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A Convenient Synthesis of Polyoxamic Acid, 5-*O*-Carbamoylpolyoxamic Acid, and Their Unnatural D Isomers

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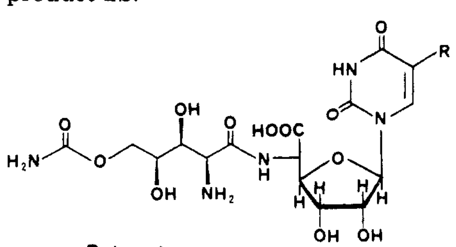
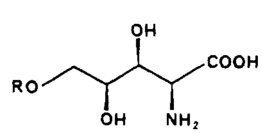
Polyoxins, e.g., **1a–d** are a family of antifungal antibiotics that has been extensively studied for some time.[1] They are widely used in Japan against phytopathogenic fungi,[1d–g] acting as competitive inhibitors of the enzyme chitin synthetase,[1b,2] leading to blockade of the biosynthesis of chitin, an essential component of the fungal cell wall.[3] A common structural feature of the polyoxins is a dipeptide comprised of a unique functionalized polyhydroxynorvaline commonly named 5-*O*- or δ-carbamoylpolyoxamic acid (**2a**) coupled to one of several related nucleoside amino acids. The name polyoxamic acid is given to the decarbamoylated natural product **2b**.[1a]

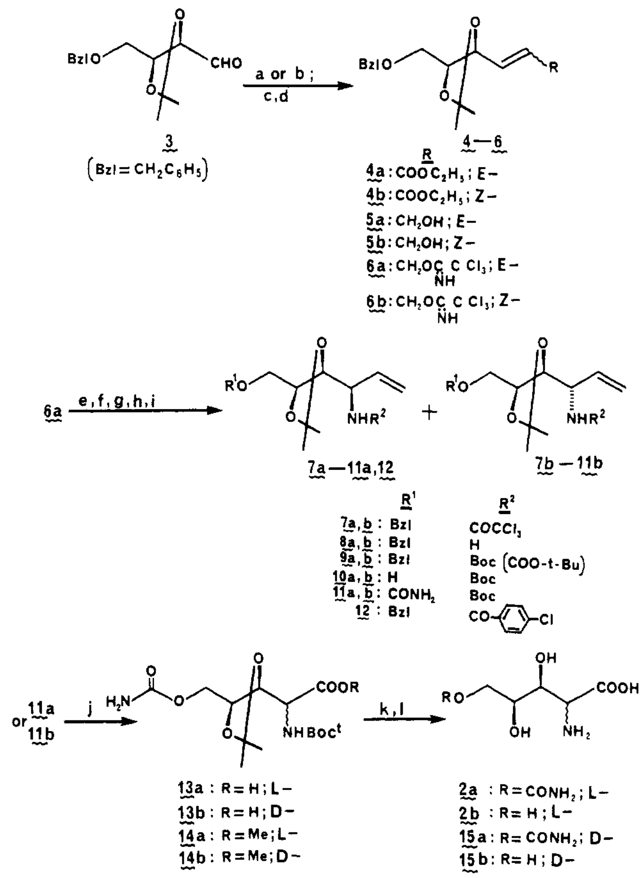


	Polyoxins	R
1a:	B	CH_2OH
1b:	D	COOH
1c:	J	CH_3
1d:	L	H



2a: R = $CONH_2$
2b: R = H

Scheme I[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, rt,[17] (quant.); (b) $Ph_3P{=}CHCOOEt$, MeOH, rt (98%); (c) DIBAL-H, toluene, rt (85%); (d) Cl_3CCN, Et_2O, Et_2O, NaH (cat.); (e) xylene, reflux, 48 h (28% each diastereomer from **5**); (f) NaOH, $THF–H_2O$, 60 °C (82%); (g) $(BOC)_2O$, Et_3N, Et_2O (quant.); (h) Na, NH_3 (96%); (i) *p*-nitrophenyl chloroformate, Et_3N, Et_2O, 0 °C, 18 h, NH_3–MeOH (75% overall); (j) $NaIO_4$, $RuCl_3$ (cat.), $CH_3CN–CCl_4–H_2O$ (70%); (k) MeOH (5–8 equiv), trifluoroacetic acid, rt, 45 min (73%); (l) 0.6 N NaOH, 60 °C, 2 h (58%).

In seeking a practical route to **2a**, and more usefully still a derivative with suitable protection for peptide coupling, use of L-tartaric acid with its inherent C-2 axis of symmetry appeared to us to be most appropriate. A purported synthesis of **2a** also utilizing L-tartaric acid has been described by Mukaiyama et al.,[4] the crucial step in which was stereoselective addition of a titanium acetylide species to the aldehyde **3**. A lengthy synthesis of **2b** based on higher carbohydrate starting materials has also appeared,[5] as well as an aldol condensation based synthesis[6] from D-erythrose of a protected D-**15a** derivative.

Our own strategy for the introduction of the α-amino acid functionality involved the use of the Overman–Claisen imidate rearrangement[7,8] as a key step, since we needed both the natural L and unnatural D isomers of the title compounds. In the course of our present work we noted some inconsistencies in the earlier report[4] (vide infra). This led us to confirm rigorously the authenticity of our

(1) (a) Isono, K; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7499. (b) Hori, M.; Kakiki, K.; Misato, T. *Agric. Biol. Chem.* **1974**, *38*, 691; (c) **1974**, *38*, 699. (d) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333. (e) Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A. S.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518. (f) Emmer, G.; Ryder, N. S.; Grassberger, M. A. *J. Med. Chem.* **1985**, *28*, 278. (g) Naider, F.; Shenbagamurthi, P.; Steinfeld, A. S.; Smith, H. A.; Boney, C.; Becker, J. M. *Antimicrob. Agents Chemother.* **1983**, *24*, 787.

(2) Becker, J. M.; Covert, N. L.; Shenbagamurthi, P.; Steinfeld, A. S.; Naider, F. *Antimicrob. Agents Chemother.* **1983**, *23*, 926.

(3) Sasaki, S.; Ohta, N.; Eguchi, J.; Furakawa, Y.; Suzuki, S. *Ann. Phytopathol. Soc. Jpn.* **1968**, *34*, 272.

(4) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.

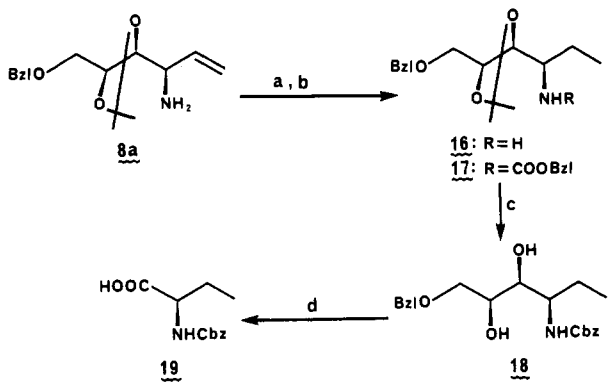
(5) Kizuhara, H.; Kimura, M.; Emoto, S. *Carbohydr. Res.* **1975**, *45*, 245.

(6) Ohdan, S.; Okamota, T.; Maeda, S.; Ichikawa, T.; Araki, Y.; Ishido, Y., *Bull. Chem. Soc. Jpn.* **1973**, *46*, 981.

(7) Takano, S.; Akiyama, M.; Ogosawara, K., *J. Chem. Soc., Chem. Commun.* **1984**, 770.

(8) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597; (b) **1976**, *98*, 2901.

Scheme II[a]



[a] Reagents and conditions: (a) H_2, Pd–C (95%); (b) benzyl chloroformate, Et_3N, THF, 0 °C (quant.); (c) 10% aqueous oxalic acid–THF, 60 °C (91%); (d) $NaIO_4$, $RuCl_3$ (cat.), CH_3CH–H_2O–CCl_4 (80%).

own synthetic materials by chemical degradation and X-ray analysis.

The aldehyde **3**[9] (Scheme I) was converted to the acrylate **4** followed by DIBAL reduction to the allylic alcohol **5**.[10] Treatment of **5** with trichloroacetonitrile provided the trichloroacetimidate **6**[7,8] which rearranged thermally to give a crude mixture (1:1) of diastereomeric amides[11] **7a** and **7b**, isolated by preparative HPLC in a combined yield of 56% from **5**. The less polar trichloroacetamide **7a** was hydrolyzed to the amine **8a**, which was converted to the *N*-Boc olefin **9a**. Debenzylation of **9a** furnished the alcohol **10a**, $[\alpha]^{24}_D$ +26° (*c* 1.0, acetone). Treatment of the more polar **7b** in the same manner provided the alcohol **10b**, $[\alpha]^{26}_D$ −45° (*c* 1.1, acetone). Surprisingly, neither **10a** nor **10b** showed rotations close to the reported value of $[\alpha]^{24}_D$ −1.98° (*c* 1.0, acetone)[4] for **10a**.[12]

In order to resolve the above discrepancy, **8a** was converted to the known *N*-Cbz-α-aminobutyric acid (**19**) (Scheme II), $[\alpha]^{26}_D$ +9.3° (*c* 2.0, absolute EtOH), which proved to be the D isomer [lit.[13] $[\alpha]^{21}_D$ +9.1° (*c* 2.8, absolute EtOH)]. Accordingly, the *R* (pro-L) configuration was assigned to **10a**, and this was confirmed by single-crystal X-ray analysis[14] of *p*-chlorobenzamide **12**.

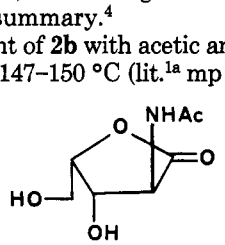
Carbamoylation of **10a** and **10b** by the reported procedure[4] furnished **11a** and **11b**, which were cleanly oxidized[7,15] to yield, respectively, the ultimately desired protected L-carbamoylpolyoxamic acid **13a** and its D isomer **13b** as amorphous solids (essentially pure by HPLC) suitable for peptide coupling. Treatment of **13a** and **13b** with CH_2N_2 provided the corresponding methyl esters **14a** and **14b** for comparison purpose.[4,16]

The absolute configuration of **13a** was further verified by deblocking with TFA followed by ion exchange chromatography to provide, as an amorphous solid, 5-*O*-carbamoyl-L-polyoxamic acid (**2a**), $[\alpha]^{23}_D$ +1.1° (*c* 0.91, H_2O), mp 208–213 °C dec [lit.[1a] $[\alpha]^{22}_D$ +1.3° (*c* 1.04, H_2O), mp 226–232 °C dec, crystalline)]. Like treatment of **13b** provided the D isomer **15a**, invariably contaminated with some decarbamoylated material **15b** (TLC).

Hydrolysis of **2a** with dilute NaOH[1a] followed by ion exchange chromatography provided, as an amorphous solid, L-polyoxamic acid (**2b**), $[\alpha]^{23}_D$ +2.1° (*c* 1.0, H_2O), mp 162–168 °C dec [lit.[1a] $[\alpha]^{23}_D$ +2.8° (*c* 1.0, H_2O), mp 171–173 °C, crystalline)]. Similar treatment of **15a** provided D-polyoxamic acid (**15b**), $[\alpha]^{23}_D$ +4.7° (*c* 1.1, H_2O), mp 90–125 °C dec.

It should be mentioned here that although formation of "polyoxamic acid, mp 167–170 °C dec" (from their structure **22**) is described by previous workers,[4] it is not supported by the relevant data.[16] In addition, they have not cited any transformation leading to 5-*O*-carbamoylpolyoxamic acid (**2a**) even though such a claim is made in the introductory summary.[4]

Finally, treatment of **2b** with acetic anhydride[1a] afforded the lactone **20**, mp 147–150 °C (lit.[1a] mp 150–152 °C) whose



20

structure was also confirmed by single-crystal X-ray analysis.[14] The syntheses of these rare amino acids (**2a**, **2b**, **14a**, **14b**) by the above route presented no problems in large-scale runs.

Experimental Section

All products, unless otherwise noted, were chromatographed to obtain samples homogeneous by TLC for spectral analysis. ^1H NMR spectra were obtained on Varian XL-400, XL-200, EM 390, and CFT 20 spectrometers using tetramethylsilane as an internal reference. Mass spectra were obtained on Finnigan MAT 312 and Varian MAT CH5 spectrometers; correct molecular ions were obtained for all compounds. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were obtained on a JASCO DIP-140 or a Rudolf Research Autopol III polarimeter. Correct microanalyses (C, H, N) of noncrystalline products were not always obtained; in such cases, NMR and mass spectral data were entirely consistent with the assigned structures. Solvents were dried by conventional methods; commercial reagents were the best available grades and were used without further purification. All evaporations were done on a rotary evaporator at reduced pressure.

Ethyl (*E*)-3-[(4*S*-*trans*)-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]propenoate[4,10] (4a). To a mechanically stirred solution of 31 g (140 mmol) of triethyl phosphonoacetate in 200 mL of dry THF at 0 °C was added 5.4 g of 60% Na-H/oil dispersion (140 mmol). After 30 min the temperature returned to 0–5 °C, and to the clear solution was added dropwise a solution of 35 g (140 mmol) of 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[9] (**3**) in 100 mL of dry THF at 0–10 °C. After being stirred 2 h at room temperature, the supernatant solution was decanted from the gum residue and concentrated to about $^1/_5$ volume. The concentrate and gum were both transferred to a separatory funnel with 150 mL each of water and hexane. The aqueous layer was separated and extracted with hexane, and the combined organics were washed with cold water and then brine, and dried over Na_2SO_4. Solvent was evaporated to leave 44 g **4a** (oil, 93% net), containing oil from NaH, suitable for the subsequent procedure. A portion was chromatographed (silica gel, 5–10% v/v EtOAc–hexane): ^1H NMR ($CDCl_3$) δ 1.29 (t, 3 H, CH_3CH_2), 1.43 and 1.46 (ss, 6, acetonide CH_3), 3.64 (d, 2 H,

(9) Hungerbuhler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.
(10) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949.
(11) The *Z* isomer **5b** required higher temperature and produced significantly more byproducts.
(12) Our $[\alpha]_D$ values of the gummy products generally obtained could vary by as much as 20% depending on the history of the particular sample, but this large a discrepancy cannot be explained.
(13) Ondetti, M. A.; Thomas, P. L. *J. Am. Chem. Soc.* **1965**, *87*, 4373.
(14) The crystal structures of **12** and **20** were solved by direct methods (MULTAN11/82). Full-matrix least-squares refinement of atomic postitional and thermal parameters converged to $R = 0.050$ for **12** and $R = 0.033$ for **20** over 2011 and 775 reflections, respectively. See Experimental Section and paragraph at the end of paper regarding supplementary material.
(15) Carlsen, P. J.; Kutsuki, T.; Martin, V. S; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(16) The $[\alpha]_D$ values and NMR spectra (see Experimental Section) of their structure **22** (methyl ester)[4] clearly do not match with either **14a** or **14b** whose structures we have unambiguously established.
(17) Of several conditions tried, these alone gave >95% *E* selectivity.

CH_2OBzl), 3.96 (m, 1 H, $CHCH_2OBzl$), 4.23 (q, 2 H, CH_2CH_3), 4.44 (m, 1 H, CHCH=C), 4.62 (s, 2 H, CH_2Ph), 6.11 (d, 1 H, CHCOOEt), 6.92 (d 1 H, CH=CHCOOEt), 7.36 (s, 5 H, Ph).

Ethyl (*Z*)-3-[(4*S*-*trans*)-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]propenoate[4,10] (4b). To a stirred solution of 6.05 g (24 mmol) of **3** in 125 mL of MeOH was added 9.3 g (27 mmol) of ethyl (triphenylphosphoranylidene)acetate. After 24 h at room temperature the reaction mixture was diluted with 125 mL of water and extracted with hexane. The extracts were washed with 1:1 MeOH–water and then brine, dried over $MgSO_4$ and filtered, concentrated to 150 mL and filtered, and evaporated to leave 7.6 g of **4b** (98%) containing a minor amount of *E* isomer. Chromatography (silica gel, 5% v/v EtOAc–hexane) afforded pure **4b**: ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H, CH_3CH_2), 1.46 (s, 6 H, acetonide CH_3), 3.70 (m, 2 H, CH_2OBzl), 3.98 (m, 1 H, $CHCH_2OBzl$), 4.16 (q, 2 H, CH_2CH_3), 4.62 (q, 2 H, CH_2Ph), 5.41 (t, 1 H, CHCH=C), 5.94 (d, 1 H, CHCOOEt), 6.22 (dd, 1 H, CHC=COOEt), 7.35 (m, 5 H, Ph).

(*E*)-3-[(4*S*-*trans*)-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenol[10] (5a). To a mechanically stirred solution of 184 g (570 mmol) of ester **4a** in 3 L of dry toluene was added slowly over 1 h 1.18 mol of diisobutylaluminum hydride–toluene solution. A cold-water bath controlled the mild exotherm between 23 and 30 °C. Stirring was continued for an additional 30 min, the reaction mixture was cooled to 5–10 °C, and a solution of 113 g of MeOH in 200 mL of toluene was added slowly (<15 °C). After an additional 30 min at room temperature a solution of 64 g of water in 130 mL of MeOH was added slowly. The thick sludge was stirred 30 min, 500 g of Celite was added, the mixture was suction-filtered, and the solids were washed with toluene and hot Et_2O. The filtrate was evaporated and the oily residue triturated thoroughly with hexane several times to leave crude solid **5a**. The hexane extract was evaporated and the residue was chromatographed to obtain additional **5a**, total 135 g (85%), sufficiently pure for the subsequent procedure. A portion was further chromatographed (silica gel, 50% v/v EtOAc–hexane): ^1H NMR ($CDCl_3$) δ 1.45 (s, 6 H, acetonide CH_3), 3.62 (m, 2 H, CH_2OBzl), 3.94 (m, 1 H, $CHCH_2OBzl$), 4.18 (m, 2 H, CH_2OH), 4.30 (t, 1 H, CHCH=C), 4.62 (s, 2 H, CH_2Ph), 5.74 (dd, 1 H, $CH=CH_2OH$), 5.97 (tt, 1 H, $CHCH_2OH$), 7.37 (s, 5 H, Ph).

(*Z*)-3-[(4*S*-*trans*)-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenol (5b) was prepared by reacting ester **4b** as described above for **4a** to give **5b** in 100% yield crude. A portion was chromatographed (silica gel, 50% v/v EtOAc–hexane): ^1H NMR ($CDCl_3$) δ 1.44 (s, 6 H, acetonide CH_3), 1.94 (t, 1 H, OH), 3.64 (d, 2 H, CH_2OBzl), 3.89 (m, 1 H, $CHCH_2OBzl$), 4.18 (t, 2 H, CH_2OH), 4.62 (s, 2 H, CH_2Ph), 4.74 (t, 1 H, CHC=C), 5.59 (t, 1 H, $CH=CH_2OH$), 5.91 (m, 1 H, $CHCH_2OH$), 7.36 (s, 5 H, Ph).

***N*-[1-[[4*S*-[4α,4(*S**),5β]]-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenyl]-2,2,2-trichloroacetamide (7a) and *N*-[1-[[4*S*-[4α,4(*R**),5β]]-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenyl]-2,2,2-trichloroacetamide (7b).** To a mechanically stirred suspension of 2 g 60% NaH/oil (50 mmol) in 150 mL of dry Et_2O at 15 °C was added a solution of 135 g (490 mmol) of alcohol **5a**[11] in 450 mL of dry Et_2O gradually over 10 min. After being stirred an additional 15 min at room temperature, the mixture was cooled to −15 °C and a solution of 75 g (520 mmol) of trichloroacetonitrile in 150 mL of dry Et_2O was added over 20 min at −15 to −10 °C. The mixture was sirred 30 min while warming to room temperature, 2.8 mL of HOAc was added, and one-half of the solvent was evaporated. The remainder was diluted with 4 L of hxane, suction-filtered through a Celite pad, and completely evaporated. The crude imidate was not isolated but was dissolved in 4 L of dry xylene, which was then purged with dry N_2 for 1 h. The solution was then heated under N_2 to distill 200 mL of solvent, and set to reflux for 48 h. On cooling, the dark solution was evaporated, the residue was dissolved in 200 mL of hexane, and this solution was chromatographed (2 kg of silica gel, 2 L of hexane followed by 2 L of 20% v/v toluene–hexane). The desired diastereomers were monitroed in the complex mixture by TLC (30% v/v diisopropyl ether–cyclohexane, ca. R_f 0.28 and 0.37), and the appropriate fractions were combined and evaporated. The residue was dissolved in Et_2O, treated with charcoal and boiled, filtered, and evaporated to leave 156 g (76%) of amber oil. The oil was dissolved in 200 mL of toluene (total volume 330 mL) and divided into six portions of 55 mL each. Each portion was chromatographed on a Waters Prep 500 with two cartridges and eluted with 1:11 (v/v) Et_2O–hexane in 250-mL fractions (30). Mixed fractions were rechromatographed. There was obtained first a total of 57.7 g (28%) of the less polar isomer, **7a**. A portion was further chromatographed: ^1H NMR ($CDCl_3$) δ 1.42 and 1.45 (ss, 6 H, acetonide CH_3), 3.67 (m, 2 H, CH_2OBzl), 4.07 (m, 2 H, $CHCH_2O$ and CHN), 4.63 (s) and 4.75 (m with 4.63, 3 H total, CH_2Ph and CHCHN), 5.22 (complex s) and 5.37 (complex d, 2 H total, forming AB of ABX system, $C=CH_2$), 5.85 (m of 8 peaks, 1 H, X of ABX, $CH=CH_2$), 7.37 (s, 6 H, Ph and NH); $[\alpha]^{26}_D$ +10.4° (*c* 1.25, acetone).

There was obtained then a total 55.7 g (27%) of the more polar isomer, **7b**. A portion was further chromatographed: ^1H NMR ($CDCl_3$) δ 1.40 (s, 6 H, acetonide CH_3), 3.60 (m, 2 H, CH_2OBzl), 4.05 (m, 2 H, $CHCH_2O$ and CHN), 4.52 (m with 4.60) and 4.60 (s, 3 H total, CHCN and CH_2Ph), 5.23 (complex d) and 5.37 (complex d, 2 H total, forming AB of ABX system, $C=CH_2$), 5.83 (m of 7 peaks, 1 H, X of ABX, $CH=CH_2$), 7.17 (br d under 7.33) and 7.33 (s, 6 H total, NH and Ph); $[\alpha]^{26}_D$ −37.9° (*c* 1.3, acetone).

[4*S*-[4α,4(*S),5β]]-2,2-Dimethyl-α-ethenyl-5-[(phenylmethoxy)methyl]-1,3-dioxolane-4-methanamine (8a).** A mixture of 46.8 g (110 mmol) of amide **7a**, 350 mL of THF and 75 mL of 1 N aqueous KOH was stirred vigorously for 4 h at 60 °C and then cooled. The organic layer was decanted, the aqueous layer was extracted with Et_2O, and the combined organics were dried over solid NaOH and filtered. The filtrate was evaporated, and the residue dissolved in hexane and dried further over NaOH, filtered, and evaporated. The 31 g of crude product was flash chromatographed (1.5 kg of silica gel, 5–15% v/v EtOAc–hexane) to give 25.2 g of **8a** (gum, 82%), homogenous by TLC: ^1H NMR ($CDCl_3$) δ 1.41 (s, 6 H, acetonide CH_3), 1.48 (s, 2 H, NH_2), 3.36 (t, 1 H, CHN), 3.57 (d, 2 H, CH_2OBzl), 3.72 (dd, 1 H, CHCHN), 4.04 (m, 1, $CHCH_2O$), 4.55 (s, 2 H, CH_2Ph), 4.93–5.33 (m, 2 H, $C=CH_2$), 5.55–5.96 (m, 1 H, $CH=CH_2$), 7.27 (s, 5 H, Ph); $[\alpha]^{26}_D$ −2.0° (*c* 1.1, CCl_4).

[4*S*-[4α,4(*R),5β]]-2,2-Dimethyl-α-ethenyl-5-[(phenylmethoxy)methyl]-1,3-dioxolane-4-methanamine (8b)** was prepared by reacting 50 g of amide **7b** as described above for **7a** to give 29.8 g of **8b** (gum, 91%). A portion was further chromatographed: ^1H NMR ($CDCl_3$) δ 1.36 (s, 8 H, acetonide CH_3 and NH_2), 3.37–3.65 (dm, 3 H, CH_2OBzl and CHN), 3.71–4.15 (m, 2 H, CHCHN and $CHCH_2O$), 4.55 (s, 2 H, CH_2Ph), 4.96–5.30 (m, 2 H, $C=CH_2$), 5.58–6.09 (m, 1 H, $CH=CH_2$), 7.25 (s, 5 H, Ph); $[\alpha]^{26}_D$ −29.6° (*c* 1.3, CCl_4).

1,1-Dimethylethyl *N*-[1-[[4*S*-[4α,4(*S),5β]]-[2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenyl]carbamate (9a).** A solution of 15.6 g (56 mmol) of amine **8a** in 150 mL of Et_2O was treated with 9.8 mL (70 mmol) of Et_3N and 14.8 mL (64 mmol) of di-*tert*-butyl dicarbonate and stirred for 18 h at ambient temperature. The mixture was evaporated and the residue chromatographed (silica gel; toluene to 1:1 v/v Et_2O–hexane to 1:1 v/v Et_2O–acetone) to give 18.5 g **9a** (gum, 87%), which was used directly in the subsequent procedure: $[\alpha]^{23}_D$ +7.0° (*c* 1.0, acetone).

1,1-Dimethylethyl *N*-[1-[[4*S*-[4α,4(*S),5β]]-[2,2-dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenyl]carbamate (9b)** was prepared by reacting 27.8 g (100 mmol) of amine **8b** as described above for **8a**. The reaction solution was diluted with hexane (2 vol, 700 mL), washed successively with cold 0.1 N HCl, 2% (w/v) aqueous K_2CO_3, water, and brine, dried over $MgSO_4$, and filtered and evaporated to leave 42 g of **9b** (gum, 90%). A portion was chromatographed: ^1H NMR ($CDCl_3$) δ 1.41 and 1.46 (ss, 6 H, 15, 5 × CH_3), 3.57 (d, 2 H, CH_2OBzl), 3.7–4.4 (m, 3 H, $CHCHN$ and $CHCH_2O$), 4.59 (s, 2 H, CH_2Ph), 5.08–5.37 (m, 2 H, $C=CH_2$), 5.64–6.11 (m, 1 H, $CH=CH_2$), 7.32 (s, 5 H, Ph); $[\alpha]^{26}_D$ −45.6° (*c* 1.0, acetone). Anal. Calcd for $C_{21}H_{31}NO_5$ (377.48): C, 66.82; H, 8.28; N, 3.71. Found: C, 66.78; H, 8.18; N, 3.42.

1,1-Dimethylethyl *N*-[1-[[4*S*-[4α,4(*S),5β]]-2,2-Dimethyl-5-(hydroxymethyl)-1,3-dioxolan-4-yl]-2-propenyl]-carbamate (10a).** To a stirred solution of 18.8 g (49 mmol) of benzyl ether **9a** in 125 mL of liquid NH_3 at −20 °C was added small pieces of sodium at 5 min intervals for 1 h until a blue color persisted (2.3 g, 100 mmol). Et_2O was added, the mixture was

allowed to warm to room temperature, and $MgSO_4$ was added. The mixture was filtered through a Celite pad, and the filtrate was evaporated to leave 13.5 g of **10a** (gum, 96%). A portion was chromatographed: ^1H NMR ($CDCl_3$) δ 1.43 (s, 16 H, 5 × CH_3 and OH), 3.75 (br s, 2 H, CH_2OH), 3.94 (m, 2 H, OCHCHO), 4.30 (m, 1 H, CHN) 4.99 (br d, 1 H, NH), 5.08–5.43 (m, 2 H, C=CH_2), 5.66–6.09 (m, 1 H, C*H*=CH_2); $[\alpha]^{24}_D$ +26.3° (*c* 1.0, acetone).

1,1-Dimethylethyl *N*-[1-[[4*S*-[4α,4(*R),5β]]-2,2-dimethyl-5-(hydroxymethyl)-1,3-dioxolan-4-yl]-2-propenyl]carbamate (10b)** was prepared by reacting 9.1 g of benzyl ether **9b** and 1.5 g of Na as described above for **9a** to give 5.7 g of **10b** (gum, 82%): $[\alpha]^{26}_D$ −35.8° (*c* 1.2, acetone). A portion was subjected to molecular distillation to give a colorless gum: $[\alpha]^{26}_D$ −38.4° (*c* 1.0, acetone). Another portion was chromatographed: ^1H NMR ($CDCl_3$) δ 1.42 and 1.45 (ss, 15 H, 5 × CH_3), 2.12 (q, 1 H, OH), 3.58–3.72 (m, 1 H, OC*H*CHN), 3.77–4.06 (m, 3 H, OC*HCH*$_2$OH), 4.26 (br s, 1 H, CHN), 4.84 (br d, 1 H, NH), 5.21–5.35 (m, 2 H, C=CH_2), 5.82–6.02 (m, 1 H, C*H*=CH_2); $[\alpha]^{26}_D$ −45.3° (*c* 1.1, acetone). Anal. Calcd for $C_{14}H_{25}NO_5 \cdot 0.5H_2O$ (296.37): C, 56.74; H, 8.84; N, 4.73. Found: C, 56.43; H, 8.43; N, 4.61.

1,1-Dimethylethyl *N*-[1-[[4*S*-[4α,4(*S),5β]]-5-[[(aminocarbonyl)oxy]methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenyl]carbamate (11a).** A stirred solution of 13.4 g (47 mmol) of alcohol **10a**, 50 mL of THF, 125 mL of Et_2O, 25 mL of pyridine, and 8.5 mL of Et_3N was cooled to −20 °C; and 10.3 g (51 mmol) of 4-nitrophenyl chloroformate was added. The mixture was stirred for 18 h at 0 °C, diluted with 900 mL of hexane, and suction-filtered. The filtrate was evaporated to leave a gum, which was dissolved in 200 mL of Et_2O, cooled to 0–5 °C, and treated with 100 mL of saturated NH_3–MeOH solution. After 2 h of stirring at 0 °C, the solution was evaporated to leave a gum. The gum was dissolved in EtOAc and washed with cold 2% (w/v) aqueous K_2CO_3 (4 × 250 mL), water (2 × 300 mL), and brine and then dried over $MgSO_4$ and filtered. The filtrate was evaporated to leave 11.2 g of **11a** (gum, 73%) with a trace impurity by TLC: ^1H NMR ($CDCl_3$) δ 1.40 (s, 15 H, 5 × CH_3), 3.85–4.03 (m, 1 H, OC*H*CHN), 4.03–4.45 (m, 4 H, OC*H*NH and OC*HCH*$_2$OCONH$_2$), 4.55–4.98 (m, 3 H, NH and NH_2), 5.08–5.42 (m, 2 H, C=CH_2), 5.65–6.12 (m, 1 H, C*H*=CH_2); $[\alpha]^{26}_D$ +12.7° (*c* 1.0, acetone). Anal. Calcd for $C_{15}H_{26}N_2O_6$ (330.38): C, 54.53; H, 7.93; N, 8.48. Found: C, 55.41; H, 8.03; N, 8.08.

1,1-Dimethylethyl *N*-[1-[[4*S*-[4α,4(*R),5β]]-5-[[(aminocarbonyl)oxy]methyl]-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenyl]carbamate (11b)** was prepared from 1.2 g of alcohol **10b** as described above for **10a** to give **11b** (gum, 58%) following chromatography: ^1H NMR ($CDCl_3$) δ 1.43 (d, 15 H, 5 × CH_3), 3.73–4.43 (m, 5 H, $OCH_2CHCHCHN$), 4.83–5.43 (m, 5 H, NH, NH_2, and C=CH_2), 5.70–6.17 (m, 1 H, C*H*=CH_2); $[\alpha]^{24}_D$ −55.2° (*c* 1.0, acetone).

(3*S*,4*S*)-5-[(Aminocarbonyl)oxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-3,4-[(1-methylethylidene)dioxy]-L-norvaline[4] (13a). A stirred mixture of 10.6 g (32 mmol) of alkene **12a**, 130 mL of CH_3CN, 130 mL of CCl_4, and 190 mL of water was treated with 30.5 g (143 mmol) of $NaIO_4$, and after 15 min, 80 mg of $RuCl_3$. After being stirred for 3.5 h at ambient temperature, the mixture was diluted with 750 mL of water, and extracted with Et_2O (2 × 500 mL). The extract was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed (silica gel, 50:50:1 Et_2O–EtOAc–HOAc) to give 9.3 g of **13a** (amorphous solid foam, 83%), satisfactory for subsequent procedures. A small middle fraction from the chromatography afforded a sample that appeared homogeneous by TLC but would not analyze (C, H, N) satisfactorily: ^1H NMR (Me_2SO-d_6) δ 1.36 (d, 15 H, 5 × CH_3), 3.77–4.33 (m, 5 H, $OCH_2CHCHCHN$), 6.33–6.61 (br s, 3 H, NH and NH_2); $[\alpha]^{26}_D$ +0.3° (*c* 1.5, acetone); MS (FAB), calcd for $C_{14}H_{25}N_2O_8$ 349.1611, found 349.1589. Anal. Calcd for $C_{14}H_{24}H_2O_8$ (348.36): C, 48.27; H, 6.84; N, 8.04. Found: C, 49.61; H, 6.95; N, 7.66.

The methyl ester **14a** was prepared from **13a** by using diazomethane: ^1H NMR ($CDCl_3$) δ 1.39 (d, 6 H, 2 acetonide CH_3), 1.43 (s, 9 H, *t*-Bu), 3.79 (s, 3 H, OMe), 4.01 (m, 1 H, OC*H*CH_2), 4.26 (m, 3 H, CH_2O and OC*H*CHN), 4.49 (d, 1 H, C*H*NH), 4.86 (br s, 2 H, H_2NCO), 5.29 (d, 1 H, N*H*CH); $[\alpha]^{26}_D$ −3.6° (*c* 1.5, CH_2Cl_2); MS (FAB), calcd for $C_{15}H_{27}N_2O_8$ 363.1767, found 363.1751 [lit.[4] $[\alpha]^{25}_D$ −5.88° (*c* 4.2, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.4 (s, 15 H), 3.65 (s, 3 H), 3.7–4.2 (m, 5 H), 4.9–5.3 (m, 3 H)].[16]

(3*S*,4*S*)-5-[(Aminocarbonyl)oxy]-*N*-[(1,1-dimethylethoxy)carbonyl]-3,4-[(1-methylethylidene)dioxy]-D-norvaline (13b) was prepared from 670 mg of alkene **12b** (1.94 g of $NaIO_4$, 5 7g of $RuCl_3$) as described above for **12a** to give **13b** (gum, 69%), which was used directly for the subsequent procedure. A portion was crystallized from acetone–hexane: ^{1}NMR (Me_2SO-d_6) δ 1.37 (s, 15 H, 5 × CH_3), 3.60–4.34 (m, 5 H, $OCH_2CHCHCHN$), 6.48 (br s, 2 H, H_2NCO), 7.23 (br d, 1 H, NHCH), 16.3 (br s, 0.8 H, COOH); $[\alpha]^{24}_D$ −28.3° (*c* 1.0, acetone).

The methyl ester **14b** was prepared from **13b** by using diazomethane: ^1H NMR ($CDCl_3$) δ 1.36 (d, 6 H, 2 acetonide CH_3), 1.42 (s, 9 H, *t*-Bu), 3.77 (s, 3 H, OMe), 4.03 (dd, 1 H), 4.16 (dd, 1 H), 4.25 (m, 1 H), 4.36 (m, 1 H), and 4.62 (m, 1 H) ($OCH_2CHCHCHN$), 4.88 (br s, 2 H, H_2NCO), 5.42 (d, 1 H, N*H*CH); $[\alpha]^{24}_D$ −26.5° (*c* 1.8, CH_2Cl_2); MS (FAB), calcd for $C_{15}H_{27}N_2O_8$ 363.1767, found 363.1743.

(3*S*,4*S*)-5-[(Aminocarbonyl)oxy]-3,4-dihydroxy-L-norvaline (5-*O*-Carbamoylpolyoxamic Acid)[1a,14] (2a). **13a** (300 mg, 0.86 mmol) was dissolved in 8 mL of cold 1:10 (v/v) MeOH–trifluoroacetic acid and then the solution was stirred for 40 min at room temperature. The solution was diluted with 125 mL of Et_2O, cooled at 0 °C for 2 h, and suction-filtered to leave 310 mg of solid residue. The residue was dissolved in water, placed on a AG 50W-X8 (H^+) ion exchange column (10 mL), washed with 50 mL of water, and eluted with 0.6 N NH_4OH. Fractions were monitored by TLC using both 4:1:2 butanol–HOAc–water/silica gel and 3:1 phenol–water/cellulose.[1a] Evaporation of the middle TLC-homogeneous fractions left **2a**, white powder, mp 208–213 °C dec: $[\alpha]^{23}_D$ +1.1° (*c* 0.91, water); MS (FAB), *m/e* 209 (100, M + 1) [lit.[1a] mp 226–232 °C dec; $[\alpha]^{22}_D$ +1.3° (*c* 1.04, H_2O)]. Total yield from all fractions was 64%. Crystallization from EtOH–water raised the melting point to 214–218 °C dec.

(3*S*,4*S*)-3,4,5-Trihydroxy-L-norvaline (Polyoxamic Acid)[1a] (2b). A stirred solution of 64 mg (0.031 mmol) of **2a** in 5 mL of 0.5 N aqueous NaOH was heated for 2 h at 60 °C, cooled, and carefully acidified with HOAc. The resulting solution was placed on a AG 50W-X8 (H^+) column (10 mL), washed with 50 mL of water, and eluted with 0.6 N NH_4OH. Evaporation of the appropriate fractions gave 46 mg of **2b** (white powder, 90%), mp 162–178 °C dec: $[\alpha]^{23}_D$ +2.1° (*c* 1.0, water) [lit.[1a] mp 171–173 °C dec; $[\alpha]^{23}_D$ +2.8° (*c* 1.0, H_2O)].

(3*S*,4*S*)-3,4,5-Trihydroxy-D-norvaline (15b) was prepared by reacting 480 mg of **13** b as described above for **13a** to give (3*S*,4*S*)-5-[(aminocarbonyl)oxy]-3,4-dihydroxy-D-norvaline (**15a**), contaminated with decarbamoylated product **15b**. The mixture was hydrolyzed as described above for **2a** to give 95 mg of **15b** (white powder, 34%), homogeneous by TLC, mp 95–125 °C dec: $[\alpha]^{23}_D$ +4.7° (*c* 1.1, water); MS (FAB), *m/e* 166 (100, M^+).

Degradation of 8a to 19. A solution of 1.4 g (5 mmol) of **8a** in 50 mL of EtOH was hydrogenated at 3–4 atm over 10% Pd–C catalyst for 18 h. The mixture was filtered, and the solvent was evaporated to leave 1.3 g **16** whose ^1H NMR spectrum showed the double bond reduced and the OBzl intact. This amine was treated with benzyl chloroformate by a conventional procedure to give 2.2 g of **17**. Compound **17** was treated with 25 mL of water, 50 mL of THF, 2.5 g of oxalic acid, and 0.3 mL of 12 N HCl for 8 h at 60 °C. The mixture was cooled, poured into 5% aqueous K_2CO_3, and extracted with EtOAc, and the extract was dried over $MgSO_4$. Solvent was evaporated and the residue chromatographed (silica gel, EtOAc–hexane) to give 1.3 g of diol **18** (gum, 71% from **8a**). Diol **18** was treated with $NaIO_4$–$RuCl_3$ as described above for **11** to give a major acidic product, a portion of which was isolated by preparative TLC to give D-*N*-Cbz-2-aminobutyric acid[13] (**19**) with the expected ^1H NMR and MS: $[\alpha]^{26}_D$ +9.3° (*c* 2.0, absolute EtOH) [lit.[13] $[\alpha]^{21}_D$ +9.1° (*c* 2.8, absolute EtOH)].

***N*-[1-[[4*S*-[4α,4(*S**),5β]]-2,2-Dimethyl-5-[(phenylmethoxy)methyl]-1,3-dioxolan-4-yl]-2-propenyl]-4-chlorobenzamide (12).** A stirred solution of 0.50 g (1.8 mmol) of amine **8a** and 0.29 mL (2.1 mmol) of Et_3N in 10 mL of CH_2Cl_2 was cooled to −30 °C, and 0.24 mL (1.9 mmol) of 4-chlorobenzoyl chloride was added slowly. After an additional 1 h at room temperature, the mixture was washed with 0.5 N HCl, 5% aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. After filtering and evaporating solvent, the residue was chromatographed (silica gel, EtOAc–hexane). The appropriate fractions were combined, covered loosely with filter paper, and left undisturbed to slowly

evaporate, giving **12** as well-defined needles, mp 90 °C: ^{1}H NMR ($CDCl_3$) δ 1.42 (ss, 6 H, acetonide CH_3), 3.7 (m, 2 H, CH_2OBzl), 4.1 (m, 2 H, OCHCHO), 4.62 (s, 2 H, CH_2Ph), 4.98 (br s, 1 H, C*H*NH), 5.3 (m, 2 H, C=CH_2), 6.0 (m, 1 H, C*H*=CH_2), 6.84 (d, 1 H, NH), 7.4 (sd, 7 H, Ph and 3,5-Ar), 7.74 (d, 2 H, 2,6-Ar); $[\alpha]^{26}_D$ +19.2° (*c* 0.5, acetone); MS (FAB) *m/e* 416 (18, M + 1), 358 (100). X-ray crystallographic data[14] for $C_{23}H_{26}ClNO_4$ (415.92): orthorhombic, space group $P2_12_12_1$, a = 8.443, b = 49.540, and c = 5.203 Å, V = 2176.2 Å^3, Z = 4, D_{calc} = 1.269 g cm^{-3}.

[2*S*-(2α,3β,4β)]-2-(Acetylamino)-2,3-dihydro-3-hydroxy-4-(hydroxymethyl)-2(5*H*)-furanone (*N*-Acetylpolyoxaminolactone)[1a] (20). A suspension of 200 mg of **2b** in 20 mL of MeOH was treated with 1 mL of acetic anhydride and stirred vigorously for 18 h as described previously.[1a] After addition of water, the solution was evaporated and the residue was chromatographed (silica gel, MeOH–EtOAc). The residue obtained was triturated with CH_3CN to leave a white powder, which was crystallized from a small volume of EtOH to give **20**, mp 146–150 °C (lit.[1a] mp 150–152 °C): ^{1}H NMR ($CDCl_3$–trace Me_2SO-d_6) δ 2.26 (s, 3 H, CH_3), 3.9 (m, 3 H, C*H*(OH)C*H*(CH_2OH) and 1° OH), 4.6 (m, 3 H, CH_2 and CHN), 5.33 (d, 1 H, 2° OH), 7.50 (br s, 1 H, NH); MS (FAB), *m/e* 215 (100, M + Na), 190 (17, M + 1). X-ray crystallographic data[14] for $C_7H_{11}NO_5$ (189.17): orthorhombic, space group $P2_12_12_1$, a = 12.182, b = 13.872, and c = 4.977 Å, V = 841.1 Å^3, Z = 4, D_{calc} = 1.494 g cm^{-3}.

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Supplementary Material Available: Views of the solid-state conformations of **12** and **20**, tables of crystal data, atomic postional and thermal parameters, bond distances and angles (8 pages). Ordering information is given on current masthead page.

Pyramidal Inversion and Electron Delocalization in the Silacyclopentadienyl Anion

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Despite growing interest in the chemistry of silicon derivatives of aromatic hydrocarbons,[1] relatively little information is available on the geometric and electronic structure of these compounds. We now report the results of ab initio calculations on the silacyclopentadienyl anion (**1**)[2,3] (the monosilicon derivative of the cyclopentadienyl anion) that reveal a rigidly pyramidal ground-state structure and an extremely low resonance energy for this compound.

Calculations were performed on the planar (C_{2v}) and pyramidal (C_s) forms of **1** at the 6-31G* level of sophistication using the program Gaussian 82.[4] Complete geometry optimizations were performed on these structures under C_{2v} and C_s symmetry constraints. Selected structural parameters[5] obtained for these two conformations are reported in Figure 1. We find that the ground-state conformation of **1** is the pyramidal C_s structure (Figure 2). The planar, C_{2v} form is found to be the transition state for pyramidal inversion between equivalent C_s structures. We calculate an inversion barrier ($C_s \rightarrow C_{2v}$) for this process of 16.2 kcal/mol.[6] The structural parameters that we obtain for the C_{2v} form of **1** compare well with those obtained previously by Gordon et al.[2] at the STO-2G level of sophistication. While only the C_{2v} conformation was considered in this previous study,[2] its properties are of particular interest since favorable orbital alignment would be expected to result in electron delocalization being at a maximum in this planar conformation (see below). Inspection of Figure 1 reveals that the structure of the ground-state C_s conformation differs significantly from that found for the planar form. In this structure the geometry about silicon is markedly pyramidal with a 68.2° angle between the Si–H bond and the mean plane of the ring heavy atoms.[7] While less pronounced, this pyramidality extends to all of the heavy atom centers in the C_s conformation.[8] Also noteworthy is the much longer Si–C bond (1.924 Å) in this conformation compared to that obtained for the C_{2v} form (1.788 Å). Concomitant with this increase in Si–C bond lengths is a decrease in the C–Si–C angle from 96.7° (C_{2v}) to 86.5° (C_s) and an increase in the Si–C–C angle from 104.8° (C_{2v}) to 110.4° (C_s). In addition, while the C–C bond lengths in the C_{2v} transition state are closely similar (1.401 and 1.405 Å), in the C_s ground state these bond lengths differ significantly (1.341 and 1.472 Å) and suggest that the hydrocarbon portion of the molecule may best be described as adopting substantial butadiene-like (localized) character. Qualitatively this structural feature, along with the lengthening of the Si–C bond, suggest that electron delocalization is significantly reduced in the C_s conformation relative to the C_{2v} form.

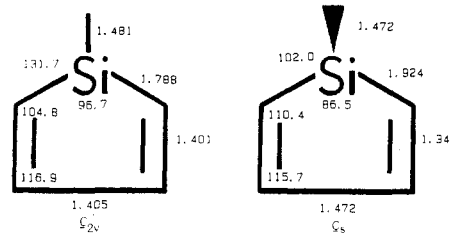

Figure 1. Calculated bonding parameters for conformations of **1** (bond lengths in Å, bond angles in degrees). Left: C_{2v} conformation. Right: C_s conformation.

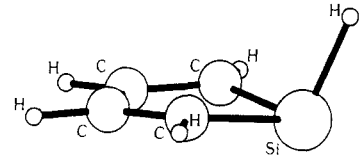

Figure 2. View of the calculated ground-state structure (C_s) for **1**.

(1) See: Clabo, D. A., Jr.; Schaefer, H. F., III. *J. Chem. Phys.* **1986**, *84*, 1664, reference 2, and references therein. See also: Gordon, M. S. In *Molecular Structure and Energy*; Liebman, J., Greenberg, A., Eds.; VCH Publishers: Dearfield Beach, FL, Vol. 1, in press.

(2) Gordon, M. S.; Boudjouk, P.; Anwari, F. *J. Am. Chem. Soc.* **1983**, *105*, 4972. In this work the C_{2v} form of **1** was investigated at the 3-21G//STO-2G level of sophistication.

(3) Portions of this work were presented at the 20th Organosilicon Symposium, April 18–19, 1986.

(4) Binkley, J. S.; Frisch, M. J.; DeFrees, D. J.; Raghavachari, K.; Whiteside, R. A.; Schlegel, H. B.; Fluder, M. J.; Pople, J. A. A copy of the program may be obtained from Carnegie-Mellon University.

(5) For C_{2v}, C–H = 1.077 (1.082) Å; for C_s, C–H = 1.082 (1.085) Å; α-C (β-C).

(6) Total energies in hartrees/molecule (6-31G*) are: C_s, −443.22440; C_{2v}, −443.19853.

(7) Structural parameters were calculated by using the program *Geom*.

(8) Pyramidality at all heavy atom centers is expected under C_s symmetry.

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