An Approach to the Total Synthesis of Dendrobine

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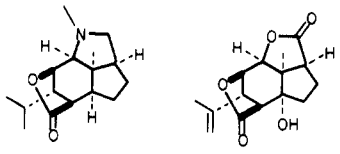
The possible rearrangement of a 5-azatricyclo[6.1.1.0^{5,9}]decane immonium ion (**3**) to the 2-azatricyclo-[5.2.1.0^{4,10}]decane carbocation **5** has been investigated as a route to the physiologically potent alkaloid dendrobine (**1**). *tert*-Butyl acetoacetate is converted in seven steps and 40% overall yield into cyclopentenone **15**, which undergoes intramolecular [2 + 2] photoaddition to the tricyclic ketone **16**. The structure of this material was vouchsafed by single-crystal X-ray analysis of the crystalline oxime, **18**. Methanolysis of the oxime benzoate **20** provides nitrile ester **21**, which is transformed by straightforward operations into lactam **24**. Reduction of **24** gives an immonium ion, which may be trapped as amino nitrile **26**. However, the immonium ion shows no propensity to rearrange to the 2-azatricyclo[5.2.1.0^{4,10}]decane system. To provide a more reactive immonium ion, oxime **18** was converted into carbinol amides **34a** and **34b** (six steps, 54% overall yield). Solvolysis of this material in 95% formic acid yields rearranged alkene **38**, tertiary formate **41**, alcohol **40**, and secondary formate **44**. When the rearrangement is carried out at 100 °C, compound **44** may be isolated in 55% yield. Lithium aluminum hydride reduction of **44** provides crystalline amino alcohol **45**. The structure of this material was firmly established by extensive proton NMR studies and single-crystal X-ray analysis. A likely mechanism for the rearrangement of **34** to **44** is put forth, and plans for the eventual use of the rearrangement in a dendrobine synthesis are discussed.

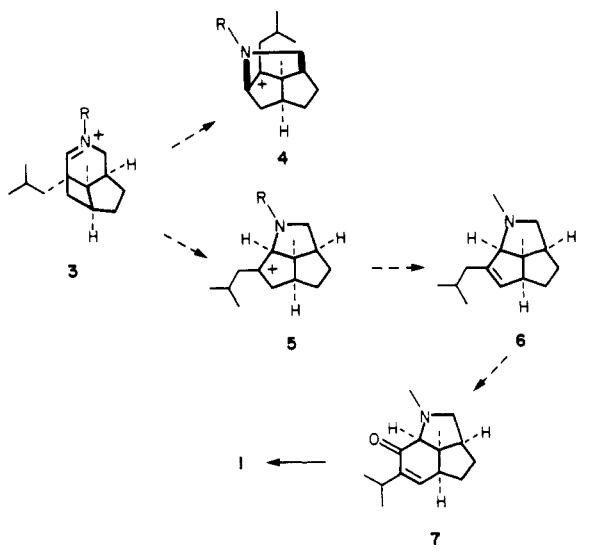
Dendrobine (**1**) is the archetypical member of a class of sesquiterpenoid alkaloids isolated from the stems of the ornamental orchid *Dendrobium nobile* and related species of the family Orchidacae. It is the major constituent of the Chinese herbal medicine Chin-Shih-Hu, which has been used for centuries as a tonic and antipyretic. Suzuki and co-workers first reported the isolation of dendrobine in the 1930s;[1] since that time a total of 13 structurally related alkaloids (seven bases and six quaternary compounds) have been extracted from *D. nobile* and other *Dendrobium* species.[2] The correct structure was independently determined in the early 1960s by three different groups,[3] and the absolute configuration was later established by circular dichroism studies on various members of the family.



1 **2**

Dendrobine is structurally similar to the potent convulsant picrotoxinin (**2**). Both compounds contain the same basic elements of a bridging lactone and a hydrindane ring system to which a second heterocyclic ring is appended. The two compounds also share similar physiological properties—high mammalian toxicity, eventually resulting in death by convulsion.[4] Because of their potent biological activity and unique polycyclic structures, both compounds have attracted considerable attention from synthetic chemists. Four total syntheses of dendrobine have appeared since 1972,[5] as well as two approaches to the skeleton[6,7] and one synthesis of an epimer.[8] More

Scheme I



3 **4** **5** **6** **7** **1**

(1) (a) Suzuki, H.; Kiematsu, I. *J. Pharm. Soc. Jpn.* **1932**, *52*, 1049; *Chem. Abstr.* **1933**, *27*, 1886. (b) Suzuki, H.; Kiematsu, I.; Ito, K. *J. Pharm. Soc. Jpn.* **1934**, *54*, 802; *Chem. Abstr.* **1935**, *29*, 798.

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(5) (a) Hayakawa, Y.; Nakamura, H.; Aoki, K.; Suzuki, M.; Yamada, K. *Tetrahedron* **1971**, *27*, 5157. (b) Yamada, K.; Suzuki, M.; Hayakawa, Y.; Aoki, K.; Nakamura, H.; Nagase, H.; Hirata, Y. *J. Am. Chem. Soc.* **1972**, *94*, 8278. (c) Inubushi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1252. (d) Inubushi, Y.; Kikuchi, T.; Ibuka, T.; Tanaka, K.; Saji, I.; Tokane, K. *Chem. Pharm. Bull.* **1974**, *22*, 349. (e) Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332. (f) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599. (g) Roush, W. R *J. Am. Chem. Soc.* **1980**, *102*, 1390. (h) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4283.

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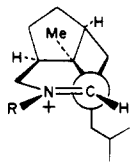


Figure 1.

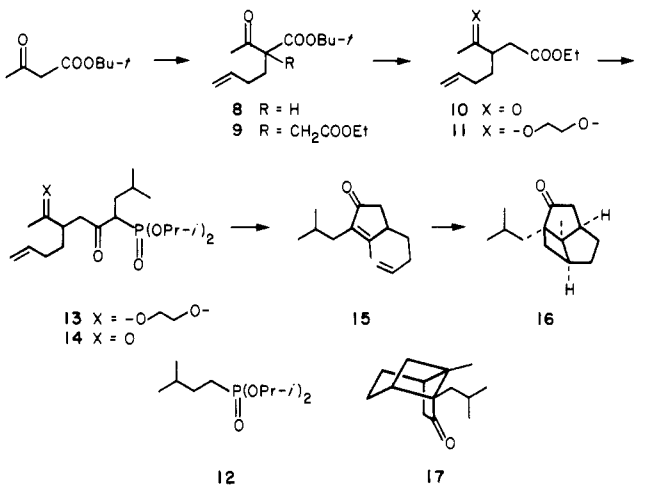
recently, two total syntheses of picrotoxinin have been published.[9]

In spite of the attention that has been given to dendrobine as a synthetic target, there has yet to be a total synthesis that is highly efficient and stereoselective in all steps. Our strategy was centered around the application of a novel and unprecedented variant of the well-known cyclobutylcarbinyl rearrangement[10,11] (Scheme I). In the key transformation, the tricyclic immonium species **3** was expected to undergo a 1,2-alkyl shift by either of two pathways: (a) migration of the exocyclic cyclobutane bond (bridged migration) to give bridged carbocation **4** or (b) migration of the endocyclic bond (fused migration) to give fused carbocation **5**. Rearrangement by the desired fused pathway would lead to tricyclic olefin **6**, which could be further elaborated to enone **7**, an intermediate in the Kende synthesis of dendrobine.[5e,12]

Prediction of the preferred mode of migration is not straightforward. On the basis of maximum continuous orbital overlap, bridged migration would seem to be favored (Figure 1). On the other hand, consideration of the thermodynamic stabilities of the two possible carbocationic products **4** and **5** favors the tricyclo[5.2.1.$0^{4,10}$]decane skeleton (**5**) rather than the tricyclo[5.2.1.$0^{4,8}$]decane skeleton (**4**). Force field calculations by Schleyer indicate that the parent hydrocarbon system for **5** is between 2.4 and 5.8 kcal/mol more stable than the parent system for **4**.[13] Examples of both fused and bridged migration pathways can be found in the literature, and there is sufficient evidence to indicate that predictions based on the principle of maximum continuous orbital overlap are often unreliable.[10b,c,d]

Apart from the important question regarding the direction of migration, an equally important problem concerns the thermodynamics of the proposed rearrangement. For the case in which the substituent on nitrogen is a methyl group, the initial migration of **3** to either **4** or **5** requires the sacrifice of a stable immonium ion for a relatively unstable tertiary carbonium ion. It can be argued that the extra strain energy (due to the cyclobutane ring) present in the reacting [6.1.1.$0^{5,9}$] system **3** might offset the difference in cation stability and allow the 1,2-shift to occur. If this were not the case, then a simple modification of the immonium species (substitution of an acyl substituent, such as formyl, for the *N*-methyl group) would serve to destabilize the reacting species **3** with respect to the carbocationic products **4** and **5** and hence reduce the activation barrier for the rearrangement.[14]

Scheme II



With these considerations in mind, we embarked upon a synthesis of the rearrangement precursor. Cyclopentenone **15** was synthesized smoothly by the seven-step procedure outlined in Scheme II. Reaction of the potassium salt of *tert*-butyl acetoacetate and 4-bromo-1-butene in refluxing *tert*-butyl alcohol provided keto ester **8** in 93% yield. A second alkylation with ethyl bromoacetate (sodium hydride, THF) gave keto diester **9** in 89% yield. The *tert*-butoxycarbonyl group was removed by heating in toluene in the presence of catalytic *p*-toluenesulfonic acid[15] to afford the 3-substituted levulinic ester **10** (79%);[16] treatment with ethylene glycol under the same conditions (with removal of water) gave ketal **11** (87%). Reaction of **11** with 2 equiv of the lithium salt of diisopropyl isoamylphosphonate (**12**, prepared by the Arbuzov reaction of isoamyl bromide and triisopropyl phosphite) in THF solution at −78 °C afforded keto phosphonate **13** as a mixture of diastereomers in excellent yield. Deprotection proceeded quantitatively to give **14**, and subsequent intramolecular Wadsworth–Emmons cyclization (NaH, THF) gave cyclopentenone **15** in 70% yield from **11**. The entire sequence was accomplished in a total of seven steps and 40% overall yield from commerically available starting materials.

Irradiation of a dilute hexane solution of **15** afforded a sweet-smelling photoproduct in 86% yield. Although proton and carbon-13 NMR spectroscopy and gas chro-

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(10) (a) For a review of the carbocation rearrangement, see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1981**, *103*, 82. (c) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1978**, 1301. (d) Duc, K.; Fetizon, M.; Kone, M. *Tetrahedron* **1978**, *34*, 3513.

(11) (a) For a review of the cyclobutylcarbinyl ketone (Cargill) rearrangement, see: Cargill, R. L.; Jackson, T.; Peet, N.; Pond, D. *Acc. Chem. Res.* **1974**, *7*, 106. (b) Cargill, R. L.; Bushey, D. F.; Dalton, J. R.; Prasad, R. S.; Dyer, R. D. *J. Org. Chem.* **1981**, *46*, 3389. (c) Yanigaya, M.; Kaneko, K.; Takashi, K.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 1761. (d) Duc, D.; Fetizon, M.; Lazare, S. *J. Chem. Soc., Chem. Commun.* **1975**, 282.

(12) It has not been our plan to end our synthesis by converging with the Kende synthesis at the stage of enone **7**. In the Kende synthesis, enone **7** is converted into dendrobine by way of a keto ester having the incorrect stereochemistry at the centers bearing the isopropyl and methoxycarbonyl groups. Although both centers are subject to base-catalyzed epimerization, the desired stereoisomer is a minor product. Rather, our intention is to investigate alternative methods of establishing the stereochemistry of these two points. We thank a referee for suggesting a clarification of this point.

(13) (a) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005. (b) In fact, of all possible tricyclodecane skeletons, the only one *more* stable than **5** is adamantane (by about 9 kcal/mole): Engler, E. M.; Farasui, M.; Sevin, A.; Cense, J. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 5771.

(14) The increased reactivity of *N*-acylammonium species in electrophilic aromatic substitution and Mannich-type reactions is well documented. (a) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. (b) Zaugg, H. E. *Synthesis* **1984**, *85*, 181. (c) Zaugg, H. E. *Synthesis* **1970**, 49. (d) Zaugg, H. E. *Org. React.* (*N.Y.*) **1965**, *14*, 52.

(15) Breslow, D. S.; Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1286.

(16) Lawesson, S.-O.; Dahlen, M.; Frisel, C. *Acta Chem. Scand.* **1962**, *16*, 1191.

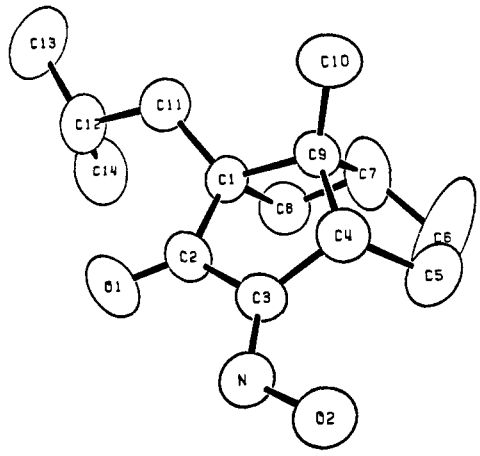
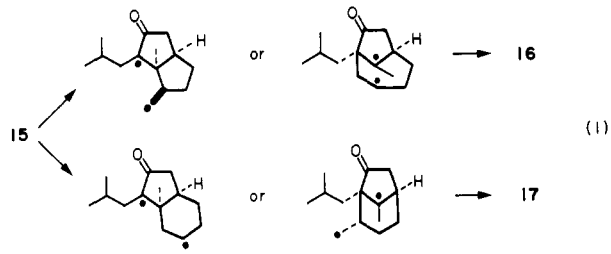


Figure 2.

matography indicated the presence of a single [2 + 2] cycloadduct, the spectral evidence was consistent with either of the two possible tricyclic products **16** or **17**. Examination of the four hypothetical diradical intermediates resulting from addition of the enone excited state to the exocyclic double bond proved to be useful, however (eq 1). Only one of these intermediates arises from the

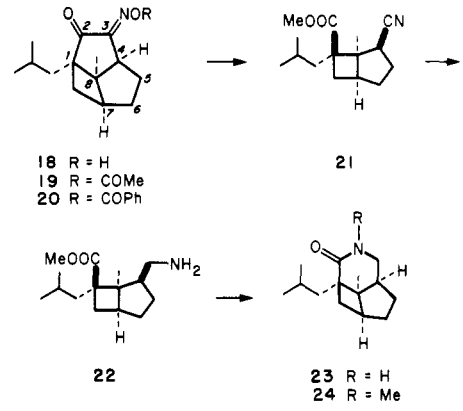


entropically favored 1,5-cyclization to form a five-membered ring diradical species. On the basis of the well-known empirical "rule of five", formation of this intermediate, and hence formation of **16**, is favored.[17] The preference of 1,6-dienes to undergo this mode of cyclization is also well precedented in the work of Georgian,[18] Pirrung,[10b] and Padwa.[19]

Encouraged by the literature precedent in favor of formation of the desired cyclized photoproduct, we began the task of converting tricyclic ketone **16** into a tricyclic lactam that could serve as a precursor to immonium ion **3**. Toward that end, **16** was treated with potassium *tert*-butoxide and isoamyl nitrite to give crystalline oximino ketone **18** in 76% yield. The X-ray structure confirms that the photoaddition has indeed proceeded in the desired manner, thereby establishing the required relative stereochemistry at the four ring junctures.[20] The ORTEP plot in Figure 2 also illustrates the cupped nature of the molecule, which nicely differentiates the endo (β) and exo (α) faces.

Acetylation of the oxime was accomplished with acetyl chloride and triethylamine in 81% yield to give acetoximino ketone **19** (Scheme III). Treatment of this compound with a 1:1 mixture of methanol and chloroform at 55 °C gave a mixture of the desired Beckmann fragmentation product **21** (42%) and oximino ketone **18** (38%). Competitive formation of **18** by methanolysis at the acetoxy carbonyl is somewhat surprising; Hassner and co-workers have reported similar fragmentations with camphor and 17-keto steroid derivatives which proceed without competing transesterification.[21] Complete suppression of the transesterification reaction, however, was accomplished by the substitution of benzoate for acetate. Benzoyloximino ketone **20** was prepared by treatment of **18** with benzoyl chloride and triethylamine. Compound **20** can be isolated in 90% yield after chromatography but was typically used in crude form; heating at reflux in methanol gives exclusively the Beckmann fragmentation product **21** in 91% yield from **18**.

Scheme III



Hydrogenation of **21** at atmospheric pressure in acetic acid using 5% rhodium on charcoal gave, after neutralization, primary amine **22**. Lactam **23** is produced in 65% yield when a dichloromethane solution of **22** is allowed to stand over anhydrous potassium carbonate. This facile ring closure is reasonable since the amine and ester substituents are held in close proximity by the rigid bicyclo[3.2.0]heptane skeleton. Methylation of **23** (NaH, methyl iodide) provides the *N*-methyl derivative **24**, which is thereby available from tricyclic ketone **16** in five steps and 39% yield. The overall transformation from *tert*-butyl acetoacetate and 4-bromo-1-butene proceeds in 12 steps and 16% yield.

We anticipated that reduction of lactam **24** to the ammonium oxidation state would be a simple matter; transformations of this type are reasonably well precedented.[22] In practice, however, the reduction of **24** with a variety of aluminum hydride based reagents was not straightforward. For ease in isolation of the monoreduced species, our standard reduction procedure involved the addition of cyanide ion to the crude reaction mixture after quenching of excess reducing agent (using the method of Rapoport and Gless).[22a] In this manner we hoped to avoid isolation of carbinol amine **25**, which we suspected would be prone

(17) (a) Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1980**, *45*, 3139. (b) Lui, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4936. (c) Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932.

(18) Georgian, V. *Tetrahedron Lett.* **1972**, 4315.

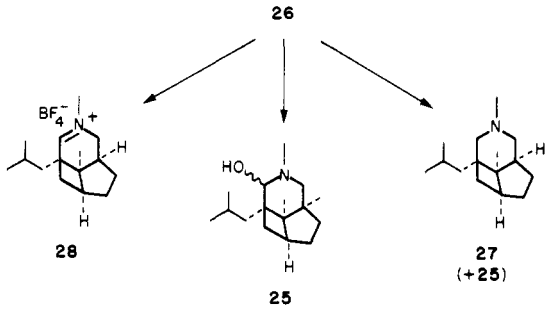
(19) Padwa, A.; Goldstein, S.; Pulver, M. *J. Org. Chem.* **1982**, *47*, 3893.

(20) The structure determination for **18** was kindly performed by G. Freeman, D. Fisher, and K. Seok-Hwan in partial fulfillment of the requirements of a course taught by the Department of Chemistry, University of California, Berkeley, and has been published: Freeman, G. E.; Fisher, D. C.; Seok-Hwan, K. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *C40*, 502.

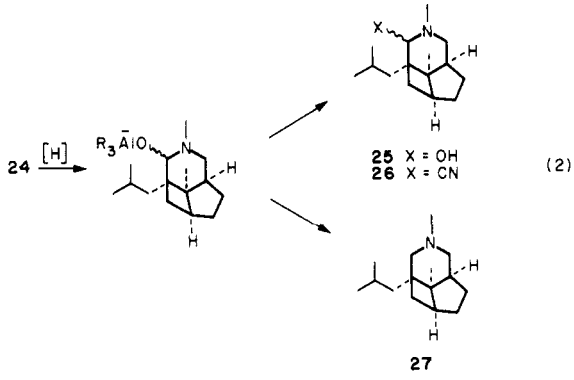
(21) (a) Hassner, A.; Pomerantz, I. H. *J. Org. Chem.* **1962**, *27*, 1760. (b) Barton, D. H. R.; Beaton, J. M. *J. Am. Chem. Soc.* **1961**, *83*, 4083. (c) Hassner, A.; Wentworth, W. A.; Pomerantz, I. H. *J. Org. Chem.* **1963**, *28*, 304. (d) Hassner, A.; Wentworth, W. A. *J. Chem. Soc., Chem. Commun.* **1965**, 44.

(22) (a) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324. (b) Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 875. (c) Sanders, E. B.; DeBardeleben, J. F.; Osdene, T. S. *J. Org. Chem.* **1975**, *40*, 2848. (d) Bohlmann, F.; Muller, H. J.; Schumann, D. *Chem. Ber.* **1973**, *106*, 3026. (e) Rueppel, M. L.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 7021. (f) Stevens, R. V.; Mehra, R. K.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1969**, 877. (g) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

Scheme IV



to dehydration to give the immonium species, and instead isolate the more stable amino nitrile **26** (eq 2).[23]

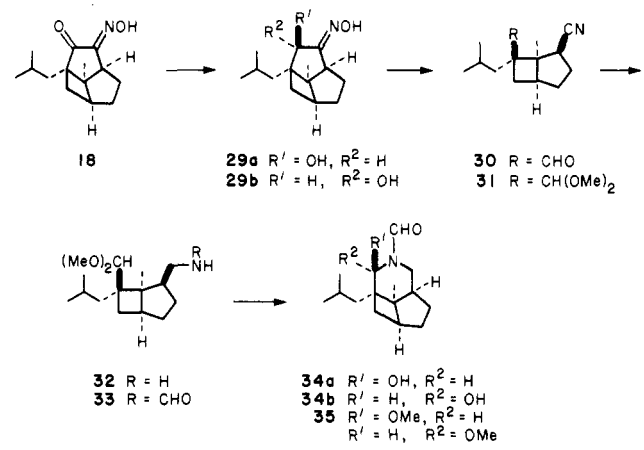


Reaction of **24** with diisobutylaluminum hydride under a variety of conditions, followed by cyanide workup, gave disappointing results.[22d,f] At 0 °C in THF solution, a 1:1 mixture of **24** and overreduction product **27** was recovered (63%), with no trace of the desired monoreduction product **26**. At lower temperatures and in hexane solution, the same behavior was observed; at the lower limit of −78 °C, no reaction at all was seen in hexane (**24** was insoluble at this temperature) or in THF even after 12 h.

Controlled reduction of **24** with lithium aluminum hydride, however, was much more successful. Treatment of the lactam with 4 equiv of hydride in THF at 0 °C (1 h) and room temperature (3 h) followed by reaction with aqueous sodium cyanide in methanol resulted in clean conversion to crystalline amino nitrile **26** (73% crude yield). Compound **26** is stable to flash chromatography on silica gel and is also surprisingly nonpolar in comparison to lactam **24** (R_f 0.51 for **26** in 1:4 ether–hexane; R_f 0.39 for **24** in 1:1 ethyl acetate–hexane). Proton and carbon-13 NMR spectroscopy revealed that **26** was formed as a single stereoisomer at the newly created stereocenter. On the basis of attack of cyanide on the less hindered (convex) face of immonium ion **3** (R = Me), we postulate an α-configuration for the cyano substituent.

One fact is clear from our reduction studies—immonium ion **3** (R = Me) does not rearrange spontaneously, at least at room temperature and in the presence of nucleophiles, because it is certainly an intermediate in the formation of **26**. We began our investigation into the potential rearrangement behavior of **26** by attempting to generate the immonium species **3** (R = Me) under nonnucleophilic conditions. Toward that end, an acetonitrile solution of **26** was treated with 1 equiv of silver tetrafluoroborate (Scheme IV). The immediate appearance of a white precipitate indicated the formation of insoluble silver cyanide and, presumably, the tetrafluoroborate salt of **3** (R = Me). Unfortunately, no rearrangement products were observed even after continued heating at 70 °C; immonium salt **28** was recovered from the reaction in poor yield. When a *p*-xylene solution of **26** was refluxed 30 h, decomposition of starting material resulted. Treatment with aqueous acetic acid resulted simply in hydrolysis to carbinol amine **25**. Finally, treatment with refluxing formic acid gave a mixture of **25** and the familiar tricyclic amine **27**, resulting from Leukart–Wallach reduction of the intermediate immonium species.[24]

Scheme V



The reluctance of **3** (R = Me) to undergo cyclobutylcarbinyl rearrangement can be rationalized on the basis of the thermodynamic stability of the immonium ion, relative to the carbonium ion that would result from rearrangement. It is apparent from the limited chemistry of amino nitrile **26** that the strain energy difference between **3** and **4** or **5** is *not* sufficient to offset the additional energy needed for generation of a tertiary carbonium ion (see Scheme I). Therefore, the only observable reactions are reactions of the immonium species as an isolated functional group. In order to remedy the situation, it is necessary to destabilize the immonium ion by transformation into a more reactive *N*-acylimmonium ion.

Our new plan called for the synthesis of carbinol amide **34**, which would serve as the precursor to an *N*-formyl version of immonium species **3** (Scheme V). Reduction of oximino ketone **18** with sodium borohydride in ethanol at 0 °C gave oximino alcohol **29** as a 10:1 mixture of isomers in 93% yield. The major compound (**29a**) was assigned the β-configuration at the carbinol center on the basis of attack of hydride on the less hindered α-face. The mixture was typically carried on without purification; subsequent treatment with 1 equiv of methanesulfonyl chloride and 2.5 equiv of triethylamine at −20 °C produced the Beckmann fragmentation product **30** in 90% yield from **18**.[25] Protection of the carbonyl was accomplished by reaction with methanol in the presence of trimethyl orthoformate and a trace of sulfuric acid to give cyano acetal **31** in 95% yield. (Without trimethyl orthoformate, acetalization is sluggish, presumably due to the inability of the carbonyl to enolize.)

Hydrogenation of **31** was attempted without success under several different conditions: platinum oxide in ethyl acetate (1 atm); rhodium on alumina in ammoniacal eth-

(23) (a) Beke, D.; Szantay, C.; Barczai-Beke, M. *Justus Liebigs Ann. Chem.* **1960**, *636*, 150. (b) Bonnett, R.; Clark, V. M.; Giddey, A.; Todd, A. *J. Chem. Soc.* **1959**, 2087. (c) Leonard, N. J.; Hay, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 1984.

(24) Moore, M. L. *Org. React. (N.Y.)* **1949**, *5*, 301.

(25) (a) Wakamatsu, T.; Fukui, M.; Ban, Y. *Synthesis* **1976**, 341. (b) Grieco, P. A.; Hiroi, K. *J. Am. Chem. Soc.* **1968**, *90*, 4924. (c) Autrey, R. L.; Scullard, P. W. *J. Am. Chem. Soc.* **1968**, *90*, 4924.

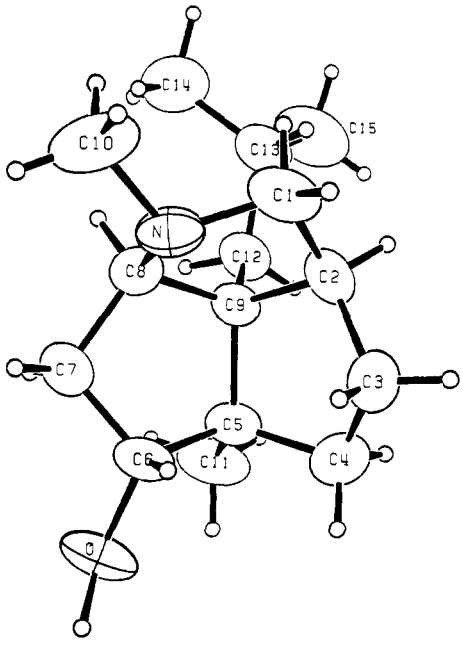
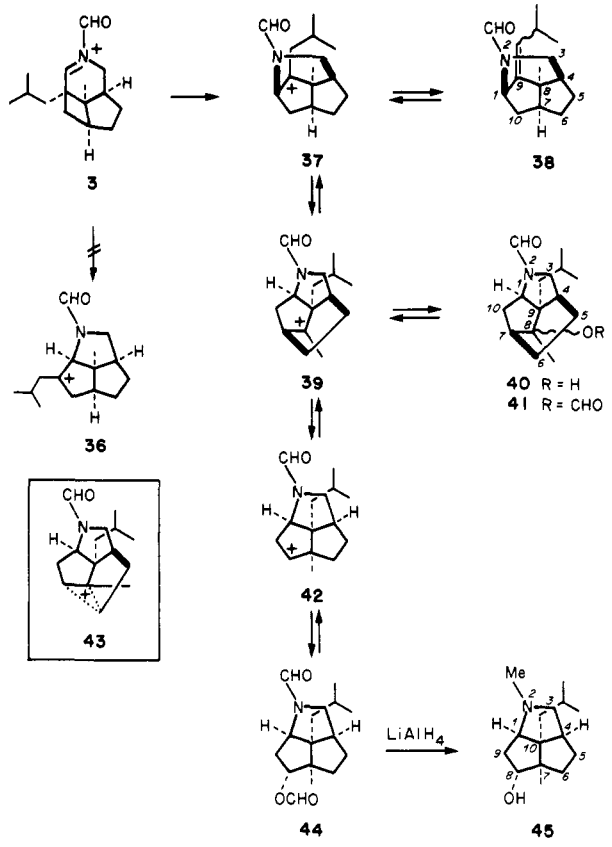


Figure 3.

anol (1 and 4 atm); rhodium on carbon in ammoniacal ethanol (1 and 4 atm). In all cases the reduction to **32** was extremely slow, and even the most vigorous conditions (4 atm, 72 h) gave only a 3:1 mixture of **31** and **32**. Hydrogenation at 1 atm over rhodium on carbon in a mixture of methanol and acetic acid, however, was successful, providing amino acetal **32** in excellent yield. Treatment of the reduction product with ethyl formate gave formamide **33** in 79% yield from **31**. Acidic hydrolysis of the acetal in aqueous THF provided an inseparable 1.6:1 mixture of epimeric carbinol amides **34** in 79% yield, along with a small amount (5%) of the corresponding *O*-methyl carbinol amides **35**. Thus, **34** is obtained in seven steps and 42% yield from tricyclic ketone **16**; the overall synthesis proceeds in 17% yield and 14 steps from commercially available starting materials.

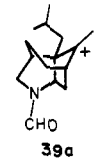
With the acylimmonium ion precursor in hand, we began the second series of experiments in our rearrangement investigation. Treatment of carbinol amide **34** with 95% formic acid at 20 °C for 12 h gives a mixture of three tricyclic rearrangement products: olefin **38** (as a mixture of double bond isomers (6%), tertiary alcohol **40** (as a 2:1 mixture of isomers, 16%), and a tertiary formate **41** (as a 1:1 mixture of isomers, 46%). Under more vigorous conditions (95% formic acid, reflux, 12 h), two rearrangement products were seen: olefin **38** (24%) and a fourth product, secondary formate **44** (as a single isomer, 55%). The latter compound (**44**) provided, upon reduction with lithium aluminum hydride, crystalline amino alcohol **45** (87%), which ultimately proved to be the key to our analysis of the rearrangement products. Extensive ^1H NMR studies, including homonuclear decoupling and two-dimensional *J*-correlated spectroscopy (COSY)[26] eventually established the correct structure for **45**. The assignment was verified by single-crystal X-ray analysis, the results of which are shown in Figure 3.[27] Structures

Scheme VI



were assigned to the remaining three compounds (**38**, **40**, and **41**) on the basis of their spectral properties and by analogy to **45**.

The likely sequence of rearrangements leading to **38**, **40**, **41**, and **44** is illustrated in Scheme VI. Initial ionization to form the acylimmonium species **3** (R = CHO) is followed by exclusive migration of the exo cyclobutane bond to give bridged tertiary carbonium ion **37**. All subsequent products in the reaction scheme arise from **37** rather than fused carbonium ion **36**, the product resulting from migration of the endo cyclobutane bond (via the desired rearrangement pathway). Once formed, **37** can lose a proton to form the isomeric mixture of olefins **38**. Alternatively, **37** can undergo a skeletally degenerate 1,2-alkyl shift to generate a second tricyclic tertiary carbonium ion **39**. Cation **39** could potentially lose a proton to generate the corresponding exo-methylene compound; since this product is not observed, however, it is likely that it protonates rapidly under the conditions of the reaction to regenerate **39**. A more likely fate for **39** is addition of an appropriate nucleophile; quenching with water and formic acid would lead to **40** and **41**. The fact that both compounds are isolated as mixtures of isomers can be rationalized by examination of a more accurate representation of the cationic species (**39a**), which reveals that the two faces of the tertiary



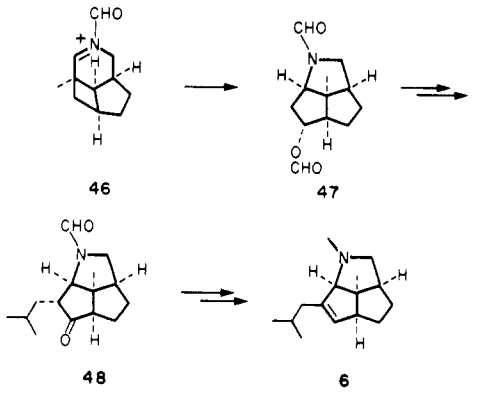
39a

carbonium ion are roughly equivalent in terms of steric congestion. A third and final 1,2-alkyl shift would convert **39** into secondary carbonium ion **42**, which is quenched by solvent to give formate **44**. However, because **44** is isolated

(26) (a) Bax, A.; Freeman, R.; Morris, G. *J. Magn. Reson.* **1981**, *42*, 169. (b) Aue, W. P.; Bartholdi, F.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229.

(27) The X-ray structure determination for **45** was performed by Dr. Fred Hollander of the Department of Chemistry, University of California, Berkeley. For full details, including tables of parameters, see: Connolly, P. J. Dissertation, University of California, Berkeley, 1984, 238–247. Photocopies of this material are available upon request from the senior author.

Scheme VII



as a single isomer at the carbinol center, its formation is perhaps better explained by the intermediacy of the nonclassical carbonium ion **43**. Nucleophilic attack at the less-hindered secondary position of **43** would account for the stereoselective production of **44**.

The selectivity observed in the initial cyclobutylcarbinyl rearrangement of **3** (R = CHO) to bridged cation **37** is best explained in stereoelectronic terms. Because the exo cyclobutane bond appears to be in much better position to overlap with the acylimmonium π-system than the endo bond, the activation barrier to 1,2-shift of the exo bond is much lower than that for the endo bond. Therefore, **37** is formed to the exclusion of **36**. As was noted previously, **37** is probably the less stable of the two possible products. Because of the apparent lower thermodynamic stability of **37**, it is possible to conclude that the initial rearrangement to give **37** is essentially irreversible—if the rearrangement were reversible, then **36** would certainly be the favored product by equilibration through **3** (R = CHO). The eventual production of secondary formate **44** can also be rationalized on this basis, since **44** possesses the more stable tricyclo[5.2.1.$0^{4,10}$]decane skeleton. Along the rearrangement pathway, equilibration of **37** to **39** would be essentially thermoneutral, but equilibration through **42** to give **44** would be exothermic in terms of strain energy. Therefore, given time, all of the intermediate products (**38**, **40**, and **41**) should funnel into the thermodynamic sink (**44**). Of the four rearrangement products, **44** is probably the most stable on kinetic grounds as well as in terms of its ability to regenerate a carbonium ion; ionization of **44** would create a secondary (or bridged) carbonium ion, while ionization of each of the other three products would generate a relatively more stable tertiary carbonium ion.

In spite of the fact that the formolysis of **34** proceeds via bridged rather than fused migration, we think that the reaction is still of potential use for the synthesis of dendrobine. Given the ease with which the rearrangement occurs and given that the ultimate thermodynamic product **44** possesses the desired tricyclo[5.2.1.$0^{4,10}$]decane skeleton, we plan to continue our work toward dendrobine with a revised synthetic plan (Scheme VII). Rearrangement of acylimmonium ion **46** should provide **47** according to the mechanism discussed above. Conversion of **47** to the corresponding tricyclic ketone and subsequent alkylation would introduce the required isobutyl substituent. Continued transformation should provide **6** and hence enone **7** in a straightforward manner.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. *tert*-Butyl alcohol was distilled from sodium and stored over 4A molecular sieves. Dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide immediately prior to use. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Triethylamine was distilled from calcium hydride and stored over 3A molecular sieves or sodium hydroxide. Throughout the paper, "hexane" refers to a commercial product that is a mixture of hexane isomers. Unless otherwise noted, solvents were removed from organic extracts under vacuum with a rotary evaporator. Melting points (Pyrex capillary) and boiling points are uncorrected. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. IR spectra were determined with a Perkin-Elmer Model 297 or Model 1420 infrared spectrophotometer in chloroform solution unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ solution, unless otherwise noted. ^{1}H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants in hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane using the δ scale. Mass spectra were obtained at 70 eV; data are tabulated as m/z (intensity expressed as percent of total ion current). Ultraviolet spectral data are reported as λ_{max} in nm (extinction coefficient). Gas–liquid partition chromatography (GLC) was done with Varian Aerograph 920 and 940 gas chromatographs using SE-30 columns. Analytical thin-layer chromatography (TLC) was performed with Analtech 250-μm silica gel plates. Column and flash[28] chromatography were done with Merck 60 silica gel (70–230 and 230–400 mesh, respectively). Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berkeley, CA.

***tert*-Butyl 2-Acetyl-5-hexenoate (8).** To a flame-dried, nitrogen-flushed 500-mL three-necked flask (equipped with a reflux condenser, addition funnel, and magnetic stirrer) charged with a hot solution made from 10.9 g (279 mmol) of potassium and 250 mL of *tert*-butyl alcohol was added, dropwise, 48.5 mL (46.3 g, 293 mmol) of *tert*-butyl acetoacetate. The mixture was brought to reflux, and 23.6 mL (31.4 g, 233 mmol) of 4-bromo-1-butene was added. After refluxing for 47 h, the resulting solution was allowed to cool, and the solvent was removed. Water (250 mL) was added, and the mixture was acidified with 10 mL of 6 N aqueous HCl and extracted with 600 mL of EtOAc. The organic phase was washed with 300 mL of brine, dried over $MgSO_4$, and concentrated to give 57 g of a brown oil. The crude product was vacuum-distilled through a 10-cm vacuum-jacketed Vigreux column to give 14.6 g of a mixture of **8** and *tert*-butyl acetoacetate (11:1, respectively, by ^{1}H NMR spectroscopy, corresponding to 13.7 g, 27%, of **8**), bp 67–69 °C (0.025 mm), and 32.5 g (66%) of pure **8**, bp 65–67 °C (0.025 mm). The two fractions were combined for a total yield of 93% and were judged to be pure enough to carry on: IR (film) 1740, 1716, 1645, 1370, 1252, 1148 cm^{-1}; ^{1}H NMR (200 MHz) 1.47 (s, 9), 1.85–2.15 (complex, 4), 2.22 (s, 3), 3.35 (t, 1, J = 7.1), 5.03 (m, 2), 5.75 (m, 1). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.08; H, 9.36.

Ethyl 3-Acetyl-3-(*tert*-butoxycarbonyl)-6-heptenoate (9). To a 500-mL round-bottomed flask (equipped with an addition funnel and magnetic stirrer) under nitrogen was added 12.5 g (262 mmol) of a 50% oil dispersion of NaH. The solids were rinsed with hexane and suspended in 200 mL of THF. Keto ester **8** (50.9 g, 240 mmol) was added dropwise during a period of 1 h, and the solution was allowed to stir for an additional 1.5 h. Ethyl bromoacetate (94% technical grade, 46.9 g, 31.2 mL, 264 mmol) was added dropwise during a period of 0.5 h. The addition funnel was replaced with a reflux condenser, and the solution was heated under reflux for 7 h. Water (200 mL) was added, and the mixture was extracted with 600 mL of EtOAc. The organic solution was washed with brine, dried over $MgSO_4$, and concentrated to yield 68.7 g of a yellow oil. Purification by vacuum-distillation through a 10-cm vacuum-jacketed Vigreux column gave 57.9 g (89%) of **9** as a colorless liquid, bp 85–135 °C (0.020 mm): IR (film) 1730, 1715, 1642, 1370, 1258, 1193, 1150 cm^{-1}; ^{1}H NMR (200 MHz) 1.24 (t, 3, J = 7.15), 1.47 (s, 9), 1.9–2.1 (m, 4), 2.27 (s, 3), 2.89 (s, 2), 4.11 (q, 2, J = 7.15), 5.01 (m, 2), 5.75 (m, 1). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.08; H, 8.69.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Ethyl 3-Acetyl-6-heptenoate (10). A solution of *p*-toluenesulfonic acid monohydrate (0.064 g, 0.34 mmol) in 14 mL of toluene under nitrogen in a 25-mL round-bottomed flask equipped with a Dean–Stark trap and reflux condenser was heated at reflux for 1 h. The solution was cooled to room temperature, and **9** (2.00 g, 6.70 mmol) was added. The mixture was heated under gentle reflux for 4.5 h and stirred at room temperature overnight. The solution was diluted with 30 mL of ether, washed with 30 mL of saturated aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. Solvent was removed, and the crude residue (1.47 g) was purified by column chromatography using 1:4 EtOAc–hexane as eluant to yield 1.05 g (79%) of **10** as a pale yellow liquid, bp 89–91 °C (0.025 mm): IR (film) 1730, 1712, 1640, 1370, 1352, 1160 cm^{-1}; ^1H NMR (250 MHz) 1.24 (t, 3, J = 7.1), 1.51 (m, 1), 1.72 (m, 1), 2.04 (q, 2, J = 6.8), 2.24 (s, 3), 2.36 (dd, 1, J = 4.5, 16.8), 2.74 (dd, 1, J = 2.7, 16.7), 3.01 (m, 1), 4.11 (q, 2, J = 7.1), 5.03 (m, 2), 5.75 (m, 1). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.48; H, 9.19.

Ethyl 3-(2-Methyl-1,3-dioxolan-2-yl)-6-heptenoate (11). In a 50-mL round-bottomed flask equipped with a Dean–Stark trap and reflux condenser, 25 mL of benzene, 2.02 mL (2.24 g, 36.1 mmol) of ethylene glycol, and 4.78 g (24.1 mmol) of **10** were combined and heated at reflux for 14 h. The reaction mixture was cooled to room temperature and poured onto 50 mL of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with 150 mL of diethyl ether; the organic phase was washed with 100 mL of water and 100 mL of brine and dried over Na_2SO_4. Removal of solvent gave 8.2 g of a yellow liquid, which was vacuum-distilled through a short-path still to yield 5.05 g of a 7.3:1 mixture (by GLC) of **11** (78%) and **10**, bp 90–98 °C (0.03 mm): IR (film) 1735, 1640, 1375, 1150, 1040 cm^{-1}; ^1H NMR (250 MHz) 1.26 (t, 3, J = 7.1), 1.28 (s, 3), 1.35 (m, 1), 1.68 (m, 1), 2.0–2.35 (m, 4), 2.42 (dd, 1, J = 6.4, 14.1), 3.92 (s, 4), 4.13 (q, 2, 7.1), 5.00 (m, 2), 5.81 (m, 1). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.73; H, 8.97.

Diisopropyl 3-Methylbutylphosphonate (12). Triisopropyl phosphite (90% technical grade, 11.6 g, 13.7 mL, 50.0 mmol) and 1-bromo-3-methylbutane (7.55 g, 5.99 mL, 50.0 mmol) were combined under nitrogen in a 25-mL round-bottomed flask equipped with a short-path distillation apparatus and heated with an oil bath to 135–140 °C for a 30-h period. During that time, approximately 4 mL of 2-bromopropane was collected. The mixture was cooled and distilled under vacuum to give 10.0 g (85%) of colorless **12**, bp 74–83 °C (0.5 mm): IR (film) 1380, 1375, 1245, 1220, 1110, 1005, 980 cm^{-1}; ^1H NMR (250 MHz) 0.90 (d, 6, J = 6.4), 1.31 (d, 12, J = 6.2), 1.4–1.8 (complex, 5), 4.69 (d septet, 2, J = 7.9, 6.2). Anal. Calcd for $C_{11}H_{25}O_3P$: C, 55.91; H, 10.66. Found: C, 55.56; H, 10.50.

Diisopropyl (4*RS*,7*RS*)- and (4*RS*,7*SR*)-2-Methyl-7-(2-methyl-1,3-dioxolan-2-yl)-5-oxo-10-undecenyl-4-phosphonate (13). To a flame-dried, nitrogen-flushed 1000-mL three-necked flask (equipped with an addition funnel and a low-temperature thermometer) charged with 48.0 g (203 mmol) of phosphonate **12** and 100 mL of THF at −70 °C was added, dropwise, 144 mL (194 mmol) of a 1.35 M solution of *n*-butyllithium in hexane at such a rate as to keep the temperature between −65 and −70 °C. The mixture was stirred at −70 °C for 0.5 h, and a solution of 22.4 g (92.4 mmol) of ester **11** in 25 mL of THF was added dropwise over a period of 0.5 h. The mixture was allowed to warm slowly to room temperature and was stirred overnight. After 21 h, the contents of the flask were poured onto 600 mL of saturated aqueous NH_4Cl, and the mixture was extracted with 1100 mL of ether. The ethereal solution was washed with brine, dried over $MgSO_4$, and concentrated to give 67.6 g of a yellow liquid. Excess **12** was removed under vacuum (0.010 mm) with a Kugelrohr apparatus to yield 36.1 g (90%) of **13** (a 1:1 mixture of isomers) as a viscous yellow oil, which was judged to be pure by ^1H NMR spectroscopy. The crude product was purified for the purpose of characterization by column chromatography using 1:2 EtOAc–hexane as eluant: IR (film) 1715, 1640, 1385, 1375, 1245, 990 cm^{-1}; ^1H NMR (250 MHz) 0.87 (m, 6), 1.2–1.8 (complex, 19), 2.08 (m, 3), 2.43 (m, 2), 2.72 (d, 1, J = 5.6), 3.15 (m, 1), 3.90 (m, 4), 4.68 (octet, 2, J = 6.6), 7.98 (m, 2), 5.90 (m, 1). Anal. Calcd for $C_{22}H_{41}O_6P$: C, 61.09; H, 9.55. Found: C, 61.04; H, 9.38.

Diisopropyl (4*RS*,7*RS*)- and (4*RS*,7*SR*)-7-Acetyl-2-methyl-5-oxo-10-undecenyl-4-phosphonate (14). A solution of 36.1 g (83.5 mmol) of crude keto phosphonate **13**, 150 mL of methanol, and 150 mL of 1.2 N aqueous HCl was stirred for 24 h. The methanol was removed with a rotary evaporator, and the aqueous residue was extracted with 700 mL of ether. The organic phase was washed with 400 mL of water and 400 mL of brine and was dried over $MgSO_4$. The solvent was removed, and the residue was pumped at high vacuum overnight to give 32.8 g (100%) of **14** (a 1:1 mixture of isomers) as a yellow-brown oil, which was judged to be pure by ^1H NMR spectroscopy. The crude product was purified for the purpose of characterization by flash chromatography using 1:2 EtOAc–hexane as eluant: IR ($CDCl_3$) 1710, 1640, 1600, 1240, 990 cm^{-1}; ^1H NMR [for one isomer] (250 MHz) 0.85 (m, 6), 1.25–1.8 (complex, 16), 2.04 (m, 3), 2.25 (s, 3), 2.9–3.35 (complex, 4), 4.77 (m, 2), 5.02 (m, 2), 5.70 (m, 1), [the other isomer showed an additional signal at 2.24 (s, 3)]. Anal. Calcd for $C_{20}H_{37}O_5P$: C, 61.84; H, 9.60. Found: C, 61.49; H, 9.48.

4-(3-Butenyl)-3-methyl-2-(2-methylpropyl)-2-cyclopenten-1-one (15). To a suspension of 4.39 g (91.8 mmol) of a 50% oil dispersion of NaH (which had been washed with hexane) and 750 mL of THF at −30 °C under nitrogen in a 2000-mL two-necked flask (equipped with an addition funnel, low-temperature thermometer, and cold bath) was added, dropwise, a solution of 32.4 g (83.5 mmol) of crude keto phosphonate **14** in 100 mL of THF at such a rate as to keep the temperature below −30 °C. The cold bath was removed, and the mixture was stirred for 20 h. Saturated aqueous NH_4Cl (500 mL) was added, and the organic layer was separated. The aqueous layer was extracted with 1500 mL of ether, and the combined organic phases were washed with 1500 mL of brine and dried over $MgSO_4$. Solvent was removed with a rotary evaporator to give 20 g of a reddish brown oil, which was vacuum-distilled through a short-path still to yield 13.3 g (78%) of **15** as a pale yellow liquid, bp 86–88 °C (0.005 mm): IR ($CDCl_3$) 1685, 1640, 1380 cm^{-1}; ^1H NMR (250 MHz) 0.83 (d, 3, J = 6.6), 0.86 (d, 3, J = 6.6), 1.28 (m, 1), 1.7–2.1 (complex, 7), 2.00 (s, 3), 2.51 (dd, 1, J = 6.5, 18.5), 2.70 (m, 1), 5.02 (m, 2), 5.81 (m, 1); UV (hexane) 345 (33), 321 (46), 309 (47), 276 (52), 228 (14000). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.33; H, 10.89.

(1*RS*,4*RS*,7*SR*,8*RS*)-8-Methyl-1-(2-methylpropyl)tricyclo[5.1.1.0^{4,8}]nonan-2-one (16). Cyclopentenone **15** (13.3 g, 64.5 mmol) was dissolved in 800 mL of HPLC grade hexane in a large immersion-well photochemical reaction vessel, and nitrogen was bubbled through the solution for 0.5 h. The mixture was irradiated with a 450-W Hanovia lamp and Pyrex filter, and the reaction was followed by GLC. After 15 h, irradiation was stopped, and the solution was dried over $MgSO_4$. Removal of solvent afforded 13.3 g of a yellow liquid, which was distilled under vacuum through a short-path still to give 11.4 g (86%) of colorless **16**, bp 67–71 °C (0.005 mm): IR (film) 1730 cm^{-1}; ^1H NMR (250 MHz) 0.86 (d, 3, J = 6.6), 0.87 (d, 3, 6.7), 1.18 (s, 3), 1.35–1.6 (complex, 5), 1.8 (m, 2), 1.95–2.3 (complex, 5), 2.59 (dd, 1, J = 9.6, 17.6); ^{13}C NMR (63 MHz) 19.6, 23.2, 24.8, 25.2, 31.6, 33.4, 34.0, 40.4, 41.8, 43.3, 46.1, 50.6, 55.8, 223.8. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.57; H, 10.54.

(*E*)-(1*RS*,4*SR*,7*SR*,8*RS*)-3-Hydroximino-8-methyl-1-(2-methylpropyl)tricyclo[5.1.1.0^{4,8}]nonan-2-one (18). To a solution of 0.680 g (6.06 mmol) of potassium *tert*-butoxide in 7 mL of *tert*-butyl alcohol under nitrogen was added 1.00 g (0.485 mmol) of tricyclic ketone **16**, dropwise with a syringe pump. After the addition was complete, the mixture was stirred for 10 min, and 0.839 mL (0.732 g, 6.06 mmol) of isoamyl nitrite was added dropwise with a syringe pump. After 2 h, 25 mL of water and 100 mL of ether were added, and the mixture was transferred to a separatory funnel. The aqueous layer was removed, and the ether layer was extracted with five 30-mL portions of 0.5 N aqueous NaOH. The basic extracts were combined with the original aqueous layer, acidified to pH 2 with 25 mL of 6 N aqueous hydrochloric acid, and extracted with 300 mL of chloroform. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give 1.2 g of brown oil, which solidified after pumping at high vacuum. The crude product was purified by flash chromatography on silica gel using 1:3 ether–hexane as eluant to give 0.87 g (76%) of **18** as a pale yellow solid, mp 98.5–100 °C: IR 3550, 3260 (br), 1725, 1625, 1365 cm^{-1}; ^1H NMR (250 MHz) 0.858 (d, 3, J = 6.6), 0.864 (d, 3, J = 6.6), 1.23 (s, 3), 1.42 (m, 2), 1.7 (m, 3), 1.85–2.4 (complex, 5), 3.08 (t,

1, J = 5.2), 9.7 (br s, 1); ^{13}C NMR (45 MHz) 20.2, 23.5, 24.5, 25.1, 31.7, 33.2, 34.6, 41.2 (double intensity), 47.7, 52.8, 53.0, 161.2, 208.6; mass spectrum, 235 (0.5), 218 (2.3), 202 (0.3), 192 (1.8), 176 (1.6), 138 (1.9), 107 (2.6), 93 (2.8), 81 (7.1); UV (methanol) 247 (11 700) (shifts to 299 upon addition of 0.1 N aqueous NaOH). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.52; H, 8.97; N, 5.91.

(*E*)-(1*RS*,4*SR*,7*SR*,8*RS*)-3-Acetoximino-8-methyl-1-(2-methylpropyl)tricyclo[5.1.1.0^{4,8}]nonan-2-one (19). Acetyl chloride (0.0266 g, 0.0241 mL, 0.339 mmol) was added dropwise to a stirring solution of 0.0400 g (0.170 mmol) of oximino ketone **18**, 0.0474 mL (0.0344 g, 0.340 mmol) of triethylamine, and 0.3 mL of CH_2Cl_2 at 0 °C under nitrogen. The mixture was stirred at 0 °C for 4 h and room temperature for 5 h. Water (5 mL) was added, and the solution was extracted with 15 mL of EtOAc. The organic phases were washed with 10 mL of 1.2 N aqueous HCl, 10 mL of saturated aqueous $NaHCO_3$, and 10 mL of brine. The organic solution was dried over $MgSO_4$ and concentrated to give 0.0457 g of oily residue, which was purified by flash chromatography using 1:2 ether–hexane as eluant to yield 0.0385 g (81%) of **19** as a pale yellow oil: IR 1775, 1730, 1625, 1365, 1175, 895 cm^{-1}; ^{1}H NMR (250 MHz) 0.87 (d, 6, J = 6.6), 1.23 (s, 3), 1.5 (m, 1), 1.7–1.8 (m, 3), 1.9–2.1 (m, 3), 2.2–2.5 (m, 3), 2.31 (s, 3), 3.13 (dd, 1, J = 4.4, 9.1). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.33; H, 8.36; N, 5.02.

(*E*)-(1*RS*,4*SR*,7*SR*,8*RS*)-3-Benzoyloximino-8-methyl-1-(2-methylpropyl)tricyclo[5.1.1.0^{4,8}]nonan-2-one (20) and Methyl (1*RS*,2*SR*,5*SR*,7*RS*)-2-Cyano-1-methyl-7-(2-methylpropyl)bicyclo[3.2.0]heptane-7-carboxylate (21). Benzoyl chloride (2.39 mL, 2.90 g, 20.6 mmol) was added to a stirring solution of 4.42 g (18.8 mmol) of oximino ketone **18**, 3.14 mL (2.28 g, 22.6 mmol) of triethylamine, and 40 mL of CH_2Cl_2 at 0 °C under nitrogen. The mixture was stirred for 1 h at 0 °C and 2 h at room temperature. Water (50 mL) was added, and the aqueous phase was washed with 150 mL of EtOAc. The organic layers were washed with 80 mL of 1.2 N aqueous HCl, 80 mL of saturated aqueous $NaHCO_3$, and brine and were dried over $MgSO_4$. The solvents were removed to give 6.40 g (100% crude yield) of benzoyloximino ketone **20** which was judged to be pure by ^{1}H NMR spectroscopy. The crude product was purified for the purpose of characterization by flash chromatography using 1:4 ether–hexane as eluant: IR 1760, 1735, 1625, 1605, 1455, 1260, 1190, 1045, 1020, 860 cm^{-1}; ^{1}H NMR (250 MHz) 0.89 (d, 3, J = 6.6), 0.90 (d, 3, J = 6.6), 1.27 (s, 3), 1.45–2.5 (complex, 10), 3.25 (dd, 1, J = 4.6, 8.7), 7.51 (t, 2, J = 7.5), 7.64 (t, 1, J = 7.5), 8.11 (d, 2, J = 7.1). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.17; H, 7.51; N, 3.98.

Crude **20** (6.40 g, 18.8 mmol) was dissolved in 50 mL of methanol and heated at reflux for 5 h. Solvent was removed with a rotary evaporator, and the residue was dissolved in 50 mL of CH_2Cl_2 and washed with 100 mL of saturated aqueous $NaHCO_3$. The aqueous phase was washed with 100 mL of CH_2Cl_2, and the combined organic layers were washed with brine and dried over $MgSO_4$. Concentration gave, after pumping at high vacuum, 4.62 g of brown residue, which was purified by flash chromatography using 1:5 ether–hexane as eluant to afford 4.27 g (91% from **18**) of cyano ester **21**: IR 2240, 1720, 1440, 1170, 1145 cm^{-1}; ^{1}H NMR (250 MHz) 0.85 (d, 3, J = 6.3), 0.90 (d, 3, J = 6.3), 1.32 (s, 3), 1.5–1.7 (m, 4), 1.9–2.2 (m, 3), 2.25–2.5 (m, 3), 2.52 (dd, 1, J = 6.1, 12.1), 3.74 (s, 3). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.98; H, 9.16; N, 5.59.

(1*RS*,5*SR*,8*SR*,9*RS*)-3-Aza-9-methyl-1-(2-methylpropyl)tricyclo[6.1.1.0^{5,9}]decan-2-one (23). Cyano ester **21** (0.137 g, 0.549 mmol) was combined with 0.080 g of 5% rhodium on charcoal in 2.5 mL of acetic acid and was stirred under 1 atm of hydrogen until the uptake had ceased. The mixture was diluted with ether, and the catalyst was removed by filtration through Celite. After neutralization with saturated aqueous $NaHCO_3$, the solution was extracted with 100 mL of CH_2Cl_2. The organic portion was washed with brine, dried over K_2CO_3 overnight, and concentrated with a rotary evaporator to give 0.104 g of an oily residue. The crude product was purified by flash chromatography using 1:1 EtOAc–hexane as eluant to yield 0.0786 g (65%) of **23**: IR 3425, 1645 cm^{-1}; ^{1}H NMR (250 MHz) 0.88 (d, 3, J = 6.6), 0.91 (d, 3, J = 6.8), 1.23 (s, 3), 1.4–2.3 (complex, 11), 3.23 (ddd, 1, J = 1.7, 6.4, 12.9), 3.51 (dd, 1, J = 2.1), 6.52 (br s, 1). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.93; H, 10.41; N, 6.27.

(1*RS*,5*SR*,8*SR*,9*RS*)-3-Aza-3,9-dimethyl-1-(2-methylpropyl)tricyclo[6.1.1.0^{5,9}]decan-2-one (24). Sodium hydride (50% oil dispersion, 0.520 g, 10.9 mmol) was placed in a flame-dried, 100-mL, two-necked, round-bottomed flask under nitrogen and was rinsed with hexane. THF (10 mL) was added, and the stirring suspension was cooled in an ice bath. Lactam **23** (2.19 g, 9.89 mmol) was dissolved in 20 mL of THF and was added to the suspension. After 10 min in the cold, the mixture was allowed to warm to room temperature, and was stirred for 2.5 h. The suspension was chilled in an ice bath, and 0.739 mL (1.68 g, 11.9 mmol) of freshly distilled methyl iodide was added dropwise. The mixture was stirred for 10 min and was allowed to warm to room temperature. After a period of 5 h, 30 mL of saturated aqueous NH_4Cl was added, and the resulting aqueous layer was extracted with 90 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give 2.44 g of a brown oil, which was purified by flash chromatography using 1:3 EtOAc–hexane as eluant to give 2.03 g (87%) of **24** as a pale yellow oil: IR (film) 1645 cm^{-1}; ^{1}H NMR (250 MHz) 0.78 (d, 3, J = 6.5), 0.89 (d, 3, J = 6.7), 1.22 (s, 3), 1.4–2.2 (complex, 11), 2.98 (s, 3), 3.12 (dd, 1, J = 1.6, 12.8), 3.69 (dd, 1, J = 1.9, 12.8); ^{13}C NMR (63 MHz) 21.5, 21.9, 24.8, 25.7, 27.4, 30.7, 35.7, 35.8, 39.0, 43.3, 45.3, 46.1, 48.7, 49.5, 175.6. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.24; H, 10.76; N, 5.97.

(1*RS*,2*RS*,5*SR*,8*SR*,9*RS*)-3-Aza-3,9-dimethyl-1-(2-methylpropyl)tricyclo[6.1.1.0^{5,9}]decane-2-carbonitrile (26). A solution of 60.4 mg (0.257 mmol) of lactam **24** in 0.5 mL of THF in an oven-dried 10-mL pear-shaped flask under nitrogen was cooled in an ice bath, and 0.298 mL (0.86 M, 0.257 mmol) of a standardized solution of $LiAlH_4$ in THF was added dropwise. The mixture was stirred in the cold for 1 h and was then allowed to warm to room temperature and stir for 3 h. Methanol (0.5 mL), water (0.5 mL), and NaCN (60 mg, 1.2 mmol) were added, and the mixture was stirred for 4 h. Water (10 mL) was added, and the aqueous solution was extracted with 25 mL of CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to give, after pumping at high vacuum, 46.2 mg (73%) of a white, crystalline solid, mp 57–59 °C, which was judged to be pure **26** by ^{1}H NMR spectroscopy. An analytical sample was prepared by flash chromatography using 1:4 ether–hexane as eluant: IR 2235, 1470, 1450 cm^{-1}; ^{1}H NMR (250 MHz) 0.96 (d, 3, J = 6.6), 1.02 (s, 3), 1.03 (d, 3, J = 6.3), 1.4–2.3 (complex, 11), 2.40 (s, 3), 2.42 (d, 1, J = 12.3), 2.56 (dd, 1, J = 3.3, 12.5), 3.39 (s, 1); ^{13}C NMR (63 MHz) 21.3, 24.1, 24.5, 25.3, 27.7, 29.6, 31.8, 40.3, 41.6, 43.6, 44.7, 44.9, 45.6, 50.6, 60.4, 115.8; mass spectrum, 246 (2.07), 231 (4.07), 220 (2.51), 203 (4.67), 189 (1.65), 178 (6.47), 165 (2.38), 124 (3.84), 82 (12.61). Anal. Calcd for $C_{16}H_{26}N_2$: C, 77.99; H, 10.64; N, 11.37. Found: C, 78.22; H, 10.48; N, 11.27.

(1*RS*,2*RS*,4*SR*,7*SR*,8*RS*)- and (1*RS*,2*SR*,4*SR*,7*SR*,8-*RS*)-3-Hydroximino-8-methyl-1-(2-methylpropyl)tricyclo-[5.1.1.0^{4,8}]nonan-2-ol (29a and 29b). Oximino ketone **18** (0.997 g, 4.24 mmol) was dissolved in 17 mL of absolute ethanol under nitrogen and cooled in an ice bath. Sodium borohydride (0.0801 g, 2.12 mmol) was added in one portion, and the solution was stirred for 1.25 h. Water (10 mL) was added, and most of the solvents were removed with a rotary evaporator. The semisolid residue was partitioned between 50 mL of saturated aqueous NH_4Cl and 50 mL of CH_2Cl_2. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give, after pumping at high vacuum, 1.04 g (>100% crude yield) of a 10:1 mixture of **29a** and **29b** as a sticky, viscous oil. The crude product was judged to be pure enough for the next reaction by ^{1}H NMR spectroscopy. The isomers were separated for the purpose of characterization by flash chromatography using 1:4 ether–hexane as eluant; data for the major isomer **29a** was as follows: IR 3590 (sharp), 3310 (br), 1475, 1455, 1375, 1080 cm^{-1}; ^{1}H NMR (250 MHz) 0.96 (d, 3, J = 6.6), 0.97 (d, 3, J = 6.6), 1.00 (s, 3), 1.2–2.5 (complex, 10), 2.87 (dd, 1, J = 6.5, 9.6), 3.45 (br s, 1), 4.44 (s, 1), 8.70 (br s, 1). Data for the minor isomer **29b** was as follows: IR 3595, 3250, 1465, 1380, 1075 cm^{-1}; ^{1}H NMR (180 MHz) 0.96 (d, 3, J = 6.5), 0.98 (d, 3, J = 6.6), 1.03 (s, 3), 1.4–2.3 (complex, 10), 2.60 (t, 1, J = 7.2), 3.70 (s, 1), 4.76 (s, 1), 8.00 (br s, 1). Anal. Calcd (mixture of **29a** and **29b**) for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N,

5.90. Found: C, 70.87; H, 10.02; N, 5.67.

(1*RS*,2*SR*,5*SR*,7*RS*)-7-Formyl-1-methyl-7-(2-methylpropyl)bicyclo[3.2.0]heptane-7-carbonitrile (30). A solution of 1.04 g (4.24 mmol) of crude hydroxy oximes **29a** and **29b** and 16 mL of CH_2Cl_2 under nitrogen was cooled in a −22 °C (aqueous $CaCl_2$/dry ice) bath. Triethylamine (1.48 mL, 1.07 g, 10.6 mmol) was added, and after 5 min, methanesulfonyl chloride (0.362 mL, 0.535 g, 4.67 mmol) was added dropwise. The solution was stirred for 30 min in the cold and 30 min at room temperature. Water (50 mL) was added, and the mixture was stirred vigorously for 5 min. Aqueous 1.2 N HCl (50 mL) was added, and the mixture was washed with 175 mL of EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated to give 0.96 g of a pale yellow oil. Purification by flash chromatography using 1:6 ether–hexane as eluant afforded, after pumping at high vacuum, 0.835 g (90% from **18**) of **30** as a white, crystalline solid, mp 48–50 °C: IR 2740, 2250, 1710 cm^{-1}; ^1H NMR (180 MHz) 0.79 (d, 3, J = 6.5), 0.88 (d, 3, J = 6.4), 1.45 (s, 3), 1.5–2.5 (complex, 11), 9.98 (s, 1). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.3. Found: C, 76.59; H, 9.49; N, 6.36.

(1*RS*,2*SR*,5*SR*,7*RS*)-7-(Dimethoxymethyl)-1-methyl-7-(2-methylpropyl)bicyclo[3.2.0]heptane-2-carbonitrile (31). Cyano aldehyde **30** (0.671 g, 3.06 mmol) was dissolved in 10 mL of methanol containing 2 mL of trimethyl orthoformate and 0.5 mL of a 0.5% solution of H_2SO_4 in methanol. After the mixture was stirred under nitrogen for 14 h, a small amount of $BaCO_3$ was added, and the solvents were removed with a rotary evaporator. The residue was diluted with 50 mL of saturated aqueous $NaHCO_3$, and the mixture was washed with 150 mL of CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated to give, after pumping at high vacuum, 0.81 g of a white solid. Purification by flash chromatography using 1:10 ether–hexane as eluant afforded 0.771 g (95%) of **31** as a white, crystalline solid, mp 64–65 °C: IR 2240, 1470, 1450, 1115, 1075 cm^{-1}; ^1H NMR (250 MHz) 0.95 (d, 3, J = 6.5), 0.96 (d, 3, J = 6.5), 1.24 (s, 3), 1.32 (dd, 1, J = 6.9, 13.7), 1.5–2.6 (complex, 10), 3.44 (s, 3), 3.54 (s, 3), 4.44 (s, 1). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.37; H, 10.10; N, 5.24.

(1*RS*,2*SR*,5*SR*,7*RS*)-1-(Aminomethyl)-7-(dimethoxymethyl)-1-methyl-7-(2-methylpropyl)bicyclo[3.2.0]heptane (32). Cyano acetal **31** (0.462 g, 1.74 mmol) and 0.47 g of 5% rhodium on charcoal were combined with 10 mL of methanol and 10 mL of acetic acid and stirred under 1 atm of hydrogen until the uptake had ceased. The catalyst was removed by suction filtration through Celite and was rinsed thoroughly with CH_2Cl_2. The combined organic solutions were concentrated. The residue was partitioned between 50 mL of CH_2Cl_2 and 25 mL of saturated aqueous K_2CO_3; the aqueous layer was washed with 100 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated to give 0.450 g (96% crude yield) of **32** as a slightly colored oil, which was judged to be pure enough for the next reaction by ^1H NMR spectroscopy: IR 3380, 3300, 1465, 1105, 1075 cm^{-1}; ^1H NMR (250 MHz) 0.92 (d, 3, J = 5.4), 0.95 (d, 3, J = 6.5), 1.18 (s, 3), 1.3–2.0 (complex, 12), 2.20 (dd, 1, J = 6.8, 15.7), 2.80 (dd, 1, J = 8.4, 12.8), 2.96 (dd, 1, J = 5.8, 12.9), 3.35 (s, 3), 3.53 (s, 3), 4.32 (s, 1); mass spectrum, (no M^+) 254 (0.15), 238 (0.28), 222 (0.92), 205 (1.24), 162 (1.17), 156 (1.72), 142 (0.97), 127 (2.51), 110 (2.02), 95 (2.68), 75 (2.48); HRMS, calcd for $C_{15}H_{28}NO_2$ (M − 15) 254.2121, found 254.2110. Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.77; H, 11.53;, N, 5.18.

(1*RS*,2*SR*,5*SR*,7*RS*)-7-(Dimethoxymethyl)-2-(formamidomethyl)-1-methyl-7-(2-methylpropyl)bicyclo[3.2.0]-heptane (33). Crude amino acetal **32** (0.430 g, 1.60 mmol) was dissolved in 10 mL of ethyl formate (distilled under nitrogen) and stirred under nitrogen at room temperature for 19 h. Solvent was removed to give, after pumping at high vacuum, 0.448 g of yellow solid. The crude product was recrystallized from hexane to give 0.336 g of **33** as a white, crystalline solid, mp 90–92 °C. The mother liquor was concentrated and purified by flash chromatography using 2:3 EtOAc–hexane as eluant to give an additional 0.044 g of **33** (82% from **32**, 79% from **31**): IR 3420, 1680, 1510, 1470, 1450, 1390, 1110, 1070 cm^{-1}; ^1H NMR [for the major rotational isomer] (250 MHz) 0.94 (d, 3, J = 6.3), 0.96 (d, 3, J = 6.4), 1.18 (s, 3), 1.2–2.0 (complex, 10), 2.21 (dd, 1, J = 7.0, 15.8), 3.28 (m, 1), 3.46 (s, 3), 3.50 (s, 3), 3.98 (m, 1), 4.26 (s, 1), 6.30 (br s, 1), 8.13 (s, 1) [the minor rotational isomer showed additional peaks at 3.44 (s, 3), 3.47 (s, 3), 4.14 (s, 1), 6.15 (br s, 1), 8.03 (d, 1, J = 12.4)]. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.51; N, 4.71. Found: C, 68.78;, H, 10.55; N, 4.70.

(1*RS*,2*RS*,5*SR*,8*SR*,9*RS*)- and (1*RS*,2*SR*,5*SR*,8*SR*,9*RS*)-3-Aza-3-formyl-9-methyl-1-(2-methylpropyl)tricyclo[6.1.1.0^{5,9}]decan-2-ol (34a and 34b). Formamide **33** (0.505 g, 1.70 mmol) was dissolved in a mixture of 10 mL of THF and 10 mL of 1.2 N aqueous HCl, and the resulting solution was stirred under nitrogen. After 4 h, TLC indicated that all **33** had been consumed, and 20 mL of 0.5 N aqueous NaOH was added until the pH of the solution was greater than 10. The mixture was washed with 120 mL of CH_2Cl_2; the organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 0.40 g of solid residue. The crude product was purified by flash chromatography using 1:2 EtOAc–hexane as eluant to give 0.337 g (79%) of white crystalline solid, mp 120–122 °C, which was found to be a 1.6:1 mixture of **34a** and **34b** by ^1H NMR spectroscopy: IR 3590 (sharp), 3380 (br), 1665, 1445 cm^{-1}; ^1H NMR [for **34a**] (250 MHz) 1.0 (m, 6), 1.08 (s, 3), 1.2–2.0 (complex, 11), 2.28 (m, 1), 3.22 (dd, 1, J = 3.5, 13.3), 3.97 (d, 1, J = 13.3), 4.68 (s, 1), 8.26 (s, 1) [the minor isomer **34b** showed additional signals at 1.07 (s, 3), 3.02 (d, 1, J = 13.3), 3.78 (dd, 1, J = 3.3, 13.4), 5.56 (s, 1), 8.11 (s, 1)]; mass spectrum, 251 (0.38), 234 (0.34), 208 (0.58), 190 (0.90), 177 (1.11), 162 (0.62), 149 (0.42), 113 (1.54), 94 (15.13), 81 (5.29), 58 (9.78). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.89; H, 10.01; N, 5.56. The *O*-methyl carbinol amide **35** (0.021 g, 5%) was isolated as a colorless oil: IR ($CDCl_3$) 1665, 1445, 1430, 1075 cm^{-1}; ^1H NMR [for the major isomer] (250 MHz) 0.96 (d, 3, J = 6.5), 0.98 (d, 3, J = 5.7), 1.03 (s, 3), 1.2–2.0 (complex, 10), 2.27 (m, 1), 2.91 (dd, 1, J = 3.6, 13.1), 3.10 (s, 3), 4.00 (d, 1, J = 13.4), 4.03 (s, 1), 8.28 (s, 1) [the minor isomer showed additional signals at 1.02 (s, 3), 2.99 (d, 1, J = 13.4), 3.16 (s, 3), 3.48 (dd, 1, J = 3.4, 13.3), 5.08 (s, 1), 8.31 (s, 1)].

Rearrangement of 34 in Formic Acid Solution: (a) At 20 °C. A solution of 104 mg (0.414 mmol) of carbinol amide **34** dissolved in 7 mL of 95% formic acid was allowed to stir under nitrogen at 20 °C for 12 h. The formic acid was removed with a rotary evaporator, and the residue was diluted with 25 mL of saturated aqueous $NaHCO_3$. The aqueous solution was extracted with 75 mL of CH_2Cl_2, and the organic phase was washed with brine and dried over Na_2SO_4. The organic solution was concentrated to give 121 mg of a yellow residue, which was purified by flash chromatography on 6 g of silica using a solvent gradient ranging from 1:2 to 2:1 EtOAc–hexane. The least polar fractions yielded 5.4 mg (6%) of a 1:1 mixture of (*E*)- and (*Z*)-(1*RS*,4*SR*,7*SR*,8*RS*)-2-aza-8-methyl-9-(2-methylpropylidene)tricyclo[5.2.1.0^{4,8}]decane-2-carboxaldehyde (**38**) and 5.7 mg of a mixture of **38** and an unidentified impurity: IR ($CDCl_3$) 3700, 1655 cm^{-1}; ^1H NMR [for one isomer of **38**] (250 MHz) 0.958 (d, 3, J = 6.5), 0.962 (d, 3, J = 6.5), 1.12 (s, 3), 1.2–2.2 (complex, 9), 2.57 (m, 1), 2.85 (d, 1, J = 12.2), 3.08 (dd, 1, J = 3.5, 12.2), 4.89 (d, 1, J = 5.1), 7.99 (s, 1) [the other isomer showed an additional signal at 5.08 (d, 1, J = 9.3)]; mass spectrum, 233 (4.72), 218 (1.30), 204 (0.37), 190 (36.89), 176 (1.42), 162 (5.71), 149 (3.22). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.87; H, 9.94; N, 6.01.

The intermediate column fractions gave 46.7 mg (46%) of a 1:1 mixture of (1*RS*,4*SR*,7*SR*,8*RS*,9*RS*)- and (1*RS*,4*SR*,7*SR*,8*SR*,9*RS*)-2-aza-8-(formyloxy)-8-methyl-9-(2-methylpropyl)tricyclo[5.2.1.0^{4,9}]decane-2-carboxaldehyde (**41**): IR ($CDCl_3$) 1725, 1660, 1380, 1190 cm^{-1}; ^1H NMR [for one isomer] (200 MHz) 0.93 (complex 6), 1.2–2.5 (complex 10), 1.66 (s, 3), 2.92 (m, 1), 3.26 (d, 1, J = 9.8), 3.64 (dd, 1, J = 4.1, 9.8), 4.14 (d, 1, J = 9.6), 7.98 (s, 1), 8.23 (s, 1) [the other isomer showed additional signals at 1.68 (s, 3), 3.45 (m, 2), 4.23 (d, 1, J = 9.4), 8.01 (s, 1), 8.34 (s, 1)]. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.66; H, 8.85; N, 4.98.

The most polar fractions yielded 15.6 mg (16%) of a 2:1 mixture of (1*RS*,4*SR*,7*SR*,8*RS*,9*RS*) and (*RS*,4*SR*,7*SR*,8*SR*,9*RS*)-2-aza-8-hydroxy-8-methyl-9-(2-methylpropyl)tricyclo[5.2.1.0^{4,9}]decane-2-carboxaldehyde (**40**): IR ($CDCl_3$) 3620, 3450 (br), 1660, 1380 cm^{-1}; ^1H NMR [for the major isomer] (250 MHz) 0.95 (d, 6, J = 6.5), 1.2–2.2 (complex, 11), 1.35 (s, 3), 2.55 (m, 1), 3.39 (d, 1, J = 11.7), 3.50 (dd, 1, J = 4.6, 11.9), 4.08 (d, 1, J = 9.7), 8.32 (s, 1) [the minor isomer gave additional signals at 0.93 (d, 6, J

= 6.5), 1.31 (s, 3), 3.24 (d, 1, J = 9.8), 3.65 (dd, 1, J = 4.0, 9.8), 4.17 (d, 1, J = 10.1), 8.22 (s, 1)]. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.67; H, 10.20; N, 5.38.

(b) At 100 °C (Reflux Temperature). A solution of 104 mg (0.414 mmol) of **34** dissolved in 7 mL of 95% formic acid was heated at reflux under nitrogen for 12 h. The formic acid was removed with a rotary evaporator, and the residue was diluted with 50 mL of 10% aqueous $NaHCO_3$. The aqueous solution was extracted with 100 mL of CH_2Cl_2, and the organic phase was washed with brine, dried over Na_2SO_4, and concentrated to give 112 mg of a yellow oil. The crude product was purified by flash chromatography on 5 g of silica using a solvent gradient ranging from 1:4 to 1:1 EtOAc–hexane. The less polar fractions gave 23.3 mg (24%) of **38**. The more polar fractions yielded 63.2 mg (55%) of (1*RS*,4*SR*,7*RS*,8*RS*,10*SR*)-2-aza-8-(formyloxy)-7-methyl-10-(2-methylpropyl)tricyclo[5.2.1.$0^{4,10}$]decane-2-carboxaldehyde (**44**) as a colorless oil: IR ($CDCl_3$) 1722, 1640, 1380 cm^{-1}; ^1H NMR [for one rotational isomer] (250 MHz) 0.95 (complex, 9), 1.2–2.4 (complex, 9), 2.65 (m, 1), 3.02 (dd, 1, J = 6.1, 12.9), 4.11 (dd, 1, J = 9.3, 12.6), 4.53 (t, 1, J = 8.8), 5.23 (t, 1, J = 3.4), 8.07 (s, 1), 8.08 (s, 1) [the other rotational isomer showed additional signals at 3.23 (dd, 1, J = 6.8, 11.5), 3.92 (dd, 1, J = 9.1, 11.5), 4.24 (t, 1, J = 7.6), 8.13 (s, 1)]; mass spectrum, 279 (2.48), 264 (0.18), 250 (1.50), 234 (38.2), 223 (3.67), 204 (0.40), 190 (1.61), 177 (3.72), 163 (1.34), 151 (1.89), 132 (1.72). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.76; H, 8.82; N, 4.87.

(1*RS*,4*SR*,7*RS*,8*RS*,10*SR*)-2-Aza-2,7-dimethyl-10-(2-methylpropyl)tricyclo[5.2.1.$0^{4,10}$]decan-8-ol (45). To a suspension of $LiAlH_4$ (95%, 10.0 mg, 0.240 mmol) in 0.5 mL of ether under nitrogen at 0 °C was added, dropwise, a solution of 32.7 mg (0.117 mmol) of **44** in 0.5 mL of ether. The mixture was stirred for 15 min at 0 °C and was allowed to warm to room temperature. After 6 h, the suspension was diluted with 5 mL of ether; 1 drop of water, 1 drop of 15% aqueous NaOH, and 3 drops of water were added in succession. Sodium sulfate was added, and the mixture was stirred for 2 h. The solids were removed by suction filtration and were washed several times with ether. The filtrate was concentrated to give 24.1 mg (87%) of **45** as a white crystalline solid, which was judged to be pure by ^1H NMR spectroscopy: IR 3625, 2785, 1460, 1445, 1075, 1050 cm^{-1}; ^1H NMR (250 MHz) 0.88 (s, 3), 0.97 (d, 6, J = 6.6), 1.28 (d, 2, J = 4.8), 1.28 (m, 1), 1.50 (m, 3), 1.73 (m, 3), 1.92 (dd, 1, J = 5.7, 12.6), 2.25 (m, 1), 2.26 (s, 3), 2.44 (dd, 1, J = 6.0, 9.1), 2.52 (d, 1, J = 5.2), 2.63 (d, 1, J = 9.0), 4.09 (dd, 1, J = 5.7, 9.6); ^{13}C NMR (63 MHz) 15.7, 25.1, 25.9, 26.2, 30.3, 36.6, 38.7, 40.7, 44.4, 48.3, 55.1, 62.0, 65.0, 71.2, 77.9; mass spectrum, 237 (5.57), 222 (1.31), 204 (0.04), 194 (5.81), 180 (3.46), 164 (2.25), 150 (2.51), 136 (9.96), 122 (0.82), 108 (1.94), 94 (1.92), 86 (4.28), 70 (3.85). An analytical sample (mp 86–87.5 °C) was prepared by recrystallization from spectrophotometric grade pentane. Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.93; H, 11.50; N, 5.93.

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Registry No. (±)-**1**, 30646-45-8; (±)-**8**, 97973-51-8; (±)-**9**, 97973-52-9; (±)-**10**, 97973-53-0; (±)-**11**, 97973-54-1; **12**, 97973-55-2; (4*RS*,7*RS*)-**13**, 97973-56-3; (4*RS*,7*SR*)-**13**, 97973-57-4; (4*RS*,7*RS*)-**14**, 97973-58-5; (4*RS*,7*SR*)-**14**, 97973-59-6; (±)-**15**, 97973-60-9; (±)-**16**, 97973-61-0; (±)-**18**, 89685-96-1; (±)-**19**, 97973-62-1; (±)-**20**, 97973-63-2; (±)-**21**, 97973-64-3; (±)-**23**, 97973-65-4; (±)-**24**, 97973-66-5; (±)-**26**, 97973-67-6; (±)-**29a**, 97973-68-7; (±)-**29b**, 98048-28-3; (±)-**30**, 97973-69-8; (±)-**31**, 97973-70-1; (±)-**32**, 97973-71-2; (±)-**33**, 97973-72-3; (±)-**34a**, 97973-73-4; (±)-**34b**, 98048-29-4; (±)-(*E*)-**38**, 97973-74-5; (±)-(*Z*)-**38**, 97973-75-6; (±)-**40** (isomer 1), 98087-64-0; (±)-**40** (isomer 2), 98168-17-3; (±)-**41** (isomer 1), 97973-76-7; (±)-**41** (isomer 2), 98048-30-7; (±)-**44**, 97973-77-8; (±)-**45**, 97973-78-9; 4-bromo-1-butene, 5162-44-7; *tert*-butyl acetoacetate, 1694-31-1; ethyl bromoacetate, 105-36-2.

Intramolecular Olefinic Aldehyde Prins Reactions for the Construction of Five-Membered Rings[1]

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Four catalysts ($Me_2AlCl \simeq SnCl_4 > EtAlCl_2 > Et_2AlCl$) for the cyclization of olefinic aldehydes by an internal Prins mechanism have been compared by using systems that afford five-membered rings by type I and type II ene processes. Stannic chloride and Me_2AlCl are clearly superior to the ethyl aluminum halides. Careful control of reaction conditions is required with Me_2AlCl in order to avoid byproducts that arise from competing ionic pathways. Chlorohydrin formation cannot be avoided with certain cyclopentane closures. These methods have been applied in the synthesis of a tricyclic trichothecane model in which the meta-fused five-membered C ring is generated by a net ene process (**4** → **5**). In this instance $SnCl_4$ effects a predominantly stepwise ionic cyclization. $TiCl_4$ is the best reagent for this transformation, affording essentially pure chloro alcohol **34**. Subsequent dehydrohalogenation completes the synthesis of **5** (86% overall yield from **4**). $TiCl_4$ has also been found to be a superior reagent for effecting cyclopentane closures in model systems; chlorohydrins are either isolated as such or deemed the likely intermediates for the resulting cyclopentenyl products. A means for controlling olefin regiochemistry in lactone eliminations (**32** → **31** or **33**, **24** → **26** or **27**) has been developed.

Meta-fused methylenecyclopentanol units are quite common in natural products. Homoallylic alcohols can generally be viewed as cyclization products of olefinic aldehydes; however, until Snider's work on R_xAlCl_{3-x}-"catalyzed" cyclizations[2] of olefinic carbonyl compounds, only a single example of five-membered ring formation (**1** → **2** + **3**) was recorded,[3] and to date only a single example of the formation of a meta-fused carbocycle by this means

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