of 1:1.4, respectively.[11] The intermediate enamido diene **6**[12] could be isolated if the reaction temperature was decreased. Hydride reduction ($LiAlH_4$, Et_2O, 25 °C, 2 h) of the mixture of lactams **7a** and **7b** produced the corresponding tertiary amines **8a** and **8b** (85%) which could be readily separated by preparative HPLC [hexane/EtOAc/Et_3N, (85:14:1), Porasil A].

Reaction of the tertiary amine **8a** with ethyl chloroformate[13] in refluxing benzene (24 h) in the presence of $NaHCO_3$ provided the urethane **9a** which underwent facile cyclization ($POCl_3$, 90 °C, 18 h) to give the unsaturated lactam **2** (mp 194–195 °C, lit.[6a] mp 196–198 °C, mmp 194–195 °C) in 78% overall yield, thereby completing the formal total synthesis of lycorine (1). The $\Delta^{2,3}$-7-oxo-α-lycorane (**2**) thus obtained was identical (^1H NMR, IR, low-resolution mass spectra, TLC) with an authentic sample.[14] Further verification of the structure of the lactam **2** was obtained by catalytic hydrogenation (HOAc, Pt, H_2, 25 °C, 4 h) to give 7-oxo-α-lycorane (**11a**) (mp 168–169 °C, lit.[3e] mp 169–171 °C) followed by hydride reduction [$LiAlH_4$, Et_2O/THF (1:1), 25 °C, 3 h] of **11a** to produce α-lycorane (**12a**) (mp 92–94 °C; lit. mp 93–94 °C,[7a] 95.5–97 °C[7h]). The lycoranes **11a** and **12a** thus obtained had identical spectral properties with those of authentic samples.[15-17]

Surprisingly, when the trans-fused tertiary amine **8b** was allowed to react with ethyl chloroformate (C_6H_6, $NaHCO_3$, reflux), the urethane **13** (34%) was isolated in addition to the desired product **9b** (61%). Upon treatment with phosphorus oxychloride (90 °C, 18 h), **9b** underwent smooth cyclization to give **10** (mp 230–232 °C) in 90% yield. Catalytic hydrogenation of **10** afforded 7-oxo-β-lycorane (**11b**) (mp 155–157 °C) which was converted to β-lycorane (**12b**) (mp 86–88 °C, lit.[7a] mp 88 °C) by reduction with lithium aluminum hydride. The infrared spectrum of the racemic β-lycorane (**12b**) thus obtained was identical with that of an authentic sample.[17]

The preparation of the tetracyclic lactam **2** represents another application of our general strategy for the syntheses of alkaloid natural products employing thermal cyclizations of enamido dienes. Further studies of the intramolecular [4 + 2] cycloaddition reactions of a variety of other substituted azatrienes are in progress, and these results will be reported independently.

Acknowledgment. We thank the National Institutes of Health (GM 25439) for their generous support of this research program.

(11) This ratio was determined by a comparison of the peak intensities of the two carbonyl carbons in the ^{13}C NMR spectrum of the mixture.

(12) Compound **6** could also be prepared directly, albeit in lower overall yield, by the acylation of the imine obtained by condensation of homopiperonal (**3**) and *p*-methoxybenzylamine with 3,5-hexadienoyl chloride.[4b]

(13) For example, see (a) Wright, W. B., Jr.; Brabander, H. J. *J. Org. Chem.* **1961**, *26*, 4057. (b) Hobson, J. D.; McCluskey, J. G. *J. Chem. Soc. C* **1967**, 2015. (c) Montzka, T. A.; Matiskeller, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325. (d) Banholzer, R.; Heusner, A.; Schulz, W. *Justus Liebigs Ann. Chem.* **1975**, 2227. (e) Brine, G. A.; Boldt, K. G.; Hart, C. K.; Carroll, F. I. *Org. Prep. Proced. Int.* **1976**, *8*, 103. (f) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567, 1571.

(14) We thank Professor K. Torssell for the ^1H NMR and IR spectra and a generous sample of the unsaturated lactam **2**.

(15) We thank Professor G. Stork for a ^1H NMR and IR spectrum of 7-oxo-α-lycorane (**11a**).[3e]

(16) We thank Professor B. Umezawa for providing an authentic sample of racemic α-lycorane (**12a**) and its ^1H NMR spectrum.

(17) We thank Professor R. K. Hill and Dr. Y. Hamada[18] (Shionogi Research Laboratories, Osaka, Japan) for IR spectra of α-, β-, and γ-lycorane.

(18) Cf. Kotera, K. *Tetrahedron* **1961**, *12*, 248.

(19) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

Registry No. (±)-**1**, 66816-51-1; (±)-**2**, 53951-02-3; **3**, 6543-34-6; **4**, 78456-77-6; (*E*)-**5**, 78456-78-7; **6**, 78456-79-8; (±)-**7a**, 78479-41-1; (±)-**7b**, 78456-80-1; (±)-**8a**, 78456-81-2; (±)-**8b**, 78456-82-3; (±)-**9a**, 78456-83-4; (±)-**9b**, 78456-84-5; (±)-**10**, 78512-54-6; (±)-**11a**, 66816-53-3; (±)-**11b**, 78512-55-7; (±)-**12a**, 63814-02-8; (±)-**12b**, 71630-03-0; (±)-**13**, 78456-85-6; *p*-methoxybenzylamine, 2393-23-9; *N*-[2-(1,3-benzodioxol-5-yl)ethylidene]-4-methoxybenzylamine, 78456-86-7.

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Highly Stereoselective Routes to Functionalized Geminal Alkyl Derivatives of Carbohydrates[1]

Summary: 2-, 3-, and 4-Keto derivatives of some α-D-hexopyranosides react with $Ph_3P{=}CHCOOEt$ to give a single geometric isomer in each case, which is readily converted into an allyl vinyl ether. Claisen rearrangements of the latter proceed with high stereoselectivities, which indicate overwhelming preference for β folding of the allyl vinyl ether intermediates.

Sir: For certain projects underway in our laboratory we need to have sugar derivatives bearing geminal alkyl substituents at one or more points on the pyranoside ring that are differentiated and functionalized for further manipulations.[2] Traditionally, geminal alkylations proceed through carbonyl groups[2,3] and the required keto sugars (i.e., hexopyranosiduloses) are readily prepared.[3] However, the choice of alkylation procedure is severely constrained by the sensitivity of these derivatives to either strong base[3a] or strong acid.[3b] In this communication we report the use of the classical Claisen rearrangement for geminal alkylation[5] in some pyranosides which proceeds under mild conditions and, in most cases, with exceptionally high stereoselectivities.

Carbonyl derivatives of sugars are usually flanked by one or more (protected) hydroxyl groups and as a consequence tend to be heavily hydrated. Olefinations with "unstabilized" Wittig reagents, therefore, give poor yields of alkenes,[6] or alternatively lead to decomposition.[7] On the other hand, stabilized Wittig reagents react well with these ketones.[8] Thus, ketone **1**[9] reacted with $Ph_3P{=}CHCO_2Et$ to give the ester **2a** as the only[10] product in 85% yield. Although the configuration of this material was not important for our overall plan, it seemed of interest to determine its structure. Accordingly, the ester **2a** was

(1) Supported in part by a research grant from the National Institutes of Health, CA-28192.

(2) Ali, Y.; Szarek, W. A. *Carbohydr. Res.* **1978**, *67*, C17. Szarek, W. A.; Vyas, D. M.; Chem, L.-Y. *Ibid.* **1977**, *53*, C1.

(3) (a) Trost, B. M.; Bodgdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 2038. (b) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanehez, E. L.; Sathe, S. S. *Ibid.* **1978**, *100*, 1267.

(4) See, for example, *Methods Carbohydr. Chem.* **1972**, *6*, Sect. 3.

(5) Corey, E. J.; Shulman, J. I. *Methods Carbohydr. Chem.* **1970**, *92*, 5522.

(6) Tam, T. F.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1980**, 556.

(7) Jordaan, J. H.; Soredlay, S. *Carbohydr. Res.* **1971**, *16*, 177. Iley, D. E.; Tam, S. Y. K.; Fraser-Reid, B. *Ibid.* **1977**, *55*, 193.

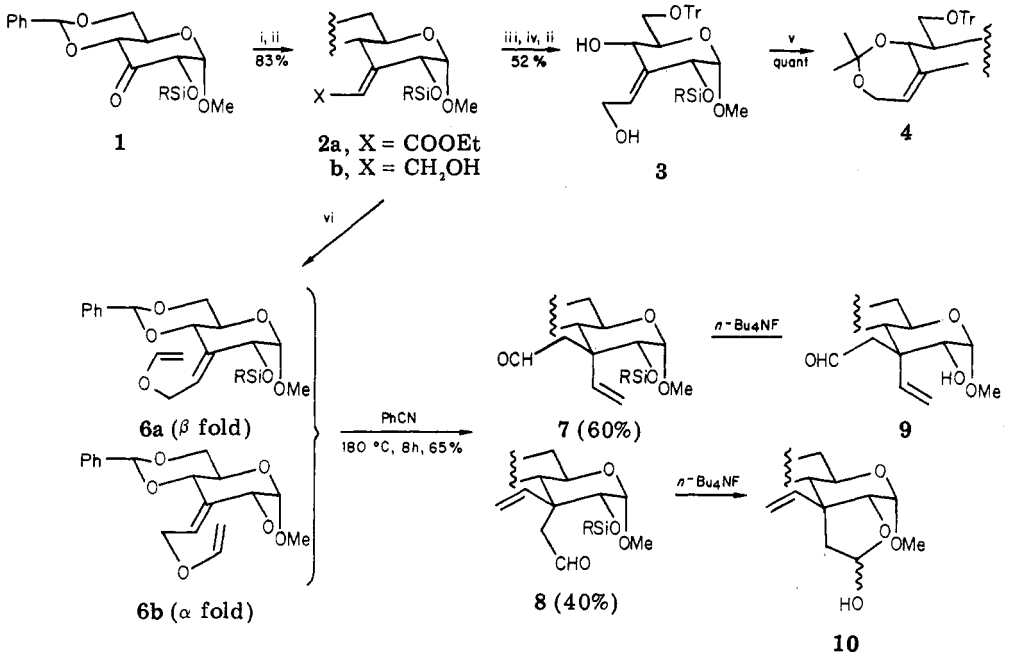
(8) See, for example: Tronchet, J. M. J.; Tronchet, J. *Helv. Chim. Acta* **1977**, *60*, 1984. Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 3870; Ohrui, H.; Moto, S. E. *Tetrahedron Lett.* **1975**, 3657.

(9) For the preparation of ketones **1** and **16**, methyl 4,6-*O*-benzylidene α-D-glucopyranoside was treated with 1 equiv of TBDMSiCl. The C2 and C3 silyl ethers were separated by column chromatography and oxidized to **1** and **16**, respectively.

(10) With the 2-*O*-benzyl analogue of **1**, both geometric isomers of the acrylate ester were produced in equal amounts.

0022-3263/81/1946-3764$01.25/0

Scheme I[a]



[a] (i) Ph_3P=CHCOOEt/CH_3CN, reflux, 4 h; (ii) $LiAlH_4$/ether, 0 °C; (iii) MeOH/TsOH; (iv) Ph_3CCl/pyridine; (v) dimethoxypropane/TsOH; (vi) ethyl vinyl ether/$Hg(CF_3COO)_2$, 23 °C, 24 h. [b] RSi = *t*-$BuMe_2Si$.

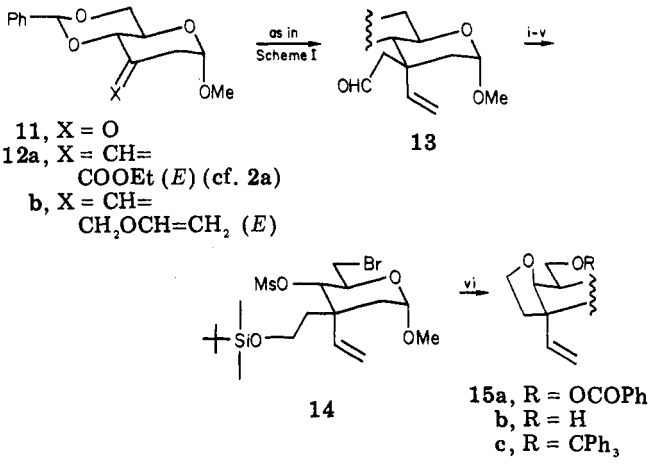
reduced, the product, **2b**, was desilylated, and the resulting diol was treated with dimethoxypropane; but an acetonide was not formed. On the other hand, when the 4-OH was exposed, as indicated in Scheme I, the resulting diol **3** did in fact afford an acetonide **4**,[11] thereby establishing the configuration of **2** as E.

Additions at a tertiary C3 center of α-D-hexopyranosides such as **1** occur preferentially from the β face,[12] and it therefore seemed that conjugate addition to **2a** should also proceed with high stereoselectivity. However, **2a** failed to react with $LiMe_2Cu$ or MeMgI/*n*-Bu_3PCuI (however, see Scheme IV). A different approach for introducing the second alkyl group was therefore required.

The alcohol **2b** was converted into the vinyl ether **6**, which proved to be somewhat unstable and was therefore used without purification. For the projected Claisen rearrangement, the β-fold **6a** corresponds to an equatorial addition at C3 and, as noted in the preceding paragraph, this should be more favorable than the α-fold **6b**, which poses a syn diaxial interaction with the aglycon. In the event, heating of **6** in refluxing benzonitrile for 8 h gave a mixture of isomeric products separable by column chromatography in a 3:2 ratio. The proof of the structure of these isomers, **7**[11] and **8**,[11] respectively, again took advantage of the neighboring hydroxyl groups. Thus, upon treatment of each with *n*-Bu_4NF, the major product remained as an hydroxy aldehyde, **9** (NMR δ 9.75; IR 1716 cm^{-1}), while the minor product cyclized spontaneously, giving a hemiacetal (NMR spectral data show no aldehyde but show an "anomeric" proton at δ 5.2).

We had hoped for greater stereoselectivity in the formation of **7** and **8** on the basis of the expected preference of the β-fold **6a**. However, the effect of the equatorial[13] C2 substituent on the rearrangement had been ignored in the foregoing analysis, and this was dramatically demonstrated with the 2-deoxy ketone **11**[14] studied in Scheme II. Pyrolysis of the allyl vinyl ether **12b** in the usual way (vide supra) proceeded in 80% yield, giving **13**[9] with only traces (2–4%) of the other isomer, detectable only by NMR. The proof of the structure of **12a** followed the protocol in Scheme I. In the case of **13**, by use of standard procedures and the Hanessian–Hular[15] reaction; the material was converted into **14**, which upon treatment with sodium benzoate in refluxing DMF gave **15a**[11] quantitatively. Proof that the benzoate was at C6 was apparent since the resulting alcohol **15b** formed a trityl derivative **15c** at room temperature.

Scheme II[a]



[a] (i) $LiAlH_4$; (ii) TBDMSiCl; (iii) NBS; (iv) NaOMe; (v) CH_3SO_2Cl; (vi) NaOCOPh/DMF.

Position 2 of the hexopyranoside ring was now studied (Scheme III) with ketone **16**[9] as substrate. Again there was only one ester formed, **17a**,[11] and there were no traces of

(11) This product gave satisfactory NMR spectra and HRMS or analytical data.

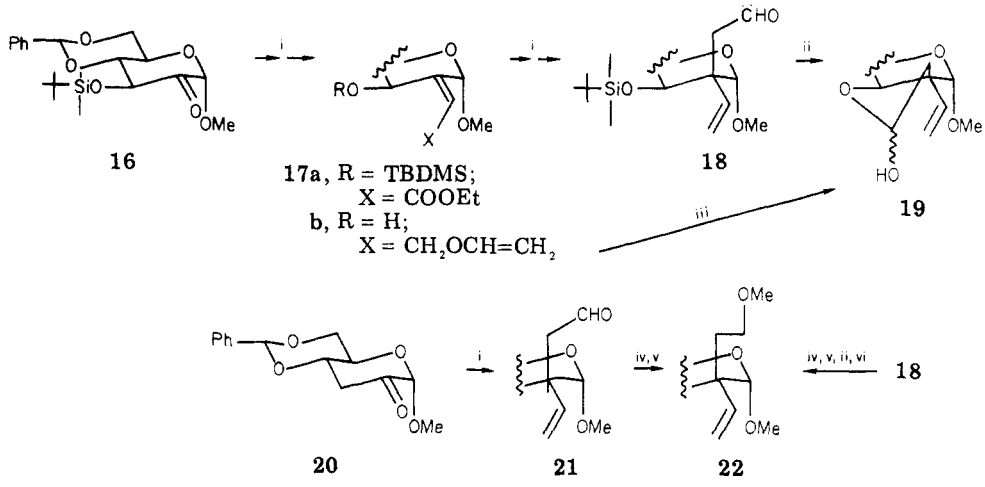
(12) See, for example: Howarth, G. B.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1974**, *96*, 1775; Jordaan, J. H.; Smedley, S. *Carbohydr. Res.* **1971**, *16*, 177; **1971**, *18*, 303.

(13) Attempts to prepare the analogue of **1** with the C2 function in axial orientation were unsuccessful, epimerization to **1** occurring spontaneously.

(14) Rosenthal, A.; Catsoulacos, P. *Can. J. Chem.* **1968**, *46*, 2868.

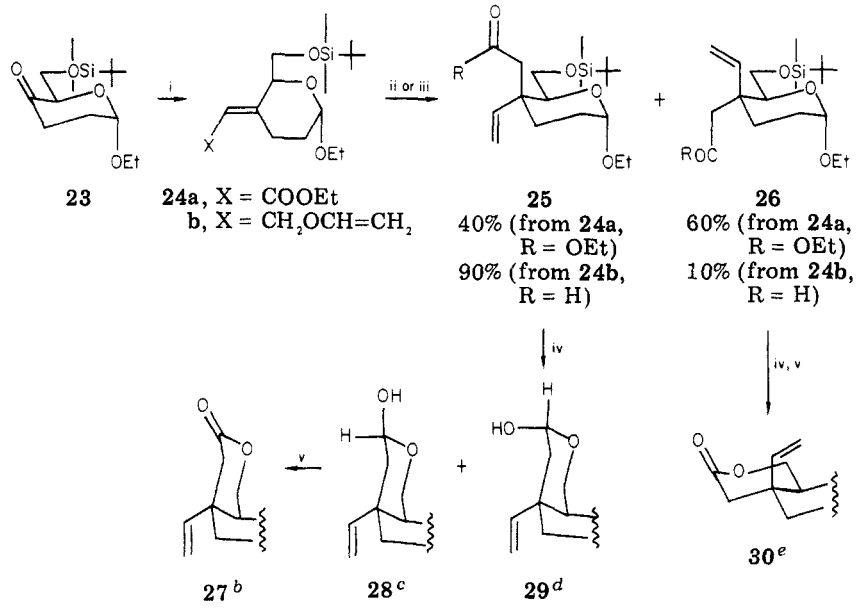
(15) Hanessian, S. *Methods Carbohydr. Chem.* **1972**, *6*, 183.

Scheme III[a]



[a] (i) As in Scheme I; (ii) n-Bu_4NF; (iii) PhCN/reflux; (iv) $LiAlH_4$; (v) MeI; (vi) Barton-McCombie deoxygenation.

Scheme IV[a]



[a] (i) As in Scheme I; (ii) for **24a**, CH_2=CHMgBr/n-Bu_3PCuI; (iii) for **24b**, PhCN, 180 °C; (iv) n-Bu_4NF; (v) Collin's oxidation. [b] $J_{5,6} = 1$ Hz, $J_{5,6'} = 6.2$ Hz. [c] $J_{5,6} = J_{5,6'} = 4.1$ Hz. [d] $J_{5,6} = 4.4$, $J_{5,6'} = 4.4$, $J_{5,4b} = 2.2$. [e] $J_{5,6} = 3.5$, $J_{5,6'} = 8.5$.

the isomer of **18**.[11] The latter was the expected product of β folding, and its configuration was established by formation of **19**. Interestingly, in this system the allyl vinyl intermediate was stable, and so the alcohol **17b** could be prepared. Upon heating, this lead directly to **19**. The 3-deoxy analogue **20**[14] also gave a single rearrangement product **21**,[11] whose structure was correlated with that of **18** by conversion to the common derivative **22**.

The 4-keto **23**[16] gave a single Wittig product judged to be **24** because the desilylated product failed to give a lactone. The Claisen rearrangement gave two products **25** and **26** (R = H) in 9:1 ratio. The major isomer upon fluorinolysis afforded two hemiacetals, **28** and **29**, whose critical 400-MHz NMR parameters are shown in Scheme IV. The long-range coupling of 2.2 Hz, confirmed in **29** by double irradiation, disappeared upon oxidation to lactone **27**. The remaining couplings in **27** of 1.0 and 6.2 Hz indicate a cis fusion of the two rings, which in turn confirms the orientation in **25**. By way of confirmation, the minor isomer of the rearrangement, **26**, gave a lactone **30** with the corresponding coupling constants indicated.

The high yield of **25** (R = H) revealed predominantly β folding of the allyl vinyl ether **24b**, which agrees with the known preference for addition from the β face to C4 trigonal sites.[16] Conjugate additions to **24a** were therefore examined, but as in the case of **2a** there was no reaction with $LiMe_2Cu$. However, with CH_2=CHMgBr/n-Bu_3PCuI, addition did occur, with **26** (R = OEt) now being the preferred isomer to **25** (R = OEt).

In summary, the Claisen rearrangements at carbons 2, 3, and 4 of α-D-hexopyranosides proceed with high stereoselectivities, which reflect a strong, and frequently total, preference for β folding.

Acknowledgment. We are grateful to Merck Sharp and Dohme and The Upjohn Company for support.[17]

(16) Fraser-Reid, B.; Walker, D. L. *Methods Carbohydr. Chem.* **1980**, *58*, 2694.

(17) Holder of Graduate Fellowship in Chemistry from (a) The Upjohn Company and (b) Merck Sharp and Dohme (Rahway, NJ).

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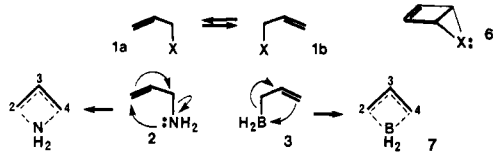
(1,3)-Sigmatropic Shifts of Allylamine and Allylborane. Flexible Models for Possible Pseudopericyclic Reactions

Summary: The degenerate 1,3-shift rearrangements of allylamine and allylborane have been mapped by the PRDDO method. It is shown that the former is neither pericyclic nor pseudopericyclic in character, but that the latter conforms to the pseudopericyclic concept when it is recognized that a general feature of electron-deficient sigmatropic migrations is the existence of polycyclic transition-state binding.

Sir: Unimolecular allylic rearrangements for simply substituted propene derivatives have traditionally been characterized by two mechanistic polar extremes. Ion pair formation accompanied by internal return has been invoked when the substituent X (**1a**/**1b**) is a good leaving group.[1] Concerted migration with inversion or the intervention of biradicals is demonstrable when carbon is the migrating atom.[2] Recently Lemal and co-workers proposed an alternative to the concerted pericyclic shift for certain cases in which the migrating atom X bears either a lone electron pair or a vacant orbital. Specifically, concerted rearrangements proceeding through a cyclically delocalized transition state in which nonbonding orbitals at X exchange roles with bonding orbitals at the same center have been designated as "pseudopericyclic".[3] The arrows in **2** and **3** depict the concept for X = NH_2 and BH_2 and imply the involvement of six and four electrons, respectively, in the delocalized transition states.



By means of approximate ab initio PRDDO calculations, we have previously shown that degenerate allylic rearrangement in the geometrically constrained 5-X-bicyclo-[2.1.0]pent-2-ene system **6** is best described as a pericyclic 1,3-shift unaccompanied by lone-pair participation at X. The calculated and experimentally correlatable variations in relative reaction rates were interpreted on the basis of transition-state structure.[4] In order to probe the nature of the cyclic transition state under conditions providing for maximum involvement of the nonbonding orbitals at X, we have evaluated the concerted migration in the more flexible, simple allylic system **1** for X = NH_2 and BH_2. While we are aware of only two cases of a 1,3-nitrogen shift,[5] dialkylboranes undergo rearrangement readily with

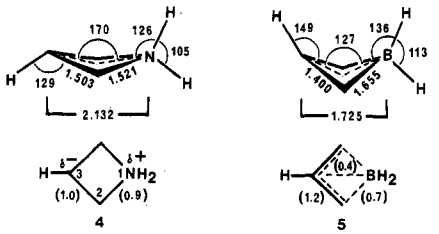


Figure 1. The PRDDO optimized C_s midpoints in the 1,3-shifts of allylamine and allylborane. Bond distances are given in angstroms and bond angles in degrees. Structures **4** and **5** represent the overall binding based on the molecular geometries and the parenthetical APS indices.

energy barriers ranging $\Delta H^{\ddagger}$ = 10–15 kcal/mol.[6]

The allyl ground states, CH_2=$CHCH_2X$, were fully geometry optimized by means of the PRDDO method[7] with no constraints. The corresponding cyclic complexes were treated similarly under the assumption of C_s symmetry (Figure 1). Linear synchronous transit (LST) pathways[8] were constructed between the endpoints (e.g., **2**/**4** and **3**/**5**). The allylamine transformation exhibited an intervening maximum and was therefore subjected to additional path-constrained optimizations. The resulting PRDDO reaction pathway **3** → **4** → **3′** accommodates the nitrogen-containing four-membered ring as an intermediate surrounded symmetrically by barriers of 4.7 kcal/mol. The final QST[8] pathways exhibit overall barriers of 98 and 11 kcal/mol for X = NH_2 and BH_2, respectively.

Can the computed reaction surfaces be characterized as pseudopericyclic? Electronic reorganization from allyl–X to the C_s cycles has been monitored by following the Armstrong–Perkins–Stewart (APS) bond indices[9] and both canonical (CMO) and Boys' localized (LMO) molecular orbitals along the QST pathways. For X = NH_2 the APS valency of the amine nitrogen varies from 3.0 to 3.7 as CH_2=$CHCH_2NH_2$ cyclizes to **4**. Simultaneously, C_3 builds up negative charge (−0.02 → −0.45) and the N–C bond orders change from 1.01/0.01 to 0.89/0.89. The near-full N–C bond formation is likewise reflected in the optimized length of 1.521 Å for the C_s intermediate (Figure 1). The latter is best formulated as a nearly flat azetidinium ylide with the carbanion center located at C_3. The transition state leading into the zwitterion is unsymmetrical and characterized by a weakened C=C bond (1.381 Å) and a developing N–C bond (1.771 Å). Thus the PRDDO 1.3-shift in **1** (X = NH_2) is distinguished by neither pericyclic nor pseudopericyclic delocalization but rather corresponds to two discrete steps initiated by the attack of NH_2: at the terminal allyl carbon. The C=C π electrons are thereby transformed into a carbanionic lone pair at C_3, giving **4**. Subsequently, analogous to the elimination of a quaternary ammonium salt, ylide **4** decomposes by cleavage of the alternate N–C bond. An obvious experimental entry onto the rearrangement surface is suggested. The very large calculated barrier to cyclization may stem in part from PRDDO's inflexible basis set and the lack of diffuse orbitals for properly handling the carbanion center

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(7) T. A. Halgren and W. N. Lipscomb, *J. Chem. Phys.*, **58**, 1569 (1973); T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. N. Lipscomb, *J. Am. Chem. Soc.*, **100**, 6595 (1978).
(8) T. A. Halgren and W. N. Lipscomb, *Chem. Phys. Lett*, **49**, 225 (1977).
(9) D. R. Armstrong, R. G. Perkins, and J. J. P. Stewart, *J. Chem. Soc., Dalton Trans.*, 838 (1973).

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