a carbonyl compound was added. The mixture was stirred for a period indicated in Tables V and VI (see Tables II and III in supplementary material for details). The mixture was poured into a stirred mixture of ether and water. After 10 min, the ethereal layer was separated and the aqueous layer was extracted 3 times with ether. The combined extract was washed with water, aqueous $NaHCO_3$, and saturated NaCl. After the mixture was dried and concentrated, the product was purified to obtain the desired 4-hydroxy ester or lactone. For unreactive substrate, 2 equiv of **5a** and 1 equiv of $Ti(OR)_4$ was used. The physical properties of the products in these tables are in the supplementary material.

**Acknowledgment.** We thank Prof. T. Yamamoto of this Institute for helpful discussion, Prof. Y. Kaizu for measurement of the Raman spectra, Toyo Stauffer Chemical for a gift of $Et_2Zn$, and Dr. J. Hasegawa of Kanegafuchi Chemical Industry for a gift of chiral 3-hydroxy-2-methylpropionates. Partial financial support from the Ministry of Education, Culture, and Science is gratefully acknowledged.

**Supplementary Material Available:** General data of experiments, tabular presentation of the experimental details of the homoenolate additions, and physical properties of the 4-hydroxy esters and the lactones obtained by these additions, including those shown in Scheme V (13 pages). Ordering information is given on any current masthead page.

# Topological Selectivity in the Intramolecular [4 + 1] Pyrroline Annulation. Formal Total Stereospecific Synthesis of (±)-Supinidine, (±)-Isoretronecanol, and (±)-Trachelanthamidine

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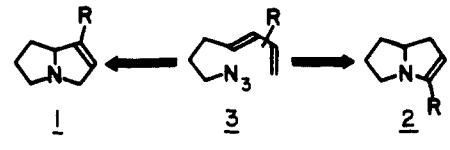
*Contribution from the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061.* *Received November 22, 1985*

**Abstract:** The preparation and cycloadditions of azidodienes **13** and **14** are described in detail. The synthesis of pyrrolines **1** and **2** is reported, and the conditions are revealed to achieve maximum selectivity in their preparation. The topography of the ultimately prepared pyrrolines depends primarily on the substitution parameters of the starting dienes and on the conditions of rearrangement of their respective vinylaziridines **15** and **16**. The former parameter is easily controlled through the vinylogous Reformatsky reaction of ethyl 4-bromocrotonate with aldehyde precursors. The latter parameter depends on the choice of thermolytic vs. nucleophilic activation of particular bonds in vinylaziridines **15** and **16**. The flexibility and practicality of this method is exemplified by several convergent approaches to substituted pyrrolines **1** and **2** and their conversion to the title pyrrolizidine alkaloids. Stereospecific preparation of saturated pyrrolizidines **35** is also described. A detailed study of the base-catalyzed elimination of β-acetoxy esters was performed, and the stereochemical consequences are reported for the formation of *E* and *Z* geometric isomers of dienes **13**.

Several years ago we implemented a strategy directed toward a system-oriented design of cyclopentanoid terpenes.[2] The key element of this strategy featured a formal [4 + 1] addition of a carbenoid across an appropriately functionalized conjugated diene. In the context of alkaloid synthesis, we have pursued a similar thought in the logical extrapolation of the above principles to the additions of electron-deficient nitrogen species to conjugated dienes. Preliminary results bode well for the synthesis of regioisomeric pyrrolizidines **1** and **2** by the internal cycloaddition of dienic azides **3**, where the topography of the pyrrolines would be controlled either by the position of the substituent in **3** or by experimental conditions through a differential activation of specific vinylaziridine bonds toward ring opening and subsequent formation of the fused pyrrolines (eq 1).[3]




1 3 2 (1)

R = H, alkyl, $CO_2R'$

It appeared that such a method would find wide applicability in the synthesis of fused pyrrolines, particularly the pyrrolizidine alkaloids, which are ubiquitous throughout the plant and animal kingdom and which are endowed with a vast array of biological properties.[4] The unsaturated ester site provides an opportunity

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1985; Recipient of the National Institutes of Health Research Career Development Award, 1984-1989 (AI-00564).

(2) For a preliminary account see: (a) Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166. (b) Hudlicky, T.; Ranu, B. C.; Naqui, S. M.; Srnak, A. *J. Org. Chem.* **1985**, *50*, 123. (c) Higgs, L.; Kavka, M.; Ranu, B. C.; Hudlicky, T. *Tetrahedron Lett.* **1984**, 2447. (d) Hudlicky, T.; Govindan, S. V.; Reddy, D. B.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422. (e) Short, R. P.; Ranu, B. C.; Revol, J. M.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453. (f) Govindan, S. V.; Hudlicky, T.; Koszyk, F. J. *J. Org. Chem.* **1983**, *48*, 3581. (g) Hudlicky, T.; Short, R. P. *J. Am. Chem. Soc.* **1982**, *47*, 1522. (h) Hudlicky, T.; Koszyk, F. J.; Dochwat, D. M.; Cantrell, G. C. *J. Org. Chem.* **1981**, *46*, 2911. (i) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (j) Hudlicky, T.; Koszyk, F. J. *Tetrahedron Lett.* **1980**, 2487. (k) Hudlicky, T.; Kutchan, T. *Tetrahedron Lett.* **1980**, 691.

(3) (a) Hudlicky, T.; Frazier, J. O.; Kwart, L. D. *Tetrahedron Lett.* **1985**, 3523. (b) See also the adjoining paper describing a conceptually identical approach: Pearson, W. H. *Tetrahedron Lett.* **1985**, 3527.

(4) For reviews of the pyrrolizidine alkaloids and their biological properties see: (a) Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247. (b) Culvenor, C. C.; Bull, L. B.; Dick, A. T. *The Pyrrolizidine Alkaloids*; North Holland: Amsterdam, 1968. (c) Warren, F. L. *Fortschr. Chem. Org. Naturst.* **1966**, *23*, 329; **1955**, *12*, 198. (d) Warren, F. L. *Alkaloids (N. Y.)* **1970**, *12*, 245. (e) Warren, F. L. In *The Alkloids, Chemistry & Physiology*; Manske, R. H. F., Ed.; Academic: New York, 1970; Vol. XII, p 319. (f) MacLean, E. K. *Pharm. Rev.* **1970**, *22*, 429. (g) Letendre, L.; Smithson, W. A.; Gilchrist, G. S.; Bergert, E. O.; Hoagland, C. H.; Ames, M. M.; Powis, G.; Korach, J. S. *Cancer* **1981**, *47*, 437.

0002-7863/86/1508-3755$01.50/0 

**Chart I**

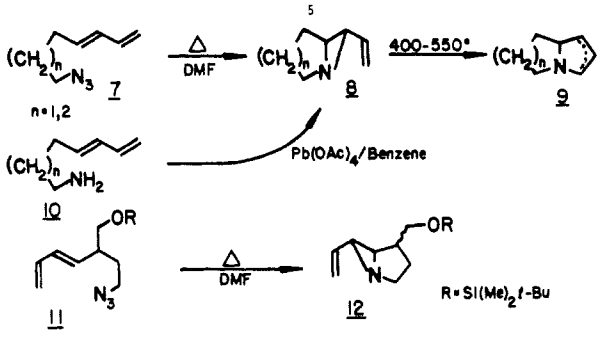
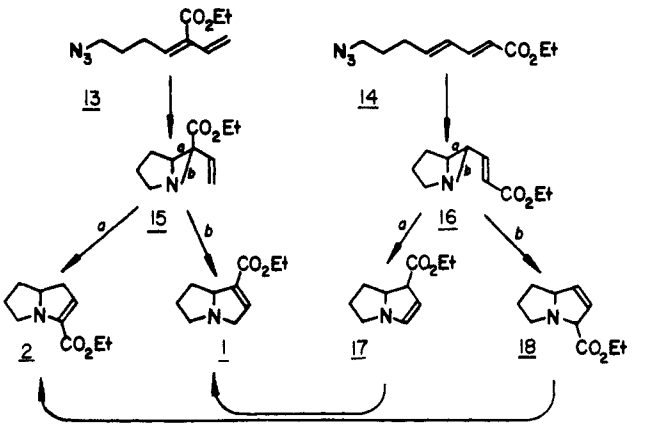
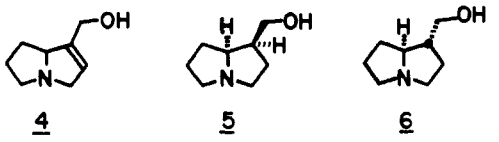


**Chart II**



for reductive and epimerizing operations as a means of absolute control of the substituent, along the lines of previously implemented strategy used in the synthesis of isocomenic acid.[2e] Of specific interest as targets of our initial study were simple pyrrolizidine alkaloids: supinidine (**4**) and the saturated stereoisomeric alkaloids isoretronecanol (**5**) and trachelanthamidine (**6**).[5]



In the interaction of carbenoids with dienes, the mechanistic pathways to vinylcyclopropanes and subsequent rearrangements to cyclopentenes are clearly defined. This is not so in the conceptually similar decomposition pathways of azidodiene **3**, for which multiple reactive options are available. The options of either the initial cycloadditions or any subsequent transformations can be greatly reduced and controlled through careful design and experimental execution. In this manuscript we report on the topologically selective preparations of pyrrolizidines **1** and **2** and the experimentally controlled parameters that impose such selectivity.

## Results and Discussion

The cycloadditions of azides to olefins and dienes have some precedent in synthetic application.[6] Because the dienic azides and the corresponding vinyltriazolines or vinylaziridines, which may be generated under a variety of experimental conditions, are disposed to undergo a multitude of mechanistically dissimilar transformations, the available studies, as well as any applications of such reactions, have been either limited or confined to special cases. Decompositions of alkyl azides containing olefins have been performed under thermal[7] and photolytic[8] conditions. Acid-catalyzed[9] and transition-metal-catalyzed[10] decomposition of azides has been reviewed. The resulting triazolines or vinylaziridines have been transformed into pyrrolines by using either thermolysis[11] or nucleophilic ring opening.[12] Some of the more serious side reactions reported to occur during the above transformations include the formation of imines[13] and diazo compounds,[14] and the mechanisms advanced for the decomposition of triazolines or vinyltriazolines to aziridines or vinylaziridines and, eventually, to pyrrolines include the postulation of diradicals,[15] azomethine ylides,[16] or the formation of allylic halides.[17] Additionally, vinylaziridines have been prepared by lead tetraacetate oxidation of certain sterically constrained dienic amines.[18] This type of behavior was documented previously for the formation of aziridines from simple olefinic amines.[19]

Faced with such a diversity of options, we tested several simple dienic azides and amines for their convertibility to pyrrolines. Azides **7** were thermally transformed to vinylaziridines **8** in poor yields (Chart I), and their further transformation to pyrrolines **9** through flash vacuum pyrolysis proved extremely sluggish.[20] The oxidation of dienic amine **10** with lead tetraacetate provided

(5) For recent synthetic efforts in this area see the following. Supinidine: (a) Chamberlin, A. R.; Nguyen, H. R.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (b) Kametani, T.; Higashiyama, K.; Otomatsu, H.; Honda, T. *Heterocycles* **1984**, *22*, 729. (c) McDonald, T. L.; Narayanan, B. A. *J. Org. Chem.* **1983**, *48*, 1129. (d) Hart, D. J.; Yang, T. K. *Tetrahedron Lett.* **1982**, 2761. (e) Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, 2619. (f) Rueger, H.; Benn, M. *Heterocycles* **1982**, *19*, 1677. (g) Terao, Y.; Imai, N.; Achiwa, K.; Sekiya, M. *Chem. Pharm. Bull.* **1982**, *30*, 3167. (h) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 909. (i) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Chem. Commun.* **1979**, 1181. (j) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1734. (k) Tufariello, Y. J.; Tette, J. P. *J. Chem. Soc., Chem. Commun.* **1971**, 469; *J. Org. Chem.* **1975**, *40*, 3860. Trachelanthamidine (see also ref 5a, 5b, 5d, 5f–5h, 5t): (l) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, 4411. (m) Pinnick, H. W.; Chang, Y. H. *Tetrahedron Lett.* **1979**, 837. (n) Danishefsky, S.; McKeee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 4783. Isoretronecanol (see also ref 5f–5i, 5m): (o) Gramain, J. C.; Remuson, R.; Vallée, D. *J. Org. Chem.* **1985**, *50*, 710. (p) Tatsuta, K.; Takahashi, H.; Amemia, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. (q) Muchowski, J. M.; Nelson, P. H. *Tetrahedron Lett.* **1980**, 4585. (r) Iwashita, T.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 1337. (s) Stevens, R. V.; Luh, Y.; Sheu, J. T. *Tetrahedron Lett.* **1976**, 3799. (t) Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225. (u) Ortiz, C.; Greenhouse, R. *Tetrahedron Lett.* **1985**, 2831. (v) Kraus, G. A.; Nevenschwander, K. *Tetrahedron Lett.* **1980**, 3841. (w) Flitsch, W.; Wernsmann, P. *Tetrahedron Lett.* **1981**, 719. (x) Pinnick, H. W.; Chang, Y. H. *J. Org. Chem.* **1978**, *43*, 4662.

(6) For general reference texts on the chemistry of azides, azidoolefins, triazolines, and aziridines, see: (a) *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970. (b) Deyrup, J. A. *Small Ring Heterocycles*—Aziridines; Hanner, A., Ed.; Interscience: New York, 1983; p 1. (c) *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic: New York, 1984. (d) Reference 9a and Supplement D, Chapters 7 and 8, 1983.

(7) (a) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676. (b) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5009. (c) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749. (d) Kozikowski, A. P.; Greco, M. N. *J. Org. Chem.* **1984**, *49*, 2310. (e) Figeys, H. P.; Jammar, R. *Tetrahedron Lett.* **1981**, *22*, 637. (f) Sundberg, R. J.; Pearce, B. C. *J. Org. Chem.* **1982**, *47*, 725. (g) Broeckx, W.; Overbergh, N.; Samyn, C.; Smets, G.; L'Abbé, G. *Tetrahedron* **1971**, *27*, 3527. (h) Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988. (i) Scheiner, P. *Tetrahedron* **1968**, *24*, 2757. (j) Scheiner, P. *J. Org. Chem.* **1965**, *30*, 7. (k) Scheiner, P. *J. Am. Chem. Soc.* **1966**, *88*, 4759. (l) Smolinsky, G. *J. Am. Chem. Soc.* **1961**, *83*, 4483. (m) Henery-Logan, K. R.; Clark, R. A. *Tetrahedron Lett.* **1968**, *7*, 801. (n) Scheiner, P. *Tetrahedron* **1967**, *24*, 349. (o) Scheiner, P. *J. Org. Chem.* **1967**, *32*, 2628.

(8) (a) Harvey, R. G.; Ratts, K. W. *J. Org. Chem.* **1966**, *31*, 3907. (b) Lwowski, W.; Rice, S. N.; Mishra, A. *J. Org. Chem.* **1968**, *33*, 481.

(9) (a) Abramovitch, R. A.; Kyba, E. P. *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, 1971. (b) Hortmann, A. G.; Koo, J. *J. Org. Chem.* **1974**, *39*, 3781.

(10) See ref 6d.

(11) (a) Rees, C. W.; Atkinson, R. S. *J. Chem. Soc., Chem. Commun.* **1967**, 1232. (b) Vessieve, R.; Gelas-Mialhe, Y.; Borel, D. *Can. J. Chem.* **1976**, *54*, 1590. (c) Pommelet, J. C.; Chuche, J. *Can. J. Chem.* **1976**, *54*, 1571. (d) See ref 8b.

(12) See ref 7a, 27.

(13) See ref 8a, 7b, 7d, 7l, 7m.

(14) See ref 7a, 7c.

(15) See ref 7g, 7h.

(16) See ref 11b, 11c.

(17) See ref 7o.

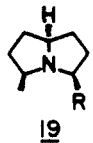
(18) Nagata, W. *Lect. Heterocycl. Chem.* **1972**, *1*, S-29.

(19) (a) Portoghese, P. S.; Sepp, D. T. *Tetrahedron* **1973**, *29*, 2253. (b) Nagata, W.; Hirai, S.; Kawata, K.; Aoki, T. *J. Am. Chem. Soc.* **1967**, *89*, 5045.

(20) Hudlicky, T.; Short, R. P.; Frazier, J. O., unpublished observations. The quality of pyrolyses has also been found to be a function of pressure. Vacuum better than $10^{-4}$ mm is a necessity.

some evidence of vinylaziridine formation, but the transformations of this type led to extremely complex mixtures. The evidence for the structures of reaction products was provided through analysis of spectra of sensitive and unpurified reaction mixtures and should be regarded with a low degree of certainty.[20] Similarly, azide **11** was transformed in low yield to vinylaziridine **12** by thermal decomposition.[20]

It became apparent that activation of the diene system must be present in order for any cycloaddition to occur under experimentally feasible conditions. We therefore prepared unsaturated esters **13** and **14**, which bear an electron-withdrawing substituent at one of the two relevant positions in the dienic systems. The substitution pattern of dienes **13** and **14** becomes important in controlling the topology of pyrrolines **1** and **2**. The recognition of the fact that two bonds (a and b) in the vinylaziridines **15** and **16** are activated toward either diradical- or nucleophile-assisted opening in a mutually orthogonal sense facilitated the projected conversion of these substrates to pyrrolizidines **1** and **2**, as shown in Chart II. Thus cleavage of bond a in **15**, brought about by thermolysis, should yield a preponderance of substituted pyrroline **2** via either a diradical or an azomethine ylide intermediate. On the other hand, opening of aziridine **15** via nucleophilic displacement at the vinyl group followed by reclosure should lead to pyrroline **1** as a major product through cleavage of bond b. Change in the position of the ester function to the terminal site in diene **14** and the subsequent ring opening of its corresponding vinylaziridine **16** should lead to pyrrolizidines **17** and **18**, whose relative ratios should be exactly opposite to those found in the reactions of **15**. That pyrrolizidines **17** and **18** can be either isomerized to **1** and **2**, respectively, or hydrogenated to identical sets of saturated esters provided additional assurance of topologically controlled preparations of **1** and **2** and their utility in accessing naturally occurring pyrrolizidine alkaloids, including those featuring the substitution pattern of ant venom **19**.[21]



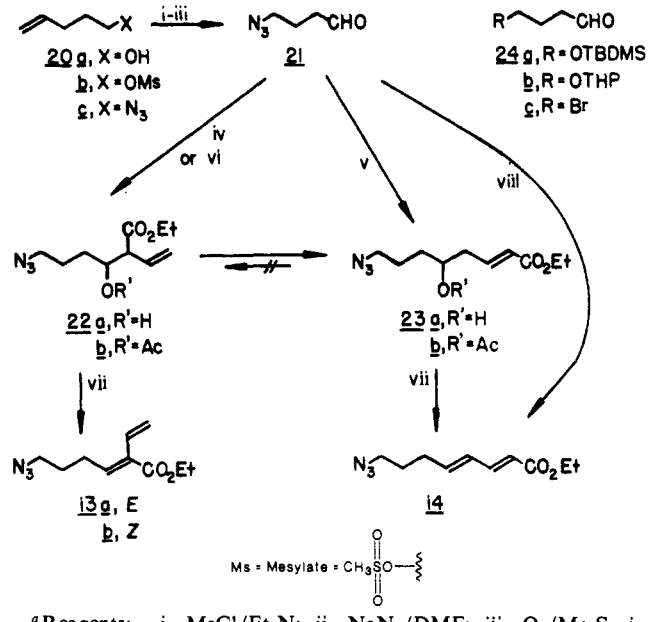
**19**

R = $C_7H_{15}$

**Preparation of Azidodienes.** A good opportunity existed to test the regioselectivity of the vinylogous Reformatsky reaction in the construction of dienes **13** and **14** since these were accessible through a controlled union of an ethyl crotonyl unit with an aldehyde. The selectivity of additions of ethyl bromocrotonate to carbonyl substrates has been shown to depend on precisely defined experimental conditions.[22] During the pursuit of syntheses of cyclopentanoid terpenes, we have utilized extensively the "$\alpha$-selectivity" of these additions in the preparation of dienic acids,[2] but the opportunity to use both $\alpha$- and $\gamma$-regioisomers from such additions in the design of cyclopentanoid terpenes did not present itself. In the approach to pyrrolizidines, this regioselection became the key element since it determines not only the position of the activating group on the diene but also the substitution pattern of the pyrrolizidines **1** and **2** or **17** and **18**.

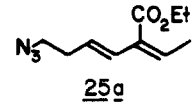
We prepared the requisite dienes **13** and **14** as shown in Chart III. 4-Penten-1-ol was converted to azidoaldehyde **21** by mesylation (95%), azide displacement (52%), and ozonolysis (70%). This procedure proved superior to the alternate preparation of **21** from commercially available pent-4-enyl bromide. (See Experimental Section.) Aldehyde **21** was purified by Kugelrohr distillation at ambient temperature and high vacuum and then used in the next step. We were surprised at the relative ease with which azidoaldehyde **21** could be manipulated. Although it could not be stored without significant decomposition, its azido group proved inert during subsequent manipulation. We therefore abandoned our earlier approach in which the azide would be introduced last into precursors such as **24a** or **24b**.[24] The tetrahydropyranyl ether proved especially cumbersome in view of the many diastereomers produced during the Reformatsky reaction. Exposure of aldehyde **21** to ethyl 4-bromocrotonate in the presence of a zinc–copper couple containing traces of acetic acid led to the formation of $\alpha$-adduct **22a** in 90% yield as a mixture of erythro and threo diastereomers (1.1:1). These isomers were not separable because of their inherent instability and tendency to decompose to the starting aldehyde and ethyl crotonate, in agreement with reported behavior for compounds of this type.[22] In practice, the crude reaction mixtures were immediately subjected to acylation conditions and converted in 85% yield to acetates **22b**, which were stable to manipulation. Careful chromatography on silica gel (hexane/ethyl acetate) provided pure erytho and threo diastereomers **22b–E** and **22b–T**.

Chart III[a]

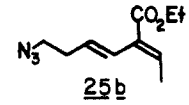



[a] Reagents: i, $MsCl/Et_3N$; ii, $NaN_3/DMF$; iii, $O_3/Me_2S$; iv, $BrCH_2CHCHCO_2Et/Zn(Cu)$, $(HOAc)/Et_2O$; v, $BrCH_2CHCHCO_2Et/Zn$/benzene; vi, $LDA/CH_3CHCHCO_2Et$/THF, −78 °C; vii, DBU/DME, 0 °C, 5 min; viii, $(EtO)_2P(O)$-$CH_2CHCHCO_2Et/n$-BuLi/−78 °C.

The initial elimination of acetates **22b** was carried out on the mixture of diastereomers to afford diene **13** as a mixture of geometric isomers. The conditions of this elimination had to be most carefully adjusted since prolonged exposure to base caused isomerization of **13** to a mixture of more substituted dienes **25a** and **25b**. The best conditions (DBU/DME, 5 min, 0 °C) pro-



**25a**



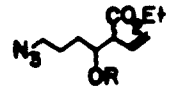
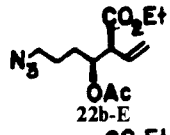
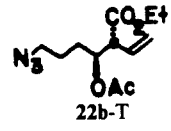
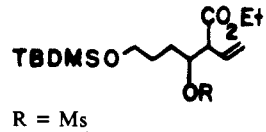
**25b**

duced a 2.5:1 mixture of *E* and *Z* isomers of **13**. We had suspected previously that such eliminations are not stereospecific since mixtures of vinyl acrylates were always obtained during similar eliminations in the terpene series. Unlike in the synthesis of cyclopentanoid terpenes, where the vinylcyclopropane rearrangement was unaffected by endo/exo ratios, in the rearrangements of vinylaziridines **15** it was necessary to maximize the content of the exo isomer. We assumed that sterospecificity in the cycloaddition of *Z* diene **13** to its triazoline would be attained, although we were uncertain about the transfer of such stereospecificity from the triazoline during its decomposition to vinylaziridine **15**. We therefore investigated the conditions of the elimination reaction in detail and found the isomeric ratio of dienes to be *independent* of the steric integrity of the acetates. Our results are summarized in Table I. Of the several leaving groups tested,

(21) Jones, T. H.; Blum, M. S. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, p 33. Stetler, H.; Basse, W.; Kuhlman, H.; Landscheidt, A.; Schlenker, W. *Chem. Ber.* **1977**, *110*, 1007.

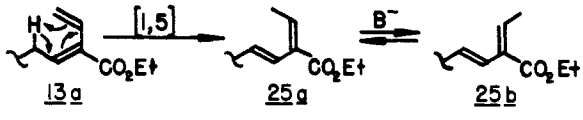
(22) Hudlicky, T.; Rice, L.; Boston, C.; Finklea, H.; Frazier, J.; Suder, B. *J. Org. Chem.* **1984**, *49*, 1845.

**Table I.** Conditions of Elimination for the Formation of Azidodienes

| substrate | conditions | products[a] 13a (*E*) | 13b (*Z*) | 25a,b |
|---|---|---|---|---|
|  | | | | |
| mixture of erythro/threo | neat DBU, 0 °C, 1 min | | | 100% |
| (1.1:1) | DME/DBU, room temp, > 15 min | | | 100% |
| R = Ac | neat DBU, −48 → −40 °C, 1 min | 1.7 | 1 | 1 |
| | DBU/toluene, 0 °C, 7 min | 2.2 | 1 | |
| | DBU/DME, 0 °C, 5 min | 2.5 | 1 | <1% |
|  22b-E | DME/DBU, 0 °C, 5 min isomer A | 4 | 1 | |
|  22b-T | isomer B | 1 | 1 | |
| R = Ms | DME/DBU, 0 °C, 6 min | 7 | 1 | |
| | DME/DBU, 0 °C, >10 min | 1.75 | 1 | 1 |
| R = Bs | DME/DBU, 0 °C, 6 min | 7 | 1 | |
| R = Ts | DME/DBU, 0 °C, 7 min | >20 | 1 | |
| | DME/DBU, 0 °C, >30 min | 1 | | 1 |
| R = $OCCF_3$ | DME/DBU, 0 °C, 5 min | 9 | 4 | 1 |
|  | | | | |
| R = Ms | $Et_3N$, room temperature | 2.5 | 1 | |
| R = Ac[b] | DME/DBU, 0 °C, 15 min | 2[b] | 1[b] | 1 |

[a] Ratios were determined by $^1H$ NMR (270 MHz). The isolated yields (chromatography) were >80%. [b] See ref 24 for spectral data of these compounds.

the largest *E*/*Z* ratio was obtained for tosylate. On the other hand, low-temperature exposure of acetates **22b** to excess DBU gave the largest *Z*/*E* ratio. It was important to maximize this ratio since the diastereomeric dienes **13** were not separable by thin-layer or column chromatography and since it was important to determine the stereospecificity parameters involved in the transformation of **13** to **15**. A similar elimination study was performed on the acetates and mesylates derived from aldehydes **24a** and **24b**. While we were unable to optimize the production of *Z* diene **13b**, we



13a 25a 25b

learned that the fully isomerized dienes **25a** and **25b** stemmed from the rearrangement of **13a** under prolonged exposure to the reaction conditions. Clearly, further investigation of the steric course of the base-catalyzed elimination of the substrates of type **22** is needed. In the future, the pure *Z* isomer of **13b** will have to be prepared by other methods such as Peterson-type olefination.

The exposure of aldehyde **21** to ethyl 4-bromocrotonate in benzene in the presence of zinc gave the expected γ-adduct **23a** in 87% yield.[22] Interestingly, this compound could also be obtained by equilibration in benzene of the zinc alkoxide of **22a**, which confirms our earlier experiments on the *reversibility* of the Reformatsky reaction.[23] The corresponding equilibration of the lithium alkoxide of **22a**, obtained by the condensation of the lithiodienolate of ethyl crotonate with aldehyde **21**, led to mixtures of **22a**, **23a**, and the conjugated isomer of **22a** (see supplementary material). In this fashion *complete* selectivity in accessing either **22** or **23** was obtained either by changes in the reaction conditions or by equilibration. Hydroxy ester **23a** was acetylated and converted to diene **14** in a manner similar to the preparation of **13**. Alternatively, this diene could be prepared in one step by the use of the Horner–Emmons-modified Wittig reaction. Ethyl 4-bromocrotonate was converted to its phosphonate ester according to a previously reported procedure.[25] The lithium salt of this ester, generated at −78 °C with *n*-butyllithium, condensed with aldehyde **21** in 70% yield to provide the fully conjugated diene **14**. We now had two sets of reliable procedures for obtaining these dienes regioselectively and were in the position to test their cycloadditions.

**Cycloadditions in the α-Series.** The exposure of diene **13** (mixture of *E* and *Z* isomers) to conditions of thermal decomposition ranging from refluxing THF to flash pyrolysis provided uniformly high yields of imine **27a**. The reaction mixtures contained traces of pyrrolines **1** and **2**, but imine **27a** constituted over 90% of such mixtures. The imine can be viewed as a product of a [1,5] hydrogen shift occurring in the endo isomer of vinylaziridine **15a**. Such behavior would be analogous to that of *cis*-alkylvinylcyclopropanes reported some time ago from our laboratory.[26] We suspected that the formation of vinylaziridines **15** from their corresponding triazolines is not subject to the stereospecificity requirements manifested in the additions of carbenoids to olefins. Although the initial triazoline formation may have been stereospecific, the decomposition may produce mixtures of endo and exo isomers of vinylaziridines **15**.[7,8] This supposition

(23) Hudlicky, T.; Natchus, G. M.; Kwart, L. D.; Colwell, B. *J. Org. Chem.* **1985**, *50*, 4300.

(24) These compounds were prepared as described in ref 3b above. Acetates: $^1H$ NMR ($CDCl_3$, 270 MHz) δ 0.07 (S, 6 H), 0.9 (S, 9 H), 1.25 (t, 3 H, *J* = 7 Hz), 1.5–1.8 (m, 4 H), 1.98 (s, 0.66 H), 2.01 (s, 0.34 H), 2.4 (m, 1 H), 3.2 (dd, 0.66 H, *J* = 14, 6 Hz), 3.32 (t, 0.34 H, *J* = 8 Hz), 3.6 (m, 2 H), 4.18 (q, 2 H, *J* = 7 Hz), 5.15 (m, 2 H), 5.9 (m, 1 H). Dienes: $^1H$ NMR ($CDCl_3$, 270 MHz) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.31 (t, 3 H, *J* = 7 Hz), 1.69 (m, 2 H), 2.39 (m, 2 H), 3.63 (t, 2 H, *J* = 7 Hz), 4.11 (q, 2 H, *J* = 7 Hz), 5.37 (d, 1 H, *J* = 12 Hz), 5.59 (d, 1 H, *J* = 18 Hz), 6.47 (dd, 1 H, *J* = 18, 6 Hz), 6.87 (t, 1 H, *J* = 6 Hz), *E* isomer. Olefin region of the *Z* isomer: 5.22 (d), 5.44 (d), 6.1 (t), 6.5 (dd).

(25) Sato, K.; Mizuno, S.; Hirayama, M. *J. Org. Chem.* **1967**, *32*, 177.

(26) Hudlicky, T.; Koszyk, F. J. *Tetrahedron Lett.* **1980**, 2487.

**Table II.** Results and Product Distribution of Thermolyses

| starting material | conditions | products[a] | | | | |
|---|---|---|---|---|---|---|
| α-Series | | **28** | **15** | **27** | **1** | **2** |
| **13** (a and b) | 0 °C, 1 week | >80 | 10 | 10 | | |
| | reflux, THF, 4 h | | | 85 | 4 | 10 |
| | reflux, benzene, 6 h | | | 88 | 3 | 9 |
| | 80 °C 0.2 mmHg, Kugelrohr | | 85 | 15 | | <1 |
| | 550 °C, $10^{-5}$ mmHg, flash vac. pyr. | | | 51 | 9 | 40 |
| | 450 °C, 0.25 mmHg | | 8 | 45 | 5 | 42 |
| **15** | reflux, THF | | 32 | 32 | 6 | 30 |
| | 550 °C, $10^{-5}$ mmHg, flash pac. pyr. | | | 45 | 10 | 45 |
| | LiI/acetone, reflux | | | <10 | 91 | |
| **15b** | 550 °C, $0.6 \times 10^{-3}$ mmHg | | | >90 | | trace |
| **27** | 550 °C, $10^{-5}$ mmHg, flash vac. pyr. | | | 67 | 7 | 26 |
| **13a**[b] | 90 °C, 0.6 mmHg | | 35 | 5 | | |
| **13a** | 550 °C, $10^{-5}$ mmHg, flash vac. pyr. | | | 51 | 9 | 40 |
| **13b** | 550 °C, $10^{-5}$ mmHg, flash vac. pyr. | | | 50 | 10 | 40 |
| **27a** | 500 °C, $10^{-4}$ mmHg, flash vac. pyr. | | | 85 | 4 | 11 |
| γ-Series | | **14** | **16** | **17** | | **18** |
| **14** | 450 °C, $10^{-5}$ mmHg | 10 | 60 | 24 | | <5 |
| **16** | 450 °C, $10^{-5}$ mmHg | | | 90 | | <5 |

[a] Ratios were determined by $^1$H NMR (270 MHz). [b] ~50% of this mixture contained isomerized diene **25** resulting from [1,5] hydrogen shift.

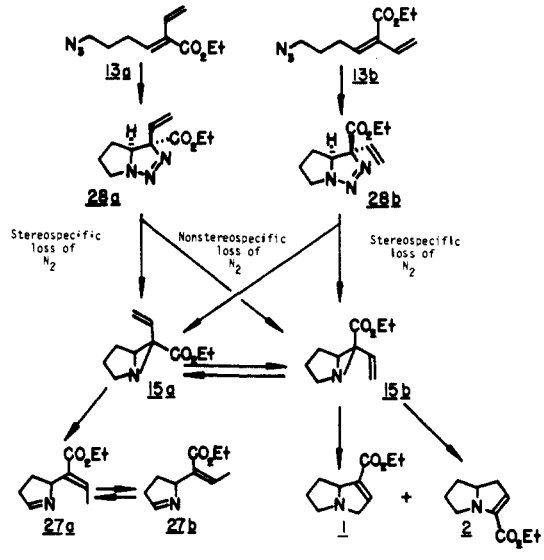



**Figure 1.** Probable mechanistic pathway in the decomposition of azidodienes.

was confirmed when sterically homogeneous *E* diene **13a** was subjected to identical conditions and produced mixtures of products identical with those obtained from thermolysis of *E* and *Z* mixtures of **13** (Table II). The pathway to imine **27a** and its geometric isomer **27b** must proceed through the corresponding triazolines and vinylaziridines, as represented in Figure 1. The triazolines were detected in the NMR spectra of crude reaction mixtures but were not subjected to purification or full characterization because of their extreme lability. Of the two vinylaziridines prepared by distillation of azidodienes at 80 °C, the exo isomer **15b** could be purified by column chromatography while **15a** rearranged to imine **27a** during the separation. Pyrolysis of either vinylaziridine or the starting azidodienes at 550 °C yielded a mixture of imines **27** and pyrrolines **1** and **2** (5:1:4). We suspect that imine **27b** resulted from an isomerization of **27a**, via intermediate **29**, since

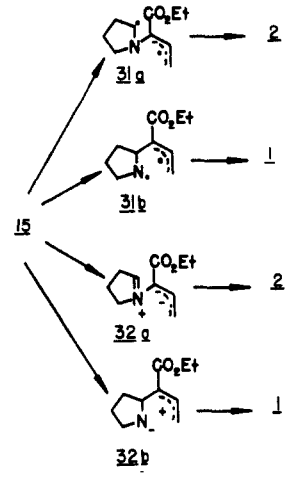
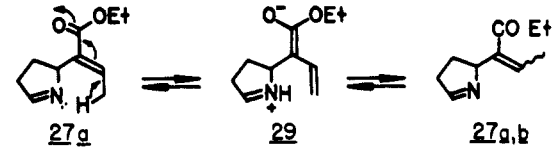
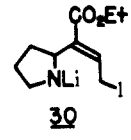



**Figure 2.** Possible intermediates in ring opening of vinylaziridines.

their relative content in thermolyses reflected the amount of time the samples were manipulated or stored prior to spectral analysis.




Vinylaziridine **15b** was completely rearranged to pyrrolizidine **1** upon refluxing in acetone containing LiI or in DME containing NaI. Such nucleophile-assisted ring opening of vinylaziridines has been reported in the literature and thought to occur via an intermediate of type **30**.[27]




Thus the synthesis of pyrrolizidine **1** was accomplished in a selective fashion through the nucelophilic opening of **15b**, while the preponderant production of **2** was achieved through pyrolysis of azidodienes **13**. This operation constituted the attainment of the title compounds through formal total syntheses since ester **1** has been converted to all of the natural products.[5]

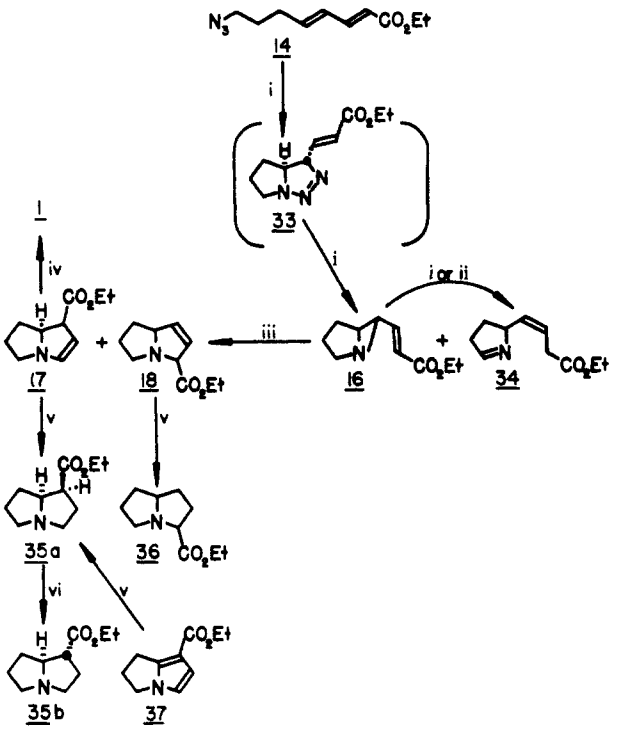
The reversibility of the [1,5] homodienyl shift of imine **27a** was addressed. In several experiments, this substance was evaporated through a hot tube in the temperature ranges at which pyrrolizidines **1** and **2** were produced. Imine **27a** furnished mixtures of products similar to those obtained on pyrolysis of **13**; however, the ratios of **1**, **2**, and **27** were different for each experiment and proved impossible to standardize (Table II). These results may reflect again on the varying content of **27b**, which would be inert to the retro [1,5] shift sequence to re-form the vinylaziridines.

Concerning the mechanism of the pyrroline rearrangements in this series, at least two options present themselves. The aziridines **15** may form either diradical or zwitterionic intermediates **31** and **32**, respectively (Figure 2). While the exact mechanism cannot be presented without further study, it is clear that diradical **31a** or azomethine ylide **32a** would be the more stable species in the above two pathways. Both ionic and diradical ring openings of vinylaziridines have been reported in the chemical literature.[15,16]

**Cycloaddition in the γ-Series.** Having completed the synthesis of pyrrolizidines **1** and **2** via the cycloadditions of dienes **13**, we turned to the investigation of similar cycloadditions using azidodiene **14**, where the activating group was a part of a fully conjugated system. The most attractive feature of this particular substrate was its stereochemical homogeneity—only the *E,E* form was produced in either the base-catalyzed eliminations of acetates

(27) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670.

Chart IV[a]



[a] Reagents: i, $PhCH_3$, reflux; ii, silica gel; iii, 450 °C; iv, basic alumina; v, $H_2$, Pd–C, HOAc, 1.5 atm; vi, alumina.

**23b** or the Horner–Emmons modification of the Wittig reaction. The reactions in this series were uniformly cleaner than in the corresponding $\alpha$-series. Refluxing diene **14** in toluene while monitoring the evolution of nitrogen provided vinylaziridine **16** in excellent yield (Chart IV). This material was suitably pure for the next step, but it contained a small amount of imine **34**, which could arise from prolonged reflux periods, on chromatography, or on distillation of vinylaziridines **16**, although the yields were not as high as for its counterpart, imine **27**.

Pyrolysis of **16** at 450 °C produced pyrroline **17** and a trace of **18**. Because of the instability of especially enamine **17**, this mixture was subjected to either isomerization to produce **1** and **2** or hydrogenation to afford **35** and **36**. The synthesis of **35** constituted formal total syntheses of isoretronecanol and trachellanthamidine.[5] We were delighted to note the high efficiency of the pyrolysis in this series. When pure **16** was pyrolyzed, almost quantitative transformation to **17** took place with a surprising and complete stereospecificity. Hydrogenation of this mixture in acetic acid gave crude **35a**, containing traces of **36**. Spectral parameters of **35a** matched exactly those reported for the hydrogenation product of pyrrole **37**.[5i,28]

Chromatography on alumina produced pure **35b**, whose spectra matched those reported for this substance by Pinnick.[5x] This unprecedented alumina-catalyzed isomerization made the syntheses of isoretronecanol and trachelanthamidine stereospecific. In previous conversions of this type, base-catalyzed isomerization of esters **35** has been reported to afford a 99:1 mixture of isomers,[29] while similar isomerizations of the corresponding amides gave ~4:1 mixtures.[30] Since the center at C-4 was unaffected during hydrogenation, these results also portend almost absolute stereospecificity of the rearrangement of **16** to **17**, thus imparting greater flexibility to the stereocontrolled preparation of the title alkaloids. The reasons for this selectivity will be addressed during future mechanistic investigations. Alumina- or base-catalyzed isomerization of **17** also provided pyrrolizidine **1** and, formally, supinidine, although these isomerizations suffered from poor reproducibilities as did the nucleophilic opening of **15** to furnish pyrrolizidine **1**. We also suspect that this compound is quite unstable since we could not obtain a pure sample by chromatography.

## Conclusions

The cycloadditions of azidodienes bearing an activating group have been shown to lead to the corresponding vinylaziridines in good yields. The vinylaziridines in either of the two series, differing only in the functional topology of the vinyl portion, were rearranged to pyrrolizidines **1** and **2** by either thermolyses or nucleophilic opening of the vinylaziridine moiety. Good selectivity was obtained for the attainment of either 2- or 4-substituted pyrrolizidine skeletons, the position of the substituent reflecting the initial placement of the activating group on the diene. This approach offers maximum flexibility in the number of experimental options available in the rearrangements. Thus the major product of the rearrangement in the $\alpha$-series was the 4-substituted pyrrolizidine when the conditions of nucleophilic opening were used, whereas under thermolytic conditions the 2-substituted pyrrolizidine predominated. By contrast, in the $\gamma$-series, the 4-substituted regioisomer was the major product of pyrolysis and was obtained in a totally stereospecific manner during the thermolysis of **16**. The title alkaloids have thus been attained in a regio- and stereoselective manner through two *convergent* approaches. Conditions need to be found to effect the nucleophilic opening of aziridine **16**, in which the electronic effect of the ester has been removed via further transformations (LiI opening of the corresponding allyl ether, for example).

This methodology has now been initiated into the compendium of methods for pyrroline synthesis. Future endeavors will address the mechanistic details of the rearrangements and the alternatives to pyrolytic transformations. Among these are oxidation of dienic amines and Michael-type additions of bis(silyl)hydroxylamines. These and other avenues are currently being explored in our laboratory as methods of access to pyrrolizidine nuclei. Further applications of this methodology in the context of alkaloid synthesis will be reported in due course.

## Experimental Section

**4-Azidobutanal (21).** For preparation of **20b**,[31] **20c**,[7c] and **24c**, see supplementary material.

**A. By Ozonolysis of 20c.** Ozone was bubbled through a solution of azidoolefin **20c**[7c] (17.4 g, 0.159 mol) and methylene chloride (70 mL) at −78 °C until a blue color persisted. This was followed by $O_2$ until the solution remained clear. Addition of dimethyl sulfide (98.7 g, 1.59 mol) at 0 °C was followed by stirring at room temperature for 24 h. The solution was diluted with ether; subsequent aqueous workup and removal of ether and methylene chloride by distillation through a 21-cm Vigreaux column yielded a gold oil, **21** (12.4 g, 70%).

**B. By Azide Displacement of 24c.** 4-Bromobutanal (1.76 g, 11 mmol) and DMF (20 mL) were stirred at room temperature for 10 min under an inert atmosphere. To this stirring solution, sodium azide (916 mg, 13 mmol) was added in one portion. Stirring was continued under an inert atmosphere for 12.5 h. An aqueous workup followed by extraction with ether and removal of solvent by distillation through a 21-cm Vigreaux column yielded a gold oil, **21** (1 g, 70%): IR (neat) 2100, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) $\delta$ 1.85 (p, 2 H, $J$ = 7 Hz), 2.5 (t, 2 H, $J$ = 7 Hz), 3.30 (t, 2 H, $J$ = 7 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.3 ($CH_2$), 40.5 ($CH_2$), 50.4 ($CH_2$), 200.7 (C).

**7-Azido-4-hydroxy-3-carboethoxyhept-1-ene (22a). A. Reformatsky Method.** To dry, powdered zinc (1.5 g, 21.2 mmol) a saturated solution of $Cu(OAc)_2$ in acetic acid (25 mL) was added, and stirring continued for 0.5 h. The resulting zinc–copper couple was rinsed with diethyl ether until no acetic acid was detected by NMR analysis of eluent. Anhydrous ether (25 mL) was added, and stirring at room temperature continued for several minutes. A solution of 5-azidobutanal (2 g, 17.64 mmol), ethyl 4-bromocrotonate (3.14 g, 21.2 mmol), and anhydrous ether (25 mL) was added dropwise via an addition funnel until half of the solution had been added. If the reaction started, addition and stirring continued; if there was no initiation, several crystals of $I_2$ were added to initiate the reaction, followed by continued addition and stirring. After addition was complete, the temperature was brought to reflux for 2.5 h. The reaction

(28) See Ref 5h, 5j, 5t. We have repeated the preparation of pyrrole **37** according to ref 5i and found the $^1H$ NMR spectrum of the hydrogenation product identical with that of **35a**.

(29) Brandange, S.; Lundin, C. *Acta. Chem. Scand.* **1971**, *25*, 2447.

(30) See ref 5l and 5v for isomerization of the corresponding amides.

(31) Pattison, F. L. M.; Millington, J. E. *Can. J. Chem.* **1956**, *34*, 757.

was quenched with saturated $NH_4Cl$ solution followed by aqueous workup to yield 3.6 g (90%) of a clear, yellow oil. Partial purification by filtration of the oil through a 5-cm plug of silica gel yielded 3.4 g (85%) of **22a** as a clear, colorless oil. This compound was used immediately in the next step because of its instability. **22a**: IR (neat) 3500, 2100, 1730, 6640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.3 (t, 3 H, $J$ = 7 Hz), 1.5–1.95 (m, 4 H), 2.75 (d, 0.33 H, $J$ = 6 Hz), 2.8 (d, 0.67 H, $J$ = 3 Hz), 3.1 (m, 1 H), 3.35 (br t, 2 H) 3.9 (m, 1 H), 4.2 (q, 2 H, $J$ = 7 Hz), 5.3 (m, 2 H), 5.8–6.0 (m, 1 H).

**B. Lithium Dienolate Method.** Diisopropylamine (1.247 mL, 8.9 mmol) was stirred at 0 °C under $N_2$, and *n*-butyllithium (3.71 mL, 8.9 mmol) was added dropwise. The mixture was stirred for 25 min, and then 10 mL THF (freshly distilled) was added to obtain a 0.9 M solution of LDA. The mixture was cooled to −78 °C, freshly distilled HMPA (1.71 mL, 9.8 mmol) was added and the mixture stirred for 30 min. Ethyl crotonate (1.11 mL, 8.9 mmol) was added, and after 15 min, followed with 4-azidobutanal (0.957 g, 8.47 mmol). Stirring was continued for 3.5 h (completion indicated by TLC) at −78 °C with warming to −50 °C during this period. The reaction mixture was diluted with 40 mL of ether (at −50 °C) and quenched with 45 mL of saturated $NH_4Cl$ solution. The aqueous layer was extracted with cold ether (2 × 10 mL). The combined organic layers were washed with 10 mL of cold water, 3 M HCl (1 × 10 mL and then 1 × 5 mL), and saturated NaCl solution (3 × 5 mL) and then dried over $Na_2SO_4$. Removal of the solvent afforded 1.743 g (91%) of **22a** of purity suitable for use in the next step.

**7-Azido-4-acetoxy-3-carboethoxyhept-1-ene (22b).** Azido alcohol **22a** (40 mg, 0.176 mmol) was stirred at 0 °C with pyridine (13.9 mg, 0.176 mmol) for 10 min. To this solution acetic anhydride (71.8 mg, 0.70 mmol) was added dropwise, followed by addition of 4-(dimethylamino)pyridine (4 mg, 0.035 mmol). The reaction mixture was stirred for 12 h, during which time the ice melted and the mixture warmed to room temperature. The reaction was quenched with saturated $NaHCO_3$ solution followed by an aqueous workup to yield 37 mg (85%) of **22b**, a clear, yellow oil. Separation of isomers was performed on silica gel using gradient elution (hexane, 95:5, 90:10...70:30 hexane/EtOAc). The reaction was scaled up to 1 g for preparative runs, in which a mixture of isomers was used.

Isomer A: **22b-E**, IR (neat) 2100, 1740, 1720 (sh) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.26 (t, 3 H, $J$ = 7 Hz), 1.60 (m, 4 H), 2.04, (s, 3 H), 3.25 (dd, 1 H, $J$ = 6, 10 Hz) 3.32 (m, 3 H), 4.12 (q, 2 H, $J$ = 7 Hz), 5.28 (m, 2 H), 5.80 (m, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 13.9 ($CH_3$), 20.7 ($CH_3$), 24.3 ($CH_2$), 28.7 ($CH_2$), 50.9 ($CH_2$), 54.8 (CH), 60.8 ($CH_2$), 72.7 (CH), 120.1 ($CH_2$), 131.5 (CH), 169.9 (C), 170.7 (C).

Isomer B: **22b-T**, IR (neat) 2980, 2940, 2100, 1740, 1720 (sh) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.25 (t, 3 H, $J$ = 7 Hz), 1.68 (m, 4 H), 2.05 (s, 3 H), 3.24 (t, 1 H, $J$ = 6 Hz), 3.28 (m, 3 H), 4.16 (q, 2 H), 5.20 (t, 3 H), 5.88 (m, 1 H); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 13.8 ($CH_3$), 20.5 ($CH_3$), 24.7 ($CH_2$), 29.1 ($CH_2$), 50.7 ($CH_2$), 54.4 (CH), 60.7 ($CH_2$), 72.2 (CH), 119.5 ($CH_2$), 131.7 (CH), 169.8 (C), 170.6 (C).

**3-Carboethoxy-7-azidohepta-1,3-diene (13a,b).** A solution of azido acetates **22b** (2:1 mixture of diastereomers) (253 mg, 1 mmol) in 3 mL of dry DME was cooled to 0 °C. Diazabicycloundecane (DBU) (167.2 mg, 1.1 mmol) was added at intervals via syringe (20 $\mu$L/20 s). After 7 min, the reaction was quenched with saturated $NH_4Cl$ solution and extracted with $Et_2O$ (3 × 20 mL). Filtration of $Et_2O$ solution through a plug of silica (1 × 0.5 cm) and evaporation gave 200 mg (96%) of diene **13**, shown to be a mixture of *E* and *Z* isomers (2:1). An analytically pure sample was obtained by flash chromatography on silica gel (hexane/$Et_2O$, 9:1) to give 61% recovery of **13**: IR (neat) 3100, 2100, 1720, 1640, 1300 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.20 (t, 3 H, $J$ = 7 Hz), 1.65 (p, 2 H, $J$ = 7 Hz), 2.34 (q, 2 H, $J$ = 7 Hz), 3.25 (t, 2 H, $J$ = 7 Hz), 4.16 (q, 2 H, $J$ = 7 Hz, *E* isomer), 4.20 (q, 2 H, $J$ = 7 Hz, *Z* isomer). [5.34 (dd, 1 H, $J$ = 20, 1 Hz), 5.5 (dd, 1 H, $J$ = 30, 1 Hz), 6.41 (dd, 1 H, $J$ = 30, 10 Hz), 6.65 (t, 1 H, $J$ = 7 Hz), *E* isomer] [5.08 (d, 1 H, $J$ = 15 Hz), 5.22 (d, 1 H, $J$ = 20 Hz), 5.84 (t, 1 H, $J$ = 7 Hz), 6.25 (dd, 1 H, $J$ = 20, 8 Hz), *Z* isomer]; $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 14.1 ($CH_3$) [25.7 ($CH_2$), *E* isomer; 26.8 ($CH_2$), *Z* isomer], 28.2 ($CH_2$), 50.8 ($CH_2$), 60.5 ($CH_2$) [115.1 ($CH_2$), 119.7 (CH), 128.9 (CH), 140.9 (C), *E* isomer], [117.0 ($CH_2$), 119.0 (CH), 135.1 (CH), 137.0 (C), *Z* isomer], 165.8 (C); mass spectrum (70 eV, rel intensity), $m/e$ 209 ($M^+$) (1), 181 ($M^+$ − nitrogen) (30), 152 (55), 136 (40), 108 (B), 106 (90), 91 (38), 80 (B), 79 (92), 65 (40), 53 (65).

Anal. Calcd for $C_{10}H_{15}O_2N_3$: 209.1164. Found: 209.1146.

**3-Carboethoxy-7-azidohepta-2,4-diene (25).** These compounds were easily prepared by allowing the above reaction mixture to warm to room temperature. After 15 min of stirring, the reaction was quenched and worked up as described above. The ratio of *E* and *Z* isomers of **25** varied with reaction times. The isomerized dienes were contaminants in the preparation of dienes **13** if the times of the reaction were not most carefully monitored. **25**: IR (neat) 2100, 1720 (br) $cm^{-1}$.

**1-Carboethoxy-7-azidohept-1-en-4-ol (23a). A. By Reformatsky Method.** Azidodiene **21** (0.62 g, 5.5 mmol) and ethyl 4-bromocrotonate (1.1 g) in 2 mL of benzene were added to dry zinc (2 equiv) in benzene (5 mL) over 5 min. The reaction was initiated with a crystal of iodine. The yellow-green mixture was brought to reflux, and after 4 h the reaction was quenched with $NH_4Cl$ solution. Extraction with ether and evaporation gave 1.1 g (86.6%) of oil. Further purification by rapid filtration of an ether solution through a plug of silica (2 × 4 cm) gave 95 mg (72%) of **23a**: IR (neat) 3500, 2120, 1730, 1660, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.2 (t, 3 H, $J$ = 7 Hz), 1.5–2.0 (m, 4 H), 2.3 (br dd, 2 H), 3.15 (br t, 2 H), 3.9 (dd, 1 H, $J$ = 16, 7 Hz), 4.05 (q, 2 H, $J$ = 7 Hz), 5.8 (d, 1 H, $J$ = 16 Hz), 6.85 (m, 1 H).

**B. By Equilibration of Zinc Alkoxide.** See supplementary material.

**1-Carboethoxy-7-azidohepta-1,3-diene (14). A. By Wittig Reaction.** In a flame-dried flask under nitrogen was placed a solution of ethyl 1-carboethoxy-4-diethylphosphonylcrotonate (2.214 g, 8.85 mmol) (prepared from ethyl 4-bromocrotonate and triethyl phosphite)[25] in dry THF (4 mL), and the mixture was cooled to −78 °C. To this solution was added *n*-BuLi in hexane (3.5 mL of 2.5 M solution, 8.85 mmol), and the orange solution was stirred for 30 min at −78 °C. 4-Azidobutanal (1 g, 8.85 mmol) was added, and stirring continued for 2 h at −78 °C. The reaction mixture was warmed to −50 °C (30 min) and the reaction quenched with saturated $NH_4Cl$ solution. Extracting ether (3 × 50 mL), drying ($Na_2SO_4$), and evaporating gave 1.38 g (75%) of oil **14**: IR (neat) 2110, 1720, 1650, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.28 (t, 3 H, $J$ = 7 Hz), 1.75 (p, 2 H, $J$ = 7 Hz), 2.27 (q, 2 H, $J$ = 7 Hz), 3.31 (t, 2 H, $J$ = 7 Hz), 4.2 (q, 2 H, $J$ = 7 Hz), 5.82 (d, 1 H, $J$ = 16 Hz), 6.16 (m, 2 H), 7.28 (dd, 1 H, $J$ = 16.4 Hz); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 14.3 ($CH_3$), 28.0 ($CH_2$), 29.9 ($CH_2$), 50.7 ($CH_2$), 60.2 ($CH_2$), 120.2 (CH), 129.5 (CH), 141.9 (CH), 144.3 (CH), 167.1 (C); mass spectrum (70 eV, rel intensity), $m/e$ 209 ($M^+$) (5), 181 (5), 149 (20), 108 (B), 97 (20), 80 (42), 67 (20), 55 (30).

Anal. Calcd for $C_{10}H_{15}N_3O_2$: 209.1164. Found: 209.1284.

**B. By Elimination of Acetate 23b.** The acetate of **23a** was prepared in a manner identical with that described for **22b** ($^1H$ NMR $\delta$ 2.09 (s, 3 H)). Elimination with DBU/DME at 0 °C for 45 min gave 81% yield of diene **14**, identical with that prepared by method A above.

**Ethyl 2-[5-(3*H*-4,5-dihydropyrrolyl)]crotonate (27).** Azido dienes **13** (2:1 mixture of *E* and *Z* isomers) (200 mg, 0.97 mmol) were refluxed in 20 mL of dry THF for 4 h. Evaporation of solvent and a quick filtration through silica gel (hexane/EtOAc, 4:1) yielded 144 mg (85%) of imine **27a** ($R_f$ = 0.29; EtOAc/hexane, 80:20). (Traces of vinylaziridine **15b** and pyrrolines **1** and **2** were detectable in the $^1H$ NMR spectrum of crude product.) **27a**: IR (neat) 1710, 1650, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.25 (t, 3 H, $J$ = 7 Hz), 1.8–2.2 (m, 2 H), 1.9 (d, 3 H, $J$ = 6 Hz), 2.5–3.0 (m, 2 H), 4.15 (q, 2 H, $J$ = 7 Hz), 5.08 (m, 1 H), 6.95 (q, 1 H, $J$ = 6 Hz), 7.65 (br d, 1 H, $J$ = 2 Hz); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 14.0 ($CH_3$, double intensity), 26.0 ($CH_2$), 38.0 ($CH_2$), 59.9 ($CH_2$), 69.7(CH), 133.9 (C), 138.9 (CH), 166.5 (C), 167.0 (CH); mass spectrum (70 eV, rel intensity), $m/e$ 181 ($M^+$) (45), 166 (20), 152 (65), 136 (70), 108 (90), 107 (95), 106 (B), 96 (75), 79 (40), 68 (52), 54 (25).

Anal. Calcd for $C_{10}H_{15}O_2N$: 181.1102. Found: 181.1098.

**1-Aza-2$\beta$-carboethoxy-2-vinyl-3$\alpha$-bicyclo[3.1.0]hexane (15b).** A sample of azidodienes **13** (100 mg) was distilled in a Büchi Kugelrohr apparatus at 80–90 °C at 0.2 mmHg over 30 min. The distillate (85 mg, 92%) was shown to contain imine **27a** (13%), vinylaziridine **15b** (85%), and traces of pyrroline **2**. Chromatography (silica gel/EtOAc) afforded pure **15b** ($R_f$ = 0.24, EtOAc; $R_f$ = 0.93, $CHCl_3$/MeOH, 1:1): IR (neat) 1730, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.27 (t, 3 H, $J$ = 7 Hz), 1.7–2.2 (m, 4 H), 2.9 (m, 1 H), 3.2 (m, 1 H), 4.12 (q, 2 H, $J$ = 7 Hz), 5.5 (m, 2 H), 5.78 (dd, 1 H, $J$ = 18, 8 Hz); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 14.0 ($CH_3$), 24.9 ($CH_2$), 46.0 (C), 50.2 ($CH_2$), 51.5 (CH), 60.2 ($CH_2$), 61.2 ($CH_2$), 123.3 ($CH_2$), 127.2 (CH), 167.0 (C); mass spectrum (70 eV, rel intensity), $m/e$ 181 ($M^+$) (35). 166 (10), 152 (50), 149 (30), 136 (30), 108 (60), 97 (25), 83 (40), 80 (50), 69 (65), 57 (B).

Anal. Calcd for $C_{10}H_{15}O_2N$: 181.1104. Found: 181.1102.

**4-Carboethoxy-3,4-dehydropyrrolizidine (1). A. From Azidodienes 13 by Thermolysis.** A sample of dienes **13** (210 mg, 1 mmol) was evaporated through a Vycor tube (1 × 50 cm; base-washed, *not* conditioned with $PbCO_3$) at 450 °C and $10^{-5}$ mmHg. The time of this distillation was kept to ~2 min by gentle warming of the flask containing the dienes. The condensate was recovered from the trap cooled with liquid $N_2$ and analyzed by $^1H$ NMR. It was shown to contain imines **27a** and **27b** (51%), pyrrolizidine **1** (9%), and pyrrolizidine **2** (40%). The crude product (190 mg, 94%) was purified by flash chromatography (chloroform on alumina) to give pure **1** ($R_f$ = 0.51, $CHCl_3$/MeOH, 1:1, $R_f$ = 0.49, $CHCl_3$/MeOH/$NH_4OH$, 55:45:2): $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.25 (t, 3 H, $J$ = 7 Hz), 1.5–3.0 (m, 6 H), 3.4 (m, 2 H), 4.15 (q, 2 H, $J$ = 7 Hz), 4.3 (m, 1 H), 6.65 (br dd, 1 H). The spectral and chromatographic

parameters were identical with those previously reported for this substance.[5i]

**B. By LiI Opening of 15b.** Vinylaziridine **15b** (7 mg) was dissolved in acetone containing 25 mg of LiI and the mixture refluxed for 8-10 h. Aqueous workup and extraction with methylene chloride gave 6 mg of pyrolizidine **1** contaminated with material resembling imine **27**. Pyrrolizidine **1** proved to be a rather sensitive material. Although isolated several times by chromatography, we were unable to obtain analytically pure samples. All spectra were contaminated with decomposition products of unknown composition.

**2-Carboethoxy-2,3-dehydropyrrolizidine (2).** The condensate from the pyrolysis of **13** was chromatographed on silica gel with hexane/EtOAc (20:80). Pyrrolizidine **2** ($R_f$ = 0.51, EtOAc/hexane, 80:20) was obtained as a clear oil, which decomposed within 2 weeks of storage: IR (neat) 1720, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.27 (t, 3 H, $J$ = 7 Hz), 1.5 (m, 1 H), 1.75 (m, 2 H), 1.95 (m, 1 H), 2.45 (m, 1 H), 2.72 (m, 1 H), 2.98 (m, 1 H), 3.25 (m, 1 H), 3.96 (m, 1 H), 4.16 (q, 2 H, $J$ = 7 Hz), 6.84 (t, 1 H, $J$ = 2 Hz); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 14.2 ($CH_3$), 25.5 ($CH_2$), 32.7 ($CH_2$), 35.7 ($CH_2$), 52.2 ($CH_2$), 60.4 ($CH_2$), 64.5 (CH), 117.2 (CH), 144.7 (C), 162.4 (C); mass spectrum (70 eV, rel intensity), $m/e$ 181 ($M^+$) (72), 179 (30), 152 (42), 134 (25), 108 (B), 80 (75).

Anal. Calcd for $C_{10}H_{15}O_2N$: 181.1102. Found: 181.1112.

**1-Aza-2-[1-(2-Carboethoxyvinyl)]bicyclo[3.1.0]hexane (16).** Azidodiene **14** (0.980 g, 47 mmol) was refluxed in dry toluene for 4 h, during which time a stoichiometric volume of nitrogen was expelled from the reaction mixture. Removal of solvent in vacuo without heating afforded 0.8 g of **16** (94%), which could be used in the next step. The crude product was contaminated with imine **34** (<8%). Attempts to purify **16** by flash chromatography led to extensive decomposition or transformation of **16** to **34**. Flash chromatography of the crude mixture yielded 122 mg (14%) of analytically pure **16**: IR (neat) 1730, 1660, 1590 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.2 (t, 3 H, $J$ = 7 Hz), 1.4-2.1 (m, 5 H), 2.4 (dd, 1 H, $J$ = 4.1 Hz), 3.0 (m, 2 H), 4.1 (q, 2 H), 5.92 (d, 1 H, $J$ = 16 Hz), 6.6 (dd, 1 H, $J$ = 16, 6 Hz); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 13.5 ($CH_3$), 19.5 ($CH_2$), 25.4 ($CH_2$), 36.9 (CH), 48.8 (CH), 52.0 ($CH_2$), 59.4 ($CH_2$), 120.5 (CH), 147.3 (CH), 165.4 (C); mass spectrum (70 eV, rel intensity), $m/e$ 181 ($M^+$) (5), 177 (2), 152 (4), 124 (10), 108 (B), 84 (30).

Anal. Calcd for $C_{10}H_{15}NO_2$: 181.1102. Found: 181.1064.

**4β-Carboethoxy-4α-pyrrolizidine (35a).** Chromatographed vinylaziridine **16** (90 mg, 0.49 mmol) was evaporated through a horizontally situated hot tube (1 × 40 cm) at 450 °C and $10^{-5}$ mmHg, and the condensate was collected in a trap cooled with liquid $N_2$. The total time of evaporation was kept under 2 min by gently warming the distillation flask. The $^1H$ NMR of the product (80 mg, 89%) indicated the presence of only pyrroline **17** [$^1H$ NMR $\delta$ 4.6 (d, 1 H, $J$ = 5.5 Hz) 5.85 (m, 1 H)] and trace amounts of pyrroline **18** [$^1H$ NMR $\delta$ 5.6 (m, 2 H)] in a ratio of at least 95:5. Thin-layer chromatography showed a clean conversion of **16** ($R_f$ = 0.75, $Al_2O_3$, $CHCl_3$) to **17** ($R_f$ = 0.38, $Al_2O_3$, $CHCl_3$) and **18** ($R_f$ = 0.1, $Al_2O_3$, $CHCl_3$). Because of the instability of enamines of the type **17**, no attempts were made at isolation of this substance. The pyrolysis mixture (70 mg) was hydrogenated over 5% Pd/C (25 mg) in HOAc (3 mL) at 23 psi for 24 h. The mixture was filtered through Celite, the filter washed with EtOH, and the filtrate evaporated to yield 66 mg (73%) of clear oil **35a**: IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 1.27 (t, 3 H, $J$ = 7 Hz), 1.5 (m, 1 H), 2.25 (m, 4 H), 2.75 (m, 2 H), 3.0 (m, 1 H), 3.4 (q, 1 H, $J$ = 8 Hz), 3.6 (m, 1 H), 3.75 (m, 1 H), 4.2 (q, 2 H, $J$ = 7 Hz), 4.38 (q, 1 H, $J$ = 8 Hz). Spectral data of this material were identical with those reported for **35a**, which was prepared by the method of Robins.[5i] Repetition of this preparation and hydrogenation of the intermediate pyrrole gave **35a**, identical with the material obtained in the pyrolysis/hydrogenation sequence.

**4α-Carboethoxy-4α-pyrrolizidine (35b).** The product of hydrogenation **35a** (45 mg) (>90% pure) was adsorbed on basic alumina and slowly eluted (~2 h) through a column (1 × 25 cm) with $CH_2Cl_2$. Evaporation of solvent gave pure **35b**: $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 3.72 (q, 1 H, $J$ = 8 Hz), 4.11 (q, 2 H, $J$ = 7 Hz); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 14.3 ($CH_3$), 26.4 ($CH_2$), 26.9 ($CH_2$), 28.4 ($CH_2$), 47.4 ($CH_2$), 53.7 ($CH_2$), 55.5 ($CH_2$), 60.4 ($CH_2$), 66.0 (CH), 173.4 (C). The $^{13}C$ NMR chemical shifts of this material matched exactly those reported by Pinnick for the trans isomer of **35**.[5x]

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**Supplementary Material Available:** Experimental procedures and data for compounds **20b**, **20c**, **24c**, zinc alkoxide, and lithium alkoxide equilibration data (3 pages). Ordering information given on any current masthead page.

# Sterically Hindered Free Radicals. 14.[1] Substituent-Dependent Stabilization of Para-Substituted Triphenylmethyl Radicals[2]

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**Abstract:** This is a contribution to the problem of stabilization of free organic radicals by resonance in general and to the recent discussion of "captodative" stabilization in particular. It has been found that substituent-dependent relative stabilities of 4,4'-disubstituted triarylmethyl radicals **1** can be sensitively determined by ESR spectroscopic measurement of the equilibria of dissociation of the quinonoid dimers **2** in 21 cases. Most of the compounds **1** and **2** were prepared for the first time. Both donor and acceptor substituents act as stabilizers; in combination they cooperate. A quantitative evaluation based on ESR, ENDOR, and UV/vis data leads to a Hammett-like equation containing $\sigma^\bullet$ and $\sigma$ parameters which is discussed.

Many attempts, beginning in 1920,[4] have been made in order to define what resonance stabilization of a radical means. Kinetic studies have been developed for measuring the relative stabilities of free organic radicals, beginning with important approaches by

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