Harpagide (15) from Penta-*O*-acetylantirrhinoside.[20] The residue (70 mg) after chromatography on silica gel (6 g) in *n*-butyl alcohol/methanol/water (14:1:4) afforded **15**: 50 mg; ^{1}H NMR and ^{13}C NMR spectra superimposable on those of natural harpagide.

6-Epiharpagide (16) from Penta-*O*-acetylprocumbide. The residue (80 mg) after chromatography on silica gel (7 g) in chloroform/methanol (4:1) afforded **16**: 55 mg; ^{1}H NMR (D_2O) δ 1.21 (1 H, s, CH_3-10), 1.69 (2 H, o, J_{AB} = 14 Hz, J_{AX} = 7 Hz, J_{BX} = 12 Hz, 2H-7), 2.33 (1 H, brs, H-9), 4.26 (1 H, q, $J_{6,7}$ = 7 Hz, $J_{6,7}$ = 12 Hz, H-6), 5.06 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.64 (1 H, brs, H-1), 6.42 (1 H, d, $J_{3,4}$ = 6 Hz, H-3). Anal. Calcd for $C_{15}H_{24}O_{10}$: C, 49.45; H, 6.64. Found: C, 48.97; H, 6.92.

Preparation of Hexa-*O*-methylmacfadyenoside (17). CH_3I (1 mL) and Ag_2O (1.2 g, freshly prepared) were added to **3** (250 mg) dissolved in dry DMF (10 mL) with stirring at room temperature and in the dark. After 24 h, CH_3I (0.5 mL) and Ag_2O (0.6 g) were added and stirring continued for 12 h. The suspension was filtered on a gooch funnel and the salts were washed with chloroform. A white precipitate was filtered off and washed repeatedly with chloroform. The combined solutions were concentrated in vacuo. The residue was chromatographed on silica gel (25 g), and elution with chloroform/methanol (24:1) afforded pure hexa-*O*-methylmacfadyenoside (**17**): 188 mg; ^{1}H NMR ($CDCl_3$) δ 2.86 (1 H, d, $J_{1,9}$ = 5 Hz, H-9), 3.2–3.6 (18 H, 6 OCH_3), 3.61 (2 H, s, 2H-10), 3.4–3.8 (1 H, H-7), 3.94 (1 H, m, H-6, partly masked), 4.65 (1 H, d, $J_{1',2'}$ = 7 Hz, H-1'), 4.98 (1 H, d, $J_{3,4}$ = 6 Hz, H-4), 5.50 (1 H, d, $J_{1,9}$ = 5 Hz, H-1), 6.48 (1 H, d, $J_{3,4}$ = 6 Hz, H-3).

Reaction of 17 with Sodium Hydroxide. Compound **17** (450 mg) was dissolved in methanol (1 mL). NaOH (2 N, 10 mL) was added, and the solution was heated for 10 h at 80 °C. After cooling, the solution was neutralized with 2 N HCl and extracted twice with chloroform. The combined organic solutions were evaporated in vacuo, and the residue was chromatographed on silica gel (40 g). Elution with chloroform/methanol (24:1) afforded hepta-*O*-methylcynanchoside (**19**, 170 mg) and hexa-*O*-methylcynanchoside (**18**, 200 mg): ^{1}H NMR of **19** ($CDCl_3$) δ 2.60 (1 H, dd, $J_{1,9}$ = 1.5 Hz, $J_{4,9}$ = 1 Hz, H-9), 3.1–3.7 (23 H, 7 OCH_3 and 2H-10 signals), 3.80 (1 H, d, $J_{6,7}$ = 7 Hz, H-7), 4.56 (1 H, d, $J_{6,7}$ = 7 Hz, H-6), 5.06 (1 H, dd, $J_{3,4}$ = 6.5 Hz, $J_{4,9}$ = 1 Hz, H-4), 5.67 (1 H, d, $J_{1,9}$ = 1.5 Hz, H-1), 6.38 (1 H, d, $J_{3,4}$ = 6.5 Hz, H-9); ^{1}H NMR of **18** ($CDCl_3$) δ 2.54 (1 H, d, $J_{1,9}$ = 3.5 Hz, H-9), 3.5–4.2 (21 H, H-7, 2H-10 and 6 OCH_3 signals), 4.50 (1 H, d, $J_{6,7}$ = 7 Hz, H-6), 5.04 (1 H, d, $J_{3,4}$ = 6.5 Hz, H-4), 5.47 (1 H, d $J_{1,9}$ = 3.5 Hz, H-1), 6.30 (1 H, d, $J_{3,4}$ = 6.5 Hz, H-3).

Preparation of Hexa-*O*-methylcynanchoside (19) from Cynanchoside (1). Cynanchoside (1, 150 mg), methylated as described for **3** (0.6 mL of CH_3I and 720 mg of Ag_2O), afforded a crude residue which on chromatography on silica gel (8 g) and elution with chloroform/methanol (97:3) afforded pure **19** (60 mg).

Registry No. **1**, 80666-56-4; **2**, 81892-75-3; **3**, 54835-65-3; **3** hexaacetate, 54621-31-7; **4**, 2415-24-9; **4** hexaacetate, 6910-20-9; **5**, 20770-65-4; **5** hexaacetate, 20770-66-5; **6**, 30688-55-2; **7**, 79549-53-4; **8**, 86372-54-5; **9**, 86362-15-4; **10**, 20486-27-5; **10** hexaacetate, 35993-19-2; **11**, 36476-17-2; **12**, 73366-31-1; **13**, 73366-30-0; **14**, 86309-49-1; **15**, 6926-08-5; **16**, 86362-16-5; **17**, 86309-50-4; **18**, 86309-52-6; **19**, 86309-51-5.

(20) In ref 5 the reduction was carried out with Li/NH_3.
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Syntheses and Reactivity of *trans*-6-Azabicyclo[3.1.0]hexan-2-ol Derivatives and Indano[1,2-*b*]aziridine. Structural Analogues of Mitomycin C

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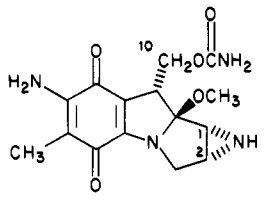
Received December 27, 1982

The synthesis and reactivity of three annelated aziridines (**4–6**) are described. *trans*-6-Azabicyclo[3.1.0]hexan-2-ol (**4**) and *cis*-2-methyl-*trans*-6-azabicyclo[3.1.0]hexan-2-ol (**5**) undergo regio- and stereospecific ring opening of the aziridine ring in aqueous HCl and $HClO_4$ acid solutions. In each case, reaction proceeds at carbon-5 to give the trans-ring-opened product. Correspondingly, treatment of indano[1,2-*b*]aziridine (**6**) with aqueous $HClO_4$ acid gave a 2.7:1 mixture of *cis*- and *trans*-2-amino-1-indanol (**39** and **40**, respectively). Comparison of these results with those previously reported for the acid-promoted hydrolysis of mitomycin C (**1**) suggests that hydrolysis in the latter case may proceed by initial loss of methanol to give the indoloquinone, followed by regiospecific ring opening of the aziridine ring by an S_N1-type process.

Mitomycin C (**1**) is a clinically useful antineoplastic



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antibiotic compound. Its mechanism of action at the molecular level both in vitro and in vivo is ill-defined.[2] Extensive studies have indicated that the biological event of primary importance induced by the mitomycins is probably the alkylation of DNA.[1] A series of mechanisms have been advanced that invoke the involvement of both the aziridine and the carbamate moieties.[3] The initial step is believed to be reduction of the quinone moiety to a semiquinone. This is suggested to be a necessary step for efficient, noncovalent binding of the drug with the substrate DNA. Subsequent reduction of the complexed semiquinone radical to the hydroquinone is followed by loss of methanol at C-9 and C-9a to give an indolohydroquinone ring system. This then fully activates the drug by unmasking electrophilic centers at carbon-1 of the aziridine ring and carbon-10 adjacent to the carbamate

(1) Alfred P. Sloan Foundation Fellow, 1977–1981. Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977–1982.
(2) (a) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; Vol. 1, pp 221–276. (b) Crooke, S. T.; Bradner, W. T. *Cancer Treat. Rev.* **1976**, *3*, 121–140. (c) Comis, R. L.; Carter, S. K. *Cancer* **1974**, *34*, 1576–1586 and references therein.
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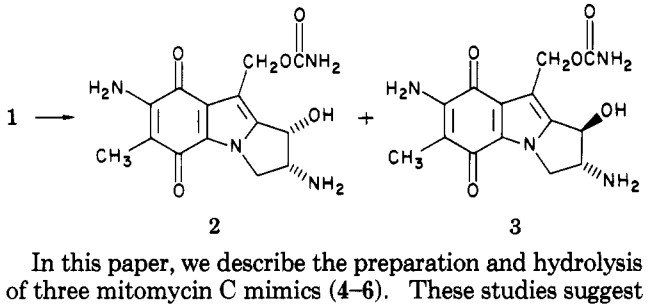
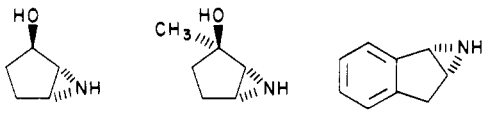
group. Reaction of the biological substrate DNA at either or both of these sites would lead to mono- or difunctional (cross-linking) alkylation of the genetic material.

These proposals have led to a significant number of chemical studies.[4-12] The results that have been obtained tend to support the bioreductive alkylation pathway. They also have been proven inadequate to fully account for the chemistry of mitomycins in vitro.[4-7] Attention has been focused on the stereochemistry of the alkylation step. Chief among these is the report that mitomycin C (1) undergoes aqueous acid hydrolysis to give predominantly the cis-diastereomer 2 over the trans-isomer 3 (4:1 ratio).[4,5] This finding is in contradiction to the normal observation that aziridines in which both carbons are secondary undergo ring opening under acidic conditions with *inversion* at the reaction site.[13]



2 3

In this paper, we describe the preparation and hydrolysis of three mitomycin C mimics (4–6). These studies suggest



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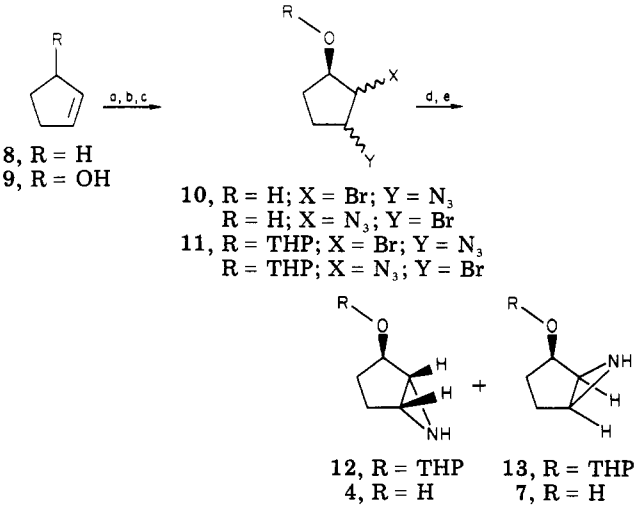
various controlling factors that may dictate the stereochemical outcome for the acid-promoted hydrolysis of mitomycin C (1). Specifically, we provide evidence that alkylation may proceed by an S_N1-type process that leads to the formation of a diastereomeric mixture of 2 and 3.

Synthesis

The first target compound was the rigid *trans*-6-azabicyclo[3.1.0]hexan-2-ol (4). An expeditious synthesis for both the cis (7) and the trans (4) adducts was developed beginning with cyclopentene (8, Scheme I). Conversion of 8 to cyclopeneten-1-ol[14] (9; 64% overall yield) was accomplished by allylic oxidation with *tert*-butyl perbenzoate and cuprous bromide[15] followed by reductive removal of

Scheme I[a]



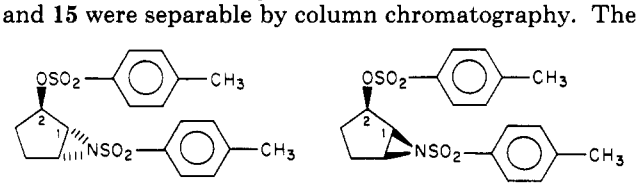
8, R = H
9, R = OH

10, R = H; X = Br; Y = N_3
R = H; X = N_3; Y = Br
11, R = THP; X = Br; Y = N_3
R = THP; X = N_3; Y = Br

12, R = THP 13, R = THP
4, R = H 7, R = H

[a] a (8 → 9): (1) $PhCO_2OC(CH_3)_3$, 1% CuBr, benzene, (2) $LiAlH_4$, ether, 64%. b (9 → 10): NaN_3, NBS, DME-H_2O, 69%. c (10 → 11): dihydropyran, *p*-TSA, CH_2Cl_2, 93%. d (11 → 12, 13): $LiAlH_4$, ether, 82%. e (12, 13 → 4, 7): (1) 6 N HCl, THF-MeOH, (2) NH_4OH, 51%.

the benzoyl group with lithium aluminum hydride. Treatment of 9 with *N*-bromosuccinimide and sodium azide according to the procedure of Krief[16] led to the bromo azide 10 (69% yield), which gave one spot on TLC analysis. Carbon-13 NMR spectroscopy, however, indicated the presence of two isomers in a ratio of 1.7:1. The precise structures of these two adducts were not ascertained, and both products were carried through the synthetic sequence. Protection of the hydroxyl group in 10 with dihydropyran (93% yield), followed by reductive cyclization of the bromo azide 11, yielded a mixture of the tetrahydropyranyl ethers of *trans*- and *cis*-6-azabicyclo-[3.1.0]hexan-2-ol (12 and 13, respectively) in 82% yield. As expected, TLC and ^{13}C NMR analyses of mixtures 11 as well as 12 and 13 each indicated the presence of four compounds. Mixture 11 could be partially separated by careful column chromatography. The inefficiency of this step, however, precluded the general use of this procedure. Deprotection of the tetrahydropyranyl group in the last step (12,13 → 4,7) was achieved by treatment of the mixture with a slight molar excess of acid (51% yield). Carbon-13 NMR analysis indicated the presence of two compounds in a 2.5:1 ratio. Comparison of the NMR spectrum with a purified sample (see Scheme II) indicated that the major compound was the desired trans-adduct 4. Attempted separation of the trans/cis diastereomeric mixture by column and gas chromatography proved unsuccessful. Further information concerning the correct identity of these two aziridines was provided by conversion of 7 and 4 to the ditosylates. The two stereoisomers 14 and 15 were separable by column chromatography. The



14 15

assignment of the diastereomers was achieved by selective decoupling experiments. Irradiation of the multiplet region

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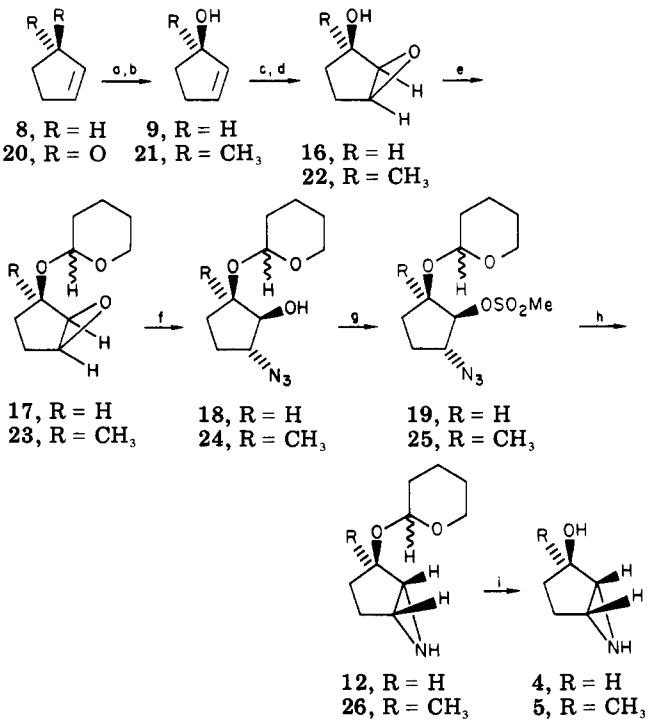
Scheme II[a]



8, R = H; 9, R = H; 16, R = H
20, R = O; 21, R = CH_3; 22, R = CH_3

17, R = H; 18, R = H; 19, R = H
23, R = CH_3; 24, R = CH_3; 25, R = CH_3

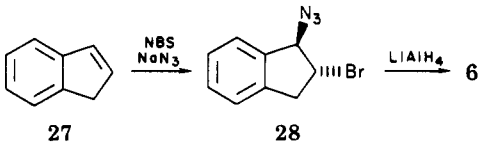
12, R = H; 4, R = H
26, R = CH_3; 5, R = CH_3

[a] a (8 → 9): (1) $PhCO_2OC(CH_3)_3$, 1% CuBr, benzene, (2) $LiAlH_4$, ether, 64%. b (20 → 21): CH_3Li, ether, 67%. c (9 → 16): $(CH_3)_3CO_2H$, $VO(AcAc)_2$, benzene, 60%. d (21 → 22): *m*-ClPBA, $CHCl_3$, 90%. e: dihydropyran, *p*-TSA, CH_2Cl_2, 16 → 17 (96%), 22 → 23 (82%). f: KN_3, 18-crown-6, CH_3CN-H_2O, 17 → 18 (83%), 23 → 24 (85%). g: CH_3SO_2Cl, pyridine, 18 → 19 (88%), 24 → 25 (87%). h: $LiAlH_4$, ether, 19 → 12 (55%), 25 → 26 (54%). i: (1) HCl, THF-MeOH, (2) NH_4OH, 12 → 4 (88%), 26 → 5 (57%).

for the H_3 and H_4 protons (δ 1.50–2.05) of the cis compound **15** indicated that the H_1–H_2 coupling constant was ~2 Hz, while a similar experiment for the trans-adduct **14** gave only a sharp singlet for the C-2 proton.

Our inability to separate the mixture of **4** and **7** prompted an alternate synthesis of *trans*-6-azabicyclo-[3.1.0]hexan-2-ol (**4**). Compound **4** was independently prepared beginning again with **8** (Scheme II). Conversion of **8** to **9**, followed by selective epoxidation of **9** with vanadyl acetylacetonate and *tert*-butyl hydroperoxide according to the method of Teranishi and co-workers gave the known *cis*-2,3-epoxycyclopentan-1-ol (**16**).[17] The epoxy alcohol **16** was then protected with dihydropyran to yield a diastereomeric mixture of tetrahydropyranyl ethers **17** (^{13}C NMR analysis). Stereospecific ring opening of the epoxide with potassium azide in the presence of 18-crown-6 in aqueous acetonitrile gave presumably azido alcohol **18** (no definitive evidence for the regiochemistry of attack was obtained) in 83% yield.[18] TLC and ^{13}C NMR analyses of the reaction product indicated the presence of only two compounds. Use of anhydrous acetonitrile in this reaction resulted in the isolation of only starting material.[20] Although the two diastereomers (**18**) were separable by column chromatography, in most cases the mixture was directly treated with methanesulfonyl chloride to yield the corresponding mesylate **19**. Lithium aluminum hydride reduction of **19** gave upon workup the fused *trans*-6-azabicyclo[3.1.0]hexan-2-ol ether **12** (55% yield). Deprotection of the tetrahydropyranyl ring with aqueous acid in the last step produced the desired product **4** in 12% overall yield (eight steps) from cyclopentene (**8**).

Scheme III



27 28

trans-6-Azabicyclo[3.1.0]hexan-2-ol (**4**) is a colorless liquid that undergoes significant decomposition within a week upon standing either neat or in solution (methylene chloride, K_2CO_3; −15 °C). Key features in the ^1H NMR spectrum of **4** were the appearance of multiplets at δ 2.49–2.65 and 4.25–4.28, which have been assigned to the aziridine (H_1 and H_5) and C-2 methine protons, respectively. Selective irradiation of the methylene protons at carbons 3 and 4 (δ 1.50–2.17) collapsed the C-2 proton signal to a sharp singlet, indicating that a small coupling constant existed between H_1 and H_2. The carbon-13 proton-decoupled NMR spectrum for **4** exhibited the expected five-line pattern.[22] Treatment of **4** with excess *p*-toluenesulfonyl chloride and base gave ditosylate **14**. This adduct (**14**) was identical with the major product isolated from the derivatization of the diastereomeric mixture (**4** and **7**) obtained in the previous synthetic sequence (Scheme I). The dissociation constant, pK_a, for the corresponding aziridinium ion **4a** was determined to

4 4a

be 6.14. One should note that this value is between that reported for *cis*-dimethylaziridine (pK_a = 8.72[23,13a]) and the aziridine in mitomycin C (**1**; pK_a = 3.2–4.3[4,24]). Several factors[23,25–27] may be responsible for this downward trend in basicity. Among these are potential adverse steric interactions at the nitrogen atom in **4** and **1**[25,26] and hybridizational changes at nitrogen resulting from the annelation of a five-membered ring system.[27]

The synthesis of the methyl analogue **5** (Scheme II) paralleled that of compound **4**. The corresponding alcohol **21** was prepared by treatment of 2-cyclopentenone (**20**) with methyllithium (72% yield). Use of the Grignard reagent, methylmagnesium bromide, led to reduced amounts of the tertiary alcohol **21**. Epoxidation of **21** with *m*-chloroperbenzoic acid in chloroform[28] gave **22** and a small amount of unidentified material. The methodology in the remaining steps in the sequence is identical with

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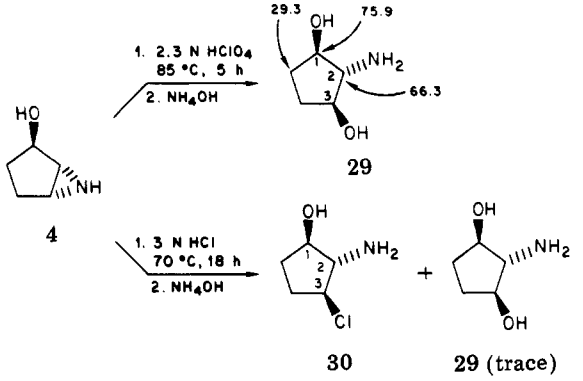
(28) For a related process, see: Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958–1965.

those described for the preparation of 4. The overall yield for 5 from 2-cyclopentenone was 11% (seven steps).

The last mitomycin mimic 6 was readily prepared in two steps (44% overall yield) from distilled indene 27 (Scheme III). Treatment of 27 with *N*-bromosuccinimide and an excess of NaN_3[11] gave presumed bromo azide 28 (85% yield). Carbon-13 NMR analysis indicated the presence of only one compound. Lithium aluminum hydride reduction of 28 in the second step gave the known indano-[1,2-*b*]aziridine (6).[29]

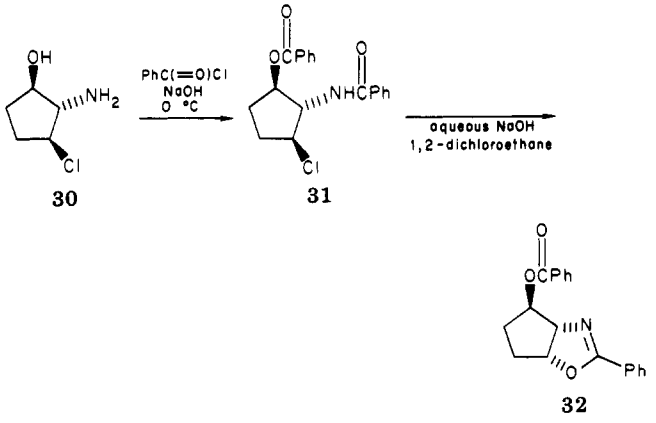
Results and Discussion

Treatment of the three annelated aziridines (4–6) with aqueous acid resulted in ring-opened products. Dissolution of 4 in aqueous 14% $HClO_4$ (2.3 N) acid (85 °C, 5 h) led to the formation of the symmetrical 1,3-dihydroxy-2-cyclopentylamine (29), while use of aqueous 3 N HCl (70 °C, 18 h) produced principally the chloro derivative 30 as well as a trace amount of 29. Employment of stronger acid

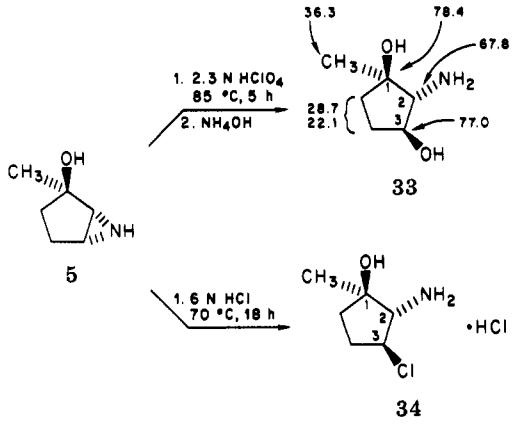


conditions (6 N HCl, 70 °C, 18 h) gave only 30. The rate of ring opening of 4 in aqueous 2.3 N $HClO_4$ acid (85 °C) could be qualitatively monitored by carbon-13 NMR spectroscopy. The approximate half-life for this conversion was 74 min. Significantly, no other products were observed.

Identification of 29 was simplified by the appearance of only three lines in the decoupled ^{13}C NMR spectrum. In addition, the ^1H NMR spectrum was in agreement with the inherent symmetry present in this molecule. Evidence in support of the proposed stereochemical assignment for 30 was secured by conversion of this compound to the dibenzoylated derivative 31, followed by cyclization to the cis-fused annelated oxazoline 32 with aqueous NaOH in 1,2-dichloroethane.

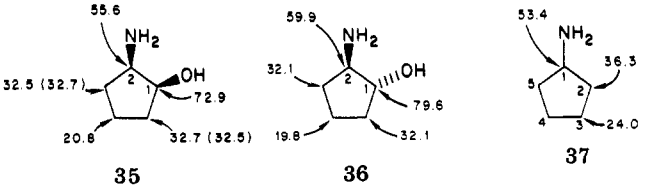


Similar results were obtained for the methyl analogue 5 in aqueous $HClO_4$ and HCl acid solutions. Cleavage of the aziridine ring in 5 in 2.3 N $HClO_4$ acid (85 °C) proceeded cleanly with an approximate half-life of 66 min.



Our tentative assignment of structure 33 rests on a series of ^1H and ^{13}C NMR observations. The regiochemistry of the ring-opening process is supported by the appearance in the ^1H NMR spectrum of 33 in D_2O of a doublet (J = 7.58 Hz) at δ 2.66 for the C-2 hydrogen atom and a multiplet at δ 3.40–3.60 for the C-3 hydrogen. Selective irradiation of the multiplet at δ 1.14–1.95 (C_4H_2 and C_5H_2) simplified the multiplet at δ 3.40–3.60 and did not alter the doublet at δ 2.66. Correspondingly, irradiation of the multiplet at δ 3.40–3.60 collapsed the doublet at δ 2.66 to a sharp singlet. A similar pattern was obtained from selective decoupling experiments performed on the protonated salt of 33.

One should be aware that the large proton–proton coupling constant observed for H_2 and H_3 in 33 does not insure that these two hydrogen atoms are trans to one another. It has been previously noted that the magnitude of this vicinal coupling constant in five-membered rings is not indicative of stereochemistry.[5,30] Our assignment of trans stereochemistry at carbons 2 and 3 stems from two independent ^{13}C NMR observations. First, a consistent pattern has been discerned in the ^{13}C NMR spectra of a wide variety of isomeric cis- and trans-1,2-disubstituted five-membered ring compounds (eight examples).[31,32] In each case the chemical shift value for the functionalized carbon atoms in the cis adduct absorbed at higher field than the corresponding resonances in the trans isomer.[33] No coherent pattern, however, was detected for any of the remaining carbon atoms in the ring. This effect is typified by *cis*- and *trans*-2-aminocyclopentanol (35 and 36, respectively).[34,13b] The chemical shift values for carbons 1



and 2 in 35 occurred at 72.9 and 55.6 ppm, respectively, while the corresponding resonances for 36 were located at

(29) (a) Horwell, D. C.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1969**, 1428. (b) Schmitz, E.; Janisch, K. *Khim. Geterot. Soed.* **1974**, *12*, 1629–1638. (c) Hassner, A.; Heathcock, C. *Tetrahedron* **1964**, *20*, 1037–1042.

(30) Huebner, C. F.; Donoghue, E. M.; Novak, C. J.; Dorfman, L.; Wenkert, E. *J. Org. Chem.* **1970**, *35*, 1149–1154.

(31) Cortes, S.; Kohn, H. *J. Org. Chem.*, in press.

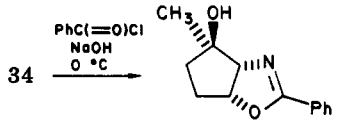
(32) Kohn, H.; Chiu, I.-C.; Jung, S H., unpublished results.

(33) For a related effect in isomeric *cis*- and *trans*-dimethylcyclopropanes, please see: Monti, J. P.; Faure, R.; Vincent, E.-J. *Org. Magn. Reson.* **1976**, *8*, 611–617.

(34) McCasland, G. E.; Smith, D. A. *J. Am. Chem. Soc.* **1950**, *72*, 2190–2195. Bannard, R. A.; Gibson, N. C. C.; Parkkari, J. H. *Can. J. Chem.* **1971**, *49*, 2064–2072.

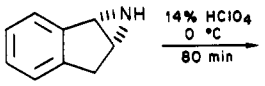
79.6 and 59.9 ppm. The second important NMR observation was the recognition that introduction of a hydroxyl group adjacent to the amino group in cyclopentylamine (**37**) (**37** → **35**, **36**) led to an upfield shift (Δ ppm ~ 4) for the other carbon atom flanking the amino group. The magnitude of this shift was independent of the stereochemical relationship of the two functional groups. Utilization of both these substituent effects led to the prediction that if opening of the aziridine ring in compounds **4** and **5** had proceeded in a trans fashion at C-5 then the chemical shift values for C-2 and C-3 should be approximately 66 and 76 ppm, respectively. Correspondingly, cis ring cleavage at C-5 would have led to signals at approximately 62 and 69 ppm for C-2 and C-3, respectively. The experimentally obtained values for compounds **29** and **33** are in excellent agreement with those predicted for the trans-ring-opened product.

Treatment of **5** with aqueous 6 N HCl led to the formation of a single product, which has been assigned structure **34**. Treatment of this compound with benzoyl choride and base yielded the cis-fused oxazoline **38**.

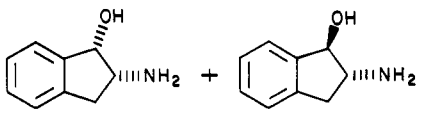


38

The complete stereoselectivity of the ring-opening process for compounds **4** and **5** is in contrast with that observed for **6**. Dissolution of indano[1,2-*b*]aziridine (**6**) in aqueous 14% $HClO_4$ acid (2.3 N; 0 °C, 80 min) gave a 2.7:1 mixture of *cis*- and *trans*-2-amino-1-indanol (**39** and **40**, respectively). The physical and chemical properties observed for both diastereomers compare favorably with those previously reported.[30,36] The approximate half-life for the ring opening of **6** in 2.3 N $HClO_4$ acid (0 °C) was 13.5 min. Compounds **39** and **40** did not epimerize at room temperature in aqueous 14% $HClO_4$ acid (2.3 N; TLC analysis). However, both adducts underwent epimerization in refluxing aqueous $HClO_4$ acid (1 h) to give a mixture of **39** and **40**, respectively (^{13}C NMR analysis).[37]



6

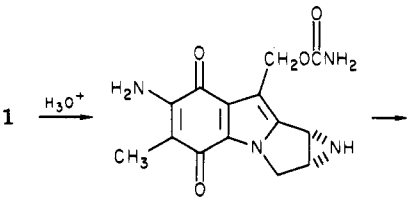


39 **40**

Conclusions

These results suggest that both **4** and **5** undergo ring opening under acidic conditions by an S_N2-type process to give the trans adducts. Moreover, these reactions proceed regiospecifically, with nucleophilic attack occurring preferably at the electronically most favorable carbon-5 site.[19] On the other hand, **6** appears to undergo hydrolysis under the employed acidic conditions by formally an S_N1 process to give the benzylic carbocation, which is then captured by water to give **39** and **40**. Variations in the precise nature of this process are conceivable. An analogous situation exists in rigid benzylic epoxides and diol epoxides of polycyclic hydrocarbons.[38-40] Research aimed at sorting out the mechanistic distinctions in this area is in progress.

Comparison of these general findings with those previously reported for the in vitro acid-promoted ring opening of mitomycin C[4,5] (**1**) suggests a likely sequence in the latter reaction is the loss of methanol, which forms indoloquinone **41**. This is followed by regiospecific opening of the aziridine ring to yield the stabilized, benzylic-like carbocation **42**. Subsequent capture of **42** by water would give the diastereomeric mixture **2** and **3**.



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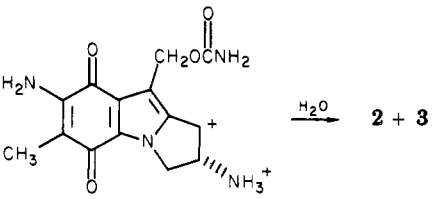

42

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. Infrared spectra (IR) were run on a Beckman IR 4250 spectrophotometer and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Associates Model T-60 and FT80A instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on a Varian Associates Model FT80A spectrometer. Chemical shifts are in parts per million relative to Me_4Si, and coupling constants (*J* values) are in hertz. In those cases where the reaction led to diastereomeric mixtures, the observed ^{13}C chemical shift value for the minor isomer(s) is given in parentheses. Small letters that appear in brackets after select ^{13}C resonances indicate the multiplicity of the signal in the corresponding proton-coupled ^{13}C NMR spectrum. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hewlett-Packard 5930 gas chromatograph–mass spectrometer. High-resolution (EI mode) mass spectra were performed by Dr. James Hudson at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Exact masses were determined by peak matching. pK_a measurements were determined with a Radiometer pHM 62 pH meter equipped with a TTT60 Titrator, REC 61 Servograph, and an ABU12 Autoburette. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, MI.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. All reactions were run under nitrogen and all glassware was dried before use unless otherwise noted. Short-path, medium-pressure (5–20 psi) liquid chromatography[41] was conducted with Merck

(35) Similar substituent effects have been previously noted in acyclic systems, please see: Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: New York, 1976; p 37.

(36) Irino, O.; Tateishi, M.; Miura, C.; Fukawa, K. *Chem. Pharm. Bull.* **1972**, *20*, 734–740. Thrift, R. I. *J. Chem. Soc. C* **1967**, 288–293.

(37) See ref 30 for a related study.

(38) (a) Sayer, J. M.; Yagi, H.; Silverton, J. V.; Friedman, S. L.; Whalen, D. L.; Jerina, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 1972–1978. (b) DiRaddo, P.; Chan, T. H. *J. Org. Chem.* **1982**, *47*, 1427–1431 and references therein. (c) Ross, A. M.; Pohl T. M.; Piazza, K.; Thomas, M.; Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658–1665.

(39) Balsamo, A.; Berti, G.; Crotti, P.; Ferretti, M.; Macchia, B.; Macchia, F. *J. Org. Chem.* **1974**, *39*, 2596–2598.

(40) Gagis, A.; Fusco, A.; Benedict, J. T. *J. Org. Chem.* **1972**, *37*, 3181–3182.

silica gel 60 PF254 (catalog no. 7747). Thin-layer chromatographic analyses were run on Analtech precoated silica G microscope slides (2.5 × 10 cm; catalog no. 01521).

Treatment of 9 with *N*-Bromosuccinimide and Sodium Azide. *N*-Bromosuccinimide (2.49 g, 14 mmol) was added in several portions (10 min) into a stirred mixture containing **9** (0.84 g, 10 mmol) and sodium azide (3.25 g, 50 mmol) in ethylene glycol dimethyl ether–H_2O (4:1, 80 mL) at −5 °C. The mixture was maintained at −5 °C for 0.5 h and then raised to 0 °C for another 0.5 h. Ether (200 mL) was added and the aqueous layer was separated. The aqueous layer was extracted with ether (2 × 50 mL), and the organic layers were combined, dried (K_2CO_3), filtered, and evaporated to dryness. The resulting yellow oily residue slowly solidified upon standing. Methylene chloride (10 mL) was added to the solid and cooled in an ice bath. The white crystalline succinimide was filtered off and the precipitate was washed with cold methylene chloride (2 × 5 mL). The combined methylene chloride solution was evaporated to dryness and the residue distilled through a Vigreaux column (10 cm) at 74 °C (0.6 mm) to afford 1.42 g (69% yield) of colorless azidobromohydrin **10** (two diastereomers). The mixture gave one spot on TLC (R_f 0.42, 20% ethyl acetate–hexanes): IR (neat, NaCl) 3400, 2960, 2110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–2.69 (m, 4 H), 2.73 (br s, 1 H, exchanged with D_2O), 3.89–4.33 (m, 3 H); ^{13}C NMR (benzene-d_6) 27.2 (27.7), 29.1 (30.3), 60.8 (59.5), 67.0 (67.6), 72.7 (78.6) ppm.

Anal. Calcd for $C_5H_8BrN_3O$: C, 29.14; H, 3.91; Br, 38.78; N, 20.39. Found: C, 29.22; H, 3.89; Br, 38.69; N, 20.42.

Treatment of 10 with Dihydropyran. A solution containing **10** (7.73 g, 37.5 mmol), dihydropyran (6.30 g, 75 mmol), and a catalytic amount of *p*-toluenesulfonic acid (68 mg, 0.4 mmol) in methylene chloride (72 mL) was stirred for 1 h at room temperature during which time the solution turned dark green. The solution was then diluted with methylene chloride (100 mL) and was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic layer was dried (K_2CO_3) and filtered, and the solvent was removed in vacuo. Short-path simple distillation of the remaining yellow residue at 110 °C (0.15 mm) gave 10.09 g (93% yield) of a mixture of *O*-tetrahydropyranyl derivatives **11**. The reaction product gave two overlapped spots on TLC (R_f 0.53 and 0.50, 5% ethyl acetate–hexanes): IR (neat, NaCl) 2940, 2880, 2100 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.83–2.10 (m, 10 H), 2.29–3.52 (m, 2 H), 3.52–4.24 (m, 3 H), 4.38–4.73 (m, 1 H); ^{13}C NMR ($CDCl_3$) 18.7, 18.9, 19.4, 25.4, 25.5, 25.6, 26.4, 26.7, 27.0, 27.3, 28.2, 28.4, 28.7, 29.8, 30.3, 30.6, 30.7, 56.3, 56.4, 56.8, 57.1, 61.7, 61.9, 62.5, 62.6, 67.5, 67.9, 68.0, 68.7, 74.9, 75.2, 75.8, 76.8, 95.7, 96.8, 98.6, 99.1 ppm.

Isolation of the more polar spot (R_f 0.50) from column chromatography (SiO_2, 5% ethyl acetate–hexanes), simplified the C-13 spectrum: ^{13}C NMR (benzene-d_6) 18.9 (19.6), 25.9 (25.8), 26.3 (26.7), 28.9 (27.0), 30.8 (30.6), 57.4 (57.2), 61.5 (62.3), 67.6, 75.3 (77.1), 95.5 (99.3) ppm. The signal located at 67.6 ppm was approximately twice the intensity of nearby peaks. MS, *m/e* (relative intensity) 290 (0.1), 249 (0.2), 145 (1), 133 (3), 135 (3), 119 (2), 121 (2), 85 (100).

Anal. Calcd for $C_{10}H_{16}BrN_3O_2$: C, 41.39; H, 5.56; Br, 27.54; N, 14.48. Found: C 41.50; H, 5.63; Br, 27.39; N, 14.31.

Preparation of Tetrahydropyranyl Ethers 12 and 13. To a suspension of lithium aluminum hydride (1.45 g, 34.8 mmol) in anhydrous ether (50 mL) was added dropwise a solution of **11** (5.06 g, 17.4 mmol) in anhydrous ether (50 mL) at 0 °C under N_2. The mixture was stirred at room temperature (2 h) and then diluted to 300 mL with ether. The reaction was quenched with saturated aqueous NH_4Cl. Upon addition of the NH_4Cl a white solid formed, which was filtered off, and the remaining filtrate was washed with saturated aqueous brine (2 × 10 mL). The organic layer was dried (K_2CO_3) and concentrated in vacuo. Distillation of the residue at 95 °C (0.55 mm) gave pure, colorless *O*-tetrahydropyranyl aziridines **12** and **13** (trans and cis mixture; 2.61 g, 82% yield; R_f 0.31, 8% MeOH–ethyl acetate): IR (neat, NaCl) 3260, 2960, 2900, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 1 H, exchanged with D_2O), 1.12–2.12 (m, 10 H), 2.32–2.75 (m, 2 H), 3.22–4.12 (m, 2 H), 4.18 (br d, J = 3 Hz, 1 H), 4.48–4.93 (m, 1 H); ^{13}C NMR ($CDCl_3$) 20.0 (19.4, 19.6, 20.1), 23.8, 24.8, 25.2, 25.5, 25.7, 26.6, 30.9, 31.2, 34.5, 35.0, 35.4, 35.5, 36.2, 38.0, 38.2, 38.8, 62.9 (62.1, 62.6, 63.1), 78.3 (77.5, 78.2, 79.0), 98.7 (97.8, 98.1, 98.5) ppm.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.10; H, 9.30; N, 7.67.

Preparation of *cis*- and *trans*-6-Azabicyclo[3.1.0]hexan-2-ol (7 and 4). To a stirred solution containing **13** and **12** (2.47 g, 13.54 mmol) in tetrahydrofuran (26 mL) was added 1.3 equiv of 3 N HCl (2.7 mL). The reaction mixture was stirred for 20 min, then methanol (26 mL) was added, and the reaction solution was stirred for additional 2 h. The reaction was concentrated in vacuo. Methylene chloride (50 mL) was then added to the remaining aqueous layer and the reaction mixture was basified with dilute aqueous NH_4OH. The organic layer was separated, and the aqueous layer was saturated with NaCl and repeatedly extracted with methylene chloride (4 × 50 mL). The organic layers were combined, dried (K_2CO_3), and evaporated to dryness. The residue was chromatographed (SiO_2, 20% MeOH–ethyl acetate) to give 0.68 g of **7** and **4** (51% yield; R_f 0.27, 20% MeOH–ethyl acetate): IR (neat, NaCl) 3600–3000 (br), 2940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33–2.00 (m, 4 H), 2.37–2.70 (m, 2 H), 3.07 (s, 2 H, exchanged with D_2O), 3.87–4.50 (m, 1, H); ^{13}C NMR ($CDCl_3$) 25.2 (25.8), 29.3 (26.6), 35.4 (35.2), 40.2 (39.4), 72.0 (73.0) ppm; MS, *m/e* (relative intensity) 100 (18), 99 (16), 98 (9), 84 (89), 82 (100).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.37; H, 9.30; N, 14.02.

The binary mixture of *cis*- and *trans*-6-azabicyclo[3.1.0]hexan-2-ol (**7** and **4**, respectively) could not be separated by GC, using a DB-1 bonded phase fused silica capillary column (60 M × 0.32 mm i.d.). ^{13}C NMR analysis of the mixture indicated the trans/cis ratio to be 2.5:1.

Ditosylation of *trans*- and *cis*-6-Azabicyclo[3.1.0]hexan-2-ol (4 and 7). Preparation of 14 and 15. To a stirred mixture containing **4** and **7** (ca. 3:1; 100 mg, 1.01 mmol), methylene chloride (1 mL), and 10 N aqueous sodium hydroxide (0.3 mL, 3.0 mmol) was added a solution of *p*-toluenesulfonyl chloride (490 mg, 2.6 mmol) in methylene chloride (3 mL). The reaction mixture was stirred at room temperature overnight, and then the organic layer was separated, dried (K_2CO_3), and evaporated to dryness to give 300 mg of crude product. Analysis of this material by ^{13}C NMR and TLC indicated the presence of two major compounds. Purification of the binary mixture by column chromatography (SiO_2, 30% ethyl acetate–hexanes) gave 140 mg (34% yield) of the less polar product **14** and 60 mg (15% yield) of the more polar compound **15**. The less polar product **14** (R_f 0.69, 50% ethyl acetate–hexanes) produced colorless crystals upon recrystallization from benzene–hexanes: mp 95–97 °C; IR (KBr) 3160, 2980, 2940, 1600, 1365, 1330, 1190, 1160, 1095, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44–2.00 (m, 4 H), 2.44 (s, 6 H), 3.37 (s, 2 H), 4.85 (br d, $J \sim$ 3 Hz, 1 H), 7.29–7.81 (m, 8 H). Selective irradiation of the protons at δ 1.44–2.00 collapsed the broad doublet at δ 4.85 to a singlet. ^{13}C NMR ($CDCl_3$) 21.6, 25.0, 28.3, 45.5, 45.7, 80.9, 127.8, 129.8, 130.1, 133.4, 134.7, 144.8, 145.3 ppm. The peaks at 21.6 and 127.8 ppm are approximately double the intensity of nearby peaks. MS, *m/e* (relative intensity) 252 (4), 237 (2), 236 (13), 235 (6), 155 (90), 91 (100), 80 (10), 65 (13).

Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C, 56.00; H, 5.19; N, 3.43; S, 15.74. Found: C, 56.09; H, 5.16; N, 3.40; S, 15.68.

Recrystallization of the more polar product **15** (R_f 0.56, 50% ethyl acetate–hexanes) from benzene–hexanes gave colorless crystals: mp 112–113 °C; IR (KBr) 3040, 3060, 2980, 1600, 1365, 1325, 1190, 1170, 1160, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.05 (m, 4 H), 2.48 (s, 6 H), 3.20–3.47 (m, 2 H), 4.67–5.03 (m, 1 H), 7.20–7.85 (m, 8 H). Selective irradiation of protons at δ 1.50–2.05 collapsed the multiplet at δ 4.67–5.03 to a doublet ($J \sim$ 2 Hz). ^{13}C NMR ($CDCl_3$) 21.6, 24.9, 25.0, 43.5, 46.0, 79.6, 127.8, 129.7, 129.9, 133.2, 135.1, 144.6, 145.0 ppm. The peaks at 21.6 and 127.0 ppm are approximately double the intensity of nearby peaks.

Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C, 56.00; H, 5.19; N, 3.43. Found: C, 56.36; H, 5.32; N, 3.24.

Preparation of the Tetrahydropyranyl Ether 17. A solution containing *cis*-2,3-epoxycyclopentan-1-ol[17] (**16**; 6.00 g, 60 mmol), dihydropyran (10.08 g, 120 mmol), and a catalytic amount of *p*-toluenesulfonic acid (103 mg, 0.6 mmol) in methylene chloride (120 mL) was stirred at room temperature (1 h). The solution was then diluted with methylene chloride (100 mL) and washed

(41) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351–1352.

with saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic layer was dried (K_2CO_3) and filtered, and the solvent was removed in vacuo. Distillation of the remaining pale-yellow residue through a Vigreaux column (10 cm) at 80 °C (0.38 mm) gave a diastereomeric mixture of tetrahydropyranyl derivative **17** (10.59 g, 96% yield). The mixture gave one spot on TLC (R_f 0.29, 10% ethyl acetate–hexanes): IR (neat, NaCl) 2930, 2860, 1440, 1350, 1120, 1070, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60–2.06 (m, 20 H), 3.00 (br s, 2 H), 3.18–3.52 (m, 4 H), 3.52–4.16 (m, 4 H), 4.59 (br s, 1 H), 4.76 (br s, 1 H); ^{13}C NMR (benzene-d_6) 19.5 (19.3), 24.8 (23.9), 25.4 (25.6), 25.9 (25.8), 31.1, 54.4, 55.5 (57.6), 61.8 (61.4), 79.0 (77.5), 97.8 (98.6) ppm. The signals located at 31.1 and 54.4 ppm were approximately twice the intensity of nearby peaks. MS, m/e (relative intensity) 184 (0.3), 101 (27), 99 (2), 85 (100), 83 (56), 67 (10). An analytical sample was obtained by subsequent column chromatography (SiO_2, 8% ethyl acetate–hexanes).

Anal. Calcd for $C_{10}H_{16}O_3$ (184.1099): C, 65.19; H, 8.75. Found (184.1101): C, 65.28; H, 8.90.

Treatment of 17 with KN_3. A solution of **17** (5.58 g, 30.3 mmol), potassium azide (4.91 g, 60.6 mmol), and 10% equivalent of 18-crown-6 (7.85 mg, 3 mmol) in acetonitrile–water (3:1, 80 mL) was heated to reflux (18 h). Ether (300 mL) was then added to the reaction, and the mixture was washed with H_2O (3 × 20 mL). The organic layer was dried (K_2CO_3) and then concentrated to dryness. Bulb-to-bulb distillation of the residue at 115 °C (external temperature, 0.4 mm) gave the desired trans-ring-opened azido alcohol **18** (5.72 g, 83% yield). Thin-layer analysis of the distillate showed two spots at R_f 0.50 and 0.39 (20% ethyl acetate–hexanes) corresponding to the two diastereomers. The isomers were separated by column chromatography (SiO_2, 15% ethyl acetate–hexanes). The less polar compound **18a** (R_f 0.50) exhibited the following spectral properties: IR (neat, NaCl) 3420, 2940, 2850, 2100, 1440, 1330, 1250, 1120, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–2.20 (m, 10 H), 3.23–4.18 (m, 6 H), 4.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 21.0, 25.0, 25.8, 27.3, 33.3, 64.9, 66.1, 77.1, 78.7, 100.5 ppm; MS m/e (relative intensity) 227 (12), 226 (26), 213 (13), 209 (4), 195 (5), 199 (3), 184 (100), 183 (52).

The more polar compound **18b** (R_f 0.39) exhibited the following spectral data: IR (neat, NaCl) 3405, 2940, 2100, 1340, 1260, 1140, 1070, 1030 cm^{-1}; ^1H NMR (benzene-d_6) δ 0.80–2.15 (m, 10 H), 2.57 (br d, J = 9 Hz, 1 H, exchanged with D_2O), 3.05–4.00 (m, 5 H), 4.42 (br s, 1 H); ^{13}C NMR (benzene-d_6) 19.8 [t], 25.7, 26.2, 28.3, 30.9, 62.2 [t], 66.6 [d], 77.4 [d], 77.8 [d], 99.8 [d]; MS, m/e (relative intensity) 227 (5), 226 (11), 213 (25), 209 (2), 199 (16), 195 (4), 184 (100), 183 (36).

Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.90; H, 7.61; N, 18.46.

Treatment of 18 with Methanesulfonyl Chloride. Methanesulfonyl chloride (0.45 mL, 5.81 mmol) was added to a stirred solution of **18** (diastereomeric mixture; 1.20 g, 5.28 mmol) in pyridine (dried over CaO; 6 mL). The solution was stirred for 1 h, and then the pyridinium hydrochloride salt was filtered off. The filtrate was diluted with ether (100 mL) and successively washed with 6 N aqueous HCl until the aqueous layer was acidic, saturated aqueous $NaHCO_3$ (10 mL) and a saturated brine solution (10 mL). The ethereal layer was dried (K_2CO_3) and filtered, and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, 15% ethyl acetate–hexanes) to yield azido mesylate **19** (diastereomeric mixture; 1.42 g, 88% yield). Attempted further purification by bulb-to-bulb distillation at 120 °C (external temperature, 0.2 mm) led to decomposition. Azido mesylate **19** (R_f 0.28, 20% ethyl acetate–hexanes) exhibited the following spectral properties: IR (neat, NaCl) 2950, 2110, 1360, 1185, 1025, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–2.35 (m, 10 H), 3.11 (s, 3 H), 4.35–4.45 (m, 4 H), 4.57–4.73 (m, 2 H); ^{13}C NMR ($CDCl_3$) 19.7 (18.6), 25.3 (24.1), 25.3 (24.2), 27.8 (24.5), 30.6 (29.6), 38.5 (37.4), 63.1 (61.9), 63.1 (62.3), 75.9 (73.0), 84.5 (83.8), 100.1 (96.3) ppm.

Anal. Calcd for $C_{11}H_{19}N_3O_5S$: C, 43.26; H, 6.27; N, 13.76; S, 10.50. Found: C, 43.34; H, 6.14; N, 13.54; S, 10.58.

One of the diastereomers of azido mesylate **19a** was selectively prepared by beginning with the less polar azido alcohol **18a** (R_f 0.50). The following spectral properties were observed for this mesylate: IR (neat, NaCl) 2940, 2860, 2100, 1350, 1220, 1180, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16–2.50 (m, 10 H), 3.07 (s, 3 H), 3.40–4.40 (m, 4 H), 4.40–4.83 (m, 2 H); ^{13}C NMR ($CDCl_3$) 18.6, 24.1, 24.2, 24.5, 29.6, 37.4, 61.9, 62.3, 73.0, 83.8, 96.3 ppm.

Anal. Calcd for $C_{11}H_{19}N_3O_5S$: C, 43.26; H, 6.27; N, 13.76; S, 10.50. Found: C, 43.34; H, 6.26; N, 13.69; S, 10.46.

Preparation of the Tetrahydropyranyl Ether 12. To a suspension of lithium aluminum hydride (0.40 g, 9.5 mmol) in anhydrous ether (50 mL) was added dropwise a solution of **19** (diastereomeric mixture; 2.81 g, 9.2 mmol) in anhydrous ether (20 mL) at 0 °C under N_2. The mixture was stirred at room temperature (2 h) and then diluted to 300 mL with ether. The reaction was quenched with saturated aqueous NH_4Cl. The white solid that formed was filtered off and the filtrate was washed with saturated aqueous brine (2 × 10 mL). The organic layer was dried (K_2CO_3) and evaporated to dryness to give a colorless oil (1.29 g). The crude *O*-tetrahydropyranyl aziridine was purified by column chromatography (SiO_2, 3% MeOH–ethyl acetate) to afford 0.92 g of pure **12** (diastereomeric mixture; 55% yield; R_f 0.60, 8% methanol–ethyl acetate): IR (neat, NaCl) 3300, 2960, 2860, 1450, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.57 (s, 1 H, exchanged with D_2O), 1.26–2.13 (m, 10 H), 2.52 (br s, 2 H), 3.16–4.03 (m, 2 H), 4.18 (br d, J = 4 Hz, 1 H), 4.67 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 19.9 (20.1), 25.5 (25.4), 26.6 (25.6), 31.0 (27.7), 31.2 (31.1), 35.3 (35.4), 37.9 (38.7), 62.7 (62.9), 78.1 (78.2), 98.0 (98.5) ppm; MS, m/e (relative intensity) 183 (1), 182 (3), 99 (11), 98 (6), 85 (100), 82 (37), 81 (14), 67 (28).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.36 H, 9.47; N, 7.53.

Preparation of *trans*-6-Azabicyclo[3.1.0]hexan-2-ol (4). To a stirred solution containing **12** (2.24 g, 11.5 mmol) in tetrahydrofuran (20 mL) was added 1.3 equiv of 3 N HCl (5 mL). The reaction was stirred for 20 min, then methanol (20 mL) was added, and the reaction solution was stirred for additional 2 h. The reaction was concentrated in vacuo. Methylene chloride (50 mL) was then added to the remaining aqueous layer and the reaction mixture was basified with diluted aqueous NH_4OH. The organic layer was separated, and the aqueous layer was saturated with NaCl and repeatedly extracted with methylene chloride (4 × 50 mL). The organic layers were combined, dried (K_2CO_3), and evaporated to dryness. The residue was chromatographed (SiO_2, 20% MeOH–ethyl acetate) to give 0.95 g of pure **4** (84% yield; R_f 0.27, 20% MeOH–ethyl acetate): IR (neat, NaCl) 3600–2800 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.17 (m, 6 H), 2.49–2.65 (m, 2 H), 4.25–4.28 (m, 1 H). Selective double irradiation of the protons at δ 1.50–2.17 collapsed the multiplet at δ 4.25–4.28 to a sharp singlet. ^{13}C NMR ($CDCl_3$) 25.1 [t], 29.4 [t], 35.3 [d], 40.2 [d], 72.4 [d] ppm; MS, m/e (relative intensity) 99 (1), 98 (6), 82 (100), 81 (13), 80 (54), 67 (7); mol wt 99.0686 (calcd for C_5H_9NO, 99.0684).

Preparation of 1-Methyl-2-cyclopenten-1-ol (21). To a stirred solution of 1.3 M methyllithium in ether (154 mL, 201 mmol) was added dropwise (30 min) a solution of 2-cyclopentenone (**20**; 15.0 g, 182.9 mmol) in anhydrous ether (200 mL) at 0 °C under N_2. After the addition, the reaction was stirred for an additional 0.5 h at 0 °C and then quenched with saturated aqueous NH_4Cl (20 mL). The ethereal layer was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was distilled through a Vigreaux column (10 cm) at 64 °C (38 mm) to give 12.91 g of the title compound **21** (72% yield) as a colorless liquid:[42] IR (neat, NaCl) 3370, 3070, 2980, 2960, 1620, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.73–1.97 (m, 2 H), 1.97–2.63 (m, 2 H), 2.75 (s, 1 H, exchanged with D_2O), 5.53–5.90 (m, 2 H); ^{13}C NMR ($CDCl_3$) 27.6 [q], 31.1 [t], 39.6 [t], 83.3 [s], 132.3 [d], 138.1 [d]; MS, m/e (relative intensity) 98 (5), 97 (14), 83 (100), 80 (3), 79 (11).

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.43; H, 10.24.

Preparation of 1-Methyl-*cis*-2,3-epoxycyclopentan-1-ol (22). *m*-Chloroperoxybenzoic acid (85%; 1.22 g, 6 mmol) was added in several portions (20 min) to a stirred solution of **21** (0.49 g, 5 mmol) in chloroform (20 mL) at 0 °C. After the addition, the reaction mixture was stirred for an additional 2 h at room temperature. The resulting cloudy mixture was filtered and the solid was washed with cold methylene chloride (10 mL). The combined filtrates were successively washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL),

(42) Mironov, V. A.; Akhrem, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 38–45.

dried ($MgSO_4$), filtered, and evaporated to dryness. Bulb-to-bulb distillation of the residue at 100 °C (external temperature, 50 mm) gave 0.51 g (90% yield) of **22** as a colorless liquid: IR (neat, NaCl) 3440, 2920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.27–1.90 (m, 4 H), 3.16 (d, J = 4 Hz, 1 H), 3.30–3.40 (m, 1 H), 3.50 (s, 1 H, exchanged with D_2O). Selective irradiation of the protons at δ 1.27–1.90 collapsed the multiplet at δ 3.30–3.40 to a doublet (J = 4 Hz). ^{13}C NMR ($CDCl_3$) 23.0 [t], 26.0 [t], 33.3 [q], 56.1 [d], 62.3 [d], 77.6 [s] ppm; MS, m/e (relative intensity) 99 (3), 96 (3), 43 (100); mol wt 114.0681 (calcd for $C_6H_{10}O_2$ 114.0684).

Protection of 22 with Dihydropyran. Treatment of **22** (4.00 g, 35 mmol) with dihydropyran (5.90 g, 70 mmol) and a catalytic amount of *p*-toluenesulfonic acid in methylene chloride (70 mL) according to the procedure used for the preparation of **17** gave 5.68 g (82% yield) of the colorless *O*-tetrahydropyranyl derivative **23** (diastereomeric mixture): bp 83 °C (0.6 mm); IR (neat, NaCl) 2940, 2860, 1390, 1370, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.34–2.17 (m, 10 H), 3.37 (s, 2 H), 3.37–3.75 (m, 1 H), 3.75–4.20 (m, 1 H), 4.97 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 19.7 (19.6), 20.7 (20.6), 23.0 (25.1), 25.4 (25.5), 31.2 (30.2), 31.9 (31.6), 54.3 (55.0), 60.1 (61.0), 63.5 (62.3) 82.0 (81.6), 95.1 (94.0) ppm; MS, m/e (relative intensity) 140 (4), 113 (4), 97 (71), 85 (100), 81 (10); mol wt of fragment 140.0840 (calcd for $C_8H_{12}O_2$ 140.0837).

Treatment of 23 with Potassium Azide. A procedure comparable to that described for the preparation of **18** was employed, using **23** (diastereomeric mixture; 11.40 g, 57.5 mmol), potassium azide (9.33 g, 115 mmol), and 0.10 equiv of 18-crown-6 (2.99 g, 1.15 mmol) in acetonitrile–water (3:1, 170 mL). The reaction was maintained at reflux for 3 days. After workup and simple distillation of the crude product, 11.78 g (85% yield) of the desired colorless azido alcohol **24** (diastereomeric mixture) was isolated. TLC analysis showed only one spot at R_f 0.65 (20% ethyl acetate–hexanes): bp 120 °C (0.15 mm); IR (neat, NaCl) 3400 (br), 2960, 2860, 2100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.33–2.47 (m, 10 H), 2.70 (d, 1 H, J = 9 Hz, exchanged with D_2O), 3.23–4.40 (m, 4 H), 4.55–5.03 (m, 1 H); ^{13}C NMR ($CDCl_3$) 20.8 (20.4), 21.6 (21.2), 25.1 (25.0), 25.2 (25.4), 32.3 (32.0), 32.4 (34.8), 63.6 (64.9), 67.1 (66.5), 82.2 (83.5), 84.2 (83.0), 94.4 (95.0) ppm; MS, m/e (relative intensity) 241 (0.1), 227 (0.2), 199 (0.3), 185 (0.2), 167 (3), 121 (3), 97 (8), 86 (53), 85 (100), 81 (16); mol wt 241.1437 (calcd for $C_{11}H_{19}N_3O_3$ 241.1426).

Preparation of Compound 25. Compound **24** (diastereomeric mixture) (4.22 g, 17.51 mmol) was converted to the corresponding mesylate with methanesulfonyl chloride (2.39 g, 21 mmol) in pyridine (17 mL) according to the procedure outlined for **19**, giving 5.59 g (87% yield) of crude product (diastereomeric mixture). TLC analysis indicated two spots at R_f 0.55 and 0.42 (20% ethyl acetate–hexanes). The mixture was separated by column chromatography (SiO_2, 15% ethyl acetate–hexanes). The less polar isomer (R_f 0.55) gave colorless needles from benzene–hexanes: mp 75–76 °C; IR (KBr) 2940, 2860, 2100, 1350, 1140, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14–2.67 (m, 10 H), 1.40 (s, 3 H), 3.15 (s, 3 H), 3.28–3.69 (m, 1 H), 3.69–4.48 (m, 3 H), 4.81 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 20.3, 20.4, 24.9, 25.3, 31.8, 33.4, 38.9, 63.5, 63.7, 81.1, 89.8, 94.9 ppm; MS, m/e (relative intensity) 277 (3), 193 (10), 175 (19), 122 (18), 112 (49), 113 (64), 94 (16), 85 (100), 79 (21).

Anal. Calcd for $C_{12}H_{21}N_3O_5S$ ($M^+ - N_3$, 277.1109): C, 45.15; H, 6.62; N, 13.15; S, 10.04. Found ($M^+ - N_3$, 277.1117): C, 45.18; H, 6.55; N, 13.03; S, 10.08.

The more polar isomer (R_f 0.42) formed as colorless crystals from benzene–hexanes: mp 72–73 °C; IR (KBr) 2960, 2880, 2110, 1330, 1200, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12–2.38 (m, 10 H), 1.42 (s, 3 H), 3.15 (s, 3 H), 3.25–3.69 (m, 1 H), 3.69–4.50 (m, 3 H), 4.81 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 19.7, 21.9, 25.2, 25.4, 31.7, 32.1, 39.0, 62.5, 63.7, 81.5, 89.6, 93.7 ppm; MS, m/e (relative intensity) 277 (2), 193 (12), 192 (11), 175 (24), 122 (22), 113 (8), 94 (18), 85 (100), 79 (23).

Anal. Calcd for $C_{12}H_{21}N_3O_5S$ ($M^+ - N_3$, 277.1109): C, 45.15; H, 6.62; N, 13.15; S, 10.04. Found ($M^+ - N_3$, 277.1112): C, 45.23; H, 6.52; N, 13.22; S, 10.03.

Reduction of 25 with Lithium Aluminum Hydride. Compound **25** (diastereomeric mixture; 4.88 g, 15.3 mmol) was treated with lithium aluminum hydride (1.25 g, 30.5 mmol) in anhydrous ether (200 mL) in a manner similar to that described for the synthesis of **12**. Bulb-to-bulb distillation of the reaction product at 115 °C (external temperature, 0.6 mm) gave 1.63 g (54% yield) of colorless aziridine **26**. Analysis of the distillate by TLC showed only one spot at R_f 0.58 (20% methanol–ethyl acetate): IR (neat, NaCl) 3240, 2870, 2830, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.46 (s, 1 H, exchanged with D_2O), 1.38 (s, 3 H), 1.03–2.09 (m, 10 H), 2.34–2.65 (m, 2 H), 3.23–3.65 (m, 1 H), 3.71–4.14 (m, 1 H), 4.77 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 20.7 (20.6), 21.5 (21.2), 25.5, 26.9 (26.7), 32.2 (32.8), 32.5, 36.0, 42.7 (42.6), 63.5 (63.3), 84.4 (84.5), 94.7 (94.4) ppm. The signals at 25.5, 32.5, and 36.0 ppm were larger than neighboring peaks. MS, m/e (relative intensity) 197 (0.2), 112 (34), 97 (18), 96 (100), 85 (25), 82 (29).

Anal. Calcd for $C_{11}H_{19}NO_2$ (197.1416): C, 66.97; H, 9.71; N, 7.10. Found (197.1417): C, 66.77; H, 9.53; N, 7.02.

Preparation of *cis*-2-Methyl-*trans*-6-azabicyclo[3.1.0]hexan-2-ol (5). A procedure comparable to that described for the preparation of **4** was adopted with **26** (diastereomeric mixture; 1.11 g, 5.6 mmol). Purification of the desired product was accomplished by column chromatography (SiO_2, 20% methanol–hexanes), giving 0.36 g (57%) of **5** as a colorless liquid (R_f 0.31, 20% methanol–hexanes): IR (neat, NaCl) 3600–3040, 2970, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19–1.56 (m, 2 H), 1.34 (s, 3 H), 1.71–1.98 (m, 4 H; two protons exchanged with D_2O) 2.33 (d, J = 4.0 Hz, 1 H), 2.46–2.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) 24.3, 26.1, 34.6, 35.7, 43.8, 78.4 ppm; MS, m/e (relative intensity) 114 (19), 113 (62), 112 (15), 98 (35), 96 (100), 81 (28), 80 (25); mol wt 113.0843 (calcd for $C_6H_{11}NO$ 113.0841).

Treatment of Indene (27) with Sodium Azide and *N*-Bromosuccinimide. *N*-Bromosuccinimide (10.60 g, 59.6 mmol) was added in several portions (15 min) to a stirred mixture containing freshly distilled **27** (5.48 g, 42.6 mmol) and sodium azide (11.07 g, 170.3 mmol) in 4:1 ethylene glycol dimethyl ether–H_2O (340 mL) at 0 °C. The mixture was maintained at −5 °C for 0.5 h and then raised to 0 °C for another 0.5 h. Ether (300 mL) was added and the organic layer was separated. The aqueous layer was extracted with ether (2 × 100 mL), and the organic layers were combined, dried (K_2CO_3), and evaporated. The residue was cooled (5 °C, 2 h), and then the white crystalline succinimide was filtered off. Distillation of the filtrate through a Vigreaux column (10 cm) at 95–105 °C (0.3 mm) gave 8.58 g (85% yield) of **28**: IR (neat, NaCl) 3160, 3100, 2900, 2120, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (dd, J = 5.6, 16.7 Hz, 1 H), 3.60 (dd, J = 6.7, 16.7 Hz, 1 H), 4.38 (ddd, J = 5.2, 5.6, 6.7 Hz, 1 H), 5.02 (d, J = 5.2 Hz, 1 H), 7.22–7.36 (A_2B_2 pattern, 4 H); ^{13}C NMR ($CDCl_3$) 41.6, 51.1, 73.4, 124.6, 125.0, 127.8, 129.5, 138.1, 140.2 ppm; MS, m/e (relative intensity) 130 (93), 116 (97), 115 (100), 103 (98); mol wt 236.9910 (calcd for $C_9H_8BrN_3$ 236.9902).

Preparation of Indano[1,2-*b*]aziridine (6). To a suspension of lithium aluminum hydride (0.40 g, 10.9 mmol) in anhydrous ether (40 mL) was added dropwise a solution of **28** (2.59 g, 10.9 mmol) in anhydrous ether (20 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature (1 h) and then was quenched with water. The ethereal layer was decanted, and the aqueous layer was saturated with NaCl and repeatedly extracted with ether (3 × 50 mL). The ethereal layers were combined, dried (K_2CO_3), evaporated to dryness, and then purified by column chromatography (SiO_2, 10% methanol–ethyl acetate) to yield 0.85 g (61%) of the title compound: IR (neat, NaCl) 3270–3200 (m), 3040, 2900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.43 (s, 1 H, exchanged with D_2O), 2.73–3.20 (m, 2 H), 2.92 (br s, 2 H), 6.95–7.20 (m, 4 H); ^{13}C NMR ($CDCl_3$) 35.5, 36.0, 39.9, 124.2, 126.1, 126.4, 127.1, 141.4, 145.1 ppm; MS, m/e (relative intensity) 132 (33), 131 (32), 130 (100), 116 (39), 115 (42); MS (CI) 132 (P + 1).

Treatment of **6** with phenyl isocyanate according to the procedure of Hassner and Heathcock gave crude *N*-(phenylcarbamoyl)indene[1,2]imine. Recrystallization (two times) of this derivative from acetone–hexanes gave the purified adduct: mp 137–139 °C (lit.[29c] mp 138–141 °C).

Treatment of *trans*-6-Azabicyclo[3.1.0]hexan-1-ol (4) with $HClO_4$. A solution of **4** (210 mg, 2.1 mmol) in aqueous 2.3 N $HClO_4$ (14%, 2.1 mL) was heated at 85° C (5 h). The solvent was removed in vacuo. ^{13}C NMR analysis of the residue indicated only one product: ^{13}C NMR (D_2O; reference, CH_3CN) 28.5, 64.4, 71.9 ppm. The residue was basified with aqueous NH_4OH (pH 9) and extracted with methylene chloride (5 × 20 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo, yielding a pale-yellow liquid that was identified as **29** (80 mg, 33%): IR (neat, NaCl) 3620–3050, 2950, 2835, 1220

cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.22–1.97 (m, 4 H), 2.59 (t, 1 H, J = 7.2 Hz), 3.31–3.79 (m, 2 H), 3.41 (s, 4 H, exchanged with D_2O). Selective irradiation of the signal at δ 1.22–1.97 collapsed the multiplet at δ 3.31–3.79 to a doublet (J = 7.2 Hz) but did not alter the triplet at δ 2.59. Selective irradiation of the peak at δ 2.59 narrowed the multiplet at δ 3.31–3.79. ^{13}C NMR (Me_2SO-d_6) 29.3, 66.3, 75.9 ppm; MS, m/e (relative intensity) 99 (100), 82 (68); mol wt 117.0793 (calcd for $C_5H_{11}NO_2$ 117.0790).

Treatment of *trans*-6-Azabicyclo[3.1.0]hexan-2-ol (4) with HCl. A solution of 4 (310 mg, 3.13 mmol) in 6 N HCl (6 mL) was heated at 70 °C (18 h) and then the solvent was removed in vacuo, leaving a yellow solid. ^{13}C NMR analysis of the crude product indicated only one product. The crude HCl salt was dissolved in aqueous NH_4OH and the basic aqueous solution extracted with methylene chloride (4 × 20 mL). The organic layers were combined, dried (K_2CO_3), filtered, and evaporated to dryness to give **30** (310 mg, 74% yield): IR (neat, NaCl) 3630–3000, 2930, 2860, 1595, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83–2.23 (m, 4 H), 2.56 (s, 3 H, exchanged with D_2O), 3.02 (dd, 1 H, J = 7.8, 8.7 Hz), 3.64–3.83 (m, 2 H). (Addition of DCl–D_2O shifted the doublet of doublets at δ 3.02 downfield to δ 3.58.) Selective irradiation of the signal at δ 1.83–2.23 simplified the multiplet at δ 3.64–3.83, while no change was observed in the doublet of doublets at δ 3.02. Selective irradiation of the peak at δ 3.64–3.83 collapsed the doublet of doublets at δ 3.02 to a broad singlet. ^{13}C NMR ($CDCl_3$) 29.6, 31.0, 63.5, 68.1, 75.7 ppm; MS, m/e (relative intensity) 137 (4), 135 (11), 100 (20), 85 (100), 82 (19), 72 (34), 56 (67); mol wt 135.0454 (calcd for $C_5H_{10}ClNO$ 135.0451).

Treatment of 30 with Benzoyl Chloride. To a stirred mixture of **30** (150 mg, 1.1 mmol) in acetonitrile (10 mL) and aqueous 2 N NaOH (2 mL, 4 mmol) was added a solution of benzoyl chloride (620 mg, 4.4 mmol) in acetonitrile (0.5 mL) at 0 °C. The reaction was stirred at 0 °C (2 h) and then neutralized with aqueous 3 N HCl at 0 °C. The solvent was concentrated in vacuo and the residue was extracted with methylene chloride (4 × 15 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and evaporated to dryness. Dibenzoate **31** was isolated by column chromatography (SiO_2, 20% ethyl acetate–hexanes). The desired compound was further purified by recrystallization from ethanol, yielding 190 mg (50%): mp 142–143 °C; IR (KBr) 3060, 2980, 1740, 1640, 1520, 1320, 1260, 1100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.72–2.67 (m, 4 H), 4.27–4.93 (m, 2 H), 5.20–5.61 (m, 1 H), 7.13–8.21 (m, 10 H). The NH proton was not detected. ^{13}C NMR (Me_2SO-d_6) 28.6, 32.4, 60.6, 63.9, 77.7, 127.3, 128.2, 128.3, 128.7, 129.2, 129.5, 131.5, 133.4, 165.4, 166.4; MS, m/e (relative intensity) 204 (36), 203 (16), 186 (2), 122 (27), 105 (100), 82 (9), 77 (30).

Anal. Calcd for $C_{19}H_{18}ClNO_3$ (343.0975): C, 66.37;, H, 5.28; N, 4.07; Cl, 10.31. Found (343.0998): C, 66.32; H, 5.24; N, 4.14; Cl, 10.23.

Preparation of Oxazoline Derivative (32). A mixture of dibenzoate **31** (100 mg, 0.29 mmol) and 1.3 equiv of aqueous 2 N NaOH (0.2 mL) in 1,2-dichloroethane (5 mL) was heated to reflux (18 h). The organic layer was separated, dried (K_2CO_3), and evaporated in vacuo, giving 70 mg (82% yield) of crude oxazoline **32**. Recrystallization from methylene chloride–hexanes afforded the purified adduct: mp 132–134 °C; IR (CH_2Cl_2, NaCl) 2960, 1700, 1630, 1040 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.58–2.39 (m, 4 H), 4.74 (d, 1 H, J = 7.7 Hz), 5.14–5.45 (m, 2 H), 7.23–7.64 (m, 5 H), 7.76–8.20 (m, 5 H). Selective irradiation of the signal at δ 5.14–5.45 collapsed the doublet at δ 4.74 to a broad singlet. Selective irradiation of the peaks at δ 1.58–2.39 altered the multiplet at δ 5.14–5.45 but did not change the doublet at δ 4.74. ^{13}C NMR (Me_2SO-d_6) 28.0, 31.6, 76.8, 79.8, 83.7, 127.1, 128.0, 128.5, 128.7, 129.3, 129.8, 131.7, 133.3, 163.9, 165.0 ppm; MS, m/e (relative intensity) 203 (1), 202 (4), 186 (4), 185 (24), 158 (18), 105 (100), 77 (60); mol wt 307.1210 (calcd for $C_{19}H_{17}NO_3$ 307.1208).

Treatment of *cis*-2-Methyl-*trans*-6-azabicyclo[3.1.0]hexan-2-ol (5) with $HClO_4$. A solution of **5** (370 mg, 3.27 mmol) in aqueous 2.3 N $HClO_4$ (14%, 3.27 mL) was heated at 85° C (5 h). The solvent was removed in vacuo and the ring-opened product directly analyzed: ^1H NMR (D_2O; reference, CH_3CN) δ 1.15 (s, 3 H), 1.54–2.32 (m, 4 H), 3.19 (br d, 1 H, J = 7.9 Hz), 3.88–4.20 (m, 1 H). Selective irradiation of the signal at δ 1.54–2.32 collapsed the multiplet at δ 3.88–4.20 to a doublet (J = 7.8 Hz) but did not alter the doublet at δ 3.19. Selective irradiation of the peak at δ 3.88–4.20 collapsed the doublet at δ 3.19 to a singlet. ^{13}C NMR (D_2O; reference, CH_3CN) 22.4, 29.0, 36.6, 67.5, 73.3, 76.5 ppm.

The hydrolyzed product was then basified with aqueous NH_4OH and continuously extracted with methylene chloride. The organic layer was separated, dried (K_2CO_3), and evaporated to give 130 mg (30% yield) of **33** as a yellow liquid: IR (neat, NaCl) 3300 (br), 2960, 1450, 1170, 1065 cm^{-1}; ^1H NMR (D_2O; reference, benzene) δ 0.90 (s, 3 H), 1.14–1.95 (m, 4 H), 2.66 (d, 1 H, J = 7.6 Hz), 3.40–3.60 (m, 1 H). Selective irradiation of the signal at δ 1.14–1.95 simplified the multiplet at δ 3.40–3.60, but did not alter the doublet at δ 2.66. Selective irradiation of the peak at δ 3.40–3.60 collapsed the doublet at δ 2.66 to a sharp singlet. ^{13}C NMR (D_2O; reference, CH_3CN) 22.1, 28.7, 36.3, 67.8, 77.0, 78.4 ppm; MS (CI), 132 (P + 1); mol wt 131.0940 (calcd for $C_6H_{13}NO_2$ 131.0946).

Treatment of *cis*-2-Methyl-*trans*-6-azabicyclo[3.1.0]hexan-2-ol (5) with HCl. A solution of **5** (320 mg, 2.83 mmol) in 6 N aqueous HCl (5.66 mL, 33.96 mmol) was heated at 75 °C (16 h). The solvent was removed in vacuo yielding a yellow solid (500 mg). ^{13}C NMR analysis of the crude residue indicated only one product. The solid was recrystallized (two times) from methanol–ether to give **34** as colorless crystals: mp 217–219 °C dec; IR (KBr) 3280, 3160–2660, 1630, 1600 cm^{-1}; ^1H NMR (D_2O; reference, CH_3CN) δ 1.21 (s, 3 H), 1.39–2.46 (m, 4 H), 3.47 (d, 1 H, J = 9.0 Hz), 3.94–4.33 (m, 1 H). Irradiation of the signal at δ 3.94–4.33 collapsed the doublet at δ 3.47 to a singlet, while irradiation of the peak at δ 1.39–2.46 simplified the multiplet at δ 3.94–4.44. ^{13}C NMR (D_2O; reference, CH_3CN) 22.4, 30.9, 37.1, 57.4, 68.3, 76.5 ppm; MS, m/e (relative intensity) 152 (19), 150 (58), 134 (32), 132 (100), 114 (28), 93 (31).

Anal. Calcd for $C_6H_{13}Cl_2NO$: C, 38.72; H, 7.04; Cl, 38.11; N, 7.53. Found: C, 38.80; H, 7.02; Cl, 38.04; N, 7.49.

Preparation of Oxazoline 38. Compound **34** (240 mg, 1.3 mmol) was dissolved in aqueous 2 N NaOH (2 mL, 4 mmol) and acetonitrile (10 mL) at 0 °C, and the benzoyl chloride (550 mg, 3 mmol) was added. The reaction mixture was stirred at 0 °C (2 h). The organic solvent was removed in vacuo and the aqueous layer extracted with methylene chloride (4 × 20 mL). The combined organic layers were dried (K_2CO_3), filtered, and evaporated to dryness. The product was isolated by column chromatography (SiO_2, 50% ethyl acetate–hexanes) and identified as oxazoline **38** (120 mg, 45% yield; R_f 0.30, 50% ethyl acetate–hexanes): IR (CH_2Cl_2, NaCl) 3500–3200, 3020, 2960, 2930, 1640, 1045, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07–1.78 (m, 2 H), 1.50 (s, 3 H), 1.78–2.47 (m, 2 H), 3.37 (br s, 1 H, exchanged with D_2O), 4.35 (d, 1 H, J = 7.3 Hz), 5.05–5.48 (m, 1 H), 7.20–7.68 (m, 3 H), 7.68–8.23 (m, 2 H). Selective irradiation of the signal at δ 5.05–5.48 collapsed the doublet at δ 4.35 to a broad singlet. ^{13}C NMR ($CDCl_3$) 24.0, 31.9, 36.3, 81.4, 82.6, 85.3, 126.9, 128.3, 128.4, 131.3, 167.4 ppm; MS, m/e (relative intensity) 217 (2), 202 (1), 199 (8), 174 (12), 146 (17), 122 (4), 105 (100), 77 (46); mol wt 217.1104 (calcd for $C_{13}H_{15}NO_2$ 217.1103).

Treatment of Indano[1,2-*b*]aziridine (6) with $HClO_4$. To a stirred solution of **6** (300 mg, 2.3 mmol) in H_2O (0.9 mL) was added $HClO_4$ (70%, 0.3 mL) dropwise at 0 °C. The residue was stirred (80 min) at 0 °C and then the reaction basified with dilute NH_4OH (pH ~9) at 0 °C. The solvent was concentrated in vacuo and then extracted with methylene chloride (4 × 20 mL). The organic layers were dried (K_2CO_3), filtered, and evaporated to dryness, giving 240 mg (71% yield) of a gray solid. ^{13}C NMR analysis of the residue indicated the presence of only two compounds in an approximate ratio of 2.7:1. Purification of the binary mixture was accomplished by column chromatography (SiO_2, 1% NH_4OH–methanol). The minor product was identified as *trans*-2-amino-1-indanol (**40**; R_f 0.45, 1% NH_4OH–methanol): mp 101–103 °C (benzene–hexanes) (lit.[30] mp 104–105 °C); IR (KBr) 3340, 3260, 3180, 3020, 1610, 1460, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30–2.94 (m, 1 H), 2.97–3.49 (m, 2 H), 3.00 (br s, exchanged with D_2O), 4.68 (d, 1 H, J = 6.4 Hz), 7.02–7.23 (m, 4 H); ^{13}C NMR ($CDCl_3$–Me_2SO-d_6) 38.6, 62.8, 82.5, 124.0, 124.6, 126.8, 127.8, 139.7, 143.9 ppm. The major product was identified as *cis*-2-amino-1-indanol (**39**; R_f 0.42, 1% NH_4OH–methanol): mp 99–100 °C (benzene–hexanes) (lit.[30] mp 107–108 °C); IR (KBr) 3600–3220, 3020, 2900, 1575, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (s, 3 H, exchanged with D_2O), 2.66 (dd, 1 H, J = 6.2, 15.0 Hz), 3.05 (dd,

1 H, J = 6.2, 15.0 Hz), 3.37-3.80 (m, 1 H), 4.78 (d, 1 H, J = 5.3 Hz), 7.19-7.38 (m, 4 H). Selective irradation of the signal at δ 3.37-3.80 collapsed the doublet at δ 4.78 to a singlet. ^{13}C NMR ($CDCl_3$) 39.3, 55.0, 75.3, 125.1, 125.4, 127.0, 128.4 ppm.

The *cis*-*O*,*N*-diacetate of **39** was prepared according to the procedure of Wenkert and co-workers:[30] mp 117-120 °C (benzene-hexanes) (lit.[30] mp 118-120 °C); ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3 H), 2.05 (s, 3 H), 2.72-3.50 (m, 2 H), 4.66-5.04 (m, 1 H), 6.00 (d, 1 H, J = 6.0 Hz), 7.07-7.49 (m, 4 H); ^{13}C NMR ($CDCl_3$) 21.1, 23.2, 36.9, 51.6, 76.3, 124.9, 126.7, 127.3, 129.7, 139.2, 141.7, 169.8, 169.9 ppm.

Epimerization Studies of *trans*-2-Amino-1-indanol (40). A solution of **40** (70 mg, 0.5 mmol) in aqueous 2.3 N $HClO_4$ (14%, 4 mL) was heated to reflux (1 h). The reaction was then basified with aqueous 6 N NH_4OH and the solution extracted with methylene chloride (3 × 20 mL). The organic layers were dried (K_2CO_3), concentrated in vacuo, and then analyzed directly by ^{13}C NMR. Comparison of the peak intensities of comparable carbon atoms indicated that both *cis*- and *trans*-2-amino-1-indanol (**39** and **40**, respectively) were present in an approximate ratio of 1:2.2.

Repetition of this reaction both at 0 °C (1 h) and at room temperature (30 min) did not lead to the formation of the cis-adduct **39** (TLC analysis).

Epimerization Studies of *cis*-2-Amino-1-indanol (39). The preceding reaction was repeated with a solution of **39** (70 mg, 0.5 mmol) in aqueous 2.3 N $HClO_4$ (14%, 4 mL). ^{13}C NMR analysis of the reaction after reflux (1 h) and workup indicated the presence of *cis*- and *trans*-2-amino-1-indanol (**39** and **40**, respectively) in a ratio of 1.4:1.

Repetition of this reaction both at 0 °C (1 h) and at room temperature (30 min) did not lead to the formation of the trans-adduct **40** (TLC analysis).

Kinetic Study of Ring Opening of 4 with $HClO_4$. A solution of **4** (310 mg, 3.13 mmol) in 14% $HClO_4$ in D_2O (2.3 N, 3.13 mL) was transferred to a 10-mm NMR tube. Acetonitrile (0.1 mL) was added as an internal standard and then the tube sealed with a torch. The NMR tube was then immersed in an oil bath and maintained at 85 ± 1 °C. At periodic intervals, the tube was removed and the ^{13}C NMR spectrum recorded. The reaction was monitored for 3 h. The rate of ring opening was determined by comparing the peak heights of comparable carbon signals in the starting material and product.

Kinetic Study of Ring Opening of 5 with $HClO_4$. With use of the procedure described for **4**, the rate of ring opening of **5** (370 mg, 3.27 mmol) was determined in 14% $HClO_4$ in D_2O (2.3 N, 3.27 mL) at 85 ± 1 °C. The reaction was monitored for 3 h.

Kinetic Study of Ring Opening of 6 with $HClO_4$. An ice-cold aqueous solution of 2.3 N $HClO_4$ (14%, 8 mL) was added to cold **6** (1.00 g, 7.6 mmol). The solution was stirred at 0 °C. The reaction was monitored for 40 min. At periodic intervals aliquots (2 mL) were removed and quenched with ice-cold dilute aqueous NH_4OH. The basic aqueous solution was then extracted with methylene chloride (3 × 15 mL), and the combined organic layers were dried (K_2CO_3), filtered, and evaporated to dryness. The residue was directly analyzed by ^{13}C NMR. The rate of ring opening was determined by comparing the peak heights of comparable carbon signals in the starting material and products.

Measurement of pK_a of *trans*-6-Azabicyclo[3.1.0]hexan-2-ol (4). A dilute (2.5×10^{-4} M) aqueous solution of **4** was made up with CO_2-free distilled water. The titrations were performed automatically with standardized aqueous 0.1 N HCl. The cell was thermostated at 25 ± 0.2 °C Each titration was continued beyond the end pont. The pK_a value was determined by standard graphical methods with the average value for three measurements reported.

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Registry No. **4**, 86288-25-7; **5**, 86288-26-8; **6**, 26536-31-2; **6** (*N*-phenylcarbamoyl derivative), 50673-02-4; **7**, 86333-90-6; **9**, 3212-60-0; **10**, 86307-64-4; **11**, 86307-65-5; **12** (isomer 1), 86288-27-9; **12** (isomer 2), 86333-91-7; **13** (isomer 1), 86333-92-8; **13** (isomer 2), 86333-93-9; **14**, 86288-28-0; **15**, 86333-94-0; **16**, 29782-88-5; **17** (isomer 1), 86288-29-1; **17** (isomer 2), 86333-95-1; **18** (isomer 1), 86288-30-4; **18** (isomer 2), 86333-96-2; **19** (isomer 1), 86288-31-5; **19** (isomer 2), 86333-97-3; **20**, 930-30-3; **21**, 40459-88-9; **22**, 86288-32-6; **23** (isomer 1), 86288-33-7; **23** (isomer 2), 86333-98-4; **24** (isomer 1), 86288-34-8; **24** (isomer 2), 86333-99-5; **25** (isomer 1), 86288-35-9; **25** (isomer 2), 86334-00-1; **26** (isomer 1), 86288-36-0; **26** (isomer 2), 86334-01-2; **27**, 95-13-6; **28**, 86288-37-1; **29**, 86288-38-2; **30**, 86288-39-3; **31**, 86288-40-6; **32**, 86288-41-7; **33**, 86288-42-8; **34**, 86288-43-9; **38**, 86288-44-0; **39**, 23337-80-6; **40**, 13575-72-9.

9,10-*syn*-Podocarpane Diterpenoids. An Approach to the Tricyclic Skeleton by Diels-Alder Cycloaddition. Related Crystal Structure Determination and Theoretical Aspects

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The cycloaddition of 2-carbomethoxy-1,4-benzoquinone with vinylcyclohexene is reported. The configuration at C-9 has been determined by X-ray diffraction on compound **5**, whose structure is strictly related to that of the adduct **3**, which is a useful intermediate for the total synthesis of 9,10-*syn*-podocarpane diterpenoids. It is shown that a complete PMO treatment can account for the regio- and stereochemical outcome of the reaction.

We report herein the use of the Diels-Alder reaction in a short stereospecific approach to the total synthesis of the 9,10-*syn*-podocarpane diterpenoids, a class of rather unusual natural compounds of biological interest. Many examples have been reported, such as Annonalide in *Annona coriacea*,[1] Momilactones in *Oriza sativa*,[2] Icacina and re-

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