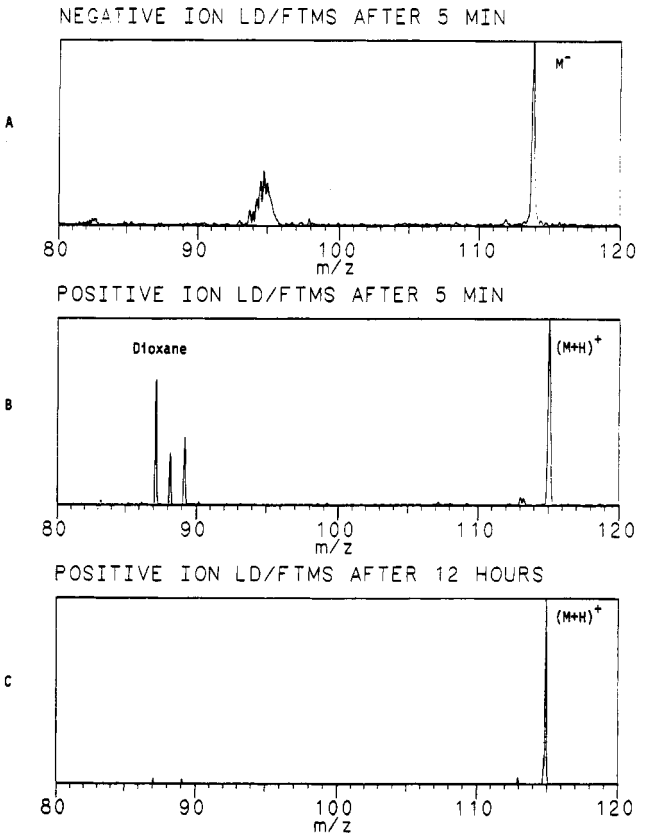


Figure 1.

lecular ion peaks for C_6Li_6 were obtained in both negative ion and positive ion modes. In the negative ion mode, m/z 114 $(C_6Li_6)^-$ dominated the spectrum (Figure 1a). In positive ion [chemical ionization (CI)] mode, m/z 115 $[(C_6Li_6+H)^+]$ dominated the spectrum (Figure 1b). After 12 h in vacuum, the 1,4-dioxane had been completely removed and the prominent mass in the positive ion spectrum was still m/z 115 (Figure 1c). These are the expected peaks for the compound in the respective ionization modes. The low resolution mass spectra do not exhibit the expected Li isotope patterns. Space charge conditions that exist in the high pressure regime used for the experiment are known to have a strong tendency under the space in LDI experiments for the neighboring peaks to colesce.[4] It appeared that the excess *tert*-butyllithium was also pumped off in the vacuum over time, leaving a gray-white material which was seen through a viewing port and is probably hexalithiobenzene. The white hexalithiobenzene reacted violently when exposed to air, yielding black decomposition products.

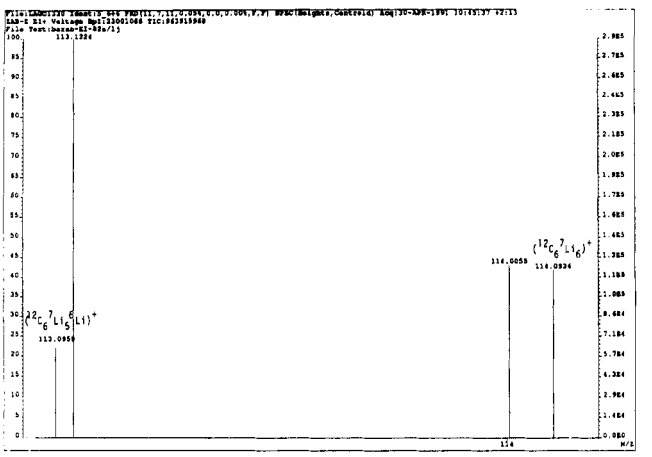


Figure 2. High resolution mass spectrum of C_6Li_6. The peak at 113.1324 comes from the coupling reaction of *tert*-butyl chloride and *tert*-butyllithium. The peak at 114.0055 is a fluorocarbon calibration peak.

High resolution spectra (Figure 2) were also run on a VG Model ZAB2-E high resolution mass spectrometer using electron impact. Peaks for $(C_6{}^7Li_6)^+$ and $(C_6{}^7Li_5{}^6Li)^+$ were observed with the following: ratios $(^{12}C_6{}^7Li_6)^+/(^{12}C_6{}^7Li_5{}^6Li)^+$ calcd 2.0868, obsd 2.047; masses $^{12}C_6{}^7Li_6$ calcd 114.093602, obsd 114.096027; $^{12}C_6{}^7Li_5{}^6Li$ calcd 113.095902, obsd 113.095146.

Hexalithiobenzene should be an exciting new reagent and both its structural chemistry and reaction chemistry should be extraordinarily interesting. With advance notice of our synthesis, Schaefer and Xie have forecast an extremely interesting planar structure for hexalithiobenzene gas-phase monomers with six lithium bridging the carbons, producing a star-like structure.[5]

One of the most surprising features of the new compound hexalithiobenzene is its relatively high vapor pressure. A conventional inlet was used to obtain the high resolution mass spectrum. This high vapor pressure may be indicative of the π system dominating the structure such that polymers, such as dimers, tetramers, and hexamers, may not be major structural features, especially in the gas phase. Perhaps the crystal structure, which is being sought,[6] will be similar to that of benzene rather than polymeric as are most organolithium compounds. If this is true perhaps the calculated molecular structure of Schaefer and Xie[5] will be seen, even in the crystal structure.

Acknowledgment. We are grateful to the National Science Foundation (CHE-9106482) and the Robert A. Welch Foundation (F-700) for support of this work.

(4) Francl, T. J.; Sherman, M. G.; Hunter, R. L.; Locke, M. J.; Bowers, W. D.; McIver, R. T., Jr. *Int. J. Mass Spectrum Ion Proc.* **1983**, *54*, 189.

(5) Schaefer, H. F., III; Xie, Y. *Chem. Phys. Lett.* **1991**, *179*, 563.

(6) In collaboration with the George Sheldrick group, Göttingen.

N-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole: A Promising Compound for Synthesis of Chiral Nonracemic Hydroxylated Pyrrolidine Derivatives

Giovanni Casiraghi,* Gloria Rassu,* Pietro Spanu, and Luigi Pinna

Dipartimento di Chimica dell'Università and Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici del CNR, Via Vienna, 2, I-07100 Sassari, Italy

Received December 3, 1991 (Revised Manuscript Received April 13, 1992)

Summary: *N*-*t*-Boc-2-(*tert*-butyldimethylsiloxy)pyrrole has been synthesized from pyrrole and used to prepare enantiomerically pure pyrrolinones **5**, **6**, **15**, and **16** and polyhydroxylated pyrrolidinones of type **11** and **12**.

The discovery that carbohydrates in which the ring

0022-3263/92/1957-3760$03.00/0

Chart I

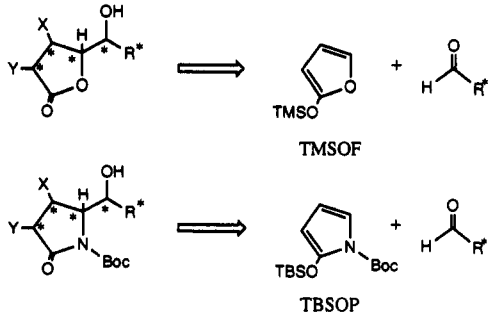
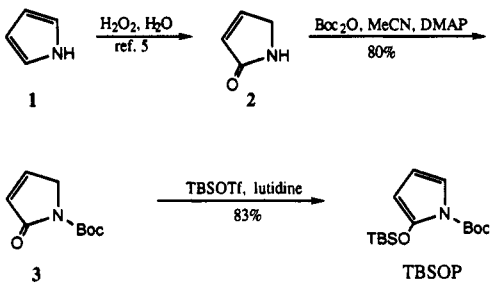


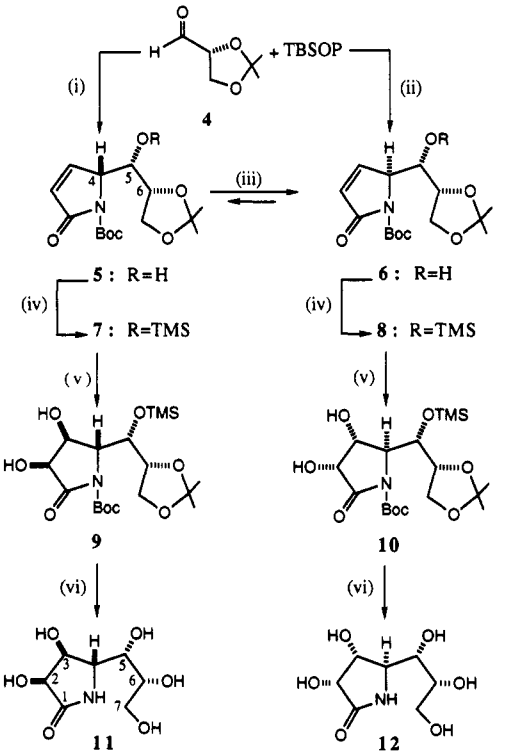
Chart II



oxygen atom has been replaced by an imino group are powerful glycosidase inhibitors[1] and the perception that such inhibition might offer a strategy for preparing novel antiviral chemotherapeutic agents[2] has led to development of many routes to such compounds.[3] Paralleling our exploitation of 2-(trimethylsiloxy)furan (TMSOF) as a key reagent in the synthesis of complex monosaccharides,[4] we reasoned that a nitrogen analogue of TMSOF [e.g. *N*-*t*-Boc-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP)] should be a promising reactant for application in azasugar synthesis. We now report preliminary results demonstrating that TBSOP is indeed a powerful compound for entry into homochiral hydroxylated pyrrolidine derivatives (Chart I).

In preparing TBSOP, we took advantage of the efficient protocol of Bocchi[5] for the oxidation of pyrrole (1) to Δ^3-pyrrolinone (2) using hydrogen peroxide under neutral conditions. Pyrrolinone 2 was then protected as *N*-*t*-Boc derivative 3 by treatment with Boc_2O in acetonitrile in the presence of (*N*,*N*-dimethylamino)pyridine (DMAP)[6,7] and finally transformed into stable TBSOP by reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate in CH_2Cl_2 in the presence of 2,6-lutidine.[8] Working on a 10-g

Scheme I. Synthesis of Pyrrolidinones 11 and 12[a]



[a] Conditions: (i) 1.5 equiv of $SnCl_4$, Et_2O, −85 °C; (ii) 1.0 equiv of BF_3 etherate, Et_2O, −85 °C; (iii) Et_3N, CH_2Cl_2, DMAP, 20 °C; (iv) TMSCl, pyridine, −30 °C; (v) $KMnO_4$, DCH-18-crown-6, CH_2Cl_2, −30 °C to −10 °C; (vi) 0.2 M CF_3COOH in CH_2Cl_2, 20 °C, then SiO_2 (EtOAc/MeOH 1:1).

(1) Paulsen, H.; Todt, K. *Adv. Carbohydr. Chem.* **1968**, *23*, 115. Elbein, A. D. *Crit. Rev. Biochem.* **1984**, *16*, 21. Sinnott, M. L. In *Enzyme Mechanisms*; Pike, M. I., Williams, A. D., Eds.; Royal Society of Chemistry: London, 1987; p 259. Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171. Fleet, G. W. J. *Chem. Brit.* **1989**, 287. Fellows, L. E. *New Scientist* **1989**, *123*, 45.

(2) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229. Tyms, A. S.; Berrie, E. M.; Ryder, T. A.; Nash, R. J.; Hegarty, M. P.; Taylor, D. L.; Mobberley, M. A.; Davis, J. H.; Bell, E. A.; Jeffries, D. J.; Taylor-Robinson, D.; Fellows, L. E. *Lancet* **1987**, *ii*, 1025. Sunkara, P. S.; Taylor, D. L.; Kang, M. S.; Bowlin, T. L.; Liu, P. S.; Tyms, A. S.; Sjoerdsma, A. *Lancet* **1989**, *i*, 1206. Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128. Fellows, L.; Nash, R. PCT Int. Appl. WO 90 12,014; *Chem. Abstr.* **1991**, *114*, 143777s.

(3) Chemical methods: Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100. Liu, P. S.; Rogers, R. S.; Kang, M. S.; Sunkara, S. *Tetrahedron Lett.* **1991**, *32*, 5853. Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Bruce, I.; Al Daher, S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1991**, *47*, 131. Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517. Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513. Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res.* **1987**, *167*, 305. Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137. Hamana, H.; Ikota, N.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5494. Liotta, L. J.; Lee, J.; Ganem, B. *Tetrahedron* **1991**, *47*, 2433. Wehner, V.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169. Jäger, V.; Hümmer, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1171. Burgess, K.; Hendeson, I. *Tetrahedron Lett.* **1990**, *31*, 6949. Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. I* **1990**, 699. Robina, I.; Gearing, R. P.; Buchanan, J. G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans I* **1990**, 2622. Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron* **1991**, *47*, 7635. Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. Reymond, J.-L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128. Burgess, K.; Chaplin, D. A.; Henderson, I.; Pan, Y. T.; Elbein, A. D. *J. Org. Chem.* **1992**, *57*, 1103. Yoon, H.; King, S. B.; Ganem, B. *Tetrahedron Lett.* **1991**, *32*, 7199. Enzymatic methods: Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280. Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849. Straub, A.; Effemberger, F.; Fisher, P. *J. Org. Chem.* **1990**, *55*, 3926. von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F., III; Pederson, R. L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924. Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187. Chen, L.; Dumas, D. P.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 741.

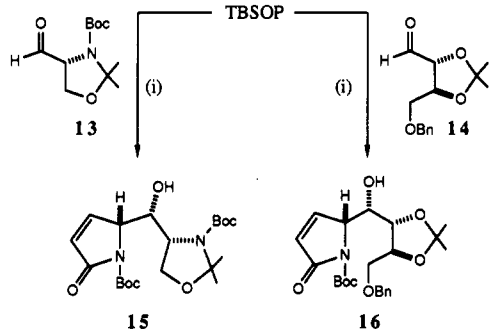
(4) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1990**, *55*, 2565. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 2135. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 6522. Rassu, G.; Spanu, P.; Casiraghi, G.; Pinna, L. *Tetrahedron* **1991**, *47*, 8025. Rassu, G.; Pinna, L.; Spanu, P.; Culeddu, N.; Casiraghi, G.; Gasparri Fava, G.; Belicchi Ferrari, M.; Pelosi, G. *Tetrahedron* **1992**, *48*, 727.

(5) Bocchi, V.; Chierici, L.; Gardini, G. P.; Mondelli, R. *Tetrahedron* **1970**, *26*, 4073.

(6) Effenberger, F.; Müller, W.; Keller, R.; Wild, W.; Ziegler, T. *J. Org. Chem.* **1990**, *55*, 3064.

(7) Treatment of **2** with the usual Boc_2O/Et_3N system in CH_2Cl_2 resulted in formation of *N*,*O*-bis(*tert*-butoxycarbonyl)-2-hydroxypyrrole. Treatment of **2** with TMSCl in Et_3N afforded *N*,*O*-bis(trimethylsilyl)-2-hydroxypyrrole; when this compound was reacted with **4**, unselective N-alkylation occurred.

Scheme II. Synthesis of Pyrrolinones 15 and 16[a]



[a] Conditions: (i) 1.5 equiv of $SnCl_4$, Et_2O, −85 °C.

scale, TBSOP can be cleanly prepared in 66% yield for the two steps. (Chart II).[9]

The synthetic potential of this new reagent was explored next, choosing pyrrolinones **5**, **6**, **15**, and **16** and pyrrolidinones **11** and **12** as first objectives. Treatment of 2,3-*O*-isopropylidene-D-glyceraldehyde (**4**) in anhydrous Et_2O with TBSOP at −85 °C in the presence of 1.5 equiv of $SnCl_4$ gave crystalline D-arabino-configurated α,β-unsaturated γ-lactam **5** *as the sole reaction product* in 80% isolated yield (Scheme I).

Extending the scope of the methodology, when **4** was allowed to react at the same temperature with TBSOP in Et_2O in the presence of 1.0 equiv of BF_3 etherate, reversal of stereochemistry occurred, resulting in predominant formation of crystalline D-ribo-configurated epimer **6** (70% yield), along with less than 20% of **5**.[10,11] Also, clean and almost quantitative epimerization at C-4 was observed when lactam **5** was treated with Et_3N in CH_2Cl_2 at room temperature in the presence of DMAP.[12] This procedure provided a good alternative preparation of the thermodynamically more stable D-ribo lactam **6**. Single-crystal X-ray analyses were performed on both **5** and **6**, firmly establishing their stereostructures.[13]

Next, after protection of the free C-5 OHs in **5** and **6** as TMS ethers (TMSCl, pyridine 90%), the double bond of both epimers **7** and **8** was selectively dihydroxylated according to a well-known procedure using solid $KMnO_4$ in CH_2Cl_2 in the presence of dicyclohexano-18-crown-6 ether,[4,14] producing diastereomeric pyrrolidinones **9** and **10** in 50% isolated yield. The stereochemistry of hydroxylation of the double bond in **7** and **8** was strictly governed by the presence of a bulky substituent at C-4 which hinders the syn face of the lactam ring. The D-glycero-D-talo and D-glycero-D-allo configurations in **9** and **10** were confirmed by the observation of ^1H NOED enhancements (ca. 8%) between H-2 and H-3, which thus have a cis relationship, and the absence of any NOE between H-2 and H-4.

Finally, the acetonide, TMS, and Boc protecting groups in **9** and **10** were cleanly removed by treatment with 0.2 M trifluoroacetic acid in CH_2Cl_2 at room temperature giving, after silica-gel chromatography (EtOAc/MeOH 1:1), the free lactams **11** and **12** in 91% and 93% yields, respectively. The overall yields for the sequences were 33% for **11** and 30% for **12**.

The synthesis of pyrrolinone templates **15** and **16** via $SnCl_4$-assisted coupling of TBSOP with protected D-serinal **13**[15] and L-threose **14**[16] was undertaken to further demonstrate application of this chemistry (Scheme II).

Much to our delight, the expected compounds were obtained both in excellent yield (75% and 91%) and with complete diastereoselectivity, following exactly the synthetic protocol described for **5**.

Since isopropylidene-protected L-glyceraldehyde *ent*-**4**,[17] L-serinal *ent*-**13**,[15] and D-threose *ent*-**14**[16] are readily available, *ent*-**5**, *ent*-**15**, *ent*-**16**, and *ent*-**11** were also synthesized, paralleling the described protocols. These materials showed ^1H and ^{13}C NMR spectral characteristics identical to those of compounds **5**, **15**, **16**, and **11**, while the same magnitude but opposite sign was observed for the optical rotations.

Extensions of this TBSOP-based method to precursors other than aldehydes **4**, **15**, and **16** and possible applications to the synthesis of biologically important pyrrolidine, pyrrolizidine, and indolizidine derivatives are currently in progress.[18]

Acknowledgment. We thank the Consiglio Nazionale delle Ricerche, Italy, and Regione Sardegna for their generous support of this work.

(8) Treatment of **3** with TMSCl in Et_3N gave rise to quite unstable *N*-(*tert*-butoxycarbonyl)-2-(trimethylsiloxy)pyrrole; this reagent failed to give appreciable coupling reactions with **4**.

(9) **Preparation of TBSOP.** (For more details, see the supplementary material). To a room temperature solution of **2** (8.3 g, 100 mmol) in CH_3CN (75 mL), di-*tert*-butyl dicarbonate (21.6 g, 100 mmol) and DMAP (600 mg) were added under stirring. The mixture was stirred at ambient temperature for 30 min and then evaporated in vacuo. The crude mixture was purified by flash chromatography on SiO_2 (8:2 EtOAc/hexane) to furnish 14.5 g (80%) of N-(*tert*-butoxycarbonyl)pyrrol-2(5*H*)-one (**3**) as a white solid. To a solution of **3** (14.5 g, 79 mmol) in anhydrous CH_2Cl_2 (60 mL) were added 2,6-lutidine (25.3 g, 236 mmol) and TBSOTf (23.2 g, 88 mmol) under argon at room temperature. After the reaction mixture was stirred for 30 min, the solvent was evaporated and the residue flash chromatographed on silica gel eluting with 1:1 EtOAc/hexane to furnish 19.6 g (83%, 66% based on **2**) of TBSOP as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, 1 H, J = 3.9, 2.1 Hz, H-4), 5.86 (t, 1 H, J = 3.7 Hz, H-3), 5.2 (dd, 1 H, J = 3.6, 2.1 Hz, H-2), 1.54 (s, 9 H, *t*-Bu), 0.97 (s, 9 H, *t*-Bu), 0.20 (s, 6 H, Me_2); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 148.20, 145.50, 112.98, 108.00, 92.35, 82.67, 28.03, 25.70, 18.33, −4.87.

(10) For remarkable examples of how the stereochemistry of Lewis acid-mediated nucleophilic additions to α-alkoxy aldehyde derivatives may be altered by changing the nature of the metal promoter, see, for example: McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 5010 and references cited herein.

(11) The 5,6-anti (erythro) selectivity observed in the $SnCl_4$-promoted homologation of **4** into **5** was expected according to the general sequence via the β-chelation-controlled addition of carbon nucleophiles to α,β-dialkoxy aldehydes. The 4,5-threo stereoselectivity can be rationalized by assuming exclusive endo approach of the reaction partners in the addition step. See, for example: Honda, T.; Hayakawa, T.; Kondoh, H.; Okuyama, A.; Tsubuki, M. *Chem. Lett.* **1991**, 1861. Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795.

(12) Base-catalyzed epimerization at C-4 is a general phenomenon in the analogous γ-lactone series; see ref 4.

(13) Compound **5**: colorless prisms (CH_2Cl_2/hexane), mp 138–140 °C; $[\alpha]_D$ +197.6° (*c* 0.83, $CHCl_3$). Compound **6**: colorless needles (Et_2O/hexane), mp 118–120 °C; $[\alpha]_D$ −120.0° (*c* 1.15, $CHCl_3$). Details of the crystal structures for **5** and **6** will be published elsewhere: Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L.; Gasparri Fava, G.; Belicchi Ferrari, M.; Pelosi, G. Manuscript in preparation.

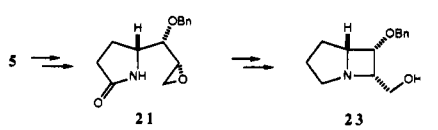
(14) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.

(15) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(16) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929.

(17) Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814. Hefele, B.; Jäger, V. *Justus Liebigs Ann. Chem.* **1987**, 85. Hubschwerlen, C. *Synthesis* **1986**, 962.

(18) Subsequent investigations in this laboratory have shown that the bicyclic "azetizidine" **23**, a quite unusual ring-contracted necine analog, can be synthesized in 36% overall yield by starting with **5**, via a sequence involving, in the key step, selective 4-exo annulation of terminal epoxide **21** (Scheme III, experimental procedures, synthetic and spectral data, see the supplementary material).



Registry No. 1, 109-97-7; 2, 4031-15-6; 3, 141293-14-3; 4, 15186-48-8; 5, 141293-15-4; *ent*-5, 141393-87-5; 6, 141393-83-1; 7, 141293-16-5; 8, 141393-84-2; 9, 141293-17-6; 10, 141393-85-3; 11, 141293-18-7; *ent*-11, 141393-90-0; 12, 141393-86-4; 13, 95715-87-0; *ent*-13, 102308-32-7; 14, 81028-12-8; *ent*-14, 81801-09-4; 15, 141293-19-8; *ent*-15, 141393-88-6; 16, 141293-20-1; *ent*-16, 141393-89-7; 17, 141293-21-2; 18, 141293-22-3; 19, 141293-23-4; 20, 141293-24-5; 21, 141293-25-6; 22, 141293-26-7; 23, 141293-27-8; TBSOP, 141293-28-9.

Supplementary Material Available: Detailed synthetic procedures and physical data for all the described compounds and Scheme III illustrating the synthesis of 23 (10 pages). Ordering information is given on any current masthead page.

Molecular Scaffolds I: Intramolecular Hydrogen Bonding in a Family of Di- and Triureas

James S. Nowick,* Noel A. Powell, Eduardo J. Martinez, Eric M. Smith, and Glenn Noronha

Department of Chemistry, University of California, Irvine, California 92717

Received May 5, 1992

Summary: Di- and triurea derivatives 1 can be prepared by an iterative procedure and are found to exist in intramolecularly hydrogen bonded 10-membered ring conformations, in which substituents R_1 and R_2 and hydrogen bonding control the direction of the urea carbonyl groups.

Hydrogen bonding is a central feature of intra- and intermolecular interactions in molecular recognition,[1] crystal packing,[2,3] and the folding of small di- and triamides in organic solvents.[4,5] In proteins, hydrogen bonding plays a fundamental role in the structure of β-sheets, α-helices, and some β-turns.[6,7] As part of a program of research aimed at developing small molecules as molecular receptors and peptide conformational templates,[8,9] we are studying intramolecular hydrogen bonding in families of oligoureas. In this paper, we report synthetic and spectroscopic studies of di- and triurea derivatives of 1,3-diaminopropane and *N*-(3-aminopropyl)-1,3-propanediamine. We find that intramolecular hydrogen bonding and substituents R_1 and R_2 provide extensive conformational control in di- and triureas of the general structure 1 (n = 2, 3).

Table I. Spectroscopic Properties of NH Groups in Compounds 1-3 at 295 K

compd	IR[a] (cm^{-1})	^1H NMR[b] (ppm)	% intramolec H bonding
1a	3306, 3463	6.88	50[c]
1b	3296, 3426 3455 (weak shoulder)	8.49, 6.17	85[d]
1c	3293, 3426, 3455 (weak shoulder)	8.67, 8.14, 6.17	95[c], 75[c]
1d	3284, 3429	5.61, 4.56	35[c]
1e	3294, 3428	5.40 (Val), 4.58 (Phe)	25[c]
2a	3464	6.24	
2b	3428	6.08	
2c	3427	6.16	
2d	3452	4.72	
2e	3424	4.62	
2f	3452	4.82	
3	3301, 3459 (weak)	8.37	85[d]

[a] IR spectra were recorded at 10 mM in $CHCl_3$ solution. [b] ^1H NMR spectra were recorded at 1.0 mM in $CDCl_3$ solution. [c] Approximate value based upon chemical shift of NH resonance. [d] Value determined by integration of infrared N-H stretch (see text).

Ureas **1b-1e** were prepared efficiently by an *iterative procedure* involving three steps: (1) conjugate addition of a primary amine to acrylonitrile;[10] (2) reaction of the resulting secondary amino group with an isocyanate; and (3) reduction of the nitrile group to generate a primary amine (eq 1).[10,11] This procedure permits the preparation

(1) (a) Hamilton, A. D.; Van Engen, D.; *J. Am. Chem. Soc.* **1987**, *109*, 5035. (b) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. (c) Rebek, J., Jr.; Askew, B.; Ballester, P.; Buhr, C.; Costero, A.; Jones, S.; Williams, K. *J. Am. Chem. Soc.* **1987**, *109*, 6866. (d) Aoyama, Y.; Tanaka, Y.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 634. (e) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. (f) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054. (g) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055. (h) Seto, C. T.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 6409. (i) Garcia-Tellado, F.; Goswami, S.; Chang, S.-K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393. (j) Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407. (k) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184. (l) Friedrichsen, B. P.; Powell, D. R.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 8931. (m) Neder, K. M.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 9412. (n) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201. (o) Aoyama, Y.; Asakawa, M.; Matsui, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 6233. (p) Ogoshi, H.; Hatakeyama, H.; Kotani, J.; Kawashima, A.; Kuroda, Y. *J. Am. Chem. Soc.* **1991**, *113*, 8181. (q) Doig, A. J.; Williams, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 338.

(2) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (b) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601.

(3) (a) Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787. (b) Brienne, M.-J.; Gabard, J.; Lehn, J.-M.; Stibor, I. *J. Chem. Soc., Chem. Commun.* **1989**, 1868. (c) Lehn, J.-M.; Mascal, M.; DeCian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 479. (d) Zerkowski, J. A.; Seto, C. H.; Wierda, D. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 9025. (e) Gallant, M.; Viet, M. T. P.; Wuest, J. D. *J. Org. Chem.* **1991**, *56*, 2284. (f) Garcia-Tellado, F.; Geib, S. J.; Goswami, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 9265.

(4) (a) Gellman, S. H.; Adams, B. R. *Tetrahedron Lett.* **1989**, *30*, 3381. (b) Gellman, S. H.; Adams, B. R.; Dado, G. P. *J. Am. Chem. Soc.* **1990**, *112*, 460. (c) Dado, G. P.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 8630. (d) Gellman, S. H.; Dado, G. P.; Laing, G.-B.; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164. (e) Laing, G.-B.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994. (f) Gellman, S. H.; Dado, G. P. *Tetrahedron Lett.* **1991**, *32*, 7377. (g) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 3138.

(5) (a) Smith, D. A.; Vijayakumar, S. *Tetrahedron Lett.* **1991**, *32*, 3613. (b) Smith, D. A.; Vijayakumar, S. *Tetrahedron Lett.* **1991**, *32*, 3617. (c) Novoa, J. J.; Whangbo, M.-H. *J. Am. Chem. Soc.* **1991**, *113*, 9017.

(6) (a) Richardson, J. S. *Adv. Protein Chem.* **1981**, *34*, 167. (b) Baker, E. N.; Hubbard, R. E. *Prog. Biophys. Molec. Biol.* **1984**, *44*, 97. (c) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1. (d) *Prediction of Protein Structure and the Principles of Protein Conformation*; Fasman, G. D., Ed.; Plenum: New York, 1989.

(7) Abbadi, A.; Mcharfi, M.; Aubry, A.; Prêmilat, S.; Boussard, G.; Marraud, M. *J. Am. Chem. Soc.* **1991**, *113*, 2729.

(8) (a) Kemp, D. S. *Trends Biotechnol.* **1990**, *8*, 249. (b) Hölzemann, G. *Kontakte* **1991**, 3. (c) Hölzemann, G. *Kontakte* **1991**, 55.

(9) (a) Feigel, M. *J. Am. Chem. Soc.* **1986**, *108*, 181. (b) Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans 1* **1986**, 1231. (c) Kahn, M.; Wilke, S.; Chen, B.; Fujita, K. *J. Am. Chem. Soc.* **1988**, *110*, 1638. (d) Kemp, D. S.; Stites, W. E. *Tetrahedron Lett.* **1988**, *29*, 5057. (e) Kemp, D. S. Bowen, B. R. *Tetrahedron Lett.* **1988**, *29*, 5077. (f) Kemp, D. S.; Bowen, B. R. *Tetrahedron Lett.* **1988**, *29*, 5081. (g) Feigel, M. *Liebigs Ann. Chem.* **1989**, 459. (h) Brandmeier, V.; Feigel, M. *Tetrahedron* **1989**, *45*, 1365. (i) Olson, G. L.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 323. (j) Diaz, H.; Kelly, J. W. *Tetrahedron Lett.* **1991**, *32*, 5725. (k) Boger, D. L.; Myers, J. B., Jr. *J. Org. Chem.* **1991**, *56*, 5385.

(10) (a) Bergeron, R. J.; Burton, P. S.; McGovern, K. A.; Kline, S. J. *Synthesis*, **1981**, 732. (b) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Phillips, D.; Rosnack, K. J.; Saccomano, N. A.; Stroh, J. G.; Volkmann, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6696.

(11) (a) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555. (b) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801. (c) Osby, J. O.; Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67.

0022-3263/92/1957-3763$03.00/0