Role of a Protected Vicinal Diol Controller in Intramolecular [3 + 2] Cycloaddition Reactions of Chiral Acyclic Alkenyl Nitrones: Syntheses of Enantiomerically Pure Tetrasubstituted Cyclobutylamines

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Summary: Intramolecular cycloaddition reactions of C_5-chain acyclic alkenyl nitrones such as *N*-[(2*S*,3*S*)-2,3-bis-(*tert*-butyldimethylsiloxy)-4-pentenylidene]benzylamine *N*-oxide and its C(5)-substituted derivatives lead to fused isoxazolidines (bicyclo[3.2.0] framework) with very high diastereomeric excess. These isoxazolidines can readily be converted to optically active tetrasubstituted cyclobutylamines.

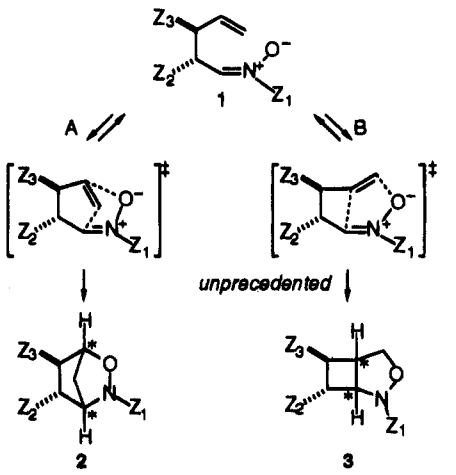
One of the most simple and convenient methods to prepare 1-amino-3-hydroxy backbones from carbon–carbon double bonds while appending a carbon chain of one or more units to them is the well-known nitrone–olefin cycloaddition reaction.[1] Although there have been countless variations of this reaction, only limited reports of its use for the construction of absolute configurations have appeared so far.[2,3] One example is the reaction of the C_6-chain alkenyl nitrone (*Z*)-D-xylonitrone, derived from D-glucose, which leads to a bicyclo[3.3.0]-type isoxazolidine (fused mode) with >99% de.[2] In contrast, the C_5-chain alkenyl nitrone **1** affords bicyclo[2.2.1] cycloadduct **2** (bridged mode; route A in Scheme 1) with almost no selectivity (1:1) with regard to the asterisked stereocenters.[3] Our recent work on processes involving the protected vicinal diol controller strategy,[4] including intermolecular nitrone–olefin [3 + 2] cycloaddition processes,[5] encouraged an effort to realize route B (Scheme 1) employing alkenyl nitrones **1** bearing a vicinal diol controller (Z_2 = Z_3 = TBDMSO).

To our delight, the effect of the controller directs a previously unknown regiochemical preference for route B. Manipulation of the cycloadducts (**3**) generates tetrasubstituted chiral cyclobutylamines which are otherwise difficult to access. In addition, the present work supports the concerted nature of the nitrone–olefin [3 + 2] cycloaddition reaction.

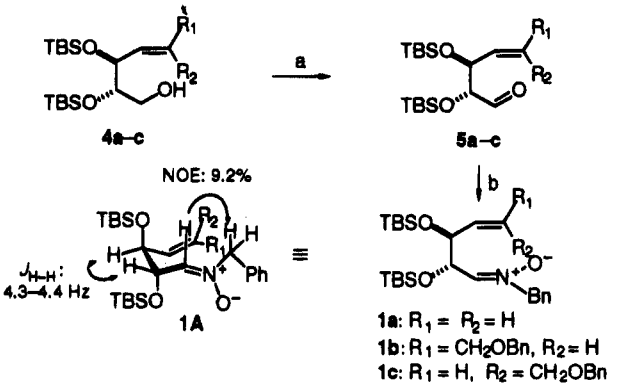
Swern oxidation of alcohols **4**[6] gives enals **5**, which are condensed with *N*-benzylhydroxylamine to afford desired alkenyl nitrones **1**[7] (≥80% yield overall, Scheme 2). The geometry of the nitrone moiety in **1** was shown to be *Z* on the basis of an NOE (9.2%) observed for the benzylic protons on irradiation of the olefinic proton of the iminium unit. Furthermore, the coupling constant (4.3–4.4 Hz) observed between the protons of the protected vicinal diol unit clearly suggests that the TBDMSO groups are anti as illustrated (**1A**).[4]

Heating a solution of vinyl nitrone **1a** in benzene at 80 °C for 12 h gives cycloadduct **6a** (62% yield) and recovered **1a** (37%) as an equilibrium mixture. The reaction does not progress upon additional heating. When recovered **1a** was subjected to the same reaction conditions, the same product ratio was obtained. These results suggest a thermal equilibrium[8] between **1a** and **6a**.

Scheme 1



Scheme 2[a]



[a] Key: (a) Swern oxidation; (b) BnNHOH/CH_2Cl_2/40 °C, 1 h.

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(1) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598 and 633–645. (b) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403–419. (c) Padwa, A. *Ibid.* **1976**, *15*, 123–136. (d) Oppolzer, W. *Ibid.* **1977**, *16*, 10–23. (e) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403. (f) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1–173. (g) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press; Oxford, 1990; pp 269–331. (h) Padwa, A.; Schoffstall, A. M. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press, Inc.: Greenwich, 1990; Vol. 2, pp 1–89.

(2) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2411–2431.

(3) Hwu, J. R.; Robl, J. A.; Gilbert, B. A. *J. Am. Chem. Soc.* **1992**, *114*, 3125–3126.

(4) (a) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535. (b) Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T. *J. Org. Chem.* **1993**, *58*, 6292–6302 and references cited therein.

(5) (a) Saito, S.; Ishikawa, T.; Moriwake, T. *Synlett* **1994**, 279–281. (b) Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282–284.

(6) Prepared from 1-*O*-(*p*-methoxybenzyl)-2,3-*O*-isopropylidene-L-threitol via five steps: (1) oxidation, (2) Wittig or Horner–Emmons olefination, (3) deprotection of the acetonide group, (4) protection of the resulting diol with a *tert*-butyldimethylsilyl group, and (5) deprotection of the *p*-methoxybenzyl group. The experimental details are given in the supplementary material.

(7) Spectroscopic [NMR (^1H, ^{13}C, ^1H-COSY, ^1H–^{13}C-HETCOR, and NOE in some cases), IR, and HRMS] and analytical data for all new compounds were satisfactory; these data are available as supplementary material.

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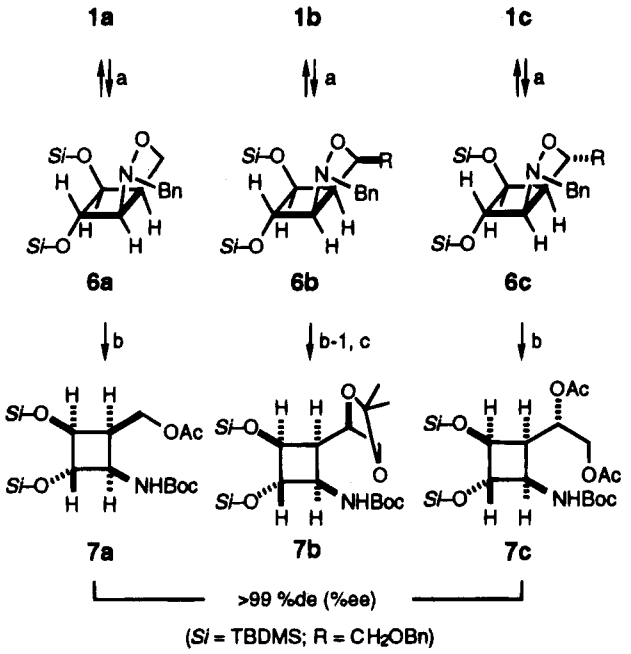
Scheme 3[a]

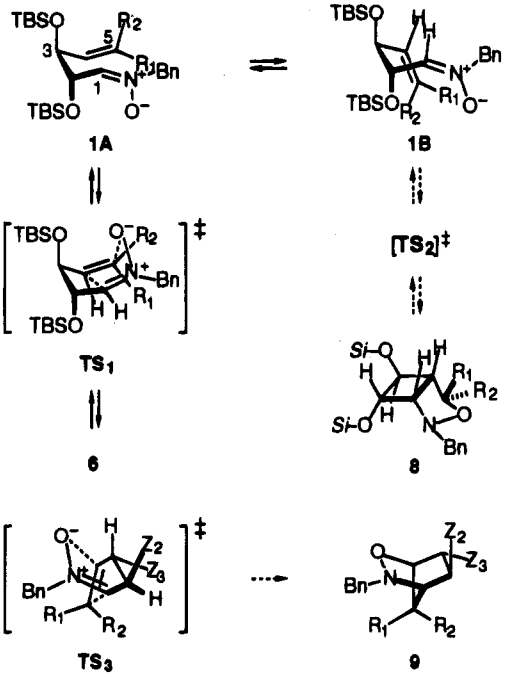


[a] Key: (a) C_6H_6/80 °C, 12 h; (b) (1) Pd–C/EtOAc/Boc_2O/rt, (2) Ac_2O/DMAP/Et_3N/CH_2Cl_2/rt; (c) $(MeO)_2CMe_2$/THF/TsOH/rt, 1 h.

A one-pot, two-stage reaction involving reductive cleavage of the isoxazolidine ring of **6a** and *N-tert*-butoxycarbonylation[9] of the resulting amino group affords chiral cyclobutylamine derivative **7a**[7] (87% yield overall) after acetylation. Careful NMR analyses, in particular, NOE experiments,[10] indicate the absolute structure of **7a** is that depicted in Scheme 3. To the best of our knowledge, this is the first example of the formation of a cyclobutane backbone from acyclic alkenyl nitrones through an intramolecular thermal cycloaddition process[11] and provides a novel method for the synthesis of chiral substituted cyclobutylamines.[12]

In addition, when heated at 80 °C in benzene, the nitrones bearing an (*E*)- or (*Z*)-alkenyl group (**1b** or **1c**) yield an equilibrium mixture of **1b** (54%) and cycloadduct **6b** (36%) or **1c** (52%) and cycloadduct **6c** (34%), respectively. These cycloadducts possess the same absolute configuration as **6a** for the stereogenic centers in the ring, as determined by NOE experiments on the corresponding cyclobutylamines **7b** and **7c**[7,13] (87% yield for both).

Scheme 4



The remarkable stereocontrol over all the stereogenic centers observed for **1a–c** suggests transition state structure $\mathbf{TS_1}$, which leads to **6a–6c**, provided the conformational rigidity (**1A**) of the controller unit remains intact throughout the course of the reaction. $\mathbf{TS_1}$ is reached as rotation around the C(1)–C(2) bond of **1A** occurs (Scheme 4). Another possible ground-state conformation, **1B**, arising from rotation around the C(3)–C(4) bond of **1A**, suffers from severe steric congestion of the alkenyl group and the TBDMSO group at C(2). The formation of cycloadduct **8**, therefore, was not realized. If rotation around the C(2)–C(3) bond were unrestricted, a transition state like $\mathbf{TS_3}$ would result, and $\mathbf{TS_3}$ is presumably more stable than $\mathbf{TS_1}$ or $\mathbf{TS_2}$ because of its bicyclo[2.2.1] array. $\mathbf{TS_3}$ would afford cycloadduct **9**, which was also not observed. Thus, the evidence indicates that the conformation of **1** is primarily governed by the controller unit to be **1A** in which an allylic conformation should be considered.[4b] The reaction has, therefore, provided high fidelity between the ground-state conformation of an acyclic substrate and the regiochemistry of an intramolecular [3 + 2] cycloaddition.

Cycloadducts **6b** and **6c** were heated in benzene under reflux for 6 h. The equilibrium mixture from each reaction was chromatographed to yield nitrones that were identical to starting nitrones **1b** or **1c**, respectively, in all respects: the olefinic geometry, nitrone geometry, and optical purity of these nitrones were perfectly retained. These findings suggest that no crossover processes (dotted arrows in Scheme 5) occurred. In particular, the lack of interconversion between the *Z* and *E* olefinic geometries indicates that a biradical mechanism is highly unlikely, although an intermediate that collapses faster than bond rotation cannot be ruled out. These facts, in any event, support the concerted nature of this reaction.

(8) Isoxazolidines have been known to undergo interconversion leading to their stereoisomers on heating. Several reports have, therefore, emphasized that product distributions for nitrone–olefin cycloaddition reactions should be rationalized by taking into account the reversibility of the reaction (a retro-1,3-dipolar cycloaddition process): (a) Delpierre, G. R.; Lamchen, M. *J. Chem. Soc.* **1963**, 4963–4701. (b) LeBel, N. A.; Lajiness, T. A. *Tetrahedron Lett.* **1966**, 2173–2176. (c) LeBel, N. A.; Banucci, E. G. *J. Org. Chem.* **1971**, *36*, 2440–2448. (d) Bianchi, G.; de Micheli, C.; Gandolfi, R. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 721–738. To the best of our knowledge, however, nobody has succeeded in obtaining starting nitrones by heating isoxazolidines.

(9) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837–838.

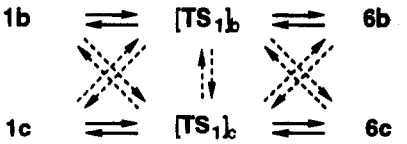
(10) The silyl protecting groups of **7a** were replaced with acetyl groups for the NOE study (see the supplementary material).

(11) For representative intermolecular [2 + 2] cycloaddition reactions leading to substituted cyclobutanes, see: (a) Slusarchyk, W. A.; Young, M. G.; Bisacchi, D. S.; Hockstein, D. R.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453–6456. (b) Jacobs, G. A.; Tino, J. A.; Zahler, R. *Ibid.* **1989**, *30*, 6955–6958. (c) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869–8885 and the references cited therein. For intramolecular [2 + 2] cycloaddition reactions, see; Chen, L.; Ghosez, L. *Tetrahedron Lett.* **1990**, *31*, 4467–4470 and references cited therein.

(12) The pharmacological activity of this class of compounds has drawn significant interest recently. See, for instance: Maruyama, T.; Sato, Y.; Horii, T.; Shiota, H.; Nitta, K.; Shirasaka, T.; Mitsuya, T.; Honjyo, M. *Chem. Pharm. Bull.* **1990**, *38*, 2719–2725. For a review, see: Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745–1768 and references cited therein.

(13) These derivatives were highly convenient for NOE experiments because all the NMR signals were distinct. Oxidative cleavage of the diol moieties of both **7b** and **7c** and ensuing reduction and acetylation afforded products identical with **7a** in all respects.

Scheme 5



The crucial role of the protected vicinal diol controller is to direct the π-faces (C=C and C=N) of **1** in such a way that they overlap each other in a fused mode via transition state $\mathbf{TS_1}$, in which the TBDMSO groups are anti to each other. Accordingly, the barriers for rotational interconversion around the C(2)—C(3) bond are large enough to prevent the reaction from going through other transition states, such as $\mathbf{TS_2}$.[14]

In summary, the chemistry presented here for the synthesis of tetrasubstituted cyclobutylamines has been enabled by the protected vicinal diol controller. The recovered alkenyl nitrones are easily separated from the cycloadducts and can be recycled. Isoxazolidines **6a–c** are stable enough to be purified by simple column chromatography and can be further elaborated to title compounds **7a–c** in high yield.

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Supplementary Material Available: Synthetic procedures, spectroscopic data, and copies of NMR spectra (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) The question may be raised as to whether we can rationalize the unusual course of the reactions on the basis of ground-state conformations in violation of the Curtin–Hammett principle. We have already discussed this issue in ref 4b.