3.77-3.66 (m, 4 H, H-3, H-4, H-6, and H-6'), 3.52-3.48 (m, 1 H, H-5), 2.83 (dd, 1 H, J = 16.35 and 4.10 Hz, CH_2CON), 2.65 (dd, 1 H, J = 16.35 and 4.10 Hz, CH_2CON), 1.88 (s, 3 H, CH_3), 1.39 (s, 9 H, $(CH_3)_3C$). Anal. Calcd for $C_{45}H_{52}N_2O_{11}$: C, 67.82; H, 6.58; N, 3.52. Found: C, 67.79; H, 6.35; N, 3.25.

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Registry No. 3, 74372-90-0; 4, 112289-38-0; 5, 132884-63-0; 6, 132884-64-1; 7, 133004-71-4; 8, 132884-65-2; 9, 132884-66-3; 10, 132884-67-4; 11, 77611-19-9; 12, 30925-18-9; 13, 132884-68-5; CH_3CN, 75-05-8.

Addition of Glycinate Enolate Equivalents to 1,4-Benzodiazepine Imino Phosphates. Preparation of Synthetically Useful 2-(Ethyl glycinat-α-ylidene)-1,4-benzodiazepines and Related Derivatives[1]

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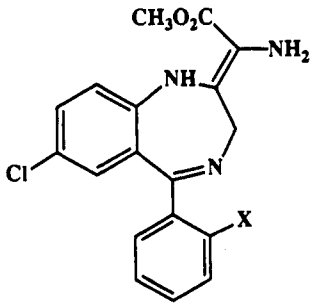
Received October 19, 1990

As part of our continuing interest in the synthesis of novel tricyclic 1,4-benzodiazepines, we required 2-dehydroglycinate-1,4-benzodiazepines of type 1 or related derivatives as precursors to compounds with a heterocyclic ring fused to the *a* face of the benzodiazepine ring. The usual approach to synthesize compounds of this type involves a linear route[2] involving a multistep construction of the dehydroglycinate portion at C-2 via a malonylidene intermediate.



1: X= H
2: X= Cl

Imino phosphates of 1,4-benzodiazepines are useful imidoyl derivatives known to be activated for nucleophilic attack.[3] We have previously reported one example of direct nucleophilic introduction of dehydroglycinate functionality[4] via reaction of a nitrone-activated glycinate

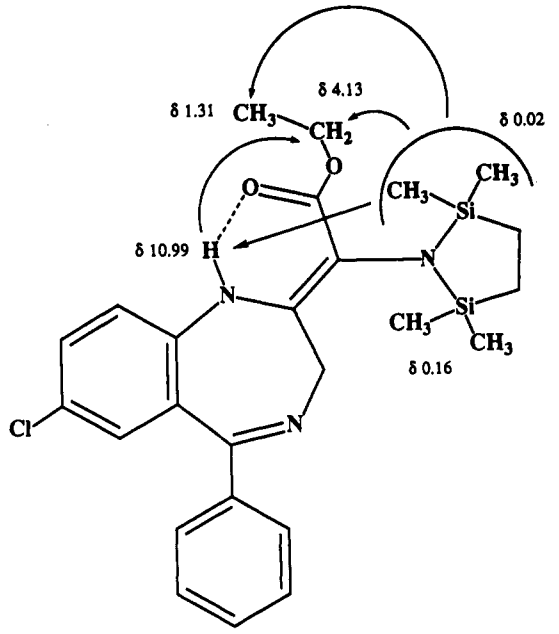
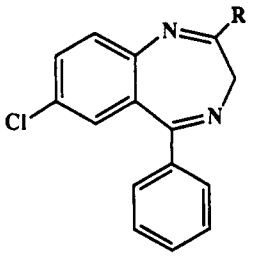
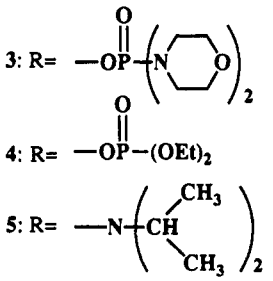


Figure 1. Observed NOE's in 2D-NOESY spectrum of 12 in $CDCl_3$.

derived carbanion and an imino phosphate. The growing number of reports of glycinate enolate synthons[5] presented us with an opportunity to explore direct nucleophilic introduction of the desired dehydroglycinate functionality via reaction of various glycinate enolates with appropriate imino phosphates. Such a method for elaborating imino phosphates derived from secondary cyclic amides should find general utility. For the present study, we chose imino dimorpholinophosphate 3[6] and imino diethylphosphate 4[2a] due to their excellent reactivity with various nucleophiles.[7]





Imino phosphate 3 was treated with the ester enolate of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetate 6[5c] (LDA, -78 °C, THF) to give the desired adduct

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(1) A preliminary account of this work has been presented at the 199th National Meeting of the American Chemical Society, ORGN 469, Boston, MA, April 22-27, 1990.

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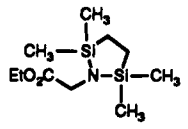
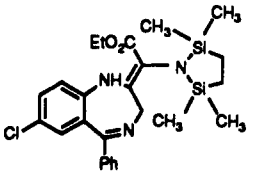
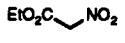
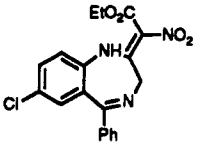
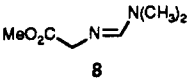
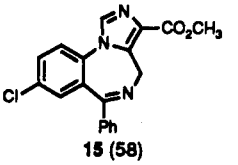
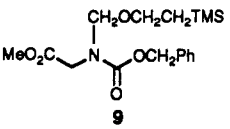
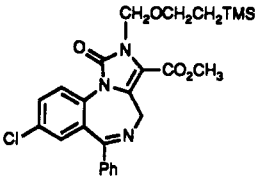
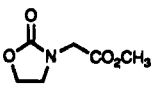
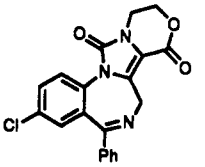
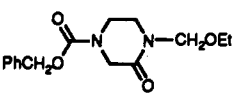
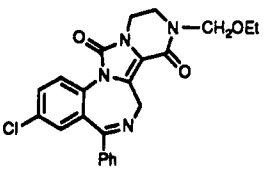
0022-3263/91/1956-3715$02.50/0

Table I. Addition of Glycinate Enolates to Imino Phosphates

entry	glycinate	imino phosphate	base	conditions[a]	product (yield, %)[b]
1	 **6**	3	LDA/THF	a	 **12** (64)
2	 **7**	4	NaH/THF	b	 **14** (15)
3	 **8**	3	LiHMDS/THF	a	 **15** (58)
4	 **9**	3	LiHMDS/THF	a	 **16** (45)
5	 **10**	3	LiHMDS/DME	c	 **18** (23)
6	 **11**	3	LDA/THF	a	 **19** (37)

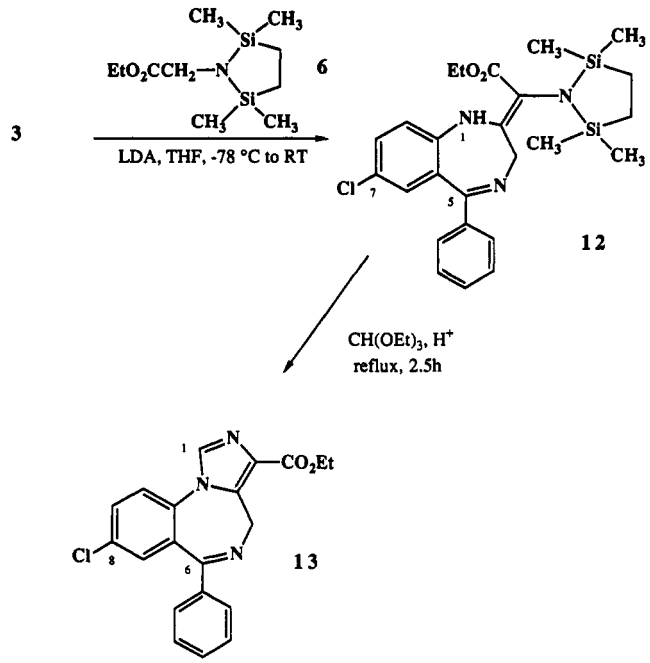
[a] Reactions were performed under an atmosphere of dry argon under the following conditions: (a) −78 °C to rt (18 h); (b) 0 °C to rt (18 h); (c) −78 °C to rt, followed by reflux for 18 h. [b] Isolated yield after crystallization or flash chromatography.

12 in good yield (Table I). Deprotonation of **6** is rather slow at −78 °C due to the bulky disilazane. If insufficient time is allowed for deprotonation of **6** (<40 min) prior to addition of the imino phosphate, variable amounts of LDA adduct **5** can be isolated, attesting to the high reactivity of **3** to even sterically demanding nucleophiles. The structure of **5** was confirmed by ^{1}H NMR as well as X-ray crystal structure. The desired adduct **12** is a stable oil that can be stored under nitrogen at room temperature for weeks without apparent decomposition. This contrasts with the unprotected glycinate **1** that appears to be less stable and has not been isolated. Compound **1** was reported[2b] to be used directly to avoid possible decomposition. Dichloro compound **2** is the only free NH_2 glycinate of this type to be isolated and characterized.[2a]

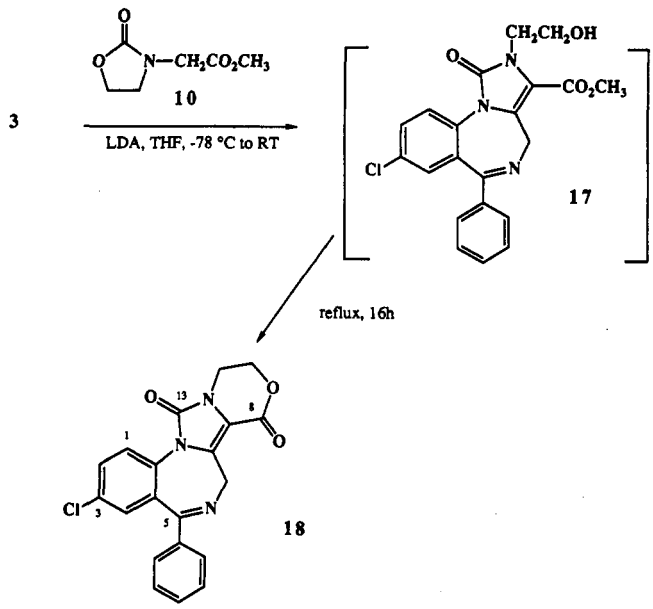
Compound **12** was isolated as a single isomer, and the *E* geometry was assigned at the exocyclic double bond on the basis of the 2D-NOESY spectrum. There was a detectable NOE between the N1 hydrogen and ester methylene protons, providing support for the assignment of cis orientation of the ester and the ring nitrogen as shown in Figure 1. Restricted rotation of the bulky cyclic disilazane resulted in ^{1}H NMR nonequivalence of the two pairs of methyl groups on the silicon atoms (singlets at δ 0.16 and 0.02),[8] which further aided the assignment of geometry at the double bond. We observed an NOE between the N1 hydrogen and the protons for only one pair of methyl groups on the disilazane. If the disilazane were cis to the N1 hydrogen, an NOE would be expected for protons from both pairs of methyl substituents. The 2D-NOESY spectrum revealed only the upfield methyl protons (δ 0.02) to have an NOE with the benzodiazepine N1 hydrogen. These same upfield methyl protons had an observable NOE with the methyl (δ 1.31) and methylene protons (δ 4.13) of the ethyl ester, further supporting *E* geometry as shown in Figure 1. *E* geometry was also suggested by the downfield shift of the benzodiazepine N1 hydrogen (δ 10.99) in **12**. This shift is most likely due to a six-membered cyclic intramolecular hydrogen bond between the N1 hydrogen and the carbonyl oxygen of the *cis*-carbeth-

(8) To unambiguously observe upfield resonances in the ^{1}H NMR ($CDCl_3$) of compound **12**, CH_2Cl_2 (δ 5.30) was used as an internal standard.

Scheme I



Scheme II



oxy group. Analogous hydrogen bonding has been suggested by Vomero[9] in a related benzodiazepine. The 2D-NOESY spectrum of **14** similarly showed an NOE between the benzodiazepine N1 hydrogen and the ester methylene, supporting *E* geometry about the exocyclic double bond in this case as well.

These assignments are not in agreement with the apparently erroneous *Z* configuration we previously assigned to the similar 2-(methyl glycinat-α-ylidene)-1,4-benzodiazepine **2** with a free amino group.[2a] This early assignment was based solely on the facile conversion of **2** to an imidazole derivative in refluxing ethyl orthoformate. In spite of the apparent *E* geometry, **12** is also readily converted to the imidazole derivative **13**[10] in excellent yield (Scheme I) by reflux with excess ethyl orthoformate in ethanol with catalytic acid. Under the reaction conditions employed, a likely sequence of events is in situ cleavage of the disilazane protection group of **12** followed by isomerization to the enol form of the ester, allowing rotation and ring closure to imidazo[1,5-*a*][1,4]benzodiazepine **13**.

Imidazo[1,5-*a*][1,4]benzodiazepines can be prepared directly from **3** by treatment with the lithium enolate of α-formamidine ester **8**[5f] (LiHMDS, THF, -78 °C). When the reaction mixture is warmed to ambient temperature, spontaneous intramolecular ring closure eliminating dimethylamine gives the imidazole derivative **15**[11] as the sole product. In fact, intermediate 2-dehydroglycinates are not isolable when such intramolecular cyclizations are possible. Due to the ease of preparation of the required glycinate formamidines[5f] this procedure compliments the known syntheses of related imidazo[1,5-*a*][1,4]benzodiazepines and imidazo[1,5-*a*][1,4]benzothiazines by additions of the anion of ethyl isocyanoacetate.[12]

The facile intramolecular cyclizations of functional groups held in close proximity by the rigid benzodiazepine skeleton were utilized for single-step synthesis of imidazolone derivatives **16**, **18**, and **19** as well as the unisolated intermediate **17**. The lithium enolate of **9** (LiHMDS, THF, -78 °C) added to **3** in the usual manner, followed by intramolecular ring closure upon warming to ambient temperature giving urethane **16**. Similarly, the enolate of methyl 2-oxazolinone-3-acetate **10** (LiHMDS, DME, -78 °C) was treated with **3**. Warming to ambient temperature followed by refluxing the reaction mixture lactonized the intermediate urethane **17** in situ to give **18** (Scheme II). This efficient procedure incorporated the glycinate "protection groups" into the novel [1,4]oxazino[4′,3′:3,4]-imidazo[1,5-*a*][1,4]benzodiazepine ring system and was the most expedient preparation of compound **18**,[13] a pivotal intermediate in an ongoing project in our laboratories. The structural assignment for **18** was confirmed by single-crystal X-ray analysis. The related novel pyrazino-[1′,2′:3,4]imidazo[1,5-*a*][1,4]benzodiazepine ring system of **19** was similarly prepared from the bis-protected 2-ketopiperizine **11** and the imino phosphate **3**.

In conclusion, nucleophilic addition of various glycinate enolates to 1,4-benzodiazepine imino phosphates **3** and **4** provides a convergent route to 2-(ethyl glycinat-α-ylidene)-1,4-benzodiazepine derivatives **12–19** in moderate to good yield, obviating lengthy linear syntheses. Further elaboration of these now readily available intermediates to highly functionalized 1,4-benzodiazepines is ongoing in our laboratories and will be reported in due course.

Experimental Section

Melting points are uncorrected. Flash chromatography was performed on fine silica (EM Sciences, 230–400 mesh). Reaction progress and purity of products were checked by analytical TLC with use of Analtech GHLF silica-coated glass plates. Elemental analyses were obtained from the Analytical Services Division of the BOC Group Technical Center (Murray Hill, NJ). All reactions were carried out under an atmosphere of dry argon. Dry tetrahydrofuran (THF), dimethoxyethane (DME), 1.0 M lithium hexamethyldisilazide in THF, and 1.5 M lithium diisopropylamide in THF/heptane were purchased in Sure/Seal bottles from

(9) Anzini, M.; Garofalo, A.; Vomero, S. *Heterocycles* **1989**, *29*, 1477–1487.

(10) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J. *J. Med. Chem.* **1989**, *32*, 2282–2291.

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(12) (a) Walser, A. U.S. Patent 4,118,386; *Chem. Abstr.* **1979**, *90*, 23054t. (b) Fryer, R. I.; Lauer, R. F.; Trybulski, E. J.; Vitone, S.; Walser, A.; Zenchoff, G. *J. Heterocycl. Chem.* **1983**, *20*, 1605–1608.

(13) The closely related deschloro analogue was originally prepared using a multistep synthesis (unpublished results).

Aldrich (Milwaukee, WI) and transferred by syringe under argon.

X-ray Crystallography. X-ray data collection was carried out with a Rigaku AFC5S diffractometer. Programs and computers used and sources of scattering data are given in ref 14. Structures of **5** and **18** were solved by direct methods and Fourier difference methods and refined by full-matrix least-squares methods. Details and crystal data are given in the supplementary material.

General Procedure for Addition of Glycinate Enolates to Imino Phosphates. The glycinate (1 mmol) was dissolved in 20 mL of THF and added to a solution of the specified base (1 mmol) in 30 mL of THF cooled to −78 °C. After 45 min, solid iminophosphate was added from a Schlenk tube under argon. The reaction mixture was allowed to warm to ambient temperature and stirred for 18 h, quenched with 1 mL of water, and concentrated under vacuum. The residue was redissolved in CH_2Cl_2, dried (anhydrous Na_2SO_4), filtered, and concentrated under vacuum. This residue was purified by flash chromatography or crystallization to give the desired dehydroglycinates.

α-(7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ylidene)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester (12) was prepared from **3** (1.15 g, 2.35 mmol), glycinate **6** (0.85 g, 3.46 mmol), and LDA (3.5 mmol) in THF by the general procedure. The crude product was purified by flash chromatography, eluting with 2:1 hexane/CH_2Cl_2 to give 750 mg (64%) of **12** as a bright yellow oil. An analytical sample was dried under vacuum (0.25 mmHg) for 48 h: ^{1}H NMR ($CDCl_3$)[8] δ 10.99 (s, 1 H), 7.19–7.58 (m, 7 H), 6.98 (d, J = 8 Hz, 1 H), 4.60 (br s, 2 H), 4.13 (q, J = 8 Hz, 2 H), 1.31 (t, J = 8 Hz, 3 H), 0.87 (s, 4 H), 0.16 (s, 6 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.61, 169.01, 156.82, 140.61, 139.59, 131.12, 130.85, 129.91, 129.50, 128.05, 127.97, 126.29, 122.81, 102.49, 59.78, 49.72, 14.26, 8.42, 0.00, −0.48; HRMS calcd for $C_{25}H_{32}N_3O_2Si_2{}^{35}Cl$ 497.1722, found 497.1712.

7-Chloro-2-(diisopropylamino)-5-phenyl-3*H*-1,4-benzodiazepine (5). If insufficient time (<40 min) was allowed for deprotonation in the previous procedure, variable amounts of LDA adduct **5** were isolated by flash chromatography. An analytical sample suitable for X-ray structure determination was crystallized from CH_2Cl_2/hexane: mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 7.10–7.57 (complex, 8 H), 5.09 (d, J = 10 Hz, 1 H), 4.22 (m, 2 H), 3.13 (d, J = 10 Hz, 1 H), 1.40 (d, J = 8 Hz, 6 H), 1.30 (d, J = 8 Hz, 6 H). Anal. Calcd for $C_{21}H_{24}N_3Cl$; C, 71.27; H, 6.84; N, 11.87. Found: C, 71.05; H, 6.65; N, 11.74.

8-Chloro-6-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic Acid Ethyl Ester (13). The disilazane compound **12** (319 mg, 0.64 mmol) was dissolved in 10 mL of triethyl orthoformate and 1 mL of absolute ethanol. Two drops of concentrated aqueous HCl were added, upon which the solution turned blood red and was heated to reflux. After 2.5 h, the now pale yellow solution was cooled, concentrated, and evaporated to dryness in vacuo. The residue was partitioned between CH_2Cl_2 and saturated aqueous Na_2CO_3, and the organic layer was separated, dried (Na_2SO_4), and concentrated to give 189 mg (80%) of **13** as a tan solid: mp 174–175 °C (lit.[10] 171–172 °C); ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.38–7.67 (complex, 8 H), 6.07 (d, J = 12.5 Hz, 1 H), 4.41 (m, 2 H), 4.06 (d, J = 12.5 Hz, 1 H), 1.42 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.11, 162.78, 139.01, 138.78, 134.07, 134.01, 133.00, 132.10, 131.75, 130.65, 129.44, 129.29, 129.21, 128.34, 124.08, 60.70, 44.87, 14.37. Anal. Calcd for $C_{20}H_{16}N_3O_2Cl$; C, 65.67; H, 4.41; N, 11.49. Found: C, 65.37; H, 4.50; N, 11.40.

α-(7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ylidene)-α-nitroacetic Acid Ethyl Ester (14). Ethyl nitroacetate (**7**, 3.5 mL, 30 mmol) in 10 mL of dry THF was added under argon to a stirred suspension of sodium hydride (50 mmol) in 30 mL of dry THF cooled in an ice bath. The mixture was stirred at ambient temperature for 1 h followed by cooling in an ice bath and successive addition of diethyl chlorophosphate (4.5 mL, 30 mmol) and then after 1 h 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[15] (3.0 g, 11 mmol). The mixture was then allowed to stir overnight at ambient temperature. After 16 h, the reaction was quenched with 100 mL of water and the organic layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 layers were washed with water, dried ($MgSO_4$), filtered, and evaporated in vacuo to afford a pale residue that was crystallized from methanol/ethyl acetate to give 600 mg (15%) of **14** as fine pale yellow needles: mp 219–221 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (br s, 1 H), 7.75 (d, J = 2.4 Hz, 1 H), 7.15–7.55 (m, 6 H), 6.95 (d, J = 8.5 Hz, 1 H), 4.35 (q, J = 7.3 Hz, 2 H), 4.27 (s, 2 H), 1.40 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 157.4, 147.2, 137.9, 132.8, 131.9, 131.3, 130.8, 130.2, 129.0, 128.2, 127.4, 123.2, 102.5, 63.5, 47.5, 14.0. Anal. Calcd for $C_{19}H_{16}N_3O_4Cl$; C, 59.15; H, 4.18; N, 10.89. Found: C, 58.98; H, 4.19; N, 10.99.

8-Chloro-6-phenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid methyl ester (15) was prepared from **3** (0.35 g, 0.72 mmol), glycinate **8** (0.25 g, 1.7 mmol), and LiHMDS (2 mmol) in THF by the given general procedure. Crude product was purified by flash chromatography, eluting with ethyl acetate/hexane (1:1) to give 147 mg (58%) of **15** as a tan solid. An analytical sample was recrystallized from ethyl acetate/CH_2Cl_2: mp 237–238 (lit.[11] 235–236 °C); ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1 H), 7.36–7.67 (m, 8 H), 6.05 (d, J = 11 Hz, 1 H), 4.03 (d, J = 11 Hz, 1 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.10, 163.10, 138.91, 138.74, 134.14, 133.91, 132.97, 132.08, 131.68, 130.62, 129.33, 129.22, 128.96, 128.27, 124.03, 51.70, 44.78. Anal. Calcd for $C_{19}H_{14}N_3O_2Cl$; C, 64.87; H, 4.01; N, 11.94. Found: C, 64.50; H, 3.99; N, 11.83.

***N*-[[(Trimethylsilyl)ethoxy]methyl]carbobenzoxyglycine Methyl Ester (9).** Carbobenzoxyglycine methyl ester (1.39 g, 6.23 mmol) was added dropwise to a stirred suspension of NaH (0.25 g, 6.25 mmol) in 50 mL of dry THF under argon. The reaction was stirred until gas evolution ceased when dry HMPA (10 mL) was added. The mixture was cooled in an ice bath, [2-(trimethylsilyl)ethoxy]methyl chloride (1.07 g, 6.42 mmol) was added dropwise, and the reaction was stirred at ambient temperature. After 48 h, the reaction mixture was evaporated in vacuo and the residue was dissolved in CH_2Cl_2, filtered through Celite, and evaporated in vacuo. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:10) to give 933 mg (42%) of **9** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.32–7.40 (m, 5 H), 5.19, 5.15 (2 × s, total 2 H), 4.84, 4.82 (2 × s, total 2 H), 4.09, 4.03 (2 × s, total 2 H), 3.74, 3.65 (2 × s, total 3 H), 3.53 (m, 2 H), 0.90 (m, 2 H). Anal. Calcd for $C_{17}H_{27}NO_5Si$; C, 57.76; H, 7.70; N, 3.96. Found: C, 57.99; H, 7.79; N, 3.98.

8-Chloro-2,4-dihydro-1-oxo-6-phenyl-2-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid methyl ester (16) was prepared from **3** (0.31 g, 0.63 mmol), the glycinate **9** (0.36 g, 1.02 mmol), and LiHMDS (1.1 mmol) in THF using the general procedure given previously. Crude product was purified by flash chromatography, eluting with ethyl acetate/CH_2Cl_2 (1:30) to give 141 mg (45%) of **16** as an orange oil: ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 1 H), 7.31–7.31 (m, 7 H), 5.84 (d, J = 12 Hz, 1 H), 5.53 (s, 2 H), 4.04 (d, J = 12 Hz, 1 H), 3.95 (s, 3 H), 3.67 (t, J = 8.25 Hz, 2 H), 0.97 (t, J = 8.25 Hz, 2 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.17, 160.06, 151.29, 138.78, 133.67, 133.26, 131.98, 131.49, 130.99, 130.88, 130.19, 129.40 128.39, 126.02, 109.56, 71.4, 66.48, 51.92, 45.44, 17.87, −1.50; HRMS calcd for $C_{25}H_{28}N_3O_4Si^{35}Cl$ 497.1538, found 497.1523.

Methyl 2-Oxazolinone-3-acetate (10). A solution of potassium *tert*-butoxide (200 mmol) in 200 mL of dry THF was added under an atmosphere of argon to a vigorously stirred suspension of 2-oxazolidone (16.21 g, 186 mmol) in 200 mL of THF/DME (1:1). The resulting pasty mixture was stirred at rt for 0.5 h and then treated by the slow dropwise addition of methyl bromoacetate (32.94 g, 215 mmol). After being stirred at ambient temperature for 18 h, the reaction was filtered and the filtrate was evaporated in vacuo. The resultant orange oil was distilled to give 23.88 g (81%) of **10** as a colorless oil: bp 126–130 °C (0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.40 (t, J = 7 Hz, 2 H), 4.06 (s, 2 H), 3.78 (s, 3 H), 3.72 (t, J = 7 Hz, 2 H). Anal. Calcd for $C_6H_9NO_4$; C, 45.28; H, 5.70; N, 8.80. Found: C, 44.81; H, 5.82; N, 8.43.

3-Chloro-10,11-dihydro-5-phenyl-13*H*-[1,4]oxazino-[4′,3′:3,4]imidazo[1,5-*a*][1,4]benzodiazepine-8,13(7*H*)-dione (18) was prepared from **3** (1.81 g, 3.70 mmol), **10** (1.22 g, 7.67 mmol), and LiHMDS (7.7 mmol) in DME following the general method given previously. The reaction mixture was heated at reflux for 18 h prior to quenching with 1 mL of water. The reaction mixture was then evaporated in vacuo, redissolved in

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CH_2Cl_2, and dried (Na_2SO_4), and 330 mg (23%) of **18** was crystallized directly from this solution by addition of an equivalent volume of ethyl ether and refrigeration. Two recrystallizations from CH_2Cl_2/Et_2O (1:1) afforded crystals suitable for X-ray structure determination: ^1H NMR ($CDCl_3$) δ 8.01 (d, J = 8 Hz, 1 H), 7.32–7.63 (m, 7 H), 5.83 (d, J = 13.5 Hz, 1 H), 4.56 (m, 2 H), 4.05 (d, J = 13.5 Hz, 1 H), 3.97 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.34, 157.01, 147.68, 138.50, 133.78, 132.48, 131.73, 131.11, 130.71, 130.49, 129.79, 128.75, 127.97, 125.28, 105.19, 66.11, 44.01, 37.21; IR (neat) 1750, 1724, 1640 cm^{-1}.

4-Carbobenzoxy-1-(ethoxymethylene)-2-ketopiperazine (11). 2-Ketopiperazine[16] (1.97 g, 19.67 mmol) and Na_2CO_3 (18 g) were dissolved in a mixture of 50 mL of water and 100 mL of ethyl acetate. The bilayer solution was then vigorously stirred during the dropwise addition of benzyl chloroformate (4.0 g, 23.4 mmol). After the mixture was stirred at ambient temperature for 16 h, the organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo to give 4.51 g (98%) of 4-carbobenzoxy-2-ketopiperazine as a white solid: mp 118–119 °C; ^1H NMR ($CDCl_3$) δ 7.36 (m, 5 H), 6.75 (br s, 1 H), 5.16 (s, 2 H), 4.16 (s, 2 H), 3.70 (t, J = 5.5 Hz, 2 H), 3.39 (m, 2 H). The solid (2.77 g, 11.82 mmol) was added in portions to a stirred suspension of NaH (12.75 mmol) in 75 mL of dry THF under argon. After gas evolution stopped, the reaction was cooled in an ice bath and chloromethyl ethyl ether (1.29 g, 13.64 mmol) in 25 mL of dry THF was added dropwise to the stirred solution. After 18 h at ambient temperature, the reaction was diluted with 25 mL of water and stirred for an additional 0.5 h. The organic layer was separated and evaporated in vacuo, and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:1) to give 3.02 g (87%) of **11** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 5.16 (s, 2 H), 4.88 (s, 2 H), 4.20 (s, 2 H), 3.74 (t, J = 7 Hz, 2 H), 3.50 (m, 4 H), 1.21 (t, J = 7 Hz, 3 H). The oil was dried under vacuum (0.25 mmHg) for 24 h and used without further purification.

3-Chloro-9-(ethoxymethyl)-10,11-dihydro-5-phenyl-7*H*,13*H*-pyrazino[1′,2′:3,4]imidazo[1,5-*a*][1,4]benzodiazepine-8,13(9*H*)-dione (19) was prepared from **3** (0.96 g, 1.96 mmol), glycinate **11** (0.82 g, 2.80 mmol), and LDA (3.0 mmol) in THF by the given general procedure. Crude product was purified by flash chromatography, eluting with ethyl acetate/hexane (1:1) followed by 100% ethyl acetate to give 320 mg (37%) of **19** as a tan foam. An analytical sample was dried under vacuum (0.25 mmHg) for 48 h: ^1H NMR ($CDCl_3$) δ 8.01 (d, J = 8 Hz, 1 H), 7.30–7.60 (m, 7 H), 5.93 (d, J = 13.5 Hz, 1 H), 4.95 (s, 2 H), 4.03 (d, J = 13.5 Hz, 1 H), 3.96 (m, 1 H), 3.88 (m, 1 H), 3.68 (t, J = 5.5 Hz, 2 H), 3.55 (q, J = 8 Hz, 2 H), 1.20 (t, J = Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.53, 158.43, 148.48, 139.13, 133.34, 131.72, 131.32, 131.03, 130.75, 130.66, 130.17, 129.33, 128.28, 125.61, 109.38, 74.65, 64.13, 44.41, 43.98, 37.93, 14 95. Anal. Calcd for $C_{23}H_{21}N_4O_3Cl$; C, 63.28; H, 4.85; N, 12.82. Found: C, 63.04; H, 4.80; N, 12.63.

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Registry No. **3**, 59318-11-5; **5**, 133473-87-7; **6**, 78605-23-9; **7**, 626-35-7; **8**, 62448-39-9; **9**, 133473-88-8; **10**, 133473-89-9; **11**, 133473-90-2; **12**, 133495-09-7; **13**, 117047-25-3; **14**, 133473-91-3; **15**, 63176-90-9; **16**, 133473-92-4; **18**, 133473-93-5; **19**, 133473-94-6; 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, 1088-11-5; 2-oxazolidone, 497-25-6; methyl bromoacetate, 96-32-2; 2-ketopiperazine, 5625-67-2; benzyl chloroformate, 501-53-1; 4-carbobenzoxy-2-ketopiperazine, 78818-15-2; chloromethyl ethyl ether, 3188-13-4.

Supplementary Material Available: X-ray structure drawings and tables listing final atomic positional parameters, atomic thermal parameters, and bond distances and angles for compounds **5** and **18** (16 pages). Ordering information is given on any current masthead page.

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Long-Range Interaction between Lone-Pair Orbitals in Diepoxynaphthalene Derivatives

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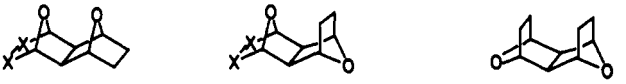
Interactions between π-subunits in "norbornylogues" **1–3** has been extensively studied both spectroscopically[1,2] and theoretically.[2,3]

1 **2** **3**

PE spectroscopic investigations have unequivocally shown that the two π-levels are split the most in **1** due to cooperative action of through-space (TS)[4] and through-bond (TB)[4] coupling mechanisms. In **2** and **3**, where the TS mode of interaction is negligible due to geometric constraints, the π-orbital splitting is still sizable as a consequence of TB-mediated coupling. Seeking further information with respect to the ability of the norbornylogue skeleton to act as a σ-bond relay, comparative studies with structurally related compounds like **4–6** were a tempting extension.



4 X-X = CH_2-CH_2 **5** X-X = CH_2-CH_2 **6**

7 X-X = Ph **8** X-X = Ph

In this paper, we present the results of PES investigations of the newly prepared **4** and **5** and their benzo-annelated analogues **7** and **8**. In all compounds considered here, ionization out of the p-type lone pair orbitals[5] associated with oxygen atoms at etheric bridges is expected to occur bellow 10 eV,[6] thus enabling their clear distinction from the higher laying σ-type bands.

The target compounds **4** and **5** were obtained by catalytic hydrogenation of *exo,exo*-1,4:5,8- and *exo,endo*-1,4:5,8-diepoxy-1,4,4a,5,8,8a-hexahydronaphthalenes. The latter compounds were accessible through a four-step procedure starting with cycloaddition of furan to dimethyl acetylenedicarboxylate.[7,8] Similarly, **7** and **8** were attained by catalytic hydrogenation of *exo,exo*-1,4:9,10- and *exo,endo*-1,4:9,10-diepoxy-1,4,4a,9,9a,10-hexahydroanthracene,[9] respectively.

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