

S0040-4039(96)00244-4

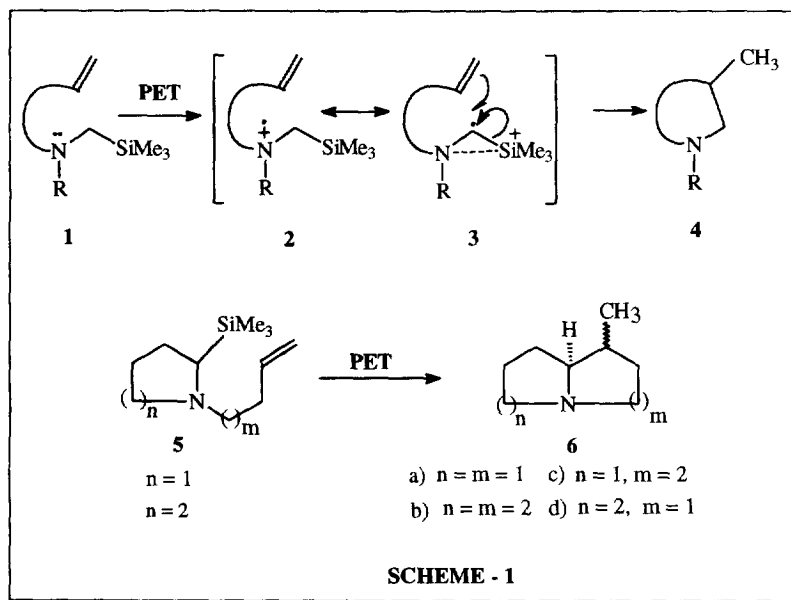
Further Evidence on the PET Cyclization of α -Silylmethylamines Tethered with Non-activated Olefins: Demonstration by the Total Synthesis of (-)-Retronecanol[#].

Ganesh Pandey* and Debasish Chakrabarti.

Division of Organic Chemistry (Synthesis)
 National Chemical Laboratory
 Pune-411 008, INDIA.
 FAX: 0212-330233.

Abstract: The total synthesis of (-)-retronecanol, in order to provide convincing evidence for the PET cyclization of α -trimethylsilylmethyl amines with tethered non-activated olefins, is reported.

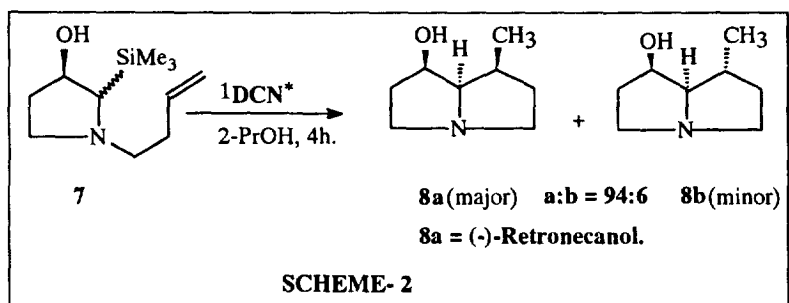
Few years back, we had reported¹ an efficient photosensitized electron transfer (PET) initiated cyclization of α -silylmethyl amines of type **1** to synthesize N-heterocycles (**4**) utilizing singlet excited state of 1,4-dicyanonaphthalene (¹DCN*) as an electron acceptor. Delocalized amine radical cation (**3**), formed by the



vertical overlap of -C-Si- σ -bond and empty p-orbital of nitrogen, was suggested² to be the intermediate in these cyclizations in contrast to the "free α -amino radical" intermediacy reported by Mariano *et al*³ in similar types of

cyclizations. Mariano's mechanistic rationale for the involvement of "free α -amino radical" was based on his claim that such cyclizations occur only when the olefin is activated³. We had also extended our cyclization strategy¹ to cyclic analogues **5** and a general stereoselective methodology for the construction of 1-azabicyclo[m.n.o]-alkanes (quinolizidines, indolizidines and pyrrolizidines)⁴ skeleton (**6**) was demonstrated⁵.

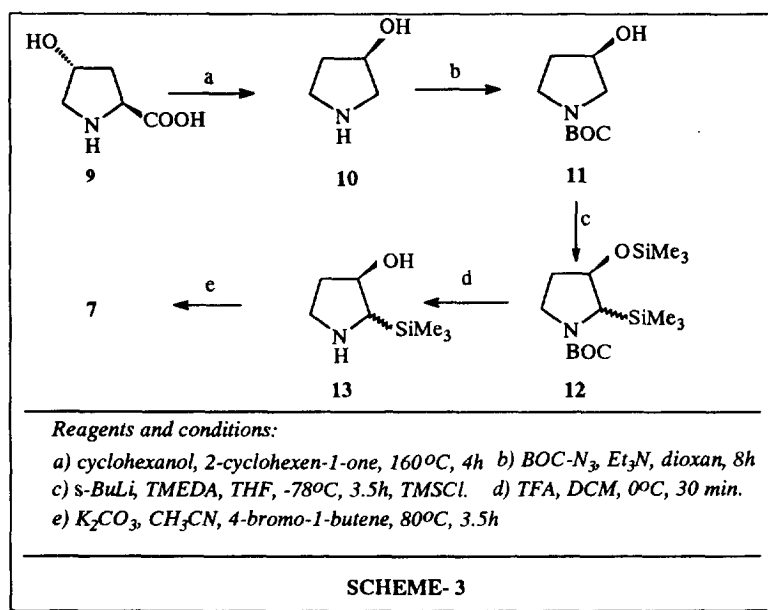
Surprisingly, following our detailed mechanistic disclosure², Mariano's group⁶ countered that the cyclization⁵ of **5** ($n=1$) to **6** is not reproducible and insisted that such cyclizations occur only when tethered olefin is activated⁷. Astonished by their report⁶ we repeated our experiments, using different experimental variations, in order to discover the discrepancy however, we always found **6** as the only photoproduct. The experimental details and the application of such cyclizations to various alkaloids are now published⁸. However, in order to provide further evidence to the authenticity of our results⁵ we continued this study with the total synthesis of (-)-retronecanol, an important "necine" base in the *senecio* series of alkaloids⁹ by the PET cyclization of **7** as shown in **Scheme 2** and disclose herein the results which provides convincing evidence that α -trimethylsilyl amines of type **7** cyclize efficiently to non-activated olefins.



As per our synthetic design precursor **7** was obtained from (R)-3-hydroxy pyrrolidine (**10**), easily obtainable¹⁰ from commercially available *trans*-(R)-4-hydroxy-L-proline (**9**), through the sequences as outlined in **Scheme 3**. Metallation¹¹ of **11** by reacting with *sec*-BuLi (2.2 eq) at -78°C in the presence of TMEDA followed by the addition of chlorotrimethyl silane (TMSCl, 2.2 eq.) and usual workup gave **12** exclusively in 86% yield. The regioselectivity of silylation at C-2 position was expected due to the directing effects of hydroxyl group for the initial metallation reaction. Usual deprotection of *tert*-BOC group from **12**, by stirring in the presence of TFA in DCM at 0°C , followed by heating (3.5h) the free amine with 4-bromo-1-butene in dry acetonitrile in the presence of anhydrous K_2CO_3 gave **7** in 75% yield¹².

PET cyclization of **7** was effected by irradiating (Pyrex filter light, $\lambda > 280$ nm, 450W medium pressure Hanovia lamp, all light absorbed by DCN only) a mixture of **7** (0.5g, 2.34 mmol) and DCN (0.1g, 0.56 mmol) in 2-propanol without removing the dissolved air¹³ from the solvent for 4h. Capillary GC analysis of the

irradiation mixture showed only two close lying product peaks in the ratio of 94:6 beside some unreacted starting material and DCN. The GC/mass of these peaks indicated them to be the diastereomeric mixture of **8a** and **b**. Concentration of the reaction mixture followed by column chromatographic purification over silica gel



gave **8a** in 78% yield. DCN was recovered quantitatively (98%). The minor diastereomer could not be isolated in sufficiently enough quantity for spectral details. Compound **8a** was characterized on the basis of satisfactory spectral data¹⁴. The stereochemistry of **8a** was established on the similar logic as reported^{5,8} earlier by comparing the chemical shift values of -CH₃ in ¹H NMR (δ 1.05) and ¹³C NMR (δ 14.17) with the minor isomer (δ 1.10 and δ 14.63 respectively) which indicated the 1,5- *cis* stereochemistry in **8a**. The optical rotation of **8a** ($[\alpha]_D^{29} = -90.8^\circ$, $c = 0.033$ EtOH) is also found comparable with the literature¹⁵ ($[\alpha]_D^{29} = -91.1^\circ$, $c = 0.06$ EtOH) report. Further authentication of the structure of **8a** could be established by comparing the ¹H NMR spectral data of the *p*-methoxybenzoate ester derivative of **8a** with the literature value¹⁴.

In summary, we have provided convincing evidence, through the synthesis of (-) retronecanol, that α -trimethylsilyl amines cyclize efficiently to non-activated olefins.

Acknowledgment: One of us (DC) thanks CSIR, New Delhi for award of Senior Research Fellowship.

REFERENCES AND NOTES:

- Pandey, G.; Kumaraswamy, G.; Bhalerao, U. T. *Tetrahedron Lett.*, **1989**, *30*, 6059-6062.
- Pandey, G.; Reddy, G. D.; Kumaraswamy, G. *Tetrahedron.*, **1994**, *50*, 8185-8194.
- Jeon, Y. T.; Lee, C-P.; Mariano, P. S. *J. Am. Chem. Soc.*, **1991**, *113*, 8847-8863.; Hasegawa, E.; Xu, W.; Mariano, P. S.; Yoon, U-C.; Kim, J-U. *J. Am. Chem. Soc.*, **1988**, *110*, 8099-8111.
- For reviews on indolizidine, pyrrolizidine and quinolizidine alkaloids see: Howard, A. S. and Michael, J. P. in *The Alkaloids. Chemistry and Pharmacology*, Brossi, A. Ed.; Academic Press, New York, **1986**, *28*, ch.3; Stevens, R. V. , in *The Total Synthesis of Natural Products*, Apsimon, A., Ed.; Wiley, New York, **1977**, *3*, 439; Nishimura, Y., in *Studies in Natural Product Chemistry*, Rahman, A. U. Ed; Elsevier, Amsterdam, **1988**, *1*, 227; and references cited therein.
- Pandey, G.; Reddy, G. D. *Tetrahedron Lett.*, **1992**, *33*, 6533-6536.
- Hoegy, S. E.; Mariano, P. S. *Tetrahedron Lett.*, **1994**, *35*, 8319-8322.
- Mariano *etal* mentioned in their paper that they repeated our work using $\lambda > 240\text{nm}$ wavelength whereas we have clearly mentioned that our cyclizations are carried out utilizing Pyrex filtered light ($\lambda > 280\text{nm}$.)
- Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc. Perk. Trans 1*, **1995**, 0000
- For isolation, extraction, structural determination and biological importance of (-)-retronecanol and other *Senecio* alkaloids see Leonard N. J.; In *The Alkaloid Chemistry and Physiology*; Manske R. H. F. Ed.; Academic Press: New York, **1960**, *6*, pp. 37-121.
- Thaning, M.; Wistrand, L-G. *Acta Chem. Scand.*, **1989**, *43*, 290-295.
- Beak, P.; Lee, W. K. *J. Org. Chem*, **1993**, *58*, 1109-1117.
- Spectral characteristics of **7**: IR.(Neat, cm^{-1}): 3500, 2900, 2800, 1225, 1050. ^1H NMR (200 MHz) (δ ppm): 0.15 (s, 9H), 1.75 (m, 1H), 2.1 (dd, $J_1 = 9.45$ Hz, $J_2 = 9.05$ Hz 1H), 2.4-2.5(m, 5H), 3.1(m, 1H), 3.45(dd appearing like d, $J = 13.5$ Hz, 1H), 4.45(bm, 1H), 5.15(m, 2H), 5.75(m, 1H). ^{13}C NMR (50.4 MHz) (δ ppm): -2.3, 32.99, 38.61, 55.05, 55.50, 64.55, 71.43, 115.61, 136.85. Mass: 212($\text{M}^+ + 1$), 196, 172, 140 (100%), 122, 73, 55.
- Pandey, G., *Synlett*, **1992**, 546-552.
- Spectral characteristics of **8a**: IR.(Neat, cm^{-1}): 3475, 2975, 2800, 1200. ^1H NMR (200 MHz) (δ ppm): 1.05 (d, $J = 6.45$ Hz, 3H), 1.85-2.05 (m, 2H), 2.15-2.25 (m, 1H), 2.4-2.6 (m, 1H), 3.0 (m, 1H), 3.2 (m, 1H), 3.5-3.6 (m, 1H), 3.8 (m, 1H), 4.1 (m, 1H), 4.55 (m, 1H). ^{13}C NMR (50.4 MHz) (δ ppm): 14.17, 30.71, 33.53, 35.57, 54.98, 60.69, 69.00, 69.80. Mass: 141(M^+), 140, 124, 99, 97, 82, 69, 55 (100%), 51.
- Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.*, **1939**, *61*, 2815-2819.
- Suri, O. P.; Jamwal, R. S.; Suri, K. A.; Atal, C. K. *Phytochem.*, **1980**, *19*, 1273-1274.

(Received in UK 19 December 1995; revised 8 February 1996; accepted 9 February 1996)