 ((CH_3)$_2$N$^+$O$^-$).

The crude *N*-oxide was heated up to 170 °C over 2 h at ca. 1 mmHg in a Kugelrohr distillation apparatus with a dry ice cooled receiver. Elimination began to occur at about 70 °C and was complete by about 120 °C. The oily product (162.5 mg) consisted of dimethylamine **24** and diene **25**. Filtration through a short plug of silica gel with hexane was sufficient to obtain 100 mg of pure alkene (0.49 mmol, 44%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.0 (s, angular CH_3), 1.7 (s, angular CH_3), 2.6 (m, allylic CH_3), 1.1–2.2 (m, 11 H), 5.03 and 5.22 (m, 2 H, C=C*H*); ^{13}C NMR (25.034 MHz, $CDCl_3$) δ 145.1 (s), 133.9 (s), 125.1 (d), 121.5 (d), 54.8 (s), 54.4 (d), 48.4 (s), 38.2 (t), 36.6 (t), 32.9 (t), 30.0 (t), 25.2 (t), 23.0 (q, C=CCH_3), 19.4 (q), 17.1 (q).

Method B. Dimethylamine **24** (47.4 mg, 0.2 mmol) in a mixture of ether and methanol was converted to its trimethylammonium iodide salt [^{1}H NMR (90 MHz, $CDCl_3$) δ 3.4 (s, NCH_3)] by the addition of ca. 10 equiv of methyl iodide. The excess methyl iodide was removed by rotary evaporation, and then water and freshly precipitated silver oxide[28a] were added to convert the iodide to hydroxide. Silver chloride precipitated and was filtered from the solution. The solution was concentrated under vacuum and then subjected to the same elimination conditions used for the *N*-oxide, yielding, after separation by an extractive, acid-base workup, 19.3 mg of amine and 18.2 mg of **25**.

1-(2-(Aminomethyl)-1-methylcyclopent-1-yl)-1-methyl-4-methylene-2-cyclohexene (27a) and 1-(2-(Aminomethyl)-1-methylcyclopent-1-yl)-1,4-dimethyl-2,4-cyclohexadiene (27b). A mixture of dienes **20a** and **20b** (242 mg, 1.12 mmol) was added

to a solution of lithium aluminum hydride (240 mg, 6.3 mmol) in 100 mL of dry ether, and the mixture was stirred for 8 h. Addition of H_2O (2.4 mL), 15% NaOH (2.4 mL), and H_2O (4.8 mL)[34] gave a white precipitate, which was removed by filtration and washed well with ether. Concentration gave 227 mg (90% yield) of product consisting mainly of diene amines **27a** and **27b**. The crude product was used directly in the next reaction.

1,4-Dimethyl-1-(2-(aminomethyl)-1-methylcyclopent-1-yl)-3-cyclohexene (28). A mixture of diene amines **27a** and **27b** (90.6 mg, 0.41 mmol) was dissolved in 10 mL of dry ether in a three-necked flask fitted with a dry ice condenser and bubbler. Anhydrous ammonia (ca. 150 mL) was condensed into the flask, and lithium metal (60 mg, 8.6 mmol) was added with stirring. After a 30-min reaction period, the blue solution was quenched by the addition of solid ammonium chloride. The ammonia was allowed to evaporate overnight, and the residue was dissolved in water and ether. The mixture was extracted with ether, and the combined ethereal extracts were dried over Na_2SO_4 and concentrated to give 83.8 mg (92% yield) of colorless amine. Evaporative distillation (100 °C, 1.2 mmHg) gave 72.1 mg of pure **28**, which contained predominantly one of the CH_2NH_2 epimers: IR (film) 3330 and 3260 (NH_2), 3010 (C=CH), 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, main peaks) δ 0.89 (s, angular CH_3), 0.93 (s, angular CH_3), 1.65 (br s, allylic CH_3), 5.27 (br s, C=CH); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 132.7 (s), 120.2 (d), 54.7, 51.1 (q), 44.5 (s), 36.1, 34.9, 32.4, 29.4, 28.6, 27.4, 24.0, 23.2 (q), 21.5 (t), 20.0 (q); HRMS calcd for $C_{15}H_{27}N$ 221.21421, found 221.213754 (2 ppm).

1-(2-((*N*,*N*-Dimethylamino)methyl)-1-methylcyclopent-1-yl)-1,4-dimethyl-3-cyclohexene (29). Amine **28** (124.3 mg, 0.56 mmol) was treated with 37% formalin solution (1.12 mL, 14 mmol) in 20 mL of acetonitrile. Sodium cyanoborohydride (159.8 mg, 2.54 mmol) was added, and the solution was stirred for 75 min. The pH of the solution was checked at 15-min intervals, and glacial acetic acid was added dropwise to maintain pH near neutrality. The solution was concentrated by rotary evaporation, and 10 mL of 10% NaOH was added to the residue. The solution was extracted with ether, and the combined extracts were dried over Na_2SO_4 and concentrated to give 132 mg (94% crude yield) of **29**, which contained predominantly one of the $CH_2N(CH_3)_2$ epimers. The crude dimethylamine was evaporatively distilled (100 °C, 1.2 mmHg) to give 101 mg (40 mmol, 72% yield) of pure **29**: IR (film) 3000, 2800, 2750, 1460, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, major peaks) δ 0.91 (s, angular CH_3), 0.93 (s, angular CH_3), 1.15–2.2 (m, 12 H), 1.66 (m, allylic CH_3), 2.2 (s, 6 H, N-$(CH_3)_2$), 5.3 (m, 1 H, C=CH); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 132.8, 112.8, 74.8 ($CH_2N(CH_3)_2$), 51.0, 48.1, 46.0 ($N(CH_3)_2$), 36.2, 35.1, 32.1, 29.6, 29.1, 27.6, 23.9, 23.4, 21.4, 20.0; HRMS calcd for $C_{17}H_{31}N$ 249.24549, found 249.244854 (2.5 ppm).

(*R,*R**)-1,4-Dimethyl-4-(1-methyl-2-methylenecyclopent-1-yl)-1-cyclohexene (Trichodiene, 1).** Dimethylamine **29** (56.8 mg, 0.23 mmol) was converted to *N*-oxide by treatment with *m*-chloroperbenzoic acid (52 mg, 0.3 mmol) and $NaHCO_3$ (42 mg, 0.5 mmol) in 10 mL of dry methylene chloride. The reaction was followed by TLC and was complete in 1 h. The mixture was diluted with methylene chloride and washed with bicarbonate and brine. The methylene chloride solution was concentrated to give 60 mg of crude amine oxide: ^1H NMR (90 MHz, $CDCl_3$) δ 0.93 (br s, CH_3), 3.17 (s, $(CH_3)_2N^+O^-$), 5.33 (m, 1 H, C=CH).

Crude amine oxide was heated to 150 °C under vacuum (ca. 1.5 mmHg) in a Kugelrohr distillation apparatus with a dry ice cooled receiver. The collected oil (38.1 mg) was chromatographed with hexane/ether (4:1) to give 26 mg (0.13 mmol, 56% yield) of pure trichodiene (**1**): IR (film) 3070 (C=CH_2), 3000 (C=CH), 1638 (C=C), 880 (C=CH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.64 (s, 3 H, allylic CH_3), 4.74 (br s, 1 H), and 4.97 (br s, 1 H) (exo methylene), 5.30 (m, 1 H, C=CH); ^{13}C NMR (50.31 MHz, $CDCl_3$) δ 159.9 (s, C=CH_2), 132.3 (s, C=CCH_3), 120.5 (d, C=CH), 106.8 (t, C=CH_2), 50.6 (s), 38.8 (t), 37.2 (t), 36.8 (s), 33.0 (t), 28.1 (t), 27.8 (t), 24.0 (q, C=CCH_3), 23.3 (t), 23.3 (q, CH_3), 17.9 (q, CH_3); signals at 0.84 (CH_3), 1.02 (CH_3), and 4.79 ppm, characteristic of the stereoisomer bazzanene (**26**)[29] were not observable in the proton NMR spectrum of the product; HRMS calcd for $C_{15}H_{24}$ 204.18768, found 204.187908 (1.1 ppm).

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Registry No. **1**, 61505-17-7; **2**, 59253-86-0; **3**, 124651-60-1; **4**, 124651-61-2; **5**, 124651-62-3; **5** (4-hydroxy derivative), 124651-63-4; **6**, 124651-64-5; **7**, 124651-65-6; **13**, 124651-66-7; **14**, 91861-30-2; **15a**, 91861-31-3; **15b**, 91926-35-1; **17a**, 124752-02-9; **17b**, 124752-03-0; **18**, 124651-67-8; **19** (diastereomer-1), 124685-86-5; **19** (diastereomer-2), 124815-35-6; **20a**, 91861-34-6; **20b**, 91861-33-5; **23**, 124651-69-0; **24**, 124651-70-3; **24** (*N*-oxide), 124651-71-4; **24** (trimethylammonium iodide salt), 124651-73-6; **25**, 124651-72-5; **27a**, 124651-74-7; **27b**, 124651-75-8; **28**, 91861-35-7; **29**, 91861-36-8; **29** (*N*-oxide), 124651-76-9; 2-methyl-1-cyclopentenecarboxylic acid, 67209-77-2; 1-methyl-1-cyclohexene, 591-49-1; 1,4-dimethylcyclohexene, 2808-79-9.

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