yielded unreacted pteroic acid, which could be recycled. The precipitate of the diethyl ester was hydrolysed with 5 equiv of 0.1 N NaOH in CH_3CN at 25 °C for 18 h; the CH_3CN was removed under vacuum, acidified to pH 4.5 with glacial HOAc, and chilled. The glutamate conjugates **2** or **3** thus formed as a precipitate were filtered and further purified by ion exchange chromatography. In a typical experiment the yield of the product after purification was 67%. The physical and spectroscopic data (UV and NMR) of target drugs **2** and **3** were identical to those published earlier.[4,5]

Acknowledgment. This investigation was supported by PHS Grant CA 32687 awarded by the National Cancer Institute, DHHS. I am also indebted to Dr. DeGraw and Dr. Sirotnak for supplying the authentic samples of **26** and **27**. Partial support was also derived from PHS Grant CA 27101 awarded by NCI, DHHS. Thanks are also due to Jayaprakash who repeated many of the reactions on a scaled-up basis.

Registry No. **2**, 52454-37-2; **2** diethyl ester, 80577-71-5; **3**, 80576-83-6; **3** diethyl ester, 80576-82-5; **5**, 6284-26-0; **6**, 96056-26-7; **7**, 1571-08-0; **8**, 96056-27-8; **9**, 96056-28-9; **10**, 96056-29-0; **11**, 17745-40-3; **12**, 96056-30-3; **13**, 96056-31-4; **15**, 96056-32-5; **16**, 96056-33-6; **17**, 96056-34-7; (*E*)-**18**, 96095-23-7; (Z)-**18**, 96056-35-8; (E)-**19**, 96056-36-9; (Z)-**19**, 96056-37-0; **20**, 96056-38-1; **21**, 96056-39-2; **22**, 96056-40-5; **22a**, 96056-41-6; **23**, 96056-42-7; **23a**, 96056-43-8; **24**, 96056-44-9; **25**, 96056-45-0; **26**, 33047-42-6; **27**, 80576-81-4; triphenylphosphine, 603-35-0; triethylphosphine, 554-70-1; (2-oxo-3-phthalimidopropyl)(triphenyl)phosphonium bromide, 96095-24-8; ethylmagnesium, 925-90-6; vinylmagnesium bromide, 1826-67-1; hydroxylamine hydrochloride, 5470-11-1; 6-chloro-2,4-diamino-5-nitropyrimidine, 6036-64-2; diethyl L-glutamate hydrochloride, 1118-89-4.

Synthesis of Spiroimidazolidin-2-ones via Intramolecular *N*-Carbamoyliminium Ion Cyclization Reactions[1]

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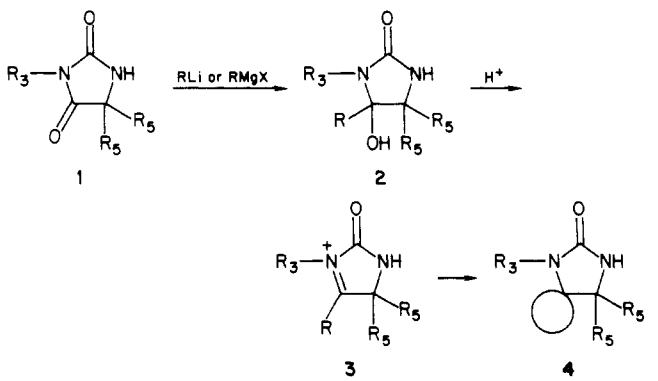
Received October 11, 1984

The use of *N*-carbamoyliminium ion initiated reactions for the generation of spiroimidazolidin-2-ones has been successfully exploited. Treatment of hydantoins with saturated alkyllithium and alkylmagnesium reagents gave the corresponding 4-hydroxyimidazolidin-2-one adducts. In the case of carbon-5 unsubstituted and carbon-5 monosubstituted hydantoins, dehydration of the intermediate 4-hydroxy derivatives occurred during workup to yield directly the 2-imidazolones. Addition of pent-4-enylmagnesium bromide (**13**) to the preformed magnesium salt of 3-benzyl-5,5-dimethylimidazolidine-2,4-dione (**5**) produced the expected tertiary 4-hydroxy adduct **14**. This intermediate upon treatment with formic acid underwent intramolecular cyclization to form a mixture containing two diastereomers of 2-(formyloxy)-7-benzyl-10,10-dimethyl-7,9-diazaspiro[4.5]decan-8-one (**15a,b**). The mechanism of these transformations is discussed.

N-Carbamoyliminium ions have proven to be versatile synthetic intermediates for the construction of annelated imidazolidinones and hydantoins.[1] In the cases examined the group that underwent addition to the cationic center was attached to the iminium ring nitrogen atom. We anticipated that access to the corresponding spiroimidazolidin-2-ones **4** (Scheme I) was possible by the initial treatment of 3-substituted hydantoins **1** with an excess of an organometallic reagent containing an olefinic moiety to give the 4-substituted 4-hydroxyimidazolidin-2-one derivatives **2**. These adducts **2** upon treatment with acid should lead to *N*-carbamoyliminium ion (**3**) formation followed by intramolecular olefinic cyclization to give the spiroimidazolidin-2-ones **4**. The successful implementation of this approach for the synthesis of **4** as well as the limitations of the method are the subject of this paper.

Scheme I. Proposed Synthetic Pathway Leading to the Formation of Spiroimidazolidin-2-one Derivatives



Results and Discussion

A key step in the proposed synthetic route is the formation of the tertiary hydroxy adducts **2**. We are unaware of any successful reports of the addition of organometallic reagents to hydantoin derivatives.[3] Compounds **5**–**7**[4-6] were chosen as test examples for this reaction. The hydantoins differed in the degree of substitution at carbon-5. Minor variation also existed at the N-3 position.

Treatment of 3-benzyl-5,5-dimethylhydantoin (**5**) with either *n*-BuLi, or *n*-BuMgCl, afforded 3-benzyl-4-*n*-bu-

(1) For previous papers in this series, see: (a) Kohn, H.; Liao, Z. K. *J. Org. Chem.* **1982**, *47*, 2787-2789. (b) Liao, Z. K.; Kohn, H. *Ibid.* **1984**, *49*, 3812-3819. (c) Liao, Z. K.; Kohn, H. *Ibid.* **1984**, *49*, 4745-4752.

(2) Taken, in part, from the Ph.D. dissertation of this author. Additional structure proof, discussion, and experimental and spectral data may be found in this reference.

(3) In a related example, the reaction of 3-phenyl-2-thiohydantoin with ethylmagnesium iodide in benzene led to the recovery of starting material. Shalaby, A. P. A.; Daboun, H. A. *J. Prakt. Chem.* **1971**, *313*, 1031-1038.

(4) Jordan, T. E.; Grinsburg, S. *J. Am. Chem. Soc.* **1949**, *71*, 2258.

(5) United States Borax and Chemical Corp., Brit. Pat. 1074999, 1967; *Chem. Abstr.* **1968**, *68*, 12974n.

(6) Finkbeiner, H. *J. Org. Chem.* **1965**, *30*, 3414-3419.

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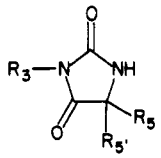
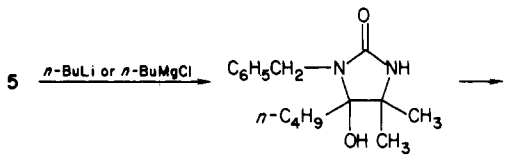


5, R_3 = $C_6H_5CH_2$; R_5, $R_{5'}$ = CH_3
6, R_3 = 2-$CH_3C_6H_4(CH_2)_2$; R_5 = CH_3, $R_{5'}$ = H
7, R_3 = $C_6H_5CH_2$; R_5, $R_{5'}$ = H

tyl-4-hydroxyimidazolidin-2-one (**8**) in 37% and 36%



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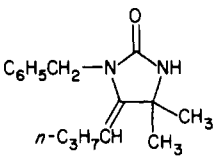

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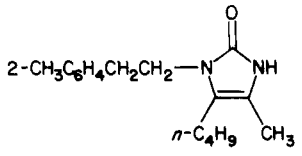
yields, respectively. Unreacted starting material (**5**) was recovered in each case. No effort was made to optimize the yield of this reaction. Compound **8** is relatively unstable and was stored at temperatures below 0 °C. The 4-hydroxyimidazolidin-2-one **8** underwent dehydration at room temperature in a chloroform solution (24 h) to yield a compound which has been tentatively identified as **9**.

An analogous situation occurred with the intermediate tertiary 4-hydroxy adducts obtained from the reactions of 5-monosubstituted hydantoin **6** with either *n*-BuLi or *sec*-BuLi and the carbon-5 unsubstituted hydantoin **8** with *n*-BuLi. In all these cases, dehydration occurred during workup and purification (i.e., flash chromatography) to give directly the 2-imidazolone adducts **10**–**12**, respectively.



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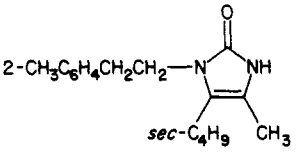

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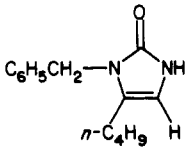

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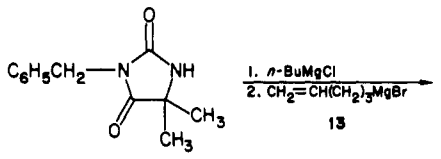
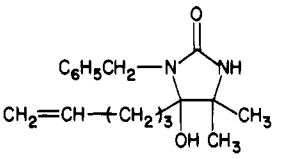
The success of these nucleophilic additions provided encouragement for the proposed *N*-carbamoyliminium ion route to spiroimidazolidin-2-ones **4** depicted in Scheme I. Accordingly, the magnesium salt of **5** (prepared by treatment of **5** with *n*-BuMgCl) was treated with pent-4-enylmagnesium bromide (**13**).[7,8] After aqueous workup, 3-benzyl-4-(pent-4-enyl)-4-hydroxy-5,5-dimethylimidazolidin-2-one (**14**) was obtained along with unreacted **5**. Due to the relative ease with which this compound underwent dehydration, no attempt was made to purify the 4-*tert*-hydroxy adduct **14**. Instead the crude product mixture was directly heated with formic acid to afford a 17:3 diastereomeric mixture of 2-(formyloxy)-7-benzyl-10,10-dimethyl-7,9-diazaspiro[4.5]decan-8-one (**15a,b**) in 28% yield (crude **14** → **15**).



5 **13**



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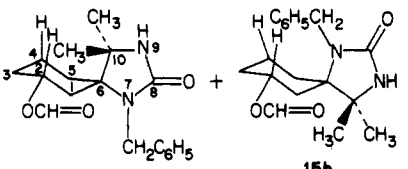


15a major **15b** minor

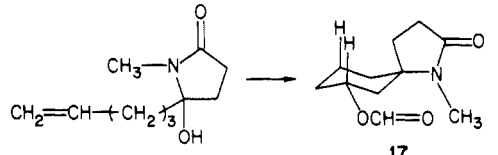
Several NMR observations provided evidence that the major and minor compounds obtained in this reaction were **15a** and **15b**, respectively. First, the detection of two large (9–12 Hz) and two small (3–4 Hz) coupling interactions in the ^1H NMR spectrum (see supplementary material section, Figure 1) for the carbon-2 methine hydrogens in the major (**15a**, δ 5.03) and the minor (**15b**, δ 5.20) adduct indicated that both of these protons occupied an axial position.[9] Second, the proton chemical shift for the carbon-2 hydrogen of the minor compound **15b** appeared downfield (0.17 ppm) from that observed for the major adduct **15a**. In previous studies, a downfield shift of this magnitude has often been associated with the presence of a 1,3-syn diaxial interaction of the ring proton with an electronegative oxygen atom.[1b,10] A comparable effect for an axial nitrogen substitutent is conceivable. Third, in the 2D-J proton-coupled ^{13}C NMR spectrum the resonances assigned to the carbon-2 atoms in **15a** and **15b** (69.1 and 69.4 ppm, respectively) were both doublets (J = 110–120 Hz) (see supplementary material section, Figure 3). Fourth, several key NOE (nuclear Overhauser effect) interactions were observed in the J-cross peak suppressed (NOESY) spectrum (2D-NOE)[11] for the diastereomeric mixture of **15a** and **15b** (see supplementary material section, Figures 4–6). A pronounced NOE was noted between the methine hydrogen (δ 5.03) at carbon-2 in the major isomer (**15a**) and the downfield methyl group (δ 1.42) of the carbon-10 *gem*-dimethyl moiety. Furthermore, an apparent NOE was also detected between this same methyl group (δ 1.42) and the upfield pair (δ 4.21) of the AB quartet for the nitrogen-7 benzylic group. This interaction, however, was not well defined in the NOESY spectrum, because of concurrent NOE effects in this spectral region [i.e., the upfield benzylic hydrogen of **15a** with a proton

(7) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 951–958.
(8) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, *20*, 411–414.
(9) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1969; pp 280–286, and references therein.
(10) (a) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163–172. (b) Carr, J. B.; Huitric, A. C. *J. Org. Chem.* **1964**, *29*, 2506–2510.
(11) (a) Hutton, W. C.; Phillips, N. J.; Garden, D. W.; Lynn, D. G. *J. Chem. Soc., Chem. Commun.* **1983**, 864–866. (b) Macura, S.; Wuthrich, K.; Ernst, R. R. *J. Magn. Reson.* **1982**, *47*, 351–357. (c) Baumann, R.; Wider, G.; Ernst, R. R.; Wuthrich, K. *Ibid.* **1981**, *44*, 402–406.

on the alicyclic ring (δ 1.40–1.45)]. The NOESY experiment suggested that the carbon-2 proton in the major product (**15a**) (δ 5.03) was close to one of the methyl groups of the carbon-10 *gem*-dimethyl moiety.

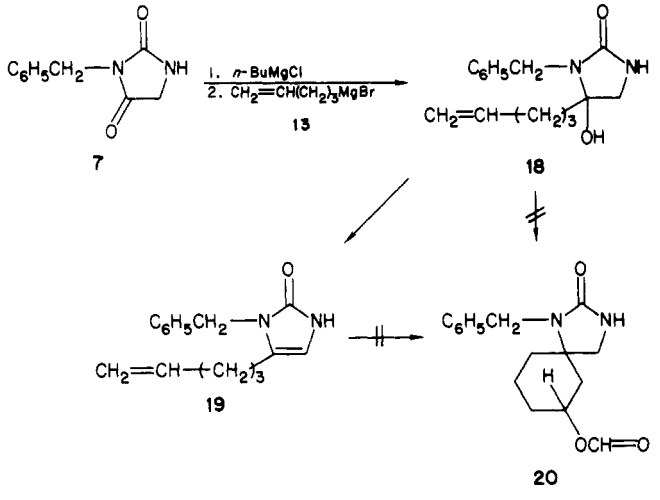
The spectral data is consistent with the proposed spiroimidazolidin-2-ones **15a** and **15b**. Moreover, molecular models suggest that the steric interactions encountered in the transition state for the formation of **15b** may be more severe than those experienced in the formation of **15a** due to the interaction of the N_3-benzyl moiety and the 1,3-syn diaxial protons of the cyclohexyl ring.

The regio- and stereoselectivity observed for the formation of **15a** and **15b** correlated favorably with the *N*-acyliminium cyclization reaction of 5-hydroxy lactam **16**.[7,8,12] In these studies, only one diastereomer (**17**) was isolated. Presumably, the absence of the *gem*-dimethyl moiety in this case led to the selective formation of **17**.



16 **17**

The generality of the spirocyclization reaction was tested with the unsubstituted derivative **18**. This compound was synthesized by the addition of **13** to the magnesium salt of **7**. Treatment of **18** with formic acid did not yield the desired intramolecular cyclization derivative **20** but rather the dehydration product, 3-benzyl-4-pent-4-enyl-2-imidazolone (**19**), was isolated in 43% overall yield from **7**. Subsequent treatment of the endo-enamide **19** with strong acid (trifluoroacetic anhydride–trifluoroacetic acid, methylene chloride, reflux, 24 h) did not lead to the desired cyclization adduct **20**. In this instance, only starting material **19** was recovered.



7 **13** **18** **19** **20**

The synthetic potential of *N*-carbamoyliminium ion initiated cyclization reactions for the generation of select spiro diamine based compounds has been documented. This study also clearly demonstrated that organometallic reagents undergo nucleophilic addition to the carbonyl-4 group in hydantoins. This reaction coupled with the ease in which these adducts undergo dehydration allow the synthesis of a wide range of new 2-imidazolones. These substrates have been of considerable recent interest due to their pronounced pharmacological activities for the treatment of cardiovascular diseases.[13]

Experimental Section

General methods are the same as those described in ref 1. The thermospray-ionization mass spectra[14] for compound **18** were performed by Dr. David Pilosof at the Department of Chemistry, University of Houston. The sample was run in 0.1 M ammonium acetate (pH 5.5). The high field NMR spectra were recorded by Dr. Gary Martin on a Nicolet NT-300 spectrometer.

Hydantoin, 5,5-dimethylhydantoin, β-(2-methylphenyl)ethyl alcohol, *n*-BuLi (2.7 M hexanes solution), *sec*-BuLi (1.4 M cyclohexane solution), and *n*-BuMgCl (2 M Et_2O solution) were purchased from Aldrich Chemical Co., while 5-bromopentene was obtained from Polysciences, Inc. The 3-benzyl-5,5-dimethylimidazolidine-2,4-dione (**5**) and the 3-benzylimidazolidine-2,4-dione (**7**) were prepared from benzyl bromide and the corresponding hydantoins (Aldrich Chemical Co.) by using the method described in ref 15. Mg turnings (Aldrich Chemical Co.) were dried at 100–120 °C for 10 min prior to use. Et_2O was distilled from Na.

Preparation of 3-Benzyl-4-*n*-butyl-4-hydroxy-5,5-dimethylimidazolidin-2-one (8). 1. Method A. To a THF solution (100 mL) of 3-benzyl-5,5-dimethylimidazolidine-2,4-dione (**5**) (1.09 g, 5 mmol) was slowly added a hexane solution of *n*-BuLi (2.7 M, 11 mL, 30 mmol) at −78 °C. The heterogeneous mixture was kept at −78 °C (10 h) and then poured into 30 mL of ice–H_2O. The solution was extracted with Et_2O (3 × 50 mL). The Et_2O solutions were combined, washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Compound **8** was purified by flash chromatography (SiO_2, 40% benzene–ethyl acetate) to give a 37% yield (0.51 g) of the desired product: R_f 0.29 (40% benzene–ethyl acetate); mp 81–84 °C dec; IR (KBr) 3300, 3250, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58–1.67 (m, 15 H), 3.73 (br s, 1 H), 4.08 (d, 1 H, J = 16 Hz), 4.67 (d, 1 H, J = 16 Hz), 6.37 (br s, 1 H), 7.27 (s, 5 H); ^{13}C NMR ($CDCl_3$, −10 to −20 °C) 22.7, 22.8, 23.1, 25.7, 26.1, 34.7, 42.0, 60.0, 92.6, 126.7, 127.0, 128.3, 140.0, 160.9 ppm. (The signals at 127.0 and 128.3 ppm were approximately twice the intensity of neighboring peaks); MS, *m/e* (relative intensity) 276 (3), 258 (27), 229 (100), 91 (30); mol wt 276.1834 (calcd for $C_{16}H_{24}N_2O_2$ 276.1838). Compound **8** was rapidly converted to 2-imidazolone **9** upon standing in chloroform (room temperature, 24 h) or upon heating to reflux in benzene (2 h). Attempts to further purify this compound by flash chromatography (SiO_2) were unsuccessful: R_f 0.83 (60% ethyl acetate–benzene); ^1H NMR ($CDCl_3$) δ 0.40–2.40 (m, 7 H), 1.50 (s, 6 H), 4.27 (t, 1 H, J = 8 Hz), 4.63 (s, 2 H), 6.93 (br s, 1 H), 7.30 (s, 5 H); MS, *m/e* (relative intensity) 258 (8), 243 (4), 229 (25), 91 (100); mol wt 258.1735 (calcd for $C_{16}H_{22}N_2O$ 258.1732).

2. Method B. To a THF solution (80 mL) containing **5** (1.09 g, 5 mmol) was added a Et_2O solution (15 mL) of *n*-BuMgCl (2 M, 30 mmol) slowly at 0 °C. The heterogeneous mixture was kept at 0 °C for 15 h. Utilizing the same workup and purification procedure outlined in method A, **8** was obtained in 36% yield (0.50 g).

Preparation of 3-[β-(2-Methylphenyl)ethyl]-5-methylimidazolidine-2,4-dione (6). Using the Mitsunobu coupling method,[16] a 20-mL THF solution of diethyl azodicarboxylate (4.80 g, 28 mmol) was slowly added to a THF solution (100 mL) containing an equimolar amount of 5-methylimidazolidine-2,4-dione[6] (2.85 g, 25 mmol), β-(2-methylphenyl)ethyl alcohol (3.40 g, 25 mmol), and Ph_3P (7.20 g, 55 mmol) at 5–10 °C. The reaction solution was maintained at room temperature (2 days) and then concentrated to dryness in vacuo. A 50% ethyl acetate–hexane solution (100 mL) was added to the syrupy residue and the mixture was placed in the refrigerator (18 h). The precipitated triphenylphosphine oxide was filtered, and the solution was concentrated to dryness in vacuo. Purification of the residue by flash chromatography (SiO_2, 50% benzene–ethyl acetate) gave **6** in 52% yield (3.00 g): R_f 0.57 (50% benzene–ethyl acetate); mp 72–75 °C; IR (KBr) 3230, 1765, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (d,

(12) (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, *19*, 4841–4844. (b) Schoemaker, H. E.; Speckamp, W. N. *Ibid.* **1978**, *19*, 1515–1518.

(13) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. *J. Med. Chem.* **1982**, *25*, 1477–1481.

(14) Blakely, C. R.; Vestal, M. L. *Anal. Chem.* **1983**, *55*, 750.

(15) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246–2254.

(16) Mitsunobu, O. *Synthesis* **1981**, *1*, 1–28.

3 H, J = 7 Hz), 2.44 (s, 3 H), 2.83–3.10 (m, 2 H), 3.63–3.73 (m, 2 H), 4.00 (q, 1 H, J = 7 Hz), 6.92 (br s, 1 H), 7.30 (s, 4 H); ^{13}C NMR ($CDCl_3$) 17.5, 19.1, 31.6, 38.4, 52.9, 126.0, 126.9, 129.7, 130.4, 135.9, 136.6, 157.6, 174.6 ppm; MS, m/e (relative intensity) 232 (33), 118 (100), 117 (49), 115 (35), 105 (35); mol wt 232.1206 (calcd for $C_{13}H_{16}N_2O_2$ 232.1212).

Preparation of 3-[β-(2-Methylphenyl)ethyl]-4-*n*-butyl-5-methyl-2-imidazolone (10). To an Et_2O solution (50 mL) of **6** (1.00 g, 4 mmol) was added a hexane solution of *n*-BuLi (2.7 M, 6 mL, 16 mmol) slowly at −20 to −25 °C. The deep-yellow heterogeneous mixture was stirred at −10 °C (7 h). The mixture was then poured into 20 mL of ice–H_2O. The Et_2O layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined Et_2O layers were then washed with a saturated aqueous NaCl solution (20 mL), dried (Na_2SO_4), and then concentrated to dryness in vacuo. Purification of the residue by flash chromatography (SiO_2, 20% EtOH–EtOAc) gave **10** in 37% yield (0.40 g): R_f 0.35 (EtOAc); IR (neat, NaCl) 3300 (br), 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63–2.38 (m, 9 H), 2.00 (s, 3 H), 2.38 (s, 3 H), 2.63–3.06 (m, 2 H), 3.44–3.88 (m, 2 H), 7.13 (s, 4 H), 10.00 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 9.5, 13.8, 19.2, 22.2, 22.5, 31.9, 33.3, 41.7, 112.4, 118.2, 126.1, 126.6, 129.7, 130.3, 136.4, 137.1, 154.4 ppm; MS, m/e (relative intensity) 272 (64), 271 (44), 167 (74), 139 (54), 125 (92), 119 (100), 91 (50); mol wt 272.1895 (calcd for $C_{17}H_{24}N_2O$ 272.1889).

Preparation of 3-[β-(2-Methylphenyl)ethyl]-4-*sec*-butyl-5-methyl-2-imidazolone (11). Using the same procedure described for the preparation of **10**, **6** (1.70 g, 7 mmol) and *sec*-BuLi (1.4 M, 16 mL, 22 mmol) in Et_2O (100 mL) gave 0.55 g (28% yield) of **11**: R_f 0.60 (EtOAc); IR (neat, NaCl) 3300 (br), 1700 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67–1.67 (m, 9 H), 2.05 (s, 3 H), 2.42 (s, 3 H), 2.72–3.28 (m, 2 H), 3.63–4.00 (m, 2 H), 7.27 (s, 4 H), 10.27 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 10.6, 12.4, 19.3, 19.7, 29.1, 31.7, 33.2, 41.5, 111.9, 121.9, 126.2, 126.6, 129.6, 130.4, 136.4, 137.0, 154.1 ppm; MS, m/e (relative intensity) 272 (95), 167 (65), 154 (27), 139 (24), 125 (100), 119 (64), 105 (41), 91 (31); mol wt 272.1893 (calcd for $C_{17}H_{24}N_2O$ 272.1889).

Preparation of 3-Benzyl-4-*n*-butyl-2-imidazolone (12). Utilizing the procedure described for **10**, **8** (0.95 g, 5 mmol) in THF (100 mL) was treated with a hexane solution of *n*-BuLi (2.7 M, 11 mL, 30 mmol) at −78 °C, and then the deep yellow heterogeneous solution was kept at this temperature for 5 h. After ice–H_2O hydrolysis, workup, and flash chromatography (SiO_2, 20% EtOH–EtOAc), **12** was obtained in 43% yield (0.51 g): R_f 0.30 (40% benzene–ethyl acetate); IR (neat, NaCl) 3300 (br), 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3 H, J = 7 Hz), 1.23–1.45 (m, 4 H), 2.21 (t, 2 H, J = 7 Hz), 4.87 (s, 2 H), 6.00 (s, 1 H), 7.18–7.33 (m, 5 H), 10.38 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 13.7, 22.1, 24.3, 29.0, 44.0, 103.8, 124.4, 126.5, 127.2, 128.6, 137.4, 153.0 ppm. (The signals at 126.5 and 128.6 ppm were approximately twice the intensity of neighboring peaks); MS, m/e (relative intensity) 230 (14), 188 (11), 187 (13), 91 (100); mol wt 230.1423 (calcd for $C_{14}H_{18}N_2O$ 230.1419).

Preparation of 2-(Formyloxy)-7-benzyl-10,10-dimethyl-7,9-diazaspiro[4.5]decan-8-one (15a,b). 1. Synthesis of Pent-4-enylmagnesium Bromide (13). To a mixture of Et_2O and Mg (0.75 g, 30 mmol) was added a small amount of the total 5-bromopentene (3.70 g, 25 mmol) at room temperature. After the reaction was initiated, the remaining amount of 5-bromopentene was carefully added in order to avoid the Et_2O from rapidly distilling away. After the addition was complete, the mixture was heated gently to reflux (15 min) and directly used.

2. Synthesis of 15a,b. To a THF solution (50 mL) of **5** (1.63 g, 8 mmol) maintained at −78 °C was added a Et_2O solution of *n*-BuMgCl (2.0 M, 5 mL, 9 mmol) slowly, and then the reaction was kept at −20 °C for 20 min. An Et_2O solution (100 mL) of **13** (~4.33 g, 25 mmol) was then added into the heterogeneous mixture. The reaction was allowed to stir at room temperature (20 h), and then the mixture was poured into 30 mL of ice–H_2O. The aqueous solution was extracted with Et_2O (3 × 100 mL). The Et_2O layers were combined, successively washed with saturated aqueous NaCl (2 × 30 mL) and H_2O (30 mL), dried (Na_2SO_4), and gently concentrated to dryness in vacuo at room temperature. ^{13}C NMR showed the residue (2.50 g) contained **14** (R_f 0.35, 40% benzene–ethyl acetate) and starting material (**5**) (R_f 0.69, 40% benzene–ethyl acetate) in a 3:2 ratio, respectively. The high intensity set of peaks in the ^{13}C NMR spectrum corresponded to **14**: ^{13}C NMR ($CDCl_3$) 22.8, 22.9, 26.0, 34.0, 34.5, 41.9, 59.0, 92.6, 114.9, 126.7, 127.0, 128.3, 137.9, 140.0, 161.0 ppm. (The signals at 126.7 and 128.3 ppm were approximately twice the intensity of neighboring peaks.) MS (CI) 289 (P + 1); mol wt. 288.1832 (calcd for $C_{17}H_{24}N_2O_2$ 288.1838). The low intensity set of peaks in the ^{13}C NMR spectrum corresponded to **5**: ^{13}C NMR ($CDCl_3$) 24.7, 42.1, 58.8, 127.7, 128.1, 128.6, 136.3, 156.6, 177.4 ppm. (The signals at 24.7, 128.1 and 128.6 ppm were approximately twice the intensity of nearby peaks.)

A CH_2Cl_2 solution (50 mL) of the crude reaction mixture containing approximately 1.13 g (4 mmol) of **14** and 0.67 g of **5** and 40 mL of HCO_2H was heated to reflux for 65 h. The solution was poured into 50 mL of ice–H_2O. The aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 solutions were successively washed with a 15% aqueous NaOH solution (30 mL) and H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated to dryness in vacuo. A mixture containing two diastereomers of 2-(formyloxy)-7-benzyl-10,10-dimethyl-7,9-diazaspiro[4.5]-decan-8-one (**15a,b**) was obtained after flash chromatography (SiO_2, 60% benzene–ethyl acetate) in 28% yield (0.35 g). High resolution ^1H and ^{13}C NMR analysis of the mixture indicated that the ratio of **15a** to **15b** was 17:3, respectively: R_f 0.39 (40% benzene–ethyl acetate); IR (neat, NaCl) 3300 (br), 1710, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (high intensity set) δ 1.20–2.30 (m, 8 H), 1.31 (s, 3 H), 1.42 (s, 3 H), 4.21 (d, 1 H, J = 16 Hz), 4.46 (d, 1 H, J = 16 Hz), 4.71 (br s, 1 H), 5.03 (dddd, 1 H, J = 4, 5, 11, 12 Hz), 7.20–7.38 (m, 5 H), 7.97 (s, 1 H). (The ^1H NMR spectrum contained several low intensity set of signals that were readily discerned. Among these included the following signals: ^1H NMR ($CDCl_3$) δ 4.42 (d, 1 H, J = 16 Hz), 4.68 (d, 1 H, J = 16 Hz), 5.20 (dddd, 1 H, J = 3, 4, 9, 12 Hz), 7.98 (s, 1 H)). ^{13}C NMR ($CDCl_3$) (high intensity set) 20.1 (t), 25.8 (q), 26.4 (q), 29.1 (t), 30.9 (t), 35.1 (t), 42.1 (t), 59.3 (s), 66.9 (s), 69.3 (d), 126.9 (d), 127.0 (d), 128.4 (d), 140.1 (s), 160.2 (s), 160.4 (d) ppm. The signals at 126.9 and 128.4 ppm were approximately twice the intensity of neighboring peaks. The ^{13}C NMR spectrum also contained a low intensity set of signals for diastereomer **15b**. Among these included the following signals: 19.0 (t), 23.4 (q), 24.7 (q), 28.1 (t), 29.7 (t), 34.5 (t), 44.0 (t), 60.0 (s), 65.9 (s), 69.4 (d) ppm; MS, m/e (relative intensity) 316 (15), 271 (21), 185 (18), 149 (18), 122 (23), 91 (100); mol wt 316.1774 (calcd for $C_{18}H_{24}N_2O_3$ 316.1787).

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 67.93; H, 7.60; N, 8.59.

Preparation of 3-Benzyl-4-(pent-4-enyl)-2-imidazolone (19). To a THF solution (35 mL) of **7** (1.43 g, 8 mmol) was added an Et_2O solution of *n*-BuMgCl (2 M, 5 mL, 9 mmol) at −78 °C, and the mixture was kept at −20 °C for 20 min. An Et_2O solution (50 mL) of **13** (~4.33 g, 25 mmol) was then added to the heterogeneous mixture and the reaction was allowed to stir at room temperature (40 h). The mixture was poured into 40 mL of ice–H_2O and the aqueous solution was extracted with Et_2O (3 × 100 mL). The combined Et_2O layers were successively washed with a saturated aqueous NaCl solution (2 × 20 mL) and then washed with H_2O (30 mL), dried (Na_2SO_4), and gently concentrated to dryness in vacuo at room temperature. TLC analysis showed the residue contained starting hydantoin **7** (R_f 0.56, 40% benzene–ethyl acetate), along with the major product **18** (R_f 0.28, 40% benzene–ethyl acetate). The thermospray-ionization mass spectrum indicated the presence of **18**: MS, m/e (relative intensity) 261 (P + 1) (8), 243 (P − OH) (100); mol wt 260.1521 (calcd for $C_{15}H_{20}N_2O_2$ 260.1525). A CH_2Cl_2 solution (30 mL) containing crude **18** and 15 mL of HCO_2H was heated to reflux (72 h). The solution was poured into 40 mL of ice–H_2O and then extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were washed successively with 15% aqueous NaOH solution (25 mL) and H_2O (2 × 40 mL), dried (Na_2SO_4), and concentrated to dryness in vacuo. Compound **19** was isolated in 43% yield (0.78 g) by flash chromatography (SiO_2, EtOAc): R_f 0.35 (40% benzene–ethyl acetate); IR (KBr) 3160, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30–2.40 (m, 6 H), 4.80 (s, 2 H), 5.00–5.90 (m, 3 H), 6.00 (s, 1 H), 7.20 (s, 5 H), 10.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 24.0, 26.3, 33.0, 44.1, 104.1, 115.2, 124.1, 126.7, 127.3, 128.7, 137.5, 137.8, 155.4 ppm (The signals at 126.7 and 128.7 ppm were approximately twice the intensity of neighboring peaks.); MS, m/e (relative intensity) 242

(10), 190 (70), 161 (37), 160 (47), 104 (65), 91 (100); mol wt 242.1427 (calcd for $C_{15}H_{18}N_2O$ 242.1419).

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Supplementary Material Available: The experimental protocol utilized as well as figures showing the high field ^1H, ^{13}C, 2D-J-resolved ^{13}C and 2D-NOE spectra of compounds **15a,b** are reported herein (7 pages). Ordering information is given on any current masthead page.

Heterodienophiles. 10.[1] Stereoselectivity in the 1,4-Cycloaddition of *N*-(Ethoxycarbonyl)-*C*-alkylaldiminium Ions with Cyclohexa-1,3-diene

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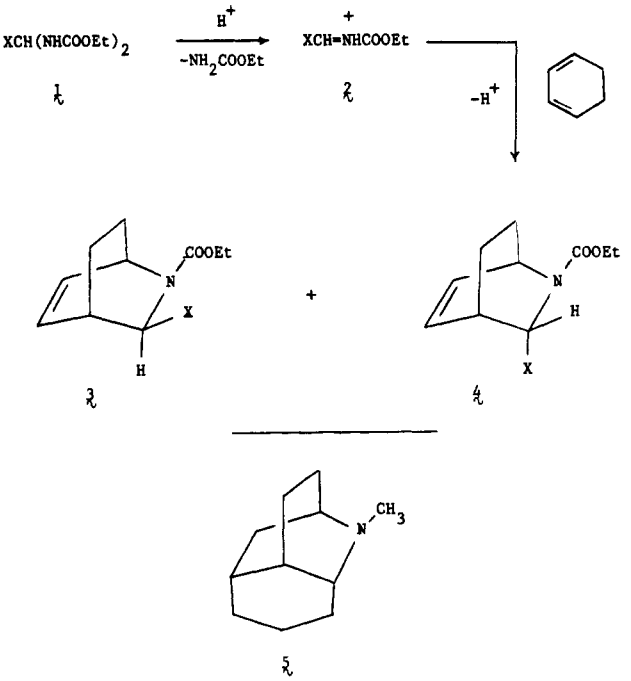
The first systematic investigation of the stereochemistry of cycloaddition reactions of *C*-alkylaldiminium ions **2** is described. *N*-(Ethoxycarbonyl)-3-*exo*- and *N*-(ethoxycarbonyl)-3-*endo*-alkyl-5,6-dehydroisoquinuclidines **3** and **4** are formed from alkylidenebis(urethanes) **1** and cyclohexa-1,3-diene under the influence of boron trifluoride catalysis. ^1H NMR chemical shift and coupling information and, in several cases, independent syntheses of 3-*endo*-alkyl isomers **4** were used to make stereochemical assignments. Major amounts of 3-*exo*-alkyl adducts **3** were found in all cases where the 3-alkyl group was primary (methyl, ethyl, propyl, isobutyl, 3-chloropropyl, and benzyl). When the 3-alkyl group was secondary (isopropyl, cyclohexyl), the percentage of 3-*endo*-alkyl adducts **4** was increased. A proposed reaction model involving cycloaddition via N-protonated (*E*)-aldiminium ions **2**-*E*, in which the allylic moiety reacts through a favored hydrogen/imine eclipsed conformation, is consistent with the observed stereochemical results. The 3-(3-chloropropyl) adduct **4h** has been reported previously as an intermediate in a discredited preparation of **5**, once proposed to be dihydrocannivonine. Our ^1H NMR and mass spectral data for **4h** are generally inconsistent with the previously reported values.

Alkylidenebis(urethanes) **1**, which are readily prepared from aldehydes and urethane,[2] undergo fragmentation in solutions containing catalytic amounts of Lewis acids to afford dienophilic *N*-(alkoxycarbonyl)iminium ions **2**. Thus, cyclohexa-1,3-diene reacts with alkylidenebis(urethanes) **1** to provide 3-substituted 5,6-dehydroisoquinuclidines (2-azabicyclo[2.2.2]oct-5-enes) **3** and **4**.[3] The stereochemical outcomes for a number of such cycloadditions are reported in Table I. For alkylidenebis(urethanes) **1a–e**, in which substituents X are aryl, carbonyl,[3b] and alkoxycarbonyl,[1] a kinetic preference[3b] for 3-exo orientation of substituents as in **3a–e** has been noted. Cycloaddition of *N*-(ethoxycarbonyl)(trichloromethyl)methanimine, the deprotonated form of **2f**, has been effected thermally without acid catalysis[4] and provides mainly 3-*endo*-(trichloromethyl) adduct **4f** with cyclohexa-1,3-diene. We have recently described a cycloaddition of alkylidenebis(urethane) **1g**, in which X is alkyl,[5] and have found mainly 3-*exo*-methyl adduct **3g** to be formed.



A second reported example in which X was alkyl utilized **1h**, X = (3-chloropropyl),[6] to give mainly 3-*exo*-alkyl adduct **3h**. The structure **3h** was described as part of a

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