reagent of 5-[(trimethylsilyl)oxy]pentyl chloride to the alcohol **35** (2.1 g, yield 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00–2.20 (4 H, m, 8-CH_2 and 11-CH_2), 4.562 (1 H, s, OCHO), 5.34–5.45 (2 H, m, olefinic protons); MS, m/z 298 (M^+), 280, 257, 215, 196.

(*R*)-17-Methyl-1-[(tetrahydropyran-2-yl)oxy]-4(*Z*)-tricosene (36). The THP ether alcohol **33** (1 g) was tosylated and reacted with the Grignard reagent of the bromide **12** (9 g) in the usual manner to give the THP ether **36** after SiO_2 chromatography (1.29 g, yield 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.830 (3 H, d, J = 6.3 Hz, RCH_3), 0.877 (3 H, t, J = 6.6 Hz, 17-CH_3), 4.573 (1 H, s, OCHO), 5.30–5.45 (2 H, m, olefinic protons); MS (70 eV), m/z (relative intensity) 334 (M^+ – 102, 1.9), 124 (2.2), 111 (3.3), 97 (4.8), 85 (100).

(*S*)-17-Methyl-1-[(tetrahydropyran-2-yl)oxy]-4(*Z*)-tricosene (38). The THP ether alcohol **35** (1 g) was tosylated and coupled with the Grignard reagent prepared from the bromide **17** (6 equiv) with Li_2CuCl_4 to give the THP ether **35** after column chromatography (1.24 g, yield 84%): ^{1}H NMR, MS identical with the enantiomer compound **36**.

(*R*)-(−)-17-Methyl-4(*Z*)-tricosen-1-ol (39). The THP ether **36** (2.2 g) was stirred at room temperature for 2 h with MeOH (30 mL) and *p*-toluenesulfonic acid (0.2 g). The usual workup and column chromatography gave the alcohol **39** (1.76 g, nearby quantitative yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.832 (3 H, d, J = 6.3 Hz, 17-CH_3), 0.879 (3 H, t, J = 6.7 Hz, RCH_3), 1.632 (1 H, quintuplet, J = 6.7 Hz, 2-CH_2), 2.031 (2 H, q, J = 6.4 Hz, 6-CH_2), 2.125 (2 H, q, J = 6.5 Hz, 3-CH_2), 3.661 (2 H, t, J = 6.6 Hz, CH_2OH), 5.34–5.45 (2 H, m, olefinic protons); MS (70 eV), m/z (relative intensity) 352 (M^+, 10.8), 334 (17.0), 264 (11.4), 137 (22.4), 124 (34.6), 110 (35.4), 96 (58.0), 82 (93.8), 71 (66.5), 68 (83.8), 57 (100), 55 (86.8), 43 (98.1); $[\alpha]^{20}_D$ −0.2° (*c* 5.58, $CHCl_3$).

(*S*)-(+)-17-Methyl-4(*Z*)-tricosen-1-ol (40) was obtained as described for its enantiomer **39**: ^{1}H NMR and MS identical with the enantiomer compound **39**; $[\alpha]^{20}_D$ +0.2° (*c* 5.99, $CHCl_3$).

(22*S*)-Methyl 22-Methyl-5(*Z*),9(*Z*)-octacosadienoate (41). The alcohol **40** (800 mg) was stirred with pyridinium dichromate (3 g) in CH_2Cl_2 (25 mL) for 8 h. Filtration through Florisil and flash column chromatography gave the aldehyde (760 mg), which was dissolved in a small amount of THF and added to a solution of the Wittig dianionic salt, prepared by addition of (4-carboxybutyl)triphenylphosphine bromide (3 g) in Me_2SO to potassium hydride (550 mg) in Me_2SO, under argon with subsequent stirring for 1 h. After 4 h at room temperature, the mixture was hydrolyzed with ice–water, acidified with 30% H_3PO_4, and extracted with hexane. Column chromatography gave the acid (276 mg, yield 35%), which was converted to the methyl ester **41** with diazomethane. The cis selectivity (>95%) was verified by reverse-phase HPLC using $AgNO_3$ (50 mM) in MeOH–H_2O (95:5, v/v) as solvent: IR (film) 3007 (CH=CH), 1740 (C=O), 721 (CH=CH, cis); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.830 (3 H, d, J = 6.4 Hz, 22-CH_3), 0.879 (3 H, t, J = 6.8 Hz, CH_3), 1.255 (30 H, s, aliphatic CH_2), 1.688 (2 H, quintuplet, J = 7.2 Hz, 3-CH_2), 1.98–2.50 (8 H, m, 4-, 7-, 8-, 11-CH_2), 2.313 (2 H, t, J = 7.4 Hz, 2-CH_2), 3.665 (3 H, s, OCH_3), 5.34–5.45 (4 H, br m, olefinic protons); MS (70 eV), m/z (relative intensity) 448 (M^+, 10.8), 416 (4.1), 306 (4.3), 182 (8.6), 168 (7.6), 164 (6.7), 150 (22.2), 141 (31.1), 136 (17.8), 125 (10.8), 123 (17.7), 109 (40.7), 97 (38.9), 81 (100), 67 (70.8), 57 (97.2); $[\alpha]^{20}_D$ +0.18° (*c* 11.9, $CHCl_3$).

(22*R*)-Methyl 22-methyl-5(*Z*),9(*Z*)-octacosadienoate (42) was obtained by following the same procedure as for **41**: ^{1}H NMR and MS of **42** were identical with those of **41**; $[\alpha]^{20}_D$ −0.17° (*c* 31.7, $CHCl_3$). This material was also identical with a sample isolated from *A. fistularis*.

Acknowledgment. Financial support was provided by the National Institutes of Health (Grants No. GM 06840 and GM 28352) and the National Science Foundation (Grant No. DMB 8606249). We thank Professor William Fenical and the Hopkins Marine Station of Stanford University for provision of facilities, Professor Robert Simoni of the Stanford Biology Department for access to his scintillation counter, and Dr. Ivan T. Stoilov for assistance and helpful comments.

A Route for the Construction of the Taxane BC Substructure

Charles S. Swindell,* Bomi P. Patel, and S. Jane deSolms[1]

Department of Chemistry, Bryn Mawr College, Bryn Mawr, Pennsylvania 19010

James P. Springer[2]

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Received October 14, 1986

A stereospecific synthesis of taxane BC intermediate **6** from photoproduct **17** is described. Vinylogous imides **12–14** were prepared in four steps from cyclohexanone cyanohydrin and dimedone. Their irradiation led to respective photoproducts **15–21**. Unequivocal identification of new photoproduct structural types exemplified by **18** and **20** was made through their X-ray crystallographic analyses. Photoproduct **17** then provided **41**, which underwent fragmentation to deliver **42**. Hydrolysis of **42** and subsequent formylation led to **43**, which then furnished **6**. An alternative sequence provided epimer **30** from photoproduct **15**. The stereochemistries and thermodynamic stereochemical preferences for the ring fusions in various intermediates as well as the **6**/**30** epimeric pair were determined through a combination of NOE difference spectroscopy and chemical interconversions. The preparation of **6** models a potentially general approach to taxane BC ring construction.

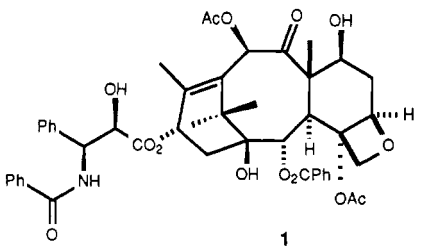
Possessing an unusual highly oxygenated and stereochemically rich diterpenoid skeleton replete with bridgehead olefin in the A ring, medium B ring, and rare 3-oxygenated oxetane fused to the C ring, taxol[3] (**1**), is recognized currently as a challenging total synthesis target of some significance. Its substantial antileukemic and antitumor activities have led to the clinical testing of taxol as an anticancer chemotherapeutic agent both in this country and in Europe. The demonstration beginning in

(1) Present address: Merck Sharp & Dohme Research Laboratories, West Point, PA 19486.

(2) Author to whom inquiries regarding the X-ray crystallographic analyses should be directed.

(3) Wani, M. C.; H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

0022-3263/87/1952-2346$01.50/0



1

1979 that taxol's antimitotic activity is expressed through its unique induction of tubulin polymerization and by the depolymerization protection that it affords tubulin-derived cytoskeletal structures[4] has continued to heighten interest in taxol on several fronts. Indeed, recent success in delineating the structural features of taxol required for biological activity[5] challenges total synthesis efforts to provide both material of proven activity and new structural analogues for further biological testing.

Our own program of taxane diterpene[6] synthesis[7] relies upon the dual strategies to the carbon skeleton (**2**, **3**) outlined in Scheme I. Given that these strategies rely on BC ring structures like **6** as pivotal intermediates, we first directed our attention to the design and implementation of their construction in a flexible and reliable way. Herein we describe in detail our work[8] toward this end which has led to a useful synthesis of enone **6**, a route which has proven sufficiently general to afford a tricyclic ABC taxane model.[9]

Preparation of Photoproducts. In putting the transformation of **8** to **6** into practice, we decided to explore nitrogen-tethered systems since the intramolecular [2 + 2] photoaddition of vinylogous imides[10] and in particular of vinylogous imide **12**[11] was already known to succeed. Vinylogous imides **12–14** were investigated to assess the role of the *N*-acyl substituent in the required fragmentation chemistry. Vinylogous amide **11**[11] was prepared from dimedone and 1-(aminomethyl)cyclohexene, the latter available as described earlier,[11] or better from the lithium aluminum hydride reduction of commercially available cyclohexanone cyanohydrin and subsequent thionyl chloride dehydration of the hydroxy amine hydrochloride.[12] From commercially available materials, the overall yield of **19** was 85%. The general preparation of the desired imides was problematic at first. Although Schell[4] reported the acetylation of **11** with acetyl chloride and pyridine, we found this method to be fraught with O, C, and polyacylation difficulties. Eventually, we discovered that N-acylation with relatively hydrolytically insensitive acylating agents was best accomplished under phase transfer conditions. This technique delivered **12**, **14**, and several related unreported imides cleanly and in good yields (Scheme II). The formation of **13** could be efficiently carried out by the direct interaction of **11** and acetic formic anhydride[13] in tetrahydrofuran.

Photolysis of **12**, the system investigated previously by Schell,[11] indeed produced known photoproduct **15**, but in addition gave lesser amounts of **18** and **20**, whose structures were proven by X-ray crystallographic analyses.[14] Likewise, photolysis of **13** proceeded in the same manner. Vinylogous imide **14** delivered major photoproduct **17** and gave minor photoproducts of the sort described above, but their isolation was not carried out in this case.

First Fragmentation Route. Schell's report[11] of the base-induced conversion of **15** into **31** prompted us to proceed along these lines in unraveling **15** to enone **6**. In particular, we hoped to make use of the ring-fusion stereochemistry of **35** in delivering appropriate taxane BC trans ring-fusion stereochemistry. However in our hands, **15** reacted with potassium *tert*-butoxide under Schell's conditions or more efficiently with sodium methoxide to provide a substance (**22**) in which the methine vinylogously α to the cyclohexenone carbonyl was epimeric to that in the previously reported structure. Since it seemed possible that the bridgehead methine could be epimerized at the bicyclo[6.4.0] stage, we involved **22** in the transformations summarized in Scheme III While treatment of enone **22**

(4) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature (London)* **1979**, *277*, 665. Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83.

(5) Parness, J.; Kingston, D. G. I.; Powell, R. G.; Harracksingh, C.; Horwitz, S. B. *Biochem. Biophys. Res. Commun.* **1982**, *105*, 1082. Mellado, W.; Magri, N. F.; Kingston, D. G. I.; Garcia-Arenas, R.; Orr, G. A.; Horwitz, S. B. *Ibid.* **1984**, *124*, 329. Lataste, H.; Senilh, V.; Wright, M.; Guénard, D.; Potier, P. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 4090. Senilh, V.; Guéritte, F.; Guénard, D.; Colin, M.; Potier, P. *C. R. Acad. Sci., Ser. 2* **1984**, *299*, 1039. Horwitz, S. B.; Lothstein, L.; Manfredi, J. J.; Mellado, W.; Parness, J.; Roy, S. N.; Schiff, P. B.; Sorbara, L.; Zeheb, R. *Ann. N. Y. Acad. Sci.* **1986**, *466*, 733.

(6) Lythgoe, B. *Alkaloids* **1968**, *10*, 597. Nakanishi, K.; et al. *Natural Products Chemistry*; Kodansha-Academic: Tokyo, 1974; Vol. I, p 281. Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(7) Taxane carbon skeleton: (a) Kato, T.; Takayanagi, H.; Suzuki, T.; Uyehara, T. *Tetrahedron Lett.* **1978**, 1201. Kende, A. S.; Benechie, M.; Curran, D. P.; Fludzinski, P.; Swenson, W.; Clardy, J. *Ibid.* **1979**, 4513. Kitigawa, I.; Shibuya, H.; Fujioka, H.; Kejiwara, A.; Tsujii, S.; Yamamoto, Y.; Takagi, A. *Chem. Lett.* **1980**, 1001. Inouye, Y.; Fukaya, C.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1117. Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886. Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190. Sakan, K.; Craven B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732. Shea, K. J.; Davis, P. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 419. Brown, P. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, *253*. Ohtsuka, Y.; Oishi, T. *Heterocycles* **1984**, *21*, 371. Clark, G. R.; Lin, J.; Nikaido, M. *Tetrahedron Lett.* **1984**, *25*, 2645. Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731. Andriamialisoa, R. Z.; Fetizon, M.; Hanna, I.; Pascard, C.; Prange, T. *Tetrahedron* **1984**, *40*, 4285. Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1984**, *25*, 4605. Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada, Y. *Ibid.* **1984**, *25*, 5389. Jackson, C. B.; Pattenden, G. *Ibid.* **1985**, *26*, 3393. Begley, M. J.; Jackson, C. B.; Pattenden, G. *Ibid.* **1985**, *26*, 3397. Kojima, T.; Inouye, Y.; Kakisawa, H. *Chem. Lett.* **1985**, 323. Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *Tetrahedron Lett.* **1985**, *26*, 3665. Fetizon, M.; Hanna, I.; Zeghdoudi, R. *Synth. Commun.* **1986**, *16*, 1. Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 203. Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. Trost, B. M.; Hiemstra, H. *Tetrahedron* **1986**, *42*, 3323. Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953. Cervantes, H.; Do Khac, D.; Fetizon, M.; Guir, F.; Beloeil, J.-C.; Lallemand, J.-Y.; Prange, T. *Tetrahedron* **1986**, *42*, 3491. Brown, P. A.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1303. Kaczmarek, R.; Blechert, S. *Tetrahedron Lett.* **1986**, *27*, 2845. Winkler, J. D.; Hey, J. P.; Williard, P. G. *J. Am. Chem. Soc.* **1986**, *108*, 6424. Winkler, J. D.; Hey, J. P.; Darling, S. D. *Tetrahedron Lett.* **1986**, *27*, 5959. (b) Swindell, C. S.; deSolms, S. J. *Tetrahedron Lett.* **1984**, *25*, 3801. (c) Neh, H.; Blechert, S.; Schnick, W.; Jansen, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 905. C-ring features: Berkowitz, W. F.; Amarasekara, A. S. *Tetrhedron Lett.* **1985**, *26*, 3663. Swindell, C. S.; Britcher, S. F. *J. Org. Chem.* **1986**, *51*, 793. A-ring side chain: Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.

(8) A portion of this work has been previously communicated. See ref 7b and: Swindell, C. S.; deSolms, S. J.; Springer, J. P. *Tetrahedron Lett.* **1984**, *25*, 3797.

(9) Swindell, C. S.; Patel, B. P., manuscript in preparation.

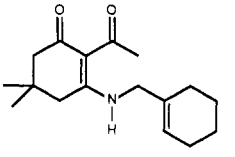
(10) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40*, 2702.

(11) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 1380.

(12) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914. Gudkova, A. S.; Utemiyazov, K.; Zavgorodnii, S. G.; Reutov, O. A. *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 1674.

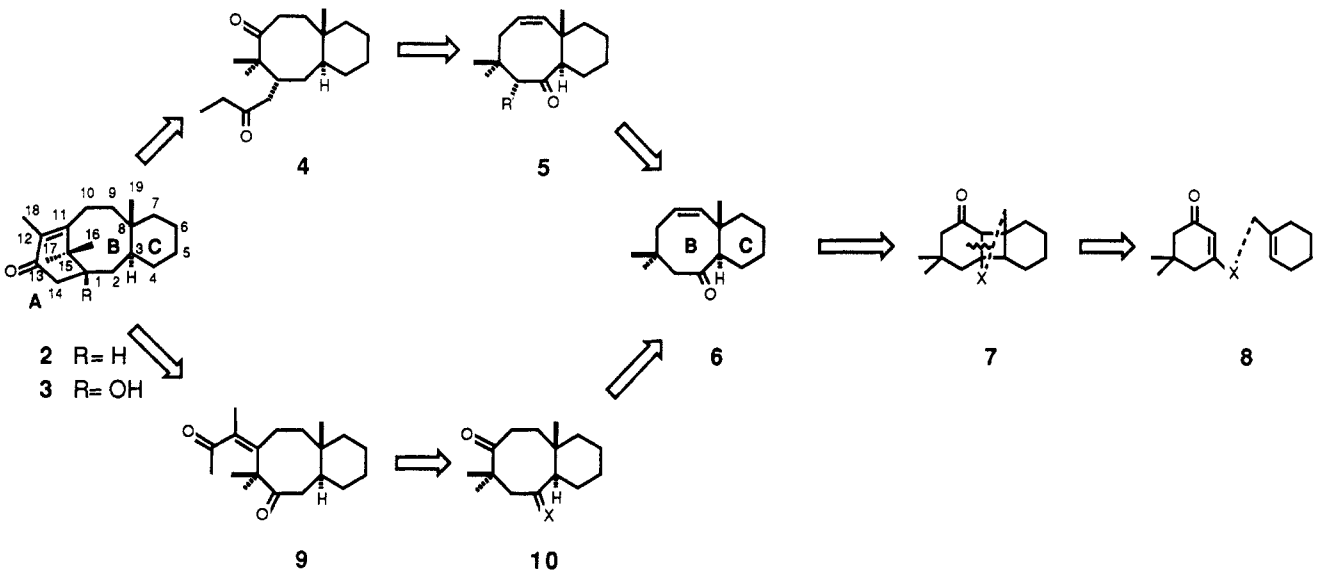
(13) Krimen, L. I. *Org. Synth.* **1970**, *50*, 1.

(14) Although Schell (ref 11) had noted the formation of i in the photolysis of **20**, we failed to detect it when scrupulously pure **20** was employed. We suggest that i might have arisen from the acetylation of **19** and not in the photochemical step.

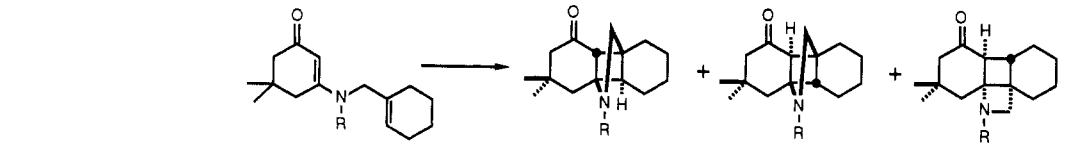


i

Scheme I



Scheme II



R = H
R = $COCH_3$
R = CHO
R = $CO_2CH_2CCl_3$

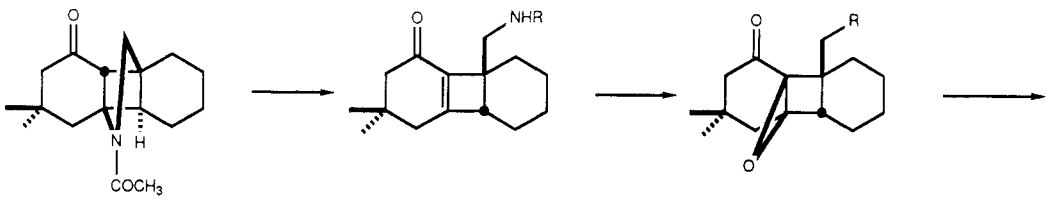
11
12
13
14

15
16
17

18
19

20
21

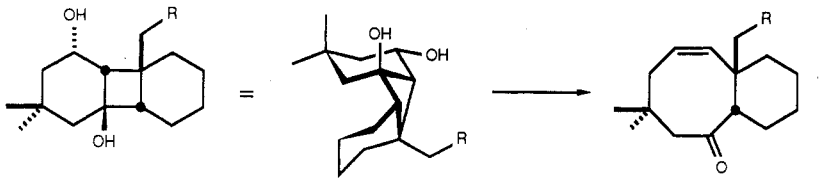
Scheme III



15

22 R = $COCH_3$
23 R = CHO

24 R = $NHCOCH_3$
25 R = NHCHO
26 R = -NC



27 R = $NHCOCH_3$
28 R = H

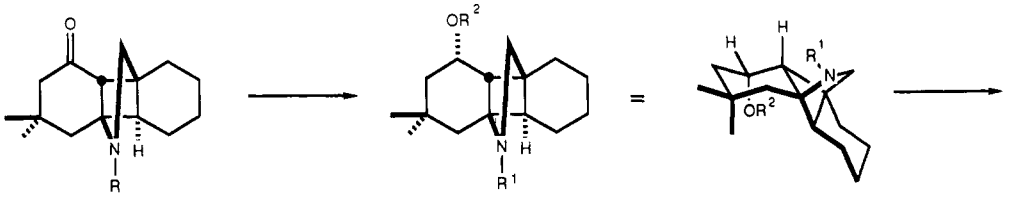
29 R = $NHCOCH_3$
30 R = H

with simple oxygen and sulfur nucleophiles under both acid- and base-catalyzed conditions led to no addition to the strained enone carbon–carbon double bond, *tert*-butyl hydroperoxide/Triton B[15] and **22** successfully gave **24**. Dissolving metal reduction[15,16] of **24** led to **27** in 17% yield. Diol **27** now had stereoelectronic features sufficient for fragmentation which could be induced directly through treatment with methanesulfonyl chloride/pyridine, thus producing **29**.

(15) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.

(16) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Rizzardo, E. *J. Am. Chem. Soc.* **1973**, *95*, 2748. Still, W. C.; Tsai, M.-Y. *Ibid.* **1980**, *102*, 3654.

Scheme IV



16 R = CHO

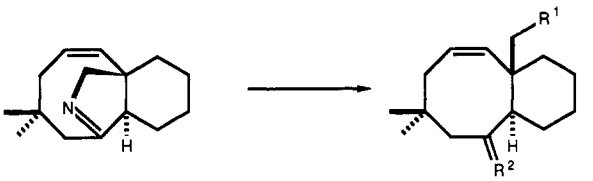
17 R = $CO_2CH_2CCl_3$

38 R^1 = CHO, R^2 = H

39 R^1 = CHO, R^2 = SO_2CH_3

40 R^1 = $CO_2CH_2CCl_3$, R^2 = H

41 R^1 = $CO_2CH_2CCl_3$, R^2 = SO_2CH_3



42

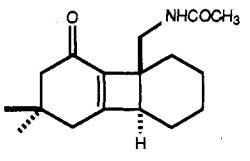
43 R^1 = NHCHO, R^2 = O

44 R^1 = NHCHO, R^2 = -OCH_2CH_2O-

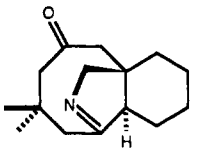
45 R^1 = -NC, R^2 = -OCH_2CH_2O-

6 R^1 = H, R^2 = O

Encouraged by these results, we next attempted to carry out a similar process starting with **16** with the intention of dehydrating the formamide at the appropriate point to an isocyanide which in turn could be cleaved reductively. This was especially appealing since an acetamide cleavage and reductive deamination[17] sequence applied to **29** failed at the latter stage. However, **16** could not be induced by base treatment to deliver corresponding enone **23** but instead either suffered nucleophilic deformylation to yield bridgehead imine ketone **32** (with potassium *tert*-butoxide, sodium methoxide) or underwent no clean reaction (with DBN, DBU). This problem was circumvented by applying to **22** a one-pot exchange of formyl for acetyl, which delivered formyl enone **23**. Its epoxidation as before provided **25**, which upon exposure to methanesulfonyl chloride/pyridine led to isocyanide **26**. Dissolving metal reduction[18] of **26** under carefully defined conditions produced in 35% yield diol **28**, which led through fragmentation of an isolable mesylate to enone **30**. Unfortunately, the cis ring-fusion stereochemistry of **30** proved to be the thermodynamic preference of this bicyclic system.

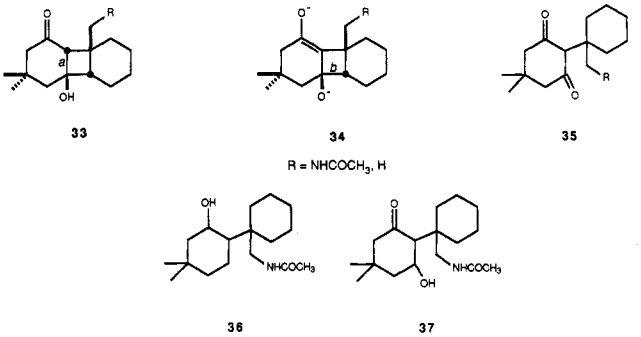


31



32

It is worth noting that the inefficiency of the dissolving metal reduction of both **24** and **26** appears not to be due to retro-aldolization involving cleavage of bond a at the stage of intermediate **33**. Indeed, similar systems are known to undergo retro-aldol reaction surprisingly slowly.[7c] Rather it appears that earlier intermediate **34** fragments through cleavage of bond b ultimately leading to **35** and further reduction products. For example, alcohol **36** and ketol **37** were isolated in experiments on acetamide system **24**, while diketone **35** (R = H) was isolated as a byproduct of the reduction of **26**.[19]



33 **34** **35**

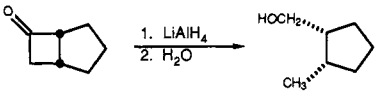
R = $NHCOCH_3$, H

36 **37**

Second Fragmentation Route. As it was clear from the above that the ring-fusion stereochemistry in less stable trans enone **6** would need to be derived directly from the corresponding ring fusion in photoproducts like **15–17**, we turned our attention to an alternative fragmentation pathway which would avoid epimerization of the site destined to become the bridgehead methine in **6**. Our second fragmentation route was suggested by the initially disappointing observation that nucleophilic deformylation of **16** led to **32**. Reduction of **16** with L-Selectride produced

(17) Dolduras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *100*, 341.
(18) Ugi, I.; Bodesheim, F. *Chem. Ber.* **1961**, *94*, 1157.

(19) Precedent for the formation of **35–37** can be found in the conversion of ii to iii below (Paquette, L. A.; Youssef, A. A.; Wise, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 5246).



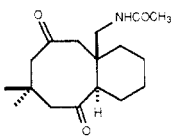
ii *iii*

axial alcohol **38** (Scheme IV). Derived mesylate **39**, upon treatment with methyllithium to induce fragmentation by amide cleavage,[20] produced **42** in 48% yield.[21] A better route to **42** employed the Zn-triggered[22] fragmentation under very mild conditions of **41**, the latter available from **17** as for the preparation of **39**. These conditions also led efficiently to **32** from **17**.[23] Evidently **39** and **41** are not restricted to the illustrated conformation and have access to one more stereoelectronically appropriate for their fragmentation to **42**.

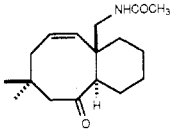
Cyclooctenone **6** could then be prepared from **42** through a sequence that began with hydrolysis and subsequent formylation of the liberated primary amine, leading to **43**. Ketalization gave **44** and dehydration then produced isocyanide **45**. Its dissolving metal reduction and deketalization finally gave **6**, which was clearly epimeric with **30**.[24] In summary, **6** could be prepared from **17** in eight steps in an overall yield of 21% with chromatography necessary only at the stages of **43** and **6**. More importantly, this chemistry has served in part as a model of a more general fragmentation route to the BC ring system of the taxanes.

Ring-Fusion Stereochemistries. As this work progressed, it became clear that the issue of ring-fusion stereochemistry of the several intermediates encountered as well as the **6**/**30** enone pair was a somewhat confused one. The intended translation of this ring fusion into the taxane BC ring juncture made it imperative that its stereochemistry and the elements involved in its control be understood at each step. Consequently, we employed both chemical and NMR spectroscopic means to establish the detailed structures of certain key substances.

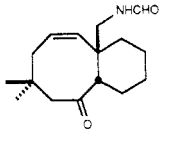
Diketone **46** which Schell[11] had prepared by hydroxide treatment of **15**, also could be obtained under milder conditions from **32** by hydrolysis in aqueous acid and capture of the primary amine with acetic anhydride. Its methine proton,[25] although obscured by a signal due to an α-keto methylene proton, could be revealed as a dd, J = 3 and 12 Hz, upon collapse of the obscurring signal by irradiating the geminal partner. Furthermore, irradiation of either the methine signal or any of the signals due to protons on the angular substituent led to no NOE[26] of the nonirradiated set. These experiments establish that the methine proton is axial and trans to the acetamidomethyl group and, from the conditions under which it can be formed from **26** and its formation from **50**, that the more stable epimer is the one depicted.



46



47



48

(20) Sawyer, J. S.; Narayanan, B. A. *Synth. Commun.* **1983**, *13*, 135.

(21) The corresponding acetamide axial mesylate derived from **15** returned its alcohol precursor upon treatment with methyllithium.

(22) Just, G.; Grozinger, K. *Synthesis* **1976**, 457.

(23) We attempted to involve benzyl and methyl urethanes analogous to photoproducts **15**–**17** in this fragmentation chemistry. While boron tribromide produced **32** from both in low yield, trimethylsilyl iodide isomerized these benzyl and methyl urethane photoproducts to the corresponding mixtures of epimeric enones analogous to **22**, **23**, and **31**.

(24) When **43** was dehydrated directly to the corresponding isocyanide and the latter subsequently subjected to n-Bu_3SnH/AIBN treatment (Barton, D. H. R.; Bringman, G.; Lamotte, G.; Motherwell, W. B.; Motherwell, R. S. H.; Porter, A. E. A. *J. Chem. Soc. Perkin Trans 1* **1980**, 2657), the isocyanide was indeed cleaved but the product was shown to have incorporated the elements of n-Bu_3SnCN. Likewise, reductive deamination (ref 17) of the amine obtained by hydrolysis of **42** failed.

(25) Methine proton signals were unambiguously located through a combination of 1D and 2D DEPT experiments.

(26) Measurements were made through NOE difference spectroscopy.

Acetyl enone **22** was available from **15** but also from **18** through its *tert*-butoxide treatment. Irradiation of its methine proton signal produced an NOE of one of the nonequivalent amidomethylene proton signals. Formyl enone **23**, available from acetyl enone **22**, was also produced from the *tert*-butoxide treatment of **19** in contrast to our experience with stereoisomer **16**. Cyclooctenone **30** was constructed from **23** and was the more stable of the **6**/**30** pair. Recalling that acetyl cyclooctenone **29** was prepared from **22** and was also the more stable epimer, these results lead to the assignment of the stereochemistry of **22**, **23**, **29** and **30**.[27]

Acetyl cyclooctenone **47** was prepared from **42** by mild aqueous acid hydrolysis followed by acetic anhydride treatment and was convertible to **29**. Formyl cyclooctenone **43**, also prepared from **42** through an analogous sequence, was epimerized in basic solution to yield **48**. Irradiation of the methine proton signal of **48** led to an NOE of the formyl proton signal while a similar experiment on **43** led to no NOE's more significant than those of cyclohexane ring proton signals. Recalling that cyclooctenone **6** was prepared from **43** and was epimerically related to **30**, these results corroborate the conclusions in the preceeding paragraph and establish the stereostructures of **6**, **43**, **47**, and **48**.[28]

Experimental Section

Reactions requiring anhydrous conditions and inert atmospheres were performed in flame-dried glassware by using anhydrous solvents under argon or nitrogen as required. Photochemical reactions were performed in an immersion reactor with a Hanovia 450-W Hg arc lamp. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Preparative high-pressure liquid chromatography was carried out on a Waters Prep 500A chromatograph. ^1H nuclear magnetic resonance spectra were determined in deuteriated chloroform, unless noted otherwise, on a Nicolet NT-360 (360 MHz), IBM AF-270 (270 MHz), or Varian EM-390 (90 MHz) spectrometer using tetramethylsilane (δ = 0) as internal standard. Coupling constants are given in hertz. ^{13}C nuclear magnetic resonance spectra were recorded in deuteriated chloroform on an IBM AF-270 (67 MHz) or Varian CFT-20 (20 MHz) spectrometer using tetramethylsilane (δ = 0) as internal standard. Infrared spectra were recorded on Perkin-Elmer 283 or 287 spectrometers. Mass spectra were recorded on a LKB-9000S, Finnigan MAT 212, MM 7035, or Hewlett-Packard 5890A/5970 GC/MS system. Ultraviolet spectra were recorded on a Beckman ACTA MVI or Perkin-Elmer Hitachi 200 spectrometer. Microanalyses were performed at Merck Sharp & Dohme Research Laboratories, West Point, PA, or at M-H-W Laboratories, Phoenix, AZ.

Acetyl Imide 12.[11] To a vigorously stirred mixture of amide **11**,[11] 50% aqueous sodium hydroxide (2 mL/mmol of **11**), Adogen-464 (1 mL/17 mmol of **11**), and methylene chloride (2 mL/mmol of **11**) at 0 °C was added dropwise 2 equiv of acetic anhydride. Stirring was continued for 10 min, at which time the organic layer was washed with water and brine and dried (sodium sulfate) and the solvent removed. Filtration of a hexane/ethyl acetate solution of the resulting oil through silica gel to remove residual phase-transfer catalyst followed by solvent removal gave **12** in 76% yield.

(2,2,2-Trichloroethoxy)carbonyl Imide 14. Prepared in 77% yield as above from 1.3 mmol of trichloroethyl chloroformate per mmol of **11**, mp 121 °C: ^1H NMR (270 MHz) δ 1.08 (6 H, s, geminal CH_3), 1.6–2.0 (8 H, m, cyclohexene CH_2), 2.26 (2 H, s, α- or vinylogously α-keto CH_2), 2.66 (2 H, s, α- or vinylogously

(27) Since the stereochemistry of acetyl enone **22** was not originally recognized as cis, the stereochemistries of these substances were incorrectly reported in earlier communications (ref 7b, 8).

(28) To reconcile the stereochemistries of these substances with those prepared from **22**, originally presumed to be trans (ref 7b, 8), we postulated earlier that hydrolysis of **42** proceeded with epimerization. We now know this is incorrect. Therefore the initially reported stereochemistries (ref 7b) of these substances are incorrect.

α-keto CH_2), 4.17 (2 H, s, CH_2N), 4.81 (2 H, s, CH_2CCl_3), 5.5-5.7 (1 H, m, $CHCH_2$), 5.85 (1 H, s, CHCO); ^{13}C NMR δ 207.48, 171.41, 158.42, 134.18, 97.81, 33.64 (quaternaries), 126.17, 123.34 (CH), 75.61, 55.61, 49.23, 41.19, 28.28, 24.61, 23.41, 21.26 (CH_2), 27.20 (CH_3, double signal); IR (CCl_4) 1770, 1710, 1590 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}NO_3Cl_3$: C, 52.89; H, 5.92; N, 3.45. Found: C, 53.07; H, 5.92; N, 3.64.

Formyl Imide 13. To a solution of 50 g (192 mmol) of **11**[11] in 300 mL of tetrahydrofuran at room temperature, there was added in a slow stream distilled aceticformic anhydride[13] prepared from 300 g of sodium formate and 267 mL of acetyl chloride. After being stirred for 12 h, the mixture was added to water and extracted with ethyl acetate, the organic layer washed with water and aqueous sodium bicarbonate and dried (sodium sulfate), and solvent removed to provide 47.8 g (84%) of **13**, mp 113–114 °C (cyclohexane): ^1H NMR (90 MHz) δ 1.20 (6 H, s, geminal CH_3), 1.6–2.1 (8 H, m, cyclohexane CH_2), 2.26 (2 H, s, α- or vinylogously α-keto CH_2), 2.55 (2 H, s, α- or vinylogously α-keto CH_2), 4.22 (2 H, s, CH_2N), 5.4–5.6 (1 H, m $CHCH_2$), 5.73 (1 H, s, CHCO), 8.82 (1 H, s, CHO); IR (KBr) 1685, 1640, 1585 cm^{-1}; ^{13}C NMR δ 160.41, 155.89, 131.26, 48.28 (quaternaries), 198.21, 123.78, 112.63 (CH), 50.47, 40.90, 33.54, 26.06, 24.89, 22.35, 22.18 (CH_2); 28.46 (double signal, CH_3); mass spectrum, *m/z* (relative intensity) 261 (M^+, 40), 95 (100); UV (CH_3OH) 281 nm.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.43; H, 8.88; N, 5.47.

Photolysis of Acetyl Imide 12. A nitrogen-purged solution of 10.9 g (40 mmol) of **12** in 1.2 L of cyclohexane was irradiated at room temperature for 4 h, at which time starting material had been consumed. GC/MS analysis of the reaction mixture indicated a 73/11/16 ratio of **15**,[11] **18**, and **20**, respectively. Concentration of the solution led to the precipitation of 6.6 g (61%) of **15**. Chromatography of the mother liquor on silica gel, eluting with hexane/ethyl acetate, gave 763 mg (7%) of **18**, mp 107–109 °C (hexane/cyclohexane): ^1H NMR (360 MHz) δ 1.0–1.9 (9 H, m, cyclohexane CH_2, CH), 1.11 (6 H, s, geminal CH_3), 1.73 (1 H, d, *J* = 14, CH_2), 1.97 (3 H, s, CH_3CO), 2.06 (1 H, $^1/_2$ AB q, *J* = 14, CH_2CO), 2.89 (1 H, s, CHCO), 2.97 (1 H, d, *J* = 7.5, CH_2), 3.25 (1 H, d, *J* = 14, CH_2), 3.66 (1 H, d, *J* = 7.5, CH_2N); ^{13}C NMR δ 209.2, 173.35, 77.09, 48.51, 37.46 (quaternaries), 51.76, 33.85 (CH), 54.05, 53.80, 52.56, 36.21, 25.35, 23.63, 21.88 (CH_2), 29.29, 23.17, 22.06 (CH_3); IR (KBr) 1710, 1660, 1390 cm^{-1}; mass spectrum, *m/z* (relative intensity) 275 (M^+, 15), 190 (100).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.74; H, 9.50; N, 5.44.

From a similar photolysis of 36 g (131 mmol) of **12**, there was isolated through chromatography as above 540 mg (2%) of **20**, mp 119–120 °C (ether): ^1H NMR (360 MHz) δ 0.99 (3 H, s, CH_3), 1.10 (3 H, s, CH_3), 1.0–1.8 (8 H, m, cyclohexane CH_2), 1.86 (1 H, dd, *J* = 1.5, 15, CH_2), 1.88 (3 H, s, CH_3), 2.1–2.2 (1 H, m, CH), 2.19 (1 H, dd, *J* = 2, 13.5, CH_2CO), 2.47 (1 H, d, *J* = 13.5, CH_CO), 2.57 (1 H, d, *J* = 15, CH_2), 2.95 (1 H, d, *J* = 10.5, CH_2CO), 3.78 (1 H, d, J = 9, CH_2N), 4.38 (1 H, d, *J* = 9, CH_2N; ^{13}C NMR δ 212.9, 171.20, 78.11, 56.54, 33.74 (quaternaries), 48.67, 31.48 (CH), 55.76, 53.49, 38.09, 33.45, 26.39, 25.48, 21.42 (CH_2), 47.42, 28.63, 20.56 (CH_3); IR (KBr) 1690, 1640, 1390 cm^{-1}; mass spectrum, *m/z* (relative intensity) 275 (M^+, 30), 190 (100).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.04; H, 9.25; N, 5.37.

Photolysis of Formyl Imide 13. A nitrogen-purged solution of 45 g (171 mmol) of **13** in cyclohexane/benzene was irradiated at room teperature for 6 h, at which time starting material had been consumed. GC/MS analysis of the reaction mixture indicated a 72/11/17 ratio of **16**, **19**, and **21**, respectively. Removal of solvent and HPLC (silica gel, ethyl acetate) of the residue gave 26.83 g (60%) of **16**, mp 136–138 °C (cyclohexane), 4.09 g (9%) of **19**, mp 172–173 °C (cyclohexane), and 6.24 g (14%) of **21**, mp 104–106 °C (pentane/ethyl acetate at room temperature).

16: ^1H NMR (360 MHz) δ 1.13 (3 H, s, CH_3), 1.20 (3 H, s, CH_3), 1.0–1.9 (8 H, m, cyclohexane CH_2), 1.98 (1 H, $^1/_2$ AB q, *J* = 13.5, CH_2CO), 2.02 (1 H, $^1/_2$ AB q, *J* = 13.5, CH_2CO), 2.19 (1 H, $^1/_2$ AB q, *J* = 13.5, CH_2), 2.2–2.3 (1 H m, CH), 2.27 (1 H, $^1/_2$ AB q, *J* = 13.5, CH_2), 2.53 (1 H, s, CHCO), 3.07 (1 H, d, *J* = 10.5, CH_2N), 3.73 (1 H, d, *J* = 10.5 CH_2N), 8.27 (1 H, s, CHO); ^{13}C NMR δ 208.13, 76.81, 47.81, 36.19 (quaternaries), 158.21, 63.28, 33.74 (CH), 54.54, 47.16, 36.96, 24.40, 23.78, 21.11, 20.26 (CH_2), 52.00, 27.93 (CH_3); IR (KBr) 1710, 1640 cm^{-1}; mass spectrum, *m/z* (relative intensity) 261 (M^+, 20), 95 (100).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.66; H, 9.27; N, 5.23.

19: ^1H NMR (360 MHz) δ 1.0–2.1 (9 H, m, cyclohexane CH_2, CH), 1.16 (3 H, s, CH_3), 1.19 (3 H, s, CH_3), 1.90 (1 H, d, *J* = 15, CH_2), 2.15 (1 H, $^1/_2$ AB q, *J* = 16.5, CH_2CO), 2.17 (1 H,d, *J* = 15, CH_2), 2.23 (1 H, $^1/_2$ AB q, *J* = 16.5, CH_2CO), 3.18 (1 H, d, *J* = 9, CH_2N), 3.42 (1 H, d, *J* = 9, CH_2N), 8.42 (1 H, s, CHO); ^{13}C NMR δ 207.92 (CO), 160.20 (CHO), 74.11 (quaternary), 52.88, 52.78, 52.18, 49.45, 49.01, 36.15, 33.94, 33.68, 32.15, 25.14, 22.89, 21.91, 21.82; IR (KBr) 1710, 1640 cm^{-1}; mass spectrum, *m/z* (relative intensity) 261 (M^+, 33), 95 (100).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.69; H, 9.20; N, 5.69.

21: ^1H NMR (360 MHz) δ 0.97 (3 H, s, CH_3), 1.0–1.8 (8 H, m, cyclohexane CH_2), 1.11 (3 H, s, CH_3), 2.03 (1 H, dd, *J* = 2, 16, CH_2), 2.05 (1 H, dt, *J* = 4, 10.5, CH), 2.11 (1 H, d, *J* = 16, CH_2), 2.18 (1 H, d, *J* = 15, CH_2CO), 2.37 (1 H, d, *J* = 15, CH_2CO), 3.07 (1 H, d, *J* = 10.5, CHCO), 3.78 (1 H, d, *J* = 10.5, CH_2N), 4.36 (1 H, d, *J* = 10.5, CH_2N), 8.16 (1 H, s, CHO); ^{13}C NMR δ 210.64, 76.43, 51.02, 33.14 (quaternaries), 158.73, 57.22, 45.98 (CH), 53.20, 52.58, 39.07, 28.45, 26.20, 25.39, 21.31 (CH_2), 32.61, 29.73 (CH_3); IR (KBr) 1690, 1640, 1370 cm^{-1}; mass spectrum, *m/z* (relative intensity) 261 (M^+, 53), 95 (100).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.58; H, 8.93; N, 5.37.

Photoproduct 17. A nitrogen-purged solution of 10 g (24.5 mmol) of **14** in 600 mL of benzene was irradiated at room temperature for 4 h, at which time starting material had been consumed. GC/MS analysis of the reaction mixture indicated a 77/23 ratio of **17** to the minor photoproducts, respectively. Removal of solvent and HPLC (silica gel, hexane/ethyl acetate) gave 7.1 g (71%) of **17**, mp 95 °C: ^1H NMR (270 MHz) δ 1.31 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 1.4–2.0 (8 H, m, cyclohexane CH_2), 2.04 (1 H, $^1/_2$ AB q, *J* = 13.6, CH_2), 2.07 (1 H, $^1/_2$ AB q, *J* = 13.6, CH_2), 2.3–2.4 (1 H, m, CH), 2.20 (1 H, $^1/_2$ AB q, *J* = 13.5, CH_2), 2.23 (1 H, $^1/_2$ AB q, *J* = 13.5, CH_2), 2.41 (1 H, s, CH), 3.17 (1 H, d, *J* = 10.1, CH_2N), 3.73 (1 H, d, *J* = 10.1, CH_2N), 4.79 (2 H, s, CH_2CCl_3); ^{13}C NMR δ 208.99, 156.32, 95.81, 47.60, 38.97, 20.90 (quaternaries), 51.34, 27.89 (CH), 74.05, 54.19, 50.46, 24.25, 23.90, 22.01, 21.19, 20.65 (CH_2), 33.71, 32.64 (CH_3); IR (CCl_4) 1770, 1710 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}NO_3Cl_3$: C, 52.89; H, 5.92; N, 3.45. Found: C, 52.94; H, 5.96; N, 3.33.

Cis Acetyl Enone 22. To a solution of sodium methoxide prepared from 386 mg (16.8 mmol) of sodium and 40 mL of methanol was added 1.2 g (4.2 mmol) of **15**, and the mixture was refluxed under argon for 24 h. After cooling and concentration, the residue was taken up in ethyl acetate, filtered, and chromatographed on silica gel, by eluting with ethyl acetate, to give 1.0 g (86%) of **22**: ^1H NMR (360 MHz) 0.9–1.9 (8 H, m, cyclohexene CH_2), 1.11 (3 H, s, CH_3), 1.13 (3 H, s, CH_3), 2.03 (3 H, s, CH_3CO), 2.04 (1 H, dd, *J* = 3, 7.5, allylic CH_2), 2.18 (1 H, d, *J* = 7.5, allylic CH_2), 2.24 (1 H, $^1/_2$ AB q, *J* = 16.5, CH_2CO), 2.32 (1 H, $^1/_2$ AB q, *J* = 16.5, CH_2CO), 2.71 (1 H, app t, *J* = 4.5, CH), 2.88 (1 H, dd, *J* = 3, 12, CH_2N), 3.82 (1 H, dd, *J* = 7.5, 12, CH_2N), 6.74 (1 H, br d, *J* = 7.5, NH); ^{13}C NMR δ 194.93, 173.50, 170.54, 144.39, 48.8, 36.65 (quaternaries), 47.93 (CH), 51.63, 47.21, 38.39, 26.31, 22.36, 18.37, 17.79 (CH_2), 28.89, 28.73, 23.08 (CH_3); IR ($CHCl_3$) 2035, 1640, 1210, 1190 cm^{-1}; UV (CH_3OH) 245 nm (ε 6830), mass spectrum, *m/z* (relative intensity) 275 (M^+, 90), 216 (100); calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1884.

Acetyl Epoxide 24. To a solution of 275 mg (1 mmol) of **22** of 1 mL of 90% *tert*-butyl hydroperoxide in 10 mL of tetrahydrofuran at room temperature was added dropwise 1 mL of Triton B (40% in methanol) over 0.5 h. After a further 4 h, the reaction mixture was added to cold aqueous sodium bisulfite and extracted with ethyl acetate and the organic layer washed with brine and dried (magnesium sulfate). Removal of solvent and trituration of the residue with hexane gave 130 mg (45%) of solid **24**, mp 109–112 °C: ^1H NMR (360 MHz) δ 1.0–1.8 (8 H, m, cyclohexane CH_2), 1.03 (3 H, s, CH_3), 1.07 (3 H, s, CH_3), 1.65 (1 H, dd, *J* = 2, 13.5, CH_2), 1.79 (1 H, dd, *J* = 2, 15, CH_2CO), 1.95 (1 H, dd, *J* = 7.5, 12, CH), 2.06 (1 H, d, *J* = 15, CH_2), 2.57 (1 H, d, *J* = 13.5, CH_2CO), 3.14 (1 H, dd, *J* = 4, 13.5, CH_2N), 3.35 (1

H, dd, J = 7, 13.5, CH_2N), 5.74 (1 H, br s, NH); IR (KBr) 3280, 3100, 1700, 1650 cm^{-1}; mass spectrum, m/z (relative intensity) 291 (M^+, 3), 219 (100).

Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.34; H, 9.13; N, 4.74.

Dissolving Metal Reduction of 24. To a mixture of 8.58 g (30 mmol) of **24** and 14.2 g (260 mmol) of ammonium chloride in 450 mL of liquid ammonia and 300 mL of tetrahydrofuran at −70 °C was added in portions 1.66 g (240 mmol) of lithium wire over 0.5 h. After being stirred a further 1.5 h at the above temperature, the reaction mixture was allowed to warm to room temperature to evaporate the ammonia and then filtered. The resulting filtrate was evaporated to leave a residue, which upon trituration with ethyl acetate gave 1.3 g (17%) of **27**, mp 243–245 °C: ^1H NMR (360 MHz; Me_2SO-d_6) δ 0.92 (6 H, s, geminal CH_3), 1.0–1.9 (13 H, m, CH_2, CH), 1.83 (3 H, s, CH_3CO), 2.23 (1 H, d, J = 7.5, C*H*CHOH), 2.68 (1 H, d, J = 13.5, CH_2N), 3.37 (1 H, d, J = 13.5, CH_2N), 3.9–4.1 (1 H, m, C*H*OH, when treated with D_2O collapses to app dt, J = 7.5, 12), 4.47 (1 H, s, tertiary OH, exchanged with D_2O), 5.06 (1 H, d, J = 4, secondary OH, exchanged with D_2O), 7.69 (1 H, br d, J = 4.5, NH, exchanged with D_2O); IR (KBr) 3280, 1650, 1550 cm^{-1}; mass spectrum, m/z (relative intensity) 295 (M^+, 0.1), 154 (100).

Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.12; H, 9.89; N, 4.74. Found: C, 69.09; H, 10.35; N, 4.45.

From other similar experiments, there could be isolated in up to 43% yield **36**, mp 155–158 °C: ^1H NMR (360 MHz; Me_2SO-d_6) δ 1.0–1.7 (17 H, m, CH_2, CH), 1.84 (3 H, s, CH_3CO), 3.25 (1 H, dd, J = 6, 15, CH_2N), 3.38 (1 H, dd, J = 7.5, 15, CH_2N), 3.5–3.6 (1 H, m, C*H*OH, when treated with D_2O collapses to app dt, J = 4.5, 10.5), 4.43 (1 H, d, J = 6, OH, exchanged with D_2O), 7.54 (1 H, br t, J = 6, NH, exchange with D_2O); ^{13}C NMR δ 170.88, 38.78, 31.82 (quaternaries), 69.10, 48.57 (CH), 51.09, 43.24, 32.66, 32.32, 30.82, 26.25, 24.94, 21.75, 21.64 (CH_2), 39.44, 23.37, 21.97 (CH_3); IR (KBr) 3350, 1620, 1540 cm^{-1}.

Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.48; H, 11.45; N, 4.99.

Likewise from yet other experiments, there could be isolated in up to 4% yield, **37**, mp 131–133 °C: ^1H NMR (360 MHz; Me_2SO-d_6) δ 0.97 (3 H, s, CH_3), 1.2–1.8 (12 H, m, CH_2), 1.80 (3 H, s, CH_3CO), 1.99 (1 H, dd, J = 2, 12, CH_2CO), 2.41 (1 H, d, J = 12, CH_2CO), 2.63 (1 H, br s, CHCO), 3.44 (2 H, d, CH_2N), 4.45–4.50 (1 H, m, C*H*OH), 4.98 (1 H, d, J = 3, OH, exchanged with D_2O), 7.64 (1 H, br t, J = 6, NH, exchanged with D_2O); IR (KBr) 3230, 3100, 1710, 1635 cm^{-1}; mass spectrum, m/z (relative intensity) 295 (M^+, 4), 154 (100); calcd for $C_{17}H_{29}NO_3$ 295.2147, found 295.2139.

Cis Acetamide Cyclooctenone 29. To a solution of 1.18 g (4 mmol) of **27** in 30 mL of pyridine at 0 °C, there was added dropwise 0.5 mL (6 mmol) of methanesulfonyl chloride. After a further 0.5 h at the same temperature followed by 18 h at room temperature, the reaction mixture was poured onto ice/water and extracted with ethyl acetate and the organic layer washed with aqueous hydrochloric acid and brine and then dried (magnesium sulfate). Removal of solvent and crystallization of the residue from ether gave 587 mg (53%) of **29**, mp 129–131 °C: ^1H NMR (360 MHz) δ 0.97 (3 H, s, CH_3), 1.14 (3 H, s, CH_3), 1.2–2.0 (10 H, m, CH_2), 2.02 (3 H, s, CH_3CO), 2.28 (1 H, app t, J = 12, CHCO), 2.5–2.6 (2 H, m, CH_2CO), 3.11 (1 H, br d, J = 12, CH_2N), 3.74 (1 H, m, CH_2N), 5.46 (1 H, d, neopentyl olefinic H), 5.7–5.9 (2 H, m, olefinic H, NH); ^{13}C NMR δ 214.56, 170.12, 42.33, 35.15 (quaternaries), 135.55, 129.97, 57.70 (CH), 50.14, 44.60, 39.54, 36.12, 25.13, 23.14, 21.53 (CH_2), 30.82, 28.07, 23.48 (CH_3); IR (KBr) 3320, 1700, 1645, 1565 cm^{-1}; mass spectrum, m/z (relative intensity) 277 (M^+, 5), 43 (100).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.29; H, 9.91; N, 5.08.

Imine Ketone 32 from 16. To a solution of sodium methoxide prepared from 193 mg (8.4 mmol) of sodium and 20 mL of methanol was added 550 mg (2.1 mmol) of **16** and the resulting mixture refluxed for 5 h. At this time, the solvent was removed, and the residue was chromatographed on silica gel, eluting with ethyl acetate, to give 371 mg (76%) of **32**, mp 83–86 °C (hexane/cyclohexane): ^1H NMR (360 MHz) δ 0.8–1.9 (8 H, m, cyclohexane CH_2), 1.11 (3 H, s, CH_3), 1.23 (3 H, s, CH_3), 1.83 (1 H, d, J = 12, CH_2CN), 2.12 (1 H, d, J = 10.5, CH_2CO), 2.23 (1 H, d, J = 12, CH_2CO), 2.24 (1 H, d, J = 10.5, CH_2CO), 2.36 (1 H, d, J = 12, CH_2CO), 2.66 (1 H, dd, J = 6, 12, CHCN), 2.77 (1 H, d, J = 12, CH_2CN), 3.46 (1 H, d, J = 15, CH_2N), 3.89 (1 H, d, J = 15, CH_2N); ^{13}C NMR δ 208.71 (CO), 185.96 (CN), 62.67, 60.63, 56.72, 51.60, 51.15, 43.15, 42.27, 33.68, 31.13, 26.44, 25.67, 23.67, 22.23; IR (KBr) 1675, 1610, 1440 cm^{-1}; mass spectrum, m/z (relative intensity) 233 (M^+, 25), 148 (100); calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1779.

Cis Formyl Enone 23. To a solution of 6.022 g (21.8 mmol) of **22** in 25 mL of methylene chloride at 0 °C was added dropwise 2.13 mL (26.3 mmol) of Magic Methyl. The resulting reaction mixture was stirred for 1 h, then warmed to room temperature for 1 h, and subsequently quenched by the addition of 2 mL of water. Evaporation of both methylene chloride and water was followed by the addition of 50 mL of dimethoxyethane and 50 mL of aqueous 2 N hydrochloric acid. This mixture was then stirred at room temperature for 1 h and evaporated and then the residue further dried by the azeotropic distillation of benzene/ethanol and then benzene. The resulting amine hydrochloride was taken up in 25 mL of pyridine and cooled to 0 °C and then a solution of approximately 50 mmol of aceticformic anhydride[13] in ether added dropwise. This was allowed to warm slowly to room temperature over 4 h, poured into aqueous 1 N hydrochloric acid, and extracted with ethyl acetate and the organic layer dried (sodium sulfate) and evaporated to provide 4.6 g (81%) of **23** as an oil: ^1H NMR (360 MHz) δ 1.11 (3 H, s, CH_3), 1.13 (3 H, s, CH_3), 1.2–1.9 (8 H, m, cyclohexane CH_2), 2.17 (1 H, $^1/_2$ AB q, J = 18, allylic CH_2), 2.23 (1 H, $^1/_2$ AB q, J = 18, allylic CH_2), 2.24 (1 H, $^1/_2$ AB q, J = 16.5, CH_2CO), 2.30 (1 H, $^1/_2$ AB q, J = 16.5, CH_2CO), 2.73 (1 H, app t, J = 4.5, CH), 2.93 (1 H, dd, J = 13.5, CH_2N), 3.89 (1 H, dd, J = 9, 13.5, CH_2N), 6.77 (1 H, br s, NH), 8.23 (1 H, s, CHO); IR (neat) 3320, 1735, 1660 cm^{-1}; UV (CH_3OH) 248 nm (ϵ 6184); mass spectrum, m/z (relative intensity) 261 (M^+, 42), 160 (100); calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1725.

Formyl Epoxide 25. To a solution of 870 mg (3.3 mmol) of **23** and 3.3 mL of *tert*-butyl hydroperoxide (90% in water) in 30 mL of tetrahydrofuran at 0 °C was added dropwise 3.3 mL of Triton B (40% in methanol). The reaction mixture was then stirred at room temperature for 4 h, added to ice/water, concentrated, and then extracted with ethyl acetate. The organic layer was washed with water, aqueous sodium bisulfite, water, and brine then dried (magnesium sulfate). Removal of solvent gave 540 mg (56%) of **25**, mp 114–117 °C (cyclohexane): ^1H NMR (360 MHz) δ 1.13 (3 H, s, CH_3), 1.18 (3 H, s, CH_3), 1.2–1.9 (8 H, m, cyclohexane CH_2), 1.65 (1 H, dd, J = 2, 13.5, CH_2CO), 1.90 (1 H, dd, J = 2, 15, CH_2), 2.06 (1 H, dd, J = 7.5, 10.5, CH), 2.16 (1 H, d, J = 15, CH_2), 2.66 (1 H, d, J = 13.5, CH_2CO), 3.29 (1 H, dd, J = 4.5, 13.5, CH_2N), 3.53 (1 H, dd, J = 7.5, 13.5, CH_2N), 8.33 (1 H, s, CHO); IR (KBr) 3300, 1700, 1660 cm^{-1}; mass spectrum, m/z (relative intensity) 277 (M^+, 5), 219 (100).

Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 68.82; H, 8.25; N, 5.24.

Isocyanide 26. To a solution of 277 mg (1 mmol) of **25** in pyridine at 0 °C under argon was added dropwise 0.155 mL (2 mmol) of methanesulfonyl chloride. After being stirred at the same temperature for 1 h and then at room temperature for 4 h, the reaction mixture was diluted with methylene chloride, washed with aqueous 0.5 N hydrochloric acid and water, dried (sodium sulfate), and passed through a short silica gel column. Removal of solvent left 258 mg (100%) of **26** as a waxy solid, mp 85–89 °C: ^1H NMR (360 MHz) δ 1.03 (3 H, s, CH_3), 1.07 (3 H, s, CH_3), 1.2–2.1 (9 H, m, cyclohexane CH_2, CH), 1.64 (1 H, dd, J = 2, 13.5, CH_2CO), 1.79 (1 H, d, J = 15, CH_2), 2.06 (1 H, d, J = 15, CH_2), 2.59 (1 H, d, J =13.5, CH_2CO), 3.28 (1 H, d, J =15, CH_2N), 3.57 (1 H, d, J = 15, CH_2N); IR (neat) 2150, 1710 cm^{-1}; mass spectrum, m/z (relative intensity) 259 (M^+, 8), 83 (100); calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.15689.

Dissolving Metal Reduction of 26. To a mixture of 4.9 g (19 mmol) of **26** and 10.7 g (200 mmol) of ammonium chloride in 200 mL of liquid ammonia and 50 mL of tetrahydrofuran at −98 °C was added as rapidly as possible 1.33 g (190 mmol) of lithium wire. When the lithium had been consumed, the reaction mixture was allowed to warm to room temperature to evaporate the ammonia, water was added, and the mixture was extracted with ethyl acetate, the organic layer was dried (sodium sulfate), and the solvent was removed. Chromatography of the residue

on silica gel, eluting with hexane/ethyl acetate, gave 564 mg (12%) of **26**, 1.4 g (35% based on recovered starting material) of **28** as a low-melting solid, and 1.178 g (30% based on recovered starting material) of **35** (R = H), mp 61–64 °C.

28: ^{1}H NMR (360 MHz) δ 0.98 (3 H, s, CH_3), 1.01 (3 H, s, CH_3), 1.1–2.4 (16 H, m, CH_2, CH, OH), 1.29 (3 H, s, CH_3), 4.25 (1 H, ddd, J = 4, 6, 12, C*H*OH); IR (KBr) 3400, 1460 cm^{-1}.

35 (R = H): ^{1}H NMR (360 MHz) δ 0.87 (3 H, s, CH_3), 1.0–1.7 (10 H, m, cyclohexane CH_2), 1.04 (3 H, s, CH_3), 1.14 (3 H, s, CH_3), 2.49 (2 H, $^1/_2$ AB q, J = 15, CH_2CO), 2.57 (2 H, $^1/_2$ AB q, J = 15, CH_2CO), 3.07 (1 H, s, COCHCO); ^{13}C NMR δ 207.92 (double signal, CO), 73.90 (CH), 55.94 (double signal, CH_2), 38.66, 32.80 (quaternaries), 37.00 (double signal, CH_2), 25.72 (CH_2), 21.79 (double signal, CH_2), 30.26, 27.16, 23.48 (CH_3); IR (KBr) 1690 cm^{-1}; mass spectrum, m/z (relative intensity) 236 (M$^+$, 2), 83 (100); calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1820.

Cis Cyclooctenone 30. To a solution of 97 mg (0.41 mmol) of **28** and 0.289 mL (2 mmol) of triethylamine in 2 mL of methylene chloride at 0 °C was added 0.077 mL (1 mmol) of methanesulfonyl chloride. After being stirred at the above temperature for 1.5 h, the reaction mixture was washed with water, aqueous 1 N hydrochloric acid, and water and dried (sodium sulfate) and the solvent removed to provide the crude mesylate. This was taken up in 1 mL of methylene chloride and 0.289 mL (2 mmol) of triethylamine. After being stirred at room temperature overnight, the reaction mixture was washed with aqueous 1 N hydrochloric acid and water and dried (sodium sulfate) and the solvent removed. Chromatography of the residue on silica gel, eluting with hexane/ethyl acetate, gave 60 mg (67%) of **30** as an oil: ^{1}H NMR (360 MHz) δ 0.95 (3 H, s, CH_3), 1.16 (3 H, s, CH_3), 1.19 (3 H, s, CH_3), 1.5–1.8 (11 H, m, CH_2, CH), 2.2–2.3 (1 H, m, CH_2CO), 2.67 (1 H, d, J = 12, CH_2CO), 5.6–5.7 (2 H, m, olefinic H); ^{13}C NMR δ 214.81, 37.02, 35.55 (quaternaries), 137.57, 128.56, 64.66 (CH), 48.09, 42.31, 39.23, 26.30, 24.52, 22.14 (CH_2), 29.88, 28.86, 27.05 (CH_3); IR (neat) 1690, 1450 cm^{-1}; mass spectrum, m/z (relative intensity) 220 (M$^+$, 20), 57 (100); calcd for $C_{15}H_{24}O$ 220.1827, found 220.1831.

Axial Alcohol 38. To a solution of 11.088 g (42.5 mmol) of **16** in 150 mL of tetrahydrofuran at −78 °C was added dropwise 50 mL (50 mmol) of L-Selectride (1 M in tetrahydrofuran). After being stirred for 3.5 h, the reaction mixture was warmed to 0 °C, and 58 mL of 15% aqueous sodium hydroxide was added dropwise followed by 42 mL of 30% hydrogen peroxide, also added dropwise. This mixture was stirred for 15 min, water added, and the mixture extracted with ethyl acetate. The organic layer was washed with aqueous sodium bisulfite and then water and dried (sodium sulfate) and the solvent removed to provide 11.1 g (99%) of **38**, mp 198–199 °C: ^{1}H NMR (360 MHz) δ 1.0–1.8 (9 H, m, cyclohexane, cyclobutane H), 1.02 (3 H, s, CH_3), 1.24 (3 H, s, CH_3), 1.60 (1 H, d, J = 13.5, CH_2), 1.61 (1 H, s, OH), 1.82 (1 H, d, J = 13.5, CH_2), 1.83 (1 H, d, J = 7.5, C*H*CHOH), 2.07 (1 H, dt, J = 6, 12, cyclohexane H), 2.97 (1 H, dd, J = 4.5, 12, CH_2CHOH), 3.03 (1 H, d, J = 10, CH_2N), 3.78 (1 H, d, J = 10, CH_2N), 4.55 (1 H, dt, J = 4.5, 7.5, C*H*OH), 8.18 (1 H, s, CHO); ^{13}C NMR δ 158.22 (CHO), 74.02, 67.23, 56.44, 49.05, 48.57, 46.66, 45.16, 37.15, 34.46, 30.56, 28.84, 24.65, 24.12, 21.63, 20.62; IR (KBr) 3260, 1640 cm^{-1}; mass spectrum, m/z (relative intensity) 263 (M$^+$, 30), 168 (100).

Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.76; H, 9.96; N, 5.70.

Axial Alcohol 40. Prepared as for **38** in 85% yield, mp 127 °C: ^{1}H NMR (270 MHz) δ 0.98 (3 H, s, CH_3), 1.19 (3 H, s, CH_3), 1.4–1.9 (9 H, m, cyclohexane, cyclobutane H), 1.70 (1 H, d, J = 12.5, CH_2), 1.82 (1 H, s, OH), 1.91 (1 H, d, J = 12.5, CH_2), 1.90 (1 H, d, J = 7, C*H*CHOH), 2.09 (1 H, dt, J = 4, 11, CH_2CHOH), 3.09 (1 H, d, J = 10, CH_2N), 3.14 (1 H, dd, J = 4.1, 11, CH_2CHOH), 3.71 (1 H, d, J = 10, CH_2N), 4.49 (1 H, dt, J = 4.1, 7, C*H*OH), 4.81 (2 H, s, CH_2CCl_3); ^{13}C NMR δ 156.62, 94.37, 46.94, 37.52, 20.27 (quaternaries), 75.39, 53.61, 29.45 (CH), 77.64, 53.91, 51.44, 25.56, 24.10, 22.68, 21.14, 19.89 (CH_2), 34.82, 33.73 (CH_3); IR (CCl_4) 3310, 1710, 735 cm^{-1}.

Anal. Calcd. for $C_{18}H_{26}NO_3Cl_3$: C, 52.63; H, 6.38; N, 3.41. Found: C, 52.83; H, 6.09; N, 3.31.

Axial Mesylate 39. To a solution of **38** and triethylamine (2.2 mmol/mmol of alcohol) in methylene chloride (12.5 mL/mmol of alcohol) at 0 °C was added dropwise methanesulfonyl chloride (2.2 mmol/mmol of alcohol). After 1 h at the above temperature, the reaction mixture was washed with water, aqueous 1 N hydrochloric acid, aqueous sodium bicarbonate, water, and brine and dried (sodium sulfate) and the solvent removed to give **39** in 83% yield, mp 148–150 °C (ether): ^{1}H NMR (360 MHz) δ 1.0–2.1 (10 H, m, cyclohexane, cyclobutane H), 1.06 (3 H, s, CH_3), 1.23 (3 H, s, CH_3), 1.68 (1 H, d, J = 13.5, CH_2), 1.87 (1 H, d, J = 13.5, CH_2), 2.09 (1 H, d, J = 7.5, C*H*CHOSO$_2$CH$_3$), 2.56 (1 H, dd, J = 4.5, 12, CH_2CHOSO$_2$CH$_3$), 3.07 (3 H, s, CH_3SO_3), 3.09 (1 H, d, J = 10.5, CH_2N), 3.83 (1 H, d, J = 10.5, CH_2N), 5.33 (1 H, dt, J = 4.5, 7.5, C*H*OSO$_2$CH$_3$), 8.23 (1 H, s, CHO); IR (KBr) 1635, 1355 cm^{-1}; mass spectrum, m/z (relative intensity) 341 (M$^+$, 4), 246 (100).

Anal. Calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10. Found: C, 60.17; H, 8.11; N, 4.33.

Axial Mesylate 41. Prepared from **40** according to the above procedure in 96% yield, mp 169–170 °C: ^{1}H NMR (270 MHz) δ 1.02 (3 H, s, CH_3), 1.18 (3 H, s, CH_3), 1.2–2.1 (10 H, m, cyclohexane CH_2, CH), 1.61 (1 H, d, J = 13, CH_2), 1.81 (1 H, d, J = 13, CH_2), 2.14 (1 H, d, J = 7, C*H*CHOSO$_2$CH$_3$), 2.66 (1 H, dd, J = 4.2, 11, CH_2CHOSO$_2$CH$_3$), 3.09 (3 H, s, OSO$_2$CH$_3$), 3.16 (1 H, d, J = 10, CH_2N), 3.72 (1 H, d, J = 10, CH_2N), 4.77 (2 H, s, CH_2CCl_3), 5.34 (1 H, dt, J = 4.2, 7, C*H*OSO$_2$CH$_3$); ^{13}C NMR δ 156.24, 94.91, 47.43, 37.02, 21.28 (quaternaries), 77.80, 54.27, 28.86 (CH), 76.91, 53.04, 51.96, 27.37, 23.40, 22.82, 21.85, 20.65 (CH_2), 68.27, 35.62, 33.35 (CH_3); IR (CCl_4) 1710, 1355, 735 cm^{-1}.

Imine Olefin 42 from 39. To a solution of 2.04 g (6 mmol) of **39** in 60 mL of tetrahydrofuran at −78 °C was added dropwise 4 mL (6 mmol) of methyllithium (1.5 M in ether). After being stirred at the above temperature for 1 h, the reaction mixture was allowed to warm to room temperature over 4 h, saturated aqueous ammonium chloride added, and the mixture extracted with methylene chloride. The organic layer was washed with brine and dried (sodium sulfate) and the solvent removed. Chromatography of the residue on alumina (activity III), eluting the hexane/ethyl acetate, gave 626 mg (48%) of **42** as an oil: ^{1}H NMR (360 MHz) δ 0.96 (3 H, s, CH_3), 1.0–2.9 (13 H, CH_2, CH), 1.09 (3 H, s, CH_3), 3.19 (1 H, d, J = 15, CH_2N), 3.94 (1 H, d, J = 15, CH_2N), 5.2–5.3 (2 H, m, olefinic H); ^{13}C NMR δ 140.72, 123.87 (olefinic C), 62.75, 41.10 (quaternaries), 50.92, 45.21, 38.91, 29.00, 24.91, 24.13, 23.98 (CH_2), 33.78, 22.06 (CH_3); IR ($CHCl_3$) 1640, 1620 cm^{-1}; mass spectrum, m/z (relative intensity) 217 (M$^+$, 24), 83 (100).

Imine Olefin 42 from 41. To a solution of 11 g (23 mmol) of **41** in 100 mL of tetrahydrofuran at room temperature was added 2.21 g (34 mmol) of zinc followed by 10 mL of 1 M potassium phosphate buffer (pH 4–5) and the mixture vigorously stirred for 8 h. After dilution with water and extraction with ethyl acetate, the organic layer was washed with water and dried (sodium sulfate), the solvent removed, and the residue chromatographed on alumina (activity III), by eluting with hexane/ethyl acetate, to give 2.05 g (83%) of **42**.

Imine Ketone 32 from 14. To a solution of 10 g (24 mmol) of **14** in 100 mL of tetrahydrofuran at room temperature was added 2.01 g (31 mmol) of zinc followed by 9 mL of 1 M sodium acetate buffer (pH 5) and the mixture vigorously stirred for 8 h. After dilution with water and extraction with ethyl acetate, the organic layer was washed with water and aqueous 1 N hydrochloric acid and dried (sodium sulfate), the solvent removed, and the residue chromatographed on silica gel, by eluting with ethyl acetate, to give 5.26 g (94%) of **32**.

Formyl Cyclooctenones 43 and 48. A solution of 272 mg (1.25 mmol) of **42** and 0.072 mL (1.25 mmol) of acetic acid in 3 mL of tetrahydrofuran and 3 mL of water was stirred at room temperature overnight. At this time, the reaction mixture was concentrated to dryness and the residue taken up in 5 mL of pyridine, cooled to 0 °C, and treated with a solution of 15 mmol of aceticformic anhydride[13] in ether. This was allowed to slowly warm to room temperature overnight, diluted with water, and extracted with ethyl acetate. The organic layer was washed with aqueous 1 N hydrochloric acid, aqueous sodium bicarbonate, and brine and dried (magnesium sulfate) and the solvent removed. Chromatography of the residue on silica gel, eluting with ethyl acetate, gave 248 mg (75%) of **43**, mp 106 °C (hexane/ethyl acetate) (ratio of **43**/**48** = 100/6 by GC/MS): ^{1}H NMR (270 MHz) δ 0.97 (3 H, s, CH_3), 1.04 (3 H, s, CH_3), 1.2–2.2 (11 H, m, CH_2, CH_2CO), 2.66

(1 H, d, J = 12, CH_2CO), 2.81 (1 H, app d, J = 12, CHCO), 3.15 (1 H, d, J = 15, CH_2N), 4.1–4.2 (1 H, m, CH_2N), 5.32 (1 H, d, J = 12, neopentyl olefinic H), 5.53 (1 H, br s, NH), 5.7–5.8 (1 H, m, olefinic H), 8.16 (1 H, s, CHO); ^{13}C NMR δ 214.36, 55.71, 33.64 (quaternaries), 165.24, 161.57, 137.43, 60.89 (CH), 54.32, 38.04, 36.52, 36.03, 24.22, 22.76, 19.38 (CH_2), 30.46, 28.42 (CH_3); IR (CCl_4) 1730, 1705 cm^{-1}; mass spectrum, m/z (relative intensity) 263 (M^+, 12), 144 (100).

Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.74; H, 9.41; N, 5.14.

Upon treatment of **43** with hot methanolic sodium methoxide, a 100/3 ratio of **48** and **43**, respectively (by GC/MS), resulted. **48**, mp 110–111 °C (hexane/ethyl acetate): ^1H NMR (270 MHz) δ 0.98 (3 H, s, CH_3), 1.12 (3 H, s, CH_3), 1.2–2.1 (11 H, m, CH_2, CH_2CO), 2.67 (1 H, d, J = 10, CH_2CO), 2.86 (1 H, app d, J = 10, CHCO), 3.12 (1 H, d, J = 12, CH_2N), 4.0–4.1 (1 H, m, CH_2N), 5.36 (1 H, d, J = 10, neopentyl olefinic H) 5.7–5.8 (2 H, m, olefinic H, NH), 8.14 (1 H, s, CHO); ^{13}C NMR δ 215.15, 54.11, 34.29 (quaternaries), 164.33, 161.08, 138.21, 60.34 (CH), 54.01, 38.87, 37.59, 36.62, 24.62, 23.35, 20.51 (CH_2), 29.66, 28.46 (CH_3); IR (CCl_4) 1765, 1745, 1690 cm^{-1}; mass spectrum, m/z (relative intensity) 263 (M^+, 16), 76 (100).

Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.84; H, 9.31; N, 5.22.

Ketal 44. A solution of 8.0 g (30.4 mmol) of **43**, 4.6 mL (82 mmol) of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid in 300 mL of benzene was refluxed overnight with continuous water separation. After cooling, the reaction mixture was washed with aqueous sodium bicarbonate, water, and brine and dried (sodium sulfate) and the solvent removed to give 9.2 g (99%) of **44**, mp 118–119 °C (hexane/ethyl acetate): ^1H NMR (270 MHz) δ 0.96 (3 H, s, CH_3), 1.11 (3 H, s, CH_3), 1.2–2.3 (13 H, m, CH_2, CH), 3.14 (1 H, d, J = 15, CH_2N), 3.6–3.7 (4 H, m, CH_2), 4.0–4.1 (1 H, m, CH_2N), 5.39 (1 H, k, J = 12, neopentyl olefinic H), 5.7–5.8 (2 H, m, olefinic N, NH), 8.15 (1 H, s, CHO); IR (CCl_4) 1740, 1580 cm^{-1}; mass spectrum, m/z (relative intensity) 307 (M^+, 6), 76 (100).

Isocyanide 45. To a solution of 9.2 g (30 mmol) of **44** in 150 mL of pyridine at 0 °C was added 5.8 mL (75 mmol) of methanesulfonyl chloride. After 1 h at 0 °C and 2 h at room temperature, the mixture was taken up in ethyl acetate, the organic phase washed with water, aqueous 2 N hydrochloric acid, sodium bicarbonate, and brine and dried (sodium sulfate), and the solvent removed to give 8.4 g (96%) of **45** as an oil: ^1H NMR (270 MHz) δ 0.98 (3 H, s, CH_3), 1.10 (3 H, s, CH_3), 1.2–2.3 (13 H, m, CH_2 CH), 3.64 (1 H, d, J = 15, CH_2N), 3.6–3.7 (4 H, m, $(CH_2O)_2$), 3.7–3.8 (1 H, m, CH_2N), 5.39 (1 H, d, J = 12, olefinic H), 5.7–5.8 (1 H, m, olefinic H); IR (neat) 2200, 1685 cm^{-1}; mass spectrum, m/z (relative intensity) 289 (M^+, 11), 76 (100).

Trans Cyclooctenone 6. To a solution of 8.4 g (29 mmol) of **45** in 200 mL of tetrahydrofuran and 300 mL of ammonia at −78 °C was added 10 g (435 mmol) of sodium. After 15 min, the reaction mixture was quenched with excess ammonium chloride and the ammonia allowed to evaporate. The residue was taken up in ethyl acetate, washed with aqueous 1 N hydrochloric acid and brine, and dried (sodium sulfate) and the solvent removed to give 7.5 g (97%) of trimethyl ketal. This was dissolved in 100 mL of tetrahydrofuran, 60 mL of acetic acid, and 40 mL of water and allowed to stand at room temperature overnight. At this time, the reaction mixture was diluted with ethyl acetate, washed with water, aqueous sodium bicarbonate, and brine, and dried (sodium sulfate) and the solvent removed to yield a residue, which upon chromatography on silica gel, eluting with hexane/ethyl acetate, gave 5.9 g (93%) of **6** (ratio of **6**/**30** = 100/7 by GC/MS) which could be kugelrohr distilled at 74 °C (0.05 torr): ^1H NMR (270 MHz) δ 0.88 (3 H, s, CH_3), 1.08 (3 H, s, CH_3), 1.11 (3 H, s, CH_3), 1.4–1.7 (10 H, m, CH_2), 2.1–2.2 (2 H, m, allylic CH_2, CHCO), 2.60 (1 H, d, J = 14, CH_2CO), 5.5–5.6 (2 H, m, olefinic H); ^{13}C NMR δ 214.67, 36.14, 35.09 (quaternaries), 136.37, 127.38, 64.01 (CH), 46.43, 42.15, 38.74, 25.97, 23.46, 21.89 (CH_2), 30.54, 28.03, 26.17 (CH_3); IR (CCl_4) 1770, 1690 cm^{-1}; mass spectrum, m/z (relative intensity) 220 (M^+, 13), 94 (100); calcd for $C_{15}H_{24}O$ 220.1827, found 220.1852.

Upon treatment of **6** with hot methanolic sodium methoxide, a 100/1 ratio of **30** and **6**, respectively (by GC/MS), resulted.

Acetamide Cyclooctanedione 46[11] from 32. A solution of 100 mg (0.4 mmol) of **32** in 10 mL of tetrahydrofuran, 5 mL of water, and 5 mL of aqueous 1 N hydrochloric acid was stirred at room temperature for 8 h and then concentrated to dryness. The residue was taken up in 7 mL of pyridine and cooled to 0 °C and then 1 mL of acetic anhydride added. After 3 h, ethyl acetate was added, and the mixture was washed with aqueous 1 N hydrochloric acid and brine and dried (sodium sulfate) and the solvent removed to provide 93 mg (80%) of **46**. Upon treatment of **46** with hot methanolic sodium methoxide, a 100/21 ratio of **46** and the cis isomer, respectively (by GC/MS), resulted.

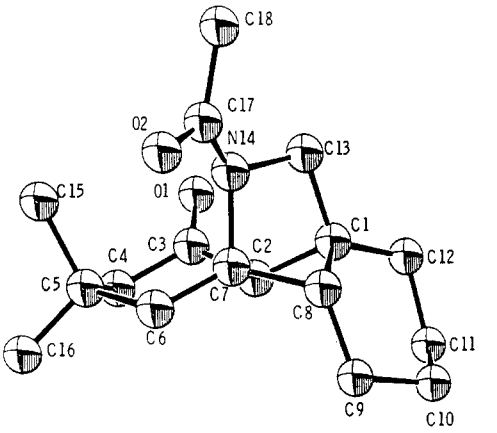


Figure 1. A perspective drawing of **18** generated from the final X-ray coordinates.

Acetamide Enone 22 and 18. A solution of 100 mg (0.36 mmol) of **22** and 100 mg (0.63 mmol) of potassium *tert*-butoxide in 5 mL of *tert*-butyl alcohol was stirred at room temperature for 15 min. At this time, the reaction mixture was concentrated and the residue taken up in ethyl acetate and chromatographed on silica gel, by eluting with hexane/ethyl acetate. There was obtained 80 mg (80%) of **18**.

Formyl Enone 23 from 19. To a suspension of 1.77 g (7 mmol) of **19** in 40 mL of *tert*-butyl alcohol at room temperature was added 1.77 g (20 mmol) of potassium *tert*-butoxide. After being stirred for 0.5 h, the reaction mixture was concentrated, taken up in ethyl acetate, and chromatographed on silica gel, by eluting with ethyl acetate, to give 870 mg (49%) of **23**.

Trans Acetamide Cyclooctenone 47. A solution of 57 mg (0.26 mmol) of **42** and 0.015 mL (0.26 mmol) of acetic acid in 1 mL of tetrahydrofuran and 1 mL of water was stirred at room temperature for 18 h. At this time, the reaction mixture was concentrated to dryness, the residue taken up in 2 mL of pyridine and cooled to 0 °C, and then 0.5 mL of acetic anhydride added. After 1 h at this temperature and 0.5 h at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate and the organic layer washed with aqueous 1 N hydrochloric acid and brine and dried (sodium sulfate). Removal of solvent gave 52 mg (72%) of **47**, mp 172–174 °C (ether): ^1H NMR (360 MHz) δ 0.98 (3 H, s, CH_3), 1.12 (3 H, s, CH_3), 1.2–2.1 (10 H, m, CH_2), 1.93 (3 H, s, CH_3CO), 2.02 (1 H, d, J = 12, CH_2CO), 2.64 (1 H, d, J = 12, CH_2CO), 2.87 (1 H, app d, J = 12, CHCO), 3.33 (1 H, d, J =15, CH_2N), 4.01 (1 H, dd, J = 10.5, 15, CH_2N), 5.39 (1 H, d, J = 12, neopentyl olefinic H), 5.52 (1 H, br s, NH) 5.73 (1 H, app dt, J = 7.5, 12, olefinic H); ^{13}C NNR δ 210.36, 169.91, 41.81, 34.45 (quaternaries), 138.79, 128.74, 60.14 (CH), 54.47, 39.05, 38.31, 37.76, 24.93, 20.92 (CH_2), 29.96, 28.43, 23.37 (CH_3); IR (KBr) 3310, 1695, 1640, 1545 cm^{-1}; mass spectrum, m/z (relative intensity) 277 (M^+, 12), 95 (100).

Upon treatment of **47** with hot methanolic sodium methoxide, a 100/20 ratio of **29** and **47**, respectively (by GC/MS), resulted.

X-ray Crystallographic Analyses.[29] **18**: Large chunky crystals of **18** formed from cyclohexane/hexane with symmetry $P2_1/n$ and cell constants of a = 10.656 (2) Å, b = 15.308 (3) Å, c =19.641 (3) Å, and β = 102.83 (2)° for Z = 8. Of the 4414 reflections measured by using Cu radiation with $2\theta \leq 114°$, 3610 were observed ($I \geq 3\sigma I$). The structure was solved by using a

(29) The following library of crystallographic programs was used: MULTAN 80, University of York, York, England, 1980. Structure Determination Package V17.0, Enraf-Nonius Corporation, Delft, Holland, 1981. ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN 1970.

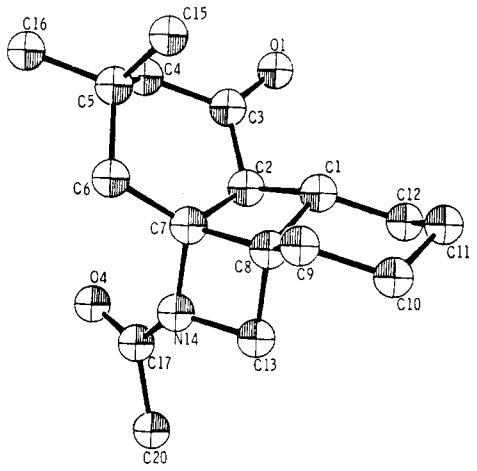


Figure 2. A perspective drawing of one of the independent molecules of **20** generated from the final X-ray coordinates.

multisolution tangent formula approach and refined by using full-matrix least squares. Anisotropic temperature parameters were used for the non-hydrogen atoms, while fixed isotropic parameters were used for the hydrogens. The function minimized was $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ to give an unweighted residual of 0.053. Tables I–III in the supplementary material contain the final fractional coordinates, temperature parameters, bond distances, and bond angles. There are no abnormally close intermolecular contacts. Figure 1 is a computer-generated drawing of **18** showing the relative configuration.

20: Crystals of **20** formed from ether with symmetry $P2_1/c$ and cell parameters of a = 16.837 (4) Å, b = 15.316 (2) Å, c = 12.557 (3) Å, and β = 100.98 (2)° for Z = 8. An automatic four-circle diffractometer equipped with Cu radiation was used to measure 4486 unique reflections with $2\theta \leq 114°$. Of these 3029 were observed ($I \geq 3\sigma I$) and corrected for Lorentz and polarization effects. A multisolution tangent formula approach to phase solution gave an initial model which was refined with least squares calculations and Fourier difference analysis. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(F_o)^2$ was minimized to give an unweighted residual of 0.064. Tables IV–VI in the supplementary material contain the final fractional coordinates, temperature parameters, bond distances, and bond angles, while Figure 2 is a drawing of one of the independent molecules of **20**.

The two independent molecules of **20** are related to each other by an approximate translation of one-half the unit cell along X. However, the conformations of the cyclohexanone rings of the two molecules differ. Both rings have half-chair conformations, but in one (shown in Figure 2) C-15 is axial, while in the other C-15′ is equatorial. Both molecules have chair conformations for the cyclohexane ring.

Acknowledgment is made to the Research Corporation (Schering-Plough Corporation Grant) and to the Bryn Mawr College Faculty Research Fund for the support of this research at Bryn Mawr. The acquisition at Bryn Mawr of the preparative liquid chromatograph was made possible by a grant from the National Science Foundation, of a GC/MS system by grants from the Camille and Henry Dreyfus Foundation and the PQ Corporation, and of the 270-MHz NMR spectrometer by grants from the W. M. Keck Foundation and Merck & Co., Inc. We are grateful for the many analytical services provided by Merck Sharp & Dohme Research Laboratories, West Point, PA.

Supplementary Material Available: Tables I–VI containing the final fractional coordinates, temperature parameters, bond distances, and bond angles for **18** and **20** (12 pages). Ordering information is given on any current masthead page.

Spiro and Bicyclic Nucleosides. Preparation of New Structural Types from Ribose Adducts of Diaminomaleonitrile

James P. Ferris* and Balekudru Devadas

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

Received December 18, 1986

The use of ribose adducts of diaminomaleonitrile (DAMN) as starting materials for the synthesis of three new nucleoside structural types is described. Oxidation of ribopyranosyl- and ribofuranosyldiaminomaleonitrile adducts (**3** and **10**, respectively) with DDQ in acetonitrile yields the iminolactones **4** and **11**, respectively, while use of DDQ in methanol yields the spiro derivatives **9** and **12**. Treatment of **4** with *t*-BuOCl and **11** with NBS results in the formation of 2,3-dicyano-5,6,7-triacetoxy-5,6,7,8-tetrahydroimidazo[2,1-*b*][1,3]oxazepine (**16**) and 2,3-dicyano-5,6-bis(benzoyloxy)-7-[(benzoyloxy)methyl]-5*H*-imidazo[2,1-*b*][1,3]oxazine (**15**), respectively. The acyclic DAMN adduct **18** also undergoes cyclization to imidazole **19** on treatment with NBS or *t*-BuOCl. The tosylate of **19** cyclizes to the pyrrolo[1,2-*a*]imidazoles **25** and **27** on heating in toluene. Compound **25** was converted to the aminoimidazolecarboxamide **31** by methanolysis to the monoimidate **29**; Hofmann rearrangement of **29** to the amino nitrile **30**; hydrolysis of **30** to **31**.

Diaminomaleonitrile (DAMN) has proven to be a versatile starting material in both the areas of organic synthesis and prebiotic synthesis.[1,2] In previous studies we reported that DAMN adducts of sugars are useful precursors for the synthesis of both C- and N-nucleosides.[3-5] The facile preparation of spiro and bicyclo nucleosides from ribose adducts of DAMN is reported herein. A preliminary report of some of our findings has appeared.[6]

Results and Discussion

The oxidation of ribopyranosyldiaminomaleonitrile (**1**) with 1 equiv of 2,3-dichloro-5,6-dicyanobenzoquinone

(1) Fukunaga, T.; Begland, R. W. *J. Org. Chem.* **1984**, *49*, 813–821, and previous papers in this series.
(2) Ferris, J. P.; Hagan, W. A., Jr. *Tetrahedron* **1984**, *40*, 1093–1120.
(3) Ferris, J. P.; Huang, H. C. *J. Chem. Soc., Chem. Commun.* **1978**, *1094*–1096.
(4) Ferris, J. P.; Badesha, S. S.; Ren, W. Y.; Huang, H. C.; Sorcek, R. J. *J. Chem. Soc., Chem. Commun.* **1981**, 110–112.
(5) Ferris, J. P.; Devadas, B.; Huang, H. C.; Ren, W. Y. *J. Org. Chem.* **1985**, *50*, 747–754.
(6) Ferris, J. P.; Devadas, B. *Tetrahedron Lett.* **1986**, *27*, 323–326.

0022-3263/87/1952-2355$01.50/0