Notes

Vobtusamine, the First Spiro *Aspidosperma*-Eburnea Alkaloid

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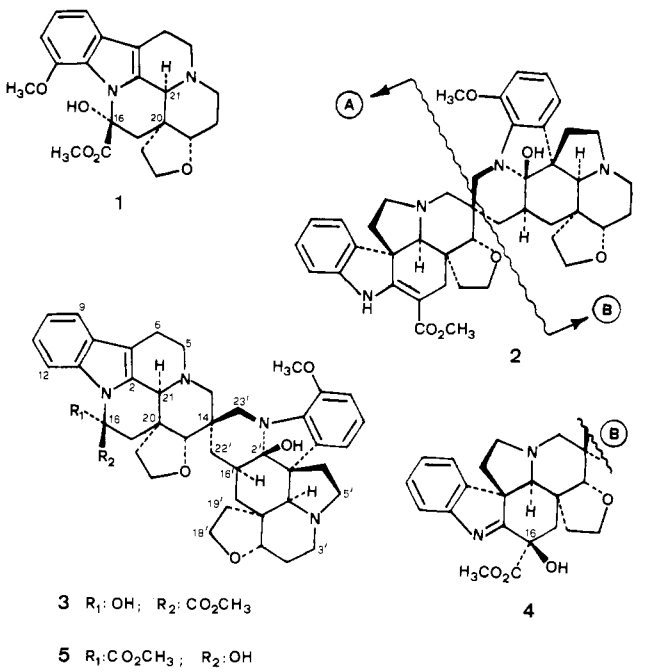
The roots of *Voacanga chalotiana* Pierre ex Stapf (Apocynaceae) native to Zaire have been investigated over many years and several monomeric indole alkaloids belonging to the sarpagine group obtained.[1] On the other hand, the root bark of the same plant collected in Angola near Quimbele has yielded, in addition to sarpagine-related alkaloids, a large amount of eburnanes [e.g., cuanzine, (1), Chart I] and spiro bisindole alkaloids (e.g., vobtusine, **2**).[2] In the course of purifying substantial quantities of vobtusine, we were able to isolate a small amount of a new dimeric alkaloid, vobtusamine (0.001% of dry weight), whose structure (**3**) was formulated on the basis of spectral data and chemical correlation. Interestingly, **3** represents the first member of a new series of sprio bisindole alkaloids containing both Eburnea (part A) and *Aspidosperma* (part B) moieties.[3]

Vobtusamine [**3**: mp 262 °C (MeOH); $[\alpha]^{21}_D$ -153° (*c* 1.0, $CHCl_3$)] showed the molecular ion at *m/z* 734 ($C_{43}H_{50}N_4O_7$ by high-resolution mass spectrum), 16 mass units higher than that for vobtusine, indicating the presence of an additional oxygen somewhere in the molecule. The UV spectrum [λ_{max} (MeOH) 228, 263, 280, 290, 310 nm] was characteristic of the addition of an indole and a 7-methoxyindoline chromophore. Weak Wenkert–Bohlmann bands[4] at 2880 and 2830 cm^{-1} (*trans*-quinolizidine) and an ester carbonyl band at 1735 cm^{-1} were observed in the IR spectrum. Inspection of the ^{13}C NMR spectrum of **3** revealed the presence of 20 carbons identical in chemical shift and multiplicity with those in the "part B" of vobtusine[5] with the exception of the methylenes C(22′) and C(23′) which appeared shifted to 27.6 and 45.8 ppm, respectively. Subtraction of these signals from the spectrum of **3** gave a set of aromatic carbons entirely consistent with a 1,2,3-trisubstituted indole, while the remainder of the resonances suggested the aliphatic moiety to be cuanzine-like.[2] In fact, the shifts of carbons 5, 6, 16, 20, and 21 were nearly identical with those of **1**, while all other carbons experienced shifts in agreement with disubstitution[6] at C(14).

Chart I



The evidence discussed so far allowed the structure **3** (without stereochemistry) to be proposed for vobtusamine in which C(22′) and C(23′) form a spiran linkage to C(14).

The mass spectrum of vobtusamine was strongly confirmatory of **3**. The major peaks at *m/z* 578 and 379 were considered to arise from the $(M - H_2O)^+\cdot$ peak through the "normal" aspidospermine-type opening of rings C and D followed by intramolecular hydrogen transfer.[7] The presence of the carbinolamine bearing a carbomethoxy group in the "part A" of vobtusamine was inferred from the observation of ions at *m/z* 518 and 319, derived from 578 and 379, respectively, by loss of HCO_2Me. Furthermore, of particular significance was the ion at *m/z* 224 diagnostic for vincamine-related alkaloids.[8]

In the 200-MHz NMR spectrum ($CDCl_3$) of **3**, two three-proton singlets were observed at δ 3.27 and 3.60 for the aromatic methoxy and carbomethoxy groups, respectively, but no NH proton was apparent. Instead, seven fully separated aromatic protons were found in the regions δ 6.50–6.75 (3 H for methoxyindoline) and δ 7.00–7.50 (four indole protons), supporting the aromatic substitution pattern in **3**. In vobtusamine both the methoxy aromatic

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(2) (a) Gabetta, B.; Martinelli, E. M.; Mustich, G. *Fitoterapia* **1974**, *45*, 32; *Chem. Abstr.* **1974**, *81*, 166291. (b) Bombardelli, E.; Bonati, A.; Gabetta, B.; Martinelli, E. M.; Mustich, G.; Danieli, B. *Tetrahedron* **1974**, *30*, 4141. (c) Danieli, B.; Lesma, G.; Palmisano, G.; Gabetta, B. *Heterocycles* **1980**, *14*, 201.

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(5) Rolland, Y.; Kunesch, N.; Poisson, J.; Hagaman, E. W.; Schell, F. M.; Wenkert, E. *J. Org. Chem.* **1976**, *41*, 3270.

(6) Stothers, J. B.; "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972.

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(8) Hesse, M. "Indolalkaloide-Fortschritte der Massenspektroscopie"; Verlag Chemie: Weinheim/Bergster., Germany, 1974; Vol. 1, p 116.

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signal, at δ 3.27 and the doublet for C(23′)H were shielded relative to the shifts in vobtusine **2** [δ 3.73 and 5.13 (^2J = 14 Hz), respectively],[7] and this could be rationalized in terms of diamagnetic anisotropy of the indole ring of the "vincamine-like half" (part A). Consistent with such a spatial interaction of two chromophores was the appearance of typical Davydov-type split Cotton bands at 231 (Δε −24.2) and 212 nm (Δε 11.6) in the CD spectrum of vobtusamine.[9,10] Consideration of models following the spectral data given above for **3** and the fact that it cooccurs with vobtusine and cuanzine led to the tentative proposal of C(14) and C(20)/C(21) having the same stereochemistry as in **2** and **1**.

A reasonable biogenetic hypothesis can be proposed for **3**, involving for "part A" of the vobtusine skeleton the oxidative *Aspidosperma* → eburnea rearrangement as predicted by Wenkert[11] and as realized in vitro with peroxy acids,[12] ozone,[13] and singlet oxygen.[14,15] The biomimetic synthesis of **3** was achieved by bubbling a stream of ozone (1.5 mol) into a 0.37 M solution of vobtusine in H_2O–AcOH (9:1) at 20 °C to give the labile 16-hydroxyvobtusine (**4**;[16] see Experimental Section). Subsequent acidic rearrangement of **4** at 45 °C led to a mixture of vobtusamine, identical with the natural compound, and a minor compound in the ratio 65:35, separable by flash chromatography (32% overall yield). By analysis of the ^1H and ^{13}C NMR spectra, the minor compound **5** was found to differ from **3** only in the stereochemistry at C(16). As the temperature was raised, the yield of **3** and **5** decreased and the presence of 16,17-anhydrovobtusamine and the 3′,16′:16,17-dianhydro derivative was observed in the reaction mixture. Finally, the 16*R* configuration for **3** was secured by spectral comparison with available models (e.g., vincamine, 16-epivincamine, cuanzine), and this conclusion was substantiated by the already observed base-induced epimerization[17] of **3** (neat tetramethylguanidine, room temperature, 90 min) leading to the most thermodynamically stable 16*S* epimer **5**.

The conversion of vobtusine **2**, whose absolute configuration had earlier been elucidated by X-ray analysis,[18] into vobtusamine establishes for it the absolute stereochemistry as depicted in **3**.

Experimental Section

Melting points are uncorrected (hot-stage microscope apparatus). Infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer, ultraviolet spectra on a Perkin-Elmer 554 UV–vis spectrophotometer, and ^1H NMR spectra on Bruker WP-80, Varian XL-100, and Varian XL-200 instruments in $CDCl_3$ as the solvent. ^{13}C NMR spectra were obtained ($CDCl_3$) on a Varian XL-200. Chemical shifts are expressed in part per million downfield from internal Me_4Si and coupling constants (J values) are given in hertz. Optical rotations were obtained with a Perkin-elmer 141 polarimeter. Circular dichroism spectra were recorded on a Jobin-Yvon Dichrograph III. Mass spectra (EI) were recorded on Varian 112 (Model 212 for high-resolution spectra) and CH-7 spectrometers.

Vobtusamine (3): mp 262 °C dec (MeOH); R_f 0.25 [silica; benzene–EtOH–NH_3 (89:10:1); blue stain with 10% ceric ammonium sulfate in 85% H_3PO_4(CAS)]; UV (MeOH) λ_{max} 228, 263, 280, 290, 310 (log ε 4.48, 4.14, 3.93, 3.85, 3.46); IR ($CHCl_3$) 2880, 2830, 1735 cm^{-1}; $[\alpha]^{21}_D$ −153° (*c* 1.0, $CHCl_3$); mass spectrum (70 eV, 210 °C) *m/z* 734 (M^+·, 33), 716 (10), 674 (15), 656 (15), 518 (10), 379 (11), 319 (11), 224 (23), 138 (100); ^1H NMR δ 3.27 (3 H, s, $ArOCH_3$), 3.60 (3 H, s, CO_2CH_3), 6.55 (1 H, dd, J = 8, 3 Hz, H-11′), 6.63 (1 H, t, J = 8 Hz, H-10′), 6.68 (1 H, dd, J = 8, 3 Hz, H-9′), 7.00-7.50 (4 H, m, aromatic); ^{13}C NMR 94.0 (C-2′), 4 8.6[a] (C-3′), 51.9 (C-5′), 30.5 (C-6′), 55.7 (C-7′), 134.8 (C-8′), 114.5 (C-9′), 118.7 (C-10′), 110.3 (C-11′), 145.1 (C-12′), 137.1. (C-13′), 25.8 (C-14′), 80.3[b] (C-15′), 30.9 (C-16′), 32.6 (C-17′), 65.2 (C-18′), 36.3 (C-19′), 44.6[c] (C-20′), 63.9 (C-21′), 27.6 (C-22′), 45.8 (C-23′), 132.9 (C-2), 48.2[a] (C-3), 51.7 (C-5), 17.6 (C-6), 106.0 (C-7), 128.6 (C-8), 117.5 (C-9), 121.3 (C-10), 120.1 (C-11), 112.7 (C-12), 136.9 (C-13), 41.9 (C-14), 80.5[b] (C-15), 83.5 (C-16), 47.6 (C-17), 65.8 (C-18), 38.3 (C-19), 44.9[c] (C-20), 56.0 (C-21), 171.8 (C=O), 52.5 (CO_2CH_3), 54.0 (OCH_3) (a–c indicates assignments may be interchanged); CD (MeOH, *c* 0.7) Δε +11.6 (212 nm), 0 (224), −24.2 (231), −8.6 (250), −10.3 (265), 0 (288), −2.5 (307), 0 (330).

Ozonation of Vobtusine to 16-Hydroxy Derivative 4. A solution of 4.3 g (5.98 mmol) of vobtusine **2** in 160 mL of H_2O–AcOH (9:1) was ozonized at 20 °C with an ozone–oxygen mixture containing 5.0 mmol of ozone/L. Ozone passage was continued until 9.0 mmol of ozone had been delivered, and the solution took on a dark violet color. Water (50 mL) was added and the pH adjusted to 8.0–9.0 by addition of dilute ammonium hydroxide. Extraction of the solution with dichloromethane (4 × 50 mL), drying (Na_2SO_4), and flash chromatography (silica; ethyl acetate–triethylamine, 9:1) yielded 1.43 g (33%) of amorphous 16-hydroxyvobtusine (**4**): R_f 0.48 [lilac (CAS)]; UV (MeOH) λ_{max} 222, 263, 290 nm (log ε 4.46, 4.13, 3.75); IR ($CHCl_3$) 2880, 2820, 1740 cm^{-1}; mass spectrum (220 °C) *m/z* 734 (M^+; 100), 674 (63), 518 (17), 393 (28), 149 (51), 138 (100); ^1H NMR δ 3.88 (3 H, s, $ArOCH_3$), 3.94 (3 H, s, CO_2CH_3), 6.65–6.80 (3 H, m, H-9′, H-10′, H-11′), 7.20–7.40 (3 H, m, H-9, H-10, H-11), 7.60 (1 H, dd, J = 8, 2 Hz, H-12); ^{13}C NMR 93.5 (C-2′), 48.7 (C-3′), 51.9 (C-5′), 31.0 (C-6′), 55.7 (C-7′), 134.5 (C8′), 114.9 (C-9′), 118.4 (C-10′), 111.4 (C-11′), 145.3 (C-12′), 137.0 (C-13′), 25.8 (C-14′), 80.4 (C-15′), 31.4 (C-16′), 32.5 (C-17′), 65.2 (C-18′), 36.6 (C-19′), 44.1 (C-20′), 63.6 (C-21′), 34.2 (C-22′), 46.5 (C-23′), 186.7 (C-2), 56.1 (C-3), 53.9 (C-5), 34.5 (C-6), 60.9 (C-7), 145.9 (C-8), 121.6 (C-9), 126.5 (C-10), 127.9 (C-11), 120.9 (C-12), 153.3 (C-13), 39.9 (C-14), 87.4 (C-15), 77.3 (C-16), 44.5 (C-17), 64.6 (C-18), 37.6 (C-19), 42.9 (C-20), 73.3 (C-21), 171.5 (C=O), 53.0 (CO_2CH_3), 55.7 (OCH_3).

Acid-Catalyzed Rearrangement of 16-Hydroxyvobtusine (4). (a) A solution of 970 mg (1.32 mmol) of **4** in 100 mL of methanol–water–acetic acid (5:5:2) containing 4.2 g of sodium acetate trihydrate was held at 45 °C under nitrogen for 1 h. The reaction mixture which then contained no starting material **4** by TLC, was diluted with water (50 mL) concentrated to half its volume in vacuo, and basified with 5% $NaHCO_3$ solution. The usual workup yielded 951 mg (98%) of **3** and **5** in a 1.85 ratio as determined by HPLC [μ-Bondapack C_{18} reverse-phase column, 1 mL/min, acetonitrile–0.01 M $(NH_4)_2CO_3$ (6:4)]. Pure epimeric components were then isolated by flash chromatography (silica gel) by eluting with ethyl acetate–diethylamine (95:5). Synthetic vobtusamine had IR, ^1H NMR, UV, TLC mobility, and HPLC (k' = 2.47) characteristics identical with those obtained with natural **3**. 16-Isovobtusamine (**5**): mp 243 °C dec (MeOH); R_f 0.32 [blue (CAS)]; UV (MeOH) λ_{max} 228, 263, 280, 289, 308 nm (log ε 4.45, 4.08, 3.93, 3.84, 3.48); IR ($CHCl_3$) 2880, 2820, 1735 cm^{-1}; mass spectrum (70 eV, 200 °C), *m/z* 734 (M^+·, 30), 674 (23), 656 (28), 224 (18), 138 (100); ^1H NMR δ 3.20 (3 H, s, $ArOCH_3$), 3.86 (3 H, s, CO_2CH_3), 4.81 (1 H, br s, OH), 6.52 (1 H, dd, J = 8, 2 Hz, H-11′), 6.58 (1 H, t, J = 8 Hz, H-10′), 6.66 (1 H, dd, J = 8, 2 Hz, H-9′), 7.10 (1 H, dd, J = 8, 2 Hz, H-12), 7.30–7.45 (2 H, m, H-9, H-10), 7.49 (1 H, dt, J = 8, 2 Hz, H-11); ^{13}C NMR 94.4 (C-2′),

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(15) That vobtusamine was not an artifact on isolation was ascertained by the stability of vobtusine under the extraction and fractionation procedure.
(16) The indicated stereochemistry at C(16) for **4** came from the ^{13}C NMR spectrum which showed a close similarity with the spectrum of 16-hydroxyvincadifformine (see ref 12 and 13).
(17) For base-catalyzed epimerization of vincamine alkaloids see: Szantay, C.; Szabo, L.; Kalaus, G. *Tetrahedron Lett.* **1973**, 191. Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Semmelhack, C. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 3702. Danieli, B.; Lesma, G.; Palmisano, G. *Gazz. Chim. Ital.* **1981**, *111*, 257.
(18) Lefebvre-Soubeyran, O. *Acta Crystallogr. Sect. B* **1973**, *29*, 2855.

48.6 (C-3′), 52.0 (C-5′), 30.5 (C-6′), 55.7 (C-7′), 134.7 (C-8′), 114.5 (C-9′), 118.4 (C-10′), 110.2[a] (C-11′), 145.1 (C-12′), 136.9 (C-13′), 25.8 (C-14′), 80.2[b] (C-15′), 31.1 (C-16′), 32.7 (C-17′), 65.3[c] (C-18′), 36.5 (C-19′), 44.6[d] (C-20′), 63.9 (C-21′), 28.4 (C-22′), 47.7 (C-23′), 131.4 (C-2), 48.6 (C-3), 51.3 (C-5), 17.8 (C-6), 105.9 (C-7), 128.7 (C-8), 117.9 (C-9), 121.7 (C-10), 120.4 (C-11), 110.7[a] (C-12), 134.4 (C-13), 42.0 (C-14), 80.6[b] (C-15), 82.1 (C-16), 43.3 (C-17), 66.3[c] (C-18), 37.6 (C-19), 43.8[d] (C-20), 56.7 (C-21), 173.6 (C=O), 54.0 (CO_2CH_3), 54.0 (OCH_3) (a–d indicate assignments may be interchanged); CD (MeOH, c 0.7) $\Delta\epsilon$ 0 (224 nm), −29.0 (230), −3.7 (243), −8.7 (265), 0 (287), −1.8 (308), 0 (325).

(b) When the addition of sodium acetate was left out of the preceding procedure and the reaction mixture (starting from 250 mg of **4**) held at reflux for 1.5 h, the development of two less polar products was observed by TLC. The usual workup followed by PLC (silica; benzene–ethanol–NH_3, 89:10:1) gave 48 mg (20%) of 2′,16′:16,17-dianhydrovobtusamine, 105 mg (43%) of 16,17-anhydrovobtusamine, 21 mg (8%) of 16-isovobtusamine **5**, and 33 mg (13%) of vobtusamine **3**.

2′,16′:16,17-Dianhydrovobtusamine had the following: R_f 0.58 [emerald green (CAS)]; UV (MeOH) λ_{max} 228, 275, 314 nm (log ϵ 4.45, 4.20, 3.92); IR ($CHCl_3$) 2840, 2800, 1725 cm^{-1}; mass spectrum (265 °C), m/z 698 ($M^{+\cdot}$, 22), 560 (23), 266 (30), 149 (64), 138 (100); ^1H NMR δ 3.60 (3 H, s, $ArOCH_3$), 4.00 (3 H, s, CO_2CH_3), 6.07 (1 H, s, H-17), 6.60–7.60 (7 H, m, aromatic protons); ^{13}C NMR (inter alia) 145.3 (C-2′), 43.7 (C-6′), 50.6 (C-7′), 102.0 (C-16′), 33.5 (C-22′), 52.3 (C-23′), 38.4 (C-14), 85.7 (C-15), 127.0 (C-16), 125.2 (C-17), 163.8 (C=O).

16,17-Anhydrovobtusamine had the following: R_f 0.46 [blue (CAS)]; UV (MeOH) λ_{max} 228, 263, 312 nm (log ϵ 4.52, 4.24, 3.98); IR ($CHCl_3$) 2840, 2800, 1725 cm^{-1}; mass spectrum (250 °C), m/z 716 ($M^{+\cdot}$, 100), 698 (14), 560 (16), 421 (14), 393 (27), 149 (37), 138 (74); ^1H NMR δ 3.46 (3 H, s, $ArOCH_3$), 4.02 (3 H, s, CO_2CH_3), 6.10 (1 H, s, H-17), 6.60–6.85 (3 H, m, H-9′, H-10′, H-11′), 7.05–7.60 (4 H, m, aromatic protons); ^{13}C NMR (inter alia) 27.8 (C-22′), 47.4 (C-23′), 130.0 (C-2), 84.5 (C-15), 127.3 (C-16), 125.8 (C-17), 163.8 (C=O).

Based-Catalyzed Epimerization of Vobtusamine (3 → 5). A solution of 15 mg (0.02 mmol) of vobtusamine (**3**) in 0.5 mL of tetramethylguanidine was stirred at room temperature for 1.5 h under nitrogen, poured into water and extracted with ether. The crude reaction mixture showed a 68:32 HPLC ratio of **5** and **3**.

Registry No. **2**, 19772-79-3; **3**, 84009-34-7; **3** (2′,16′:16,17-dianhydro), 84009-36-9; **3** (16,17-anhydro), 84009-37-0; **4**, 84009-35-8; **5**, 84048-13-5.

Conjugate Addition of 1-(Phenylthio)-1-(trimethylsilyl)-2-propene to Unsaturated Ketones

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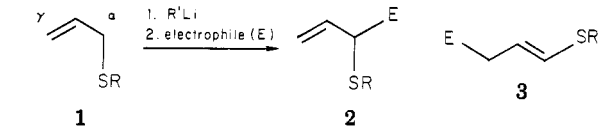
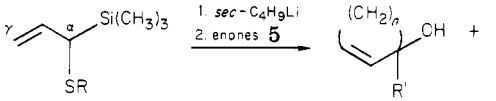
The reactions of unsymmetrical, sulfur-substituted, allyllithium reagents **1** with alkyl halides,[1] epoxides,[2] and carbonyl compounds[3] proceed with predominant α regioselectivity to give adducts **2** rather than adducts **3** (Scheme I). Exceptions to this generalization include the reactions of (alkylthio)allylcopper reagents with allylic halides,[3a,b] (arylthio)allyllithium reagents with ketones in the presence of *N,N,N′,N′*-tetramethylethylenediamine, hexamethylphosphoramide, or 1,4-diazabicyclo[2.2.2]octane,[1a] and the doubly metalated derivative of 2-propenethiol with various electrophiles.[4] In addition, the alkylation of various ketene dithioacetals exhibits similar γ regioselectivity in certain cases.[5] We recently demonstrated that 1-(phenylthio)-1-(trimethylsilyl)-2-propene (**4**) also exhibits γ regioselectivity in reactions with aldehydes and ketones,[6] and we now report the reactions of **4** with various unsaturated ketones.[7]

Scheme I



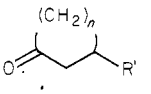
1 **2** **3**

Scheme II



4, R = C_6H_5
8, R = n-C_4H_9

6, R′ = $CH_2CH{=}C(SR)Si(CH_3)_3$



7, R′ = $CH_2CH{=}C(SR)Si(CH_3)_3$

In contrast to the high degree of α regioselectivity noted for the addition of (arylthio)- or (alkylthio)allyllithium reagents to enones,[3d] the addition of the anion of **4** to enones **5** proceeds exclusively with γ regioselectivity. Also, unlike the results reported by Binns and Haynes,[3d] 1,4-addition predominates over 1,2-addition even in the absence of hexamethylphosphoramide. With 2-cyclohexenone (**5a**), the addition furnished the γ/1,2-adduct **6** and the γ/1,4-adduct **7** (Scheme II) in a 12:88 ratio in 75% yield in the presence of hexamethylphosphoramide and in a 22:78 ratio in 61% yield in the absence of hexamethylphosphoramide. Careful scrutiny of the crude product failed to reveal any of the α/1,2- or α/1,4-adducts. Although the same degree of γ regioselectivity was maintained in other enone reactions, the proportion of 1,2- and 1,4-addition varied in a manner that was not always predictable. For example, the addition of **4** to cyclopentenone (**5c**) or cycloheptenone (**5d**) led to the γ/1,2-adducts **6** and γ/1,4-adducts **7** in 50:50 and 48:52 ratios, respectively,

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