Table II. Bromination of Aromatic Hydrocarbons with $CuBr_2/Al_2O_3$[a]

aromatics	°C/h	products	total yield, %	ratio of products, % mono-Br	di-Br
naphthalene	80/2	1-Br	98	100	0
	130/1[b]	1-Br, 1,4-Br_2	100	8	92
1-methylnaphthalene	50/2	4-Br	100	100	0
	80/16	2,4-Br_2	100	0	100
phenanthrene	80/2	9-Br	95	100	0
fluorene	80/2	2-Br	95	100	0
	80/6	2,7-Br_2	98	0	100
toluene	80/8	2-Br, 4-Br	65	100[c]	0
p-xylene	80/1.5	2-Br, 2,6-Br_2	95	85	15
mesitylene	50/1	2-Br, 2,4-Br_2	98	99	1

[a] $CuBr_2$/aromatic = 5; solvent: carbon tetrachloride. [b] Chlorobenzene. [c] Mixture (1:1) of *o*- and *p*-bromotoluene.

tetrachloride and 1,4-dibromonaphthalene was obtained from the reaction run at 130 °C in chlorobenzene. Halogenation of alkylbenzenes with metal halides gave mixtures of nuclear-halogenated compounds and side-chain-halogenated compounds.[8-10] In contrast, in similar reactions using alumina-supported copper(II) bromide, only nuclear bromination occurred and no side-chain brominated compounds were obtained. The reaction of toluene with alumina-supported copper(II) bromide gave mixture of *o*- and *p*-bromotoluene. *p*-Xylene and mesitylene were also susceptible to nuclear bromination, and the corresponding monobromo compounds were obtained in high yields. Reactivity of the alkylbenzenes toward copper(II) bromide increased with increasing number of alkyl groups, as follows: mesitylene > *p*-xylene > toluene.

The advantages of this procedure are simple workups, mild reaction conditions, and higher selectivities. Products can be isolated in good yield by simple filtration and solvent evaporation, and no extraction steps are required.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and used without further purification. Neutral alumina was purchased from ICN Biomedicals (Woelm N-Super 1). Carbon tetrachloride was dried with calcium chloride and distilled. All ^1H NMR, IR, and mass spectra were recorded by using JEOL FX-90Q, JASCO A-302, and JEOL DX-303 spectrometers, respectively. Product mixtures were analyzed by GLC on a Hitachi Model 163 flame ionization instrument equipped with a SE-30 on Chromosorb WAW column.

Preparation of Copper(II) Chloride Adsorbed on Alumina (Reagent 1). To a solution of copper(II) chloride dihydrate (10 g) in distilled water (30 mL) was added neutral alumina (20 g, Woelm N-Super 1) at room temperature. The water was evaporated by using a rotary evaporator at 80 °C under reduced pressure. The resulting reagent was then dried under vacuum (4 Torr) at 100 °C for 15 h. Preparation of alumina-supported copper(II) bromide (reagent 2) was similar to that described above.

1-Chloronaphthalene: General Procedure for Chlorination of Aromatic Hydrocarbons. A 100-mL round-bottomed flask was charged with 1 (7.14 g) and naphthalene (0.345 g, 3 mmol) dissolved in chlorobenzene (30 mL). A Teflon-coated stirring bar was added and the mixture stirred vigorously at 130 °C for 2 h. Analysis by GLC indicated the complete disappearance of naphthalene. The product mixture was filtered, and the reagent was washed with chlorobenzene (10 mL).

2,7-Dibromofluorene: General Procedure for Bromination of Aromatic Hydrocarbons. A mixture of fluorene (1.5 g, 9 mmol), 2 (30 g), and carbon tetrachloride (80 mL) was placed in a 200-mL round-bottomed flask and stirred with a Teflon-coated magnetic stirring bar at 80 °C for 5 h. The product mixture was filtered, and the spent reagent was washed with carbon tetrachloride (30 mL). Evaporation of solvent from the combined filtrate under reduced pressure yielded 2.84 g (97%) of 2,7-dibromofluorene as a pale yellow solid having ^1H NMR and IR spectra identical with those of an authentic sample, mp 157-159 °C (lit.[11] mp 162-163 °C). The purity was >96% (GLC).

Registry No. Alumina, 1344-28-1; naphthalene, 91-20-3; 1-methylnaphthalene, 90-12-0; phenanthrene, 85-01-8; fluorene, 86-73-7; anthracene, 120-12-7; toluene, 108-88-3; *p*-xylene, 106-42-3; 1,3,5-trimethylbenzene, 108-67-8; 1-chloronaphthalene, 90-13-1; 1,4-dichloronaphthalene, 1825-31-6; 4-chloro-1-methylnaphthalene, 17075-39-7; 9-chlorophenanthrene, 947-72-8; 9,10-dichlorophenanthrene, 17219-94-2; 2-chlorofluorene, 2523-44-6; 2,7-dichlorofluorene, 7012-16-0; 9-chloroanthracene, 716-53-0; 9,10-dichloroanthracene, 605-48-1; 1-bromonaphthalene, 90-11-9; 1,4-dibromonaphthalene, 83-53-4; 4-bromo-1-methylnaphthalene, 6627-78-7; 1-methyl-2,4-dibromonaphthalene, 3278-84-0; 9-bromophenanthrene, 573-17-1; 2-bromofluorene, 1133-80-8; 2,7-dibromofluorene, 16433-88-8; 2-bromotoluene, 95-46-5; 4-bromotoluene, 106-38-7; 2-bromo-1,4-dimethylbenzene, 553-94-6; 2,6-dibromo-1,4-dimethylbenzene, 66788-13-4; 2-bromo-1,3,5-trimethylbenzene, 576-83-0.

(8) Kovacic, P.; Davis, K. E. *J. Am. Chem. Soc.* **1964**, *86*, 427.
(9) Kovacic, P.; Wu, C. *J. Org. Chem.* **1961**, *26*, 759.
(10) Kovacic, P.; Wu, C. *J. Org. Chem.* **1961**, *26*, 762.
(11) *Beilstein, 4th ed.* **1922**, *5*, 628.

Intramolecular [4 + 1] Pyrroline Annulation via Azide-Diene Cycloadditions. 2. Formal Stereoselective Total Syntheses of (±)-Platynecine, (±)-Hastanecine, (±)-Turneforcidine, and (±)-Dihydroxyheliotridane

Tomas Hudlicky,*[1] Gustavo Seoane, and Thomas C. Lovelace

Chemistry Department, Virginia Polytechnic Institute, Blacksburg, Virginia 24061

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Introduction

A functional approach to simple pyrrolizidine bases such as a supinidine, trachelanthamidine, and isoretronecanol has been realized by the intramolecular cyclization of azido dienes.[2,3] In analogy with similar ring closures of carbenoids,[4] these cyclizations, combined with the subsequent thermolysis of vinylaziridines, provided a reliable pyrroline annulation technology representing a formal [4 + 1] union of a nitrene with a 1,3-diene. Following the necessary investigations of conditions of rearrangements of vinylaziridines, we decided to adapt this methodology to the preparation of pyrrolizidines oxygenated in both rings. Herein we report the synthesis of several pyrrolizidine alkaloids of the retronecine type via a fully general approach and a common set of intermediates, Figure 1.

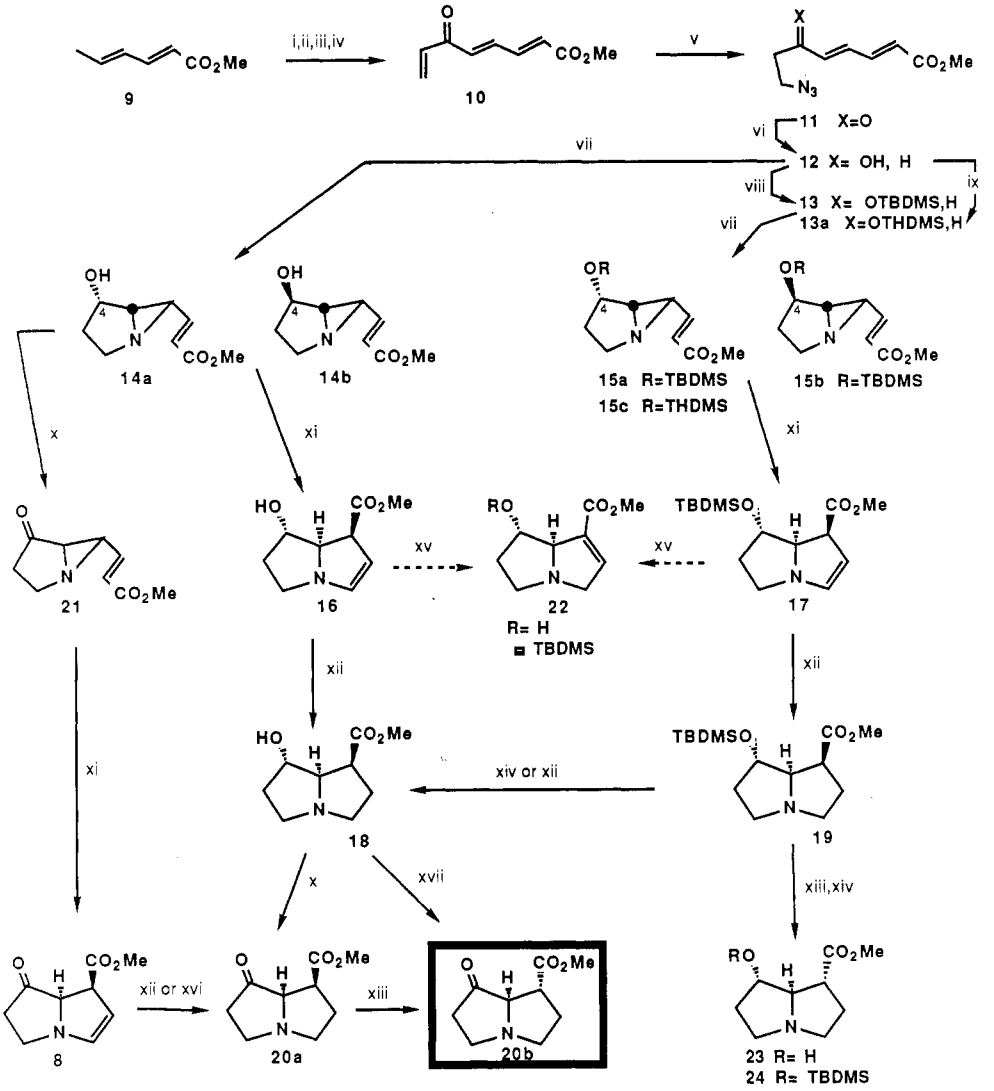
Results and Discussion

Pyrrolizidine alkaloids enjoy popularity in the synthetic community for two reasons. First, they are the basic constituents of many cytotoxic lactones,[5] and second, they

(1) Recipient of the Research Career Development Award, 1984-1989, National Institutes of Health (AI-00564).
(2) Hudlicky, T.; Frazier, J. O.; Kwart, L. D. *Tetrahedron Lett.* **1985**, *26*, 3523. See also the adjoining paper: Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527.
(3) Hudlicky, T.; Seoane, G.; Seoane, A.; Frazier, J. O.; Kwart, L. D.; Tiedje, M. H.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755.
(4) For recent applications, see: Ranu, B. C.; Short, R. P.; Frazier, J. O.; Rigby, H. L. *Synthesis* **1986**, 716. Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *J. Org. Chem.*, in press.

0022-3263/88/1953-2094$01.50/0

Scheme I[a]



[a] Reagents: (i) O_3, CH_2Cl_2; DMS, 90%; (ii) $Ph_3PCHCHO$, CH_2Cl_2, Δ, 82%; (iii) $CH_2CHMgBr$, THF, 45 °C, 85%; (iv) MnO_2, hexane/CH_2Cl_2, 1:1, room temperature, 26%; (v) NaN_3, AcOH/H_2O, 1:1, room temperature, 88%; (vi) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 64%; (vii) PhMe, Δ; (viii) TBDMSCl, imidazole, DMF, 43%; (ix) THDMSCl, imidazole, DMF, 45%; (x) MnO_2, $CHCl_3$, room temperature; (xi) FVP, 480 °C; (xii) H_2 (30 psi), 5% Pd/C, MeOH; (xiii) ref 23; (xiv) *n*-Bu_4NF, THF (xv) MeONa, MeOH; (xvi) $NaCNBH_3$, HCl(gas), THF/MeOH; (xvii) ref 10d.

provide attractive targets on which new carbon–carbon bond forming methodology can be tested. A wide variety of approaches to retronecine or platynecine bases exist, and many total syntheses of these compounds have been published.[6-11] In our endeavor, we were guided by the possibility of preparation of *either* acrylate **7** *or* its deconjugated regioisomer **8**, Figure 1. Not only should these compounds be mutually interconvertible, and thus provide for the entry to unsaturated diols **1** or **2**, but also either could serve as a source of fully saturated keto esters **20**,

(5) Biological activity: Atal, C. K. *Lloydia* **1978**, *41*, 312. General review: Robins, D. J. *Prog. Chem. Org. Nat. Prod.* **1981**, *41*, 115.

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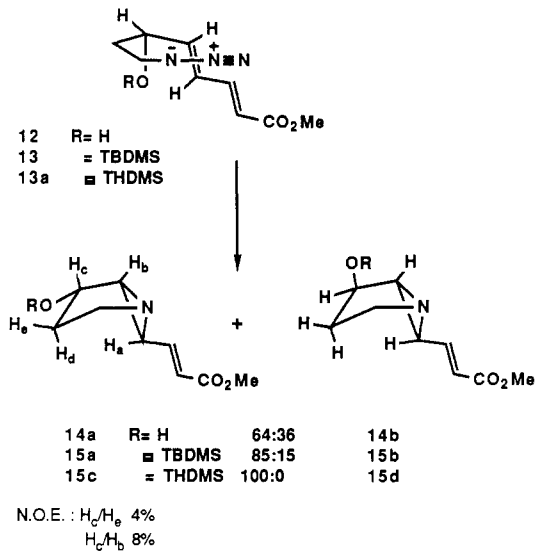
(10) Turneforcidine: (a) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *Heterocycles* **1982**, *19*, 2075. (b) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1983**, *48*, 3644. (c) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425. (d) Aasen, A. J.; Culvenor, C. C. J. *Aust. J. Chem.* **1969**, *22*, 2657.

(11) Platynecine: (a) Benn, M.; Rueger, H. *Heterocycles* **1983**, *20*, 1331. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425.

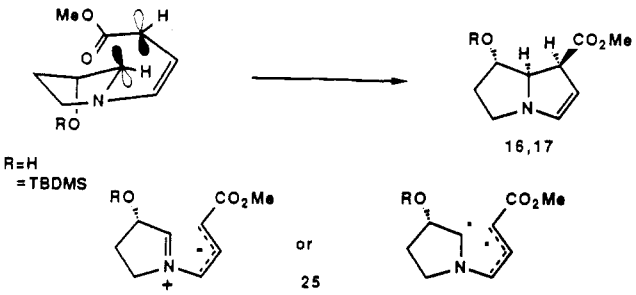
the precursors to saturated alkaloids **3–6**. The key issue of synthetic planning became the design of azido dienes that would provide, regioselectively, the precursory vinylaziridines. The question of the final regiochemistry of the carbomethoxy substituent at position 2 versus position 4 on the pyrrolizidine ring as a function of either its position on the diene or the type of bond that is cleaved in the vinylaziridines has been addressed and resolved during our earlier investigations.[2,12] We chose the so-called "γ-series" because the dienes and the vinylaziridines in this series were sterically homogeneous, and their rearrangements were not complicated by the intervening 1,5-shift of the endo isomers.[13]

The preparation of triene **10**, the precursor to azido diene **11**, was surprisingly troublesome at the outset of our studies. Several techniques of its preparation were tried, including β-keto acid condensations,[14] allylic oxidations,[15] α-keto aldehyde preparation,[16] and others, to no avail.[17] The Wittig condensation of (formylmethylene)triphenylphosphorane[18] with fumaric ester aldehyde[19] provided the dienal to which vinyl Grignard reagent was added. This material was then oxidized to **10** in an overall yield of 16% (Scheme I). The lowest yielding step in this sequence proved to be MnO_2 oxidation of the bisallylic alcohol.[20] Addition of azide ion to **10** proceeded smoothly in HOAc to give an 88% yield of **11**, which was reduced to alcohol **12** with $NaBH_4/CeCl_3$ (64%)[21] and silylated to **13** (43%, after chromatography). The potential for facile enantioselective synthesis exists at this stage provided a chiral reduction is performed.[22] The azido diene **12** was subjected to reflux in toluene for 16 h to yield approximately 50% of vinylaziridines **14a** and **14b** (64:36). By contrast, identical conditions applied to the silyl ether **13** yielded vinylaziridines **15a** and **15b** in a shorter reaction time of 12 h and with an improved yield (70%) as well as improved diastereoselectivity (85:15). The presence of the bulky silyl group favors the cycloaddition to take place from the *re* face of the diene, to a far greater extent than the directing effect of the hydroxyl group. Finally, the protection of **12** with the thexyldimethylsilyl group (THDMS) gave compound **13a**, which provided, with complete control of stereochemistry (100:0), isomer **15c**, which was carried through to final products in a manner identical with that used for **15a**. The stereochemical assignments were made by using NOE experiments, which indicated the relative



positions of hydrogens in **14a**. Irradiation of H_c produced 4% enhancement at H_e and 8% enhancement at H_b. On the other hand, irradiation of H_a only produced a small enhancement at H_d (<2%).

With the control of stereochemistry in vinylaziridines accomplished, the identification of diastereomers was carried out only for the purpose of completeness. Evaporation of vinylaziridines **14** through a horizontally situated Vycor tube [480 °C (10^{-5} mmHg)] provided unsaturated pyrrolizidine **16** as a single isomer. We were not surprised



that the C-1 substituent was present in the less stable configuration, as this observation has been made previously in the γ-series,[3] but we were pleased to note that the two isomers converged to one as a consequence of either a diradical or zwitterionic closure of the intermediate species **25**. Thus all of the diastereomeric vinylaziridines, namely, **15a–c**, **14a**, and **14b**, would be used in a stereoconvergent manner.

The pyrolysis of **15** gave the similarly silylated pyrrolizidine **17**, which possessed identical stereochemistry to its desilylated counterpart. Both compounds were hydrogenated to the saturated compounds **18** and **19** respectively. The proof of identical stereochemistry in both series became available by deprotection of **19** to **18**, which fortuitously took place on extended hydrogenation in MeOH. The synthesis of compound **18** represents a formal total synthesis of dihydroxyheliotridane (**6**).[9c]

The isomerization of the ester functionality at C-1 was accomplished in analogy with experiments in the supinidine series to provide esters **23** or **24**, thus completing the formal total synthesis of platynecine (**3**),[11b] hastanecine (**4**),[9c] turneforcidine (**5**),[10c,d] and dihydroxyheliotridane (**6**).[9c]

The preparation of **20** by either hydrogenation of **8** or oxidation of **18** completed the formal total synthesis of the title compounds[9c,10c] by this general methodology. We now turned to investigations of improved procedures toward the target compounds, keto esters **20**.

(12) Hudlicky, T.; Sinai-Zingde, G.; Seoane, G. *Synth. Commun.* **1987**, *17*, 1155.
(13) The tendency of vinylaziridines to undergo a 1,5-shift has been observed (ref 2) and parallels our observations in the vinylcyclopropane series. See: Hudlicky, T.; Koszyk, F. J. *Tetrahedron Lett.* **1980**, *21*, 2487.
(14) The condensation of β-keto acids with α,β-unsaturated aldehydes and further decarboxylative dehydration of the resulting hydroxy acid to furnish dienes is a well-known procedure: Naf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114. For the procedures of oxidation of the corresponding β-hydroxy acid, see: Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567.
(15) Several procedures for the allylic oxidation of methyl sorbate were tried according to Rabjohn: Rabjohn, N. *Org. React. (N.Y.)* **1976**, *24*, 261.
(16) Attempts were made to oxidize 4-azidopentanal to the corresponding α-keto aldehyde according to Vedejs et al: Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. The ozonolysis of 1-azido-3-oxopent-4-ene was also tried, giving the desired α-keto aldehyde in low yield.
(17) All of the approaches provided the desired enone in 5–10% yield and were abandoned in preference to the approach presented here.
(18) Commercially available, Aldrich Chemical Co., Inc.
(19) Obtained in 95% yield from methyl sorbate according to Stotter and Eppner: Stotter, P. L.; Eppner, J. B. *Tetrahedron Lett.* **1973**, 2417.
(20) See for example: (a) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1952**, 1430. (b) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717.
(21) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(22) See for example: Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

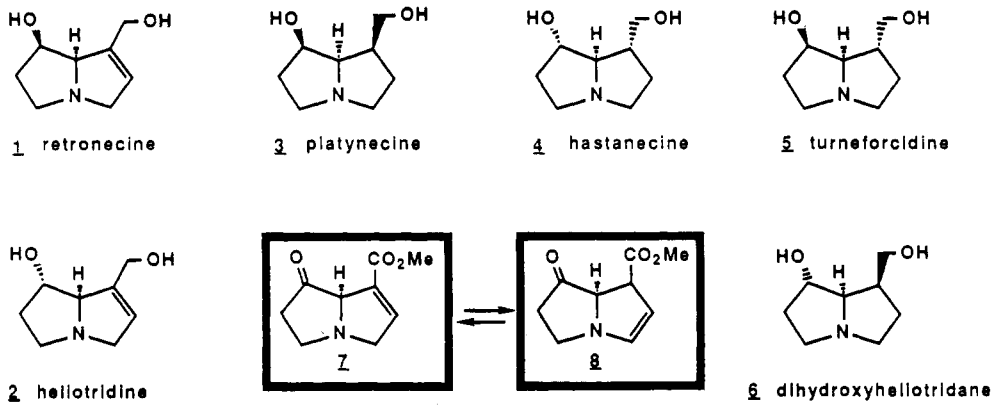


Figure 1. Oxygenated pyrrolizidine alkaloids.

The oxidation of vinylaziridines **14**, although troublesome, as were all of the oxidations in this series, did provide a 40% yield of keto aziridine **21**. The pyrolysis of **21** gave one of the crucial intermediates, unsaturated keto ester **8**, in excellent yield. Realizing that hydrogenation of *either* **7** *or* **8** produced saturated keto ester **20a** with the stereochemistry indicated, we explored the possibility of generating **7**, or rather its reduced form **22**, for access to retronecine bases **1** and **2**. The pyrrolizidines **16** and **17** were subjected to various conditions of base-catalyzed isomerization to produce fully conjugated pyrrolizidine **22**, an act that will constitute the formal total synthesis of retronecine (**1**) and heliotridine (**2**). The investigation and optimization of these procedures are now in progress.[24]

Conclusion

The title compounds became accessible via intermediates **7**, **8**, or **20** in short sequences of operations in which the key steps involved vinylaziridine generation via the intramolecular cycloaddition of azido dienes followed by thermal rearrangement of the vinylaziridines to provide annulated pyrroline systems suitable as intermediates for elaboration to the title compounds.

The method is amenable to asymmetric induction as the complete control of diastereoselectivity in the preparation of **18** will allow the entry to either enantiomeric series of pyrrolizidine alkaloids upon provision of azido dienes **12** in a chiral fashion. The keto aziridines of type **21** may become useful in nucleophilic variations of the vinylaziridine–pyrroline rearrangement as alternatives to pyrolyses. These endeavors form the basis of further research in this area.

Experimental Section

All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere, with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried with an internal inert gas sweep. THF, ether, DME, and benzene were distilled from benzophenone ketyl, dichloromethane and toluene from calcium hydride.

Analytical TLC was performed on silica gel 60F-254 plates. Flash chromatography was performed on Kieselgel 60 (230–400 mesh) by using EM reagents. Mass spectra were recorded on a DuPont 20-491 or a Varian MAT-112 instrument (low resolution) or on a double-focusing DuPont 21-110C or VGT instrument (exact mass). Infrared spectra were recorded on neat samples (NaCl plates) on a Perkin-Elmer 257 spectrometer. Proton NMR spectra were obtained on Varian EM390 or Bruker WP-270 instruments. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal reference (0.0 ppm). Carbon NMR spectra were recorded on Bruker WP-270 or NR-80 instruments. Carbon chemical shifts are reported in parts per million relative to TMS, the spectra were calibrated either to TMS or to the center line of the $CDCl_3$ triplet (77.02 ppm), and the multiplicity is indicated by CH_3, CH_2, CH, C (INEPT experiments).

Methyl 6-Oxo-2,4,7-octatrienoate (10). Methyl 5-formyl-2,4-pentadienoate[25] (0.94 g, 6.71 mmol) was dissolved in THF (60 mL) at room temperature. To this solution was added vinylmagnesium bromide (7.40 mL of 1.0 M solution in THF) dropwise. The resulting red solution was stirred at 45 °C, and the reaction was monitored by TLC. The reaction was complete after 40 min; the mixture had become a red-brown, cloudy solution. The reaction was quenched by adding saturated aqueous NH_4Cl (5 mL), and the mixture was diluted with ether (100 mL). The organic layer was washed with 3 N HCl (10 mL). The combined aqueous layers were extracted with ether (2 × 15 mL). The combined organic layers were then washed with brine, dried over Na_2SO_4, filtered, and evaporated to yield 1.0 g of crude alcohol, which was about 90% pure by NMR (85% yield) and suitable for use in the next step without further purification. An analytical sample was then purified on 5% deactivated flash silica gel with CH_2Cl_2/Et_2O (9:1) to yield pure allylic alcohol: oil; R_f 0.30 (hexane/Et_2O, 1:1); IR (neat) 3400 (br), 2960, 1720, 1640, 1620, 1440, 1140, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (br s, 1 H), 3.70 (s, 3 H), 4.72 (m, 1 H), 5.15 (dd, J_1 = 7, J_2 = 1 Hz, 1 H), 5.26 (dd, J_1 = 15, J_2 = 1 Hz, 1 H), 5.85 (m, 1 H), 5.86 (d, J = 14 Hz, 1 H), 6.08 (dd, J_1 = 11, J_2 = 4 Hz, 1 H), 6.35 (m, 1 H), 7.23 (dd, J_1 = 14, J_2 = 11 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 51.5, 72.9, 116.0, 121.5, 132.2, 138.4, 142.6, 143.9, 167.3; mass spectrum (70 eV), m/e (relative intensity) 168 (2, M^+), 166 (5), 113 (20), 85 (60), 84 (100), 55 (28).

Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0786.

To a stirred solution of the alcohol (1.0 g, 5.9 mmol) in a 1:1 mixture of hexane/CH_2Cl_2 (120 mL) was added MnO_2 (5.1 g, 59 mmol) in one portion at room temperature. The flask was protected from light by means of a blanket, and the stirring was continued at room temperature. After 26 h the suspension was filtered through Celite and rinsed with EtOAc (3 × 30 mL), and the solvent was evaporated to give 0.51 g of a yellow solid, which was chromatographed (5% deactivated silica gel, hexane/ether, 65:35) to obtain pure **10** as a pale yellow solid: 0.25 g, 26%,[26] R_f 0.35 (hexane/ether, 60:40); mp 81–82 °C; IR ($CDCl_3$) 1720, 1600, 1460, 1380, 1090, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (s, 3 H), 5.90 (dd, J_1 = 10, J_2 = 1 Hz, 1 H), 6.24 (d, J = 15 Hz, 1 H), 6.31 (dd, J_1 = 18, J_2 = 1 Hz, 1 H), 6.58 (dd, J_1 = 18, J_2 = 10 Hz, 1 H), 6.73 (d, J = 15 Hz, 1 H), 7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 51.8 (CH_3), 128.7 (CH), 129.4 (CH_2), 133.3 (CH), 135.4 (CH), 139.5 (CH), 141.5 (CH), 166.2 (C), 189.0 (C); mass spectrum (70 eV), m/e (relative

(23) Aasen, A. J.; Culvenor, C. C. J.; Smith, L. W. *J. Org. Chem.* **1969**, *34*, 4137.

(24) Preliminary experiments using NaOEt, DBU, neutral Al_2O_3, and a variety of other reagents did not produce satisfactory evidence for this isomerization. Perhaps the deconjugated isomer is more stable in that position, as suggested by analogy to carbocyclic systems. See: Agosta, W. C.; Wolf, S. *J. Org. Chem.* **1975**, *40*, 1699.

(25) Prepared in 82% yield by refluxing (formylmethylene)triphenylphosphorane[18] and fumaric ester aldehyde in dichloromethane for 4 h.

(26) One of the referees suggested that the low yield of this oxidation may be due to the quality of the reagent. Both commercial MnO_2 and purified MnO_2 were used with similar results.

intensity) 166 (57, M^+), 139 (22), 135 (21), 111 (72), 107 (100), 77 (25), 55 (82).

Calcd for $C_9H_{10}O_3$: 166.0630. Found: 166.0627.

Methyl 8-Azido-6-oxo-2,4-octadienoate (11). A stirred solution of the ketone **10** (0.80 g, 4.82 mmol) in 30 mL of a 1:1 $AcOH/H_2O$ mixture was cooled in an ice bath, and NaN_3 (0.72 g, 11 mmol) was added in one portion. The cooling bath was removed, and the yellow solution was stirred for 35 min. The reaction mixture was diluted with ether (100 mL) and washed with saturated aqueous Na_2CO_3 (50 mL). The aqueous layer was extracted with ether (1 × 50 and 1 × 70 mL); the combined organic layers were washed with saturated aqueous Na_2CO_3 until pH 8 (5×) and with brine, dried over Na_2SO_4, and filtered through a plug of silica, and the solvent was evaporated to yield pure **11** as a yellow solid: 0.89 g, 88%; mp 55–56 °C; R_f 0.32 (hexane/ether, 60:40); IR ($CDCl_3$) 2960, 2100, 1725, 1600, 910, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (t, J = 6.4 Hz, 2 H), 3.60 (t, J = 6.4 Hz, 2 H), 3.76 (s, 3 H), 6.24 (d, J = 14.5 Hz, 1 H), 6.42 (d, J = 14.5 Hz, 1 H), 7.24 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 40.0 (CH_2), 45.9 (CH_2), 51.9 (CH_3), 129.2 (CH), 134.8 (CH), 139.2 (CH), 141.1 (CH), 166.1 (C), 196.6 (C); mass spectrum (70 eV), m/e (relative intensity) 182 (3), 154 (14), 139 (60), 111 (100), 95 (70), 80 (97), 59 (60), (CI mode, isobutane) 210 (7, MH^+), 195 (6), 182 (35), 167 (52), 155 (100).

Calcd for $C_9H_{11}O_3N$ $(M - N_2)^+$: 181.0739. Found: 181.0761.

Methyl 8-Azido-6-hydroxy-2,4-octadienoate (12). To an ice-cooled solution of ketone **11** (0.89 g, 4.25 mmol) in dry MeOH (30 mL) was added $NaBH_4$ (0.22 g, 5.78 mmol) in one portion. After 2 min a catalytic amount of anhydrous $CeCl_3$ (10 mg) was added (gas evolution was observed), and the reaction was monitored by TLC. After 35 min the reaction was quenched with H_2O (0.25 mL), and the solvent was evaporated. The resulting solid was partitioned between ether (50 mL) and 3 N H_2SO_4 (5 mL). The aqueous layer was extracted with ether (2 × 15 mL), and the combined organic layers were neutralized with saturated aqueous $NaHCO_3$, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent yielded 0.87 g of a yellow oil, which was chromatographed (5% deactivated silica gel, hexane/ether, 1.6:2) to give pure **12** as a colorless oil: 550 mg, 64%; R_f 0.22 (hexane/ether, 60:40); IR (neat) 3350 (br), 2080, 1710, 1430, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (m, 2 H), 1.95 (br d, 1 H, variable), 3.45 (m, 2 H), 3.73 (s, 3 H), 4.40 (m, 1 H), 5.89 (d, J = 15.3 Hz, 1 H), 6.08 (dd, J_1 = 15.3, J_2 = 5.8 Hz, 1 H), 6.38 (ddd, J_1 = 15.3, J_2 = 10.5, J_3 = 1 Hz, 1 H), 7.25 (dd, J_1 = 15.3, J_2 = 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 35.6 (CH_2), 47.9 (CH_2), 51.5 (CH_3), 69.0 (CH), 121.4 (CH), 127.7 (CH), 143.7 (CH), 143.9 (CH), 167.3 (C); mass spectrum (CI mode), m/e (relative intensity) 212 (20, MH^+), 184 (90), 166 (100), 141 (95).

Calcd for $C_9H_{14}O_3N_3$: 212.1035. Found: 212.1152.

Methyl 8-Azido-6-[(*tert*-butyldimethylsilyl)oxy]-2,4-octadienoate (13). To a stirred solution of alcohol **12** (105 mg, 0.5 mmol) in DMF (0.8 mL) were added in portions *tert*-butyldimethylsilyl chloride (TBDMSCl, 378 mg, 2.5 mmol) and then imidazole (340 mg, 5 mmol). Upon addition of imidazole, the yellow solution turned orange. After 15 h of stirring at room temperature, more TBDMSCl (100 mg, 0.65 mmol) and imidazole (60 mg, 0.9 mmol) were added. After 25 h the mixture was diluted with 30 mL of ether and poured into 10 mL of brine. The aqueous layer was extracted with ether (2 × 10 mL); the combined organic layers were washed with cold 3 N HCl and then with brine and dried, and the solvent was evaporated to give 0.30 g of a clear oil, which was chromatographed (silica gel, hexane/ether, 90:10) to obtain pure **13** as a colorless oil: 70 mg, 43% R_f 0.68 (hexane/ether, 60:40); IR (neat) 2930, 2090, 1710, 1260, 1120, 860, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (d, J = 12.0 Hz, 6 H), 0.88 (s, 9 H), 1.75 (q, J = 6.5 Hz, 2 H), 3.35 (m, 2 H), 3.73 (s, 3 H), 4.35 (m, 1 H), 5.88 (d, J = 15.5 Hz, 1 H), 6.04 (dd, J_1 = 15.5, J_2 = 6.0 Hz, 1 H), 6.30 (m, 1 H), 7.25 (dd, J_1 = 15.5, J_2 = 11.0 Hz, 1 H).

(3α)-1-Aza-2α-(2-carbomethoxyethenyl)-4β-hydroxybicyclo[3.1.0]hexane (14a) and Its 4α Epimer (14b). A solution of alcohol **12** (550 mg, 2.6 mmol) in toluene (20 mL) was refluxed and monitored by TLC. After 16 h the resulting deep orange solution was evaporated to give a thick oil in which the ratio of β and α alcohols **14** was determined to be 64:36 by NMR. The oil was chromatographed (10% deactivated silica gel, acid-free EtOAc) to give 270 mg (49%) of a mixture of **14a** and **14b**. An analytical sample of the alcohols was obtained by preparative TLC (silica gel, EtOAc/hexane, 90:10, three elutions) of the mixture.

14a: oil; R_f 0.16 (silica gel, EtOAc); IR (neat) 3500–3300, 2960, 1725, 1650, 1440, 1270, 1150, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (m, 1 H), 1.65 (br s, 1 H, the chemical shift of this proton was variable), 1.92 (m, 1 H), 2.44 (dd, J_1 = 4.0, J_2 = 2.3 Hz, 1 H), 2.48 (dd, J_1 = 8.0, J_2 = 2.3 Hz, 1 H), 3.05 (m, 2 H), 3.65 (s, 3 H), 4.74 (ddd, J_1 = 9.0, J_2 = 8.5, J_3 = 4.0 Hz, 1 H), 5.96 (d, J = 15.5 Hz, 1 H), 6.55 (dd, J_1 = 15.5, J_2 = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.7 (CH_2), 35.9 (CH), 51.1 (CH_2), 51.3 (CH_3), 51.4 (CH), 72.4 (CH), 121.2 (CH), 146.8 (CH), 166.2 (C); mass spectrum (70 eV), m/e (relative intensity) 165 (48), 150 (100), 132 (35), 118 (33), 106 (62).

Calcd for $C_9H_{11}NO_2$ $(M - H_2O)^+$: 165.0790. Found: 165.0780.

Calcd for $C_9H_{14}NO_3$ $(MH)^+$ (CI mode): 184.0974. Found: 184.0963.

14b: oil; R_f 0.15 (silica gel, EtOAc); IR (neat) 3500–3300, 2950, 1720, 1650, 1440, 1270, 1145, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, 2 H), 1.87 (dd, J_1 = 8.0, J_2 = 2.3 Hz, 1 H), 2.45 (br s, 1 H, variable), 2.50 (br d, J = 2.3 Hz, 1 H), 3.10 (m, 1 H), 3.22 (m, 1 H), 3.66 (s, 3 H) 4.53 (m, 1 H), 5.93 (d, J = 15.5 Hz, 1 H), 6.52 (dd, J_1 = 15.5, J_2 = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.1 (CH_2), 38.7 (CH), 51.1 (CH_2), 51.6 (CH_3), 54.6 (CH), 72.4 (CH), 121.8 (CH), 146.8 (CH), 166.5 (C); mass spectrum (70 eV), m/e (relative intensity) 183 (15, M^+), 165 (10), 149 (13), 134 (10), 124 (33), 106 (40), 98 (42), 80 (100).

Calcd for $C_9H_{13}NO_3$: 183.0895. Found: 183.0895.

(3α)-1-Aza-2α-(2-carbomethoxyethenyl)-4β-[(*tert*-butyldimethylsilyl)oxy]bicyclo[3.1.0]hexane (15a) and Its 4α Epimer (15b). A solution of the ether **13** (50 mg, 0.15 mmol) in toluene (5 mL) was refluxed and monitored by TLC. After 12 h the resulting deep yellow solution was evaporated to give a thick oil in which the ratio of β and α alcohols **15** was determined to be 85:15 by NMR. The oil was chromatographed (10% deactivated silica gel, EtOAc/hexane, 30:70) to give the pure aziridines.

15a: oil, 27 mg, 61%; R_f 0.50 (hexane/EtOAc, 1:1); IR (neat) 2980, 2850, 1725, 1660, 1100, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.5 (m, 1 H), 1.9 (m, 1 H), 2.36 (dd, J_1 = 4.5, J_2 = 2.5 Hz, 1 H), 2.47 (br dd, J_1 = 7.8, J_2 = 2.5 Hz, 1 H), 3.05 (m, 2 H), 3.65 (s, 3 H), 4.73 (ddd, J_1 = 8.5, J_2 = 7.8, J_3 = 4.5 Hz, 1 H), 6.00 (br d, J = 15.5 Hz, 1 H), 6.63 (dd, J_1 = 15.5, J_2 = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.9 (CH_3), −4.7 (CH_3), 18.1 (C), 25.7 (3 CH_3) 30.0 (CH_2), 36.5 (CH), 51.4 (CH_3), 51.7 (CH_2), 52.4 (CH), 73.6 (CH), 121.2 (CH), 147.7 (CH), 178.9 (C); mass spectrum (70 eV), m/e (relative intensity) 297 (8, M^+), 282 (10), 265 (12), 238 (18), 166 (55), 139 (40), 106 (100), 73 (70).

Calcd for $C_{15}H_{27}O_3NSi$: 297.1760. Found: 297.1759.

15b: oil, 4 mg, 9%; R_f 0.65 (hexane/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.6 (m, 2 H), 1.80 (br dd, J_1 = 7.5, J_2 = 2.5 Hz, 1 H), 2.38 (d, J = 2.5 Hz, 1 H), 3.04 (ddd, J_1 = 11.5, J_2 = 7.5, J_3 = 1.5 Hz, 1 H), 3.22 (ddd, J_1 = 11.5, J_2 = 11.0, J_3 = 8.0 Hz, 1 H), 3.68 (s, 3 H), 4.52 (br d, J = 4 Hz, 1 H), 5.95 (dd, J_1 = 16.0, J_2 = 0.5 Hz, 1 H), 6.60 (dd, J_1 = 16.0, J_2 = 7.5 Hz, 1 H).

(5α)-1-Aza-4β-carbomethoxy-6α-hydroxybicyclo[3.3.0]octane (18). Vinylaziridine **14a** (9 mg, 0.05 mmol) was evaporated through a horizontally situated Vycor tube (0.6 × 55 cm) at 480 °C and about 10^{-4} mmHg, and the condensate was collected in a trap cooled with liquid N_2. The total time of evaporation was kept under 10 min by gently warming the distillation flask. Thin-layer chromatography showed a clean conversion of **14a** (R_f 0.7, neutral alumina, EtOAc) to the enamine **16** (R_f 0.2, neutral alumina, EtOAc). Because of the instability of enamines such as **16**, no attempt was made to isolate **16**. The pyrolysis mixture was hydrogenated over 5% Pd/C (10 mg) in dry methanol (3 mL) at 30 psi for 16 h. The mixture was filtered through Celite, the filter washed with EtOAc, and the filtrate evaporated to yield 5 mg of a clear oil, which was chromatographed (1.5% deactivated neutral alumina, acid-free EtOAc) to give pure **18** as a colorless oil: 4 mg, 43%; R_f 0.12 (silica gel, $CHCl_3/MeOH/NH_4OH$, 85:14:1); IR (neat) 3350 (br), 2930, 1720, 1600, 1180, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (m, 1 H), 1.85–1.95 (m, 3 H), 2.11 (m, 1 H), 2.56 (ddd, J_1 = 10.5, J_2 = 10.0, J_3 = 6.0 Hz, 1 H), 2.68 (m, 1 H), 2.91 (ddd, J_1 = 11.5, J_2 = 9.0, J_3 = 7.5 Hz, 1 H), 3.11–3.25 (m, 2 H), 3.41 (dd, J_1 = 8.0, J_2 = 6.5 Hz, 1 H), 3.71 (s, 3 H), 3.93 (dt, J_1 = 8.5, J_2 = 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.0, 34.2,

46.7, 52.0, 53.0, 54.0, 71.9, 73.8, 175.3; mass spectrum (70 eV), m/e (relative intensity) 185 (13, M^+), 167 (60), 154 (31), 141 (100), 128 (16), 126 (14), 106 (22), 88 (20).

Calcd for $C_9H_{15}O_3N$: 185.1052. Found: 185.1051.

(5α)-1-Aza-4β-carbomethoxy-6α-[(*tert*-butyldimethylsilyl)oxy]bicyclo[3.3.0]octane (19). Vinylaziridine **15a** (10 mg, 0.03 mmol) was pyrolyzed as described in the previous experiment for **14a**. The total time of evaporation was kept under 6 min by gently warming the distillation flask. Thin-layer chromatography showed a clean conversion of **15a** (R_f 0.55, silica gel, EtOAc) to the enamine **17** (R_f 0.31, silica gel, EtOAc) and trace amounts of another product of R_f 0.08 (possibly the deprotected enamine). Because of the instability of enamines such as **17**, no attempt was made to isolate **17**. The pyrolysis mixture was hydrogenated over 5% Pd/C (10 mg) in dry methanol (2 mL) at 31 psi for 8 h. The mixture was filtered through Celite, the filter washed with EtOAc, and the filtrate evaporated to yield 4 mg of a clear oil, which was chromatographed (1.5% deactivated neutral alumina, acid-free EtOAc/hexane, 1:1) to give pure **19** as a colorless oil: 3 mg, 30%; R_f 0.50 (silica gel), $CHCl_3$/MeOH/NH_4OH, 85:14:1); IR (neat) 2980, 2940, 2870, 1740, 1260, 1210, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H), 0.85 (s, 9 H), 1.75 (m, 1 H), 1.85–2.03 (m, 3 H), 2.62 (ddd, J_1 = 10.6, J_2 = 7.9, J_3 = 6.0 Hz, 1 H), 2.77 (ddd, J_1 = 11.5, J_2 = 6.9, J_3 = 5.2 Hz, 1 H), 2.96 (ddd, J_1 = 11.5, J_2 = 8.5, J_3 = 6.5 Hz, 1 H), 3.08 (ddd, J_1 = 9.0, J_2 = 8.5, J_3 = 7.9 Hz, 1 H), 3.19 (ddd, J_1 = 10.6, J_2 = 4.8, J_3 = 6.5 Hz, 1 H), 3.54 (dd, J_1 = 7.9, J_2 = 4.0 Hz, 1 H), 3.66 (s, 3 H), 4.03 (dt, J_1 = 5.2, J_2 = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.8 (CH_3), −4.3 (CH_3), 18.0 (C), 25.8 (3 CH_3), 29.4, 36.1, 46.0, 51.5, 53.2, 54.1, 74.2, 74.7, 166.8; mass spectrum (70 eV), m/e (relative intensity) 297 (7), 265 (10), 256 (9), 242 (12), 213 (6), 169 (20), 141 (50), 106 (55), 82 (100).

Calcd for $C_{11}H_{20}O_3NSi$ $(M-57)^+$: 242.1212. Found: 242.1200.

(3α)-1-Aza-2α-(2-carbomethoxyethenyl)-4-oxobicyclo[3.1.0]hexane (21). To a stirred solution of the alcohol **14a** (48 mg, 0.27 mmol) in $CHCl_3$ (1.5 mL) was added MnO_2 (100 mg) in one portion at room temperature. The mixture was protected from the light and stirred for 24 h. It was then centrifugated, and the filter was washed with $CHCl_3$. The filtrate was concentrated to about 4 mL, and more MnO_2 (100 mg) was added. After 2.5 days the suspension was centrifugated again, the filter washed with $CHCl_3$, and the filtrate evaporated to give an oil, which was chromatographed (10% deactivated silica gel, EtOAc/hexane, 9:1) to yield pure **21** as a pale yellow oil: 17 mg, 38%; R_f 0.55 (silica gel, EtOAc); IR (neat) 2930, 2860, 1740, 1720, 1660, 1260, 1020, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (ddd, J_1 = 19.1, J_2 = 9.7, J_3 = 2.9 Hz, 1 H), 2.41 (q, J = 9.7 Hz, 1 H), 2.51 (d, J = 2.0 Hz, 1 H), 2.63 (dd, J_1 = 7.6, J_2 = 2.0 Hz, 1 H), 3.35 (m, 1 H), 3.56 (m, 1 H), 3.70 (s, 3 H), 6.06 (d, J = 15.9 Hz, 1 H), 6.53 (dd, J_1 = 15.9, J_2 = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.8 (CH_2), 42.9 (CH), 49.3 (CH_2), 49.9 (CH), 51.7 (CH_3), 123.5 (CH), 143.7 (CH), 165.9 (C), 209.2 (C); mass spectrum (70 eV), m/e (relative intensity) 150 (3), 122 (26), 98 (100), 94 (19), 82 (55), 80 (54), 58 (22). Calcd for C_7H_8ON $(M-59)^+$: 122.0606. Found: 122.0604.

(5α)-1-Aza-4β-carbomethoxy-6-oxobicyclo[3.3.0]oct-2-ene (8). Vinylaziridine **21** (15 mg, 0.08 mmol) was pyrolyzed as described for **14a** and **15a**. The total time of evaporation was kept under 10 min by gently warming the distillation flask. ^1H NMR of the pyrolysate indicated the presence of only the enamine **8**, which was used in the next step without purification: pale yellow oil, 14 mg; R_f 0.18 (silica gel, EtOAC); ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 3 H), 3.3–3.6 (m, 2 H), 3.70 (s, 3 H), 3.7 (m, 1 H), 4.88 (m, 1 H), 6.07 (m, 1 H).

(5α)-1-Aza-4α-carbomethoxy-6-oxobicyclo[3.3.0]octane (20b). Method I. Enamine 8 (14 mg, 0.08 mmol) was hydrogenated over 5% Pd/C (10 mg) in glacial AcOH (2.5 mL) at 27 psi for 13 h. The mixture was filtered through Celite, the filter washed with $CHCl_3$, the filtrate passed through a plug of alumina, and the solvent evaporated, to give crude **20a** as an oil: 14 mg; R_f 0.52 (silica gel, $CHCl_3$/MeOH/NH_4OH, 85:14:1); ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 4 H), 2.7 (m, 1 H), 2.9–3.2 (m, 3 H), 3.4 (m, 1 H), 3.70 (s, 3 H), 3.7 (m, 1 H). Keto ester **20a** was epimerized to **20b** by using NaOMe/MeOH.[23] Spectroscopic data for **20b** was in agreement with that reported in the literature.[10c,d]

Method II. To a stirred solution of the alcohol **18** (4 mg, 0.22 mmol) in $CHCl_3$ (0.8 mL) at room temperature was added MnO_2 (10 mg) in one portion. After 8 h, the mixture was filtered through Celite, the filter washed with $CHCl_3$, and the filtrate evaporated to yield 2 mg of an oil, ^1H NMR of which showed signals corresponding to the keto ester **20a**. All attempts to purify **20a** were unsuccessful.

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5-Substituted-2-furoic Acids as Latent Dienes for the Preparation of Aryl Ethers and Thioethers via the Diels–Alder Reaction

James A. Cella

General Electric Company/CRD, P.O. Box 8, K1 5A-48, Schenectady, New York 12301

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The construction of aromatic rings is frequency accomplished by means of a Diels–Alder cycloaddition followed by appropriate transformations of the adducts to effect aromatization. In this context, the use of a furan derivative as the dienophilic partner is advantageous since aromatization of the adducts can be effected simply by dehydration.[1]

Use of this procedure for the preparation of aromatic ethers and thioethers provides an interesting alternative to the more conventional Williamson and Ullman methods which are incompatible with certain functionalities. The requisite furyl ethers are excellent dienophiles readily obtained by a variety of methods.[2] A potential limitation

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