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

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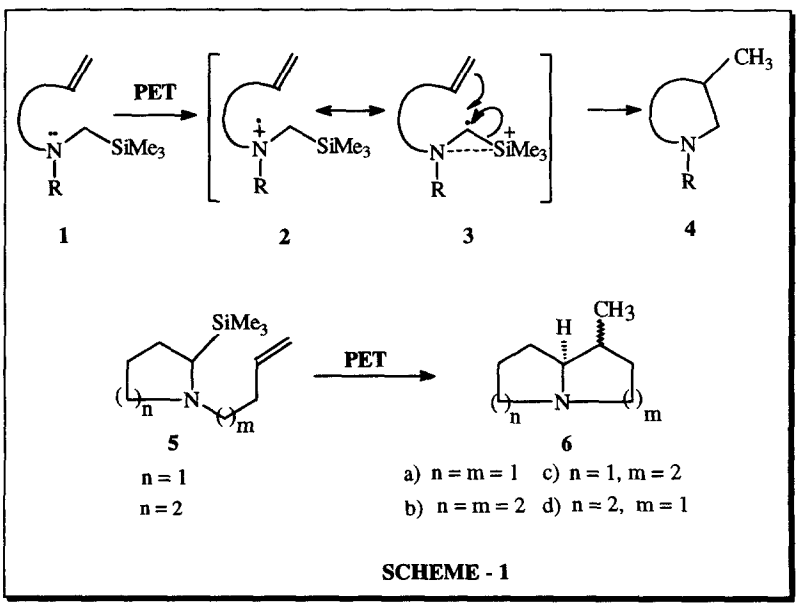
Abstract: The total synthesis of (-)-retronecanol, in order to provide convincing evidence for the PET cyclization of α-trimethylsilylmethyl amines with tethered non-activated olefins, is reported.

Few years back, we had reported[1] 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



SCHEME - 1

vertical overlap of -C-Si- σ-bond and empty p-orbital of nitrogen, was suggested[2] to be the intermediate in these cyclizations in contrast to the "free α-amino radical" intermediacy reported by Mariano *etal*[3] in similar types of

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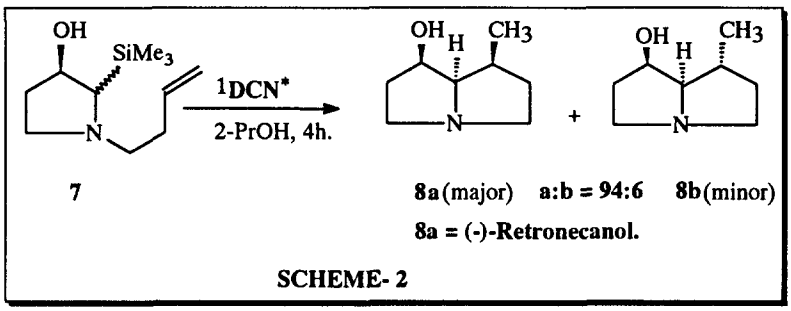
cyclizations. Mariano's mechanistic rationale for the involvement of "free α-amino radical" was based on his claim that such cyclizations occur only when the olefin is activated[3]. We had also extended our cyclization strategy[1] to cyclic analogues **5** and a general stereoselective methodology for the construction of 1-azabicyclo[m.n.o]-alkanes (quinolizidines, indolizidines and pyrrolizidines)[4] skeleton (**6**) was demonstrated[5].

Surprisingly, following our detailed mechanistic disclosure[2], Mariano's group[6] countered that the cyclization[5] of **5** (n=1) to **6** is not reproducible and insisted that such cyclizations occur only when tethered olefin is activated[7]. Astonished by their report[6] 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 published[8]. However, in order to provide further evidence to the authenticity of our results[5] we continued this study with the total synthesis of (-)-retronecanol, an important "necine" base in the *senecio* series of alkaloids[9] 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.

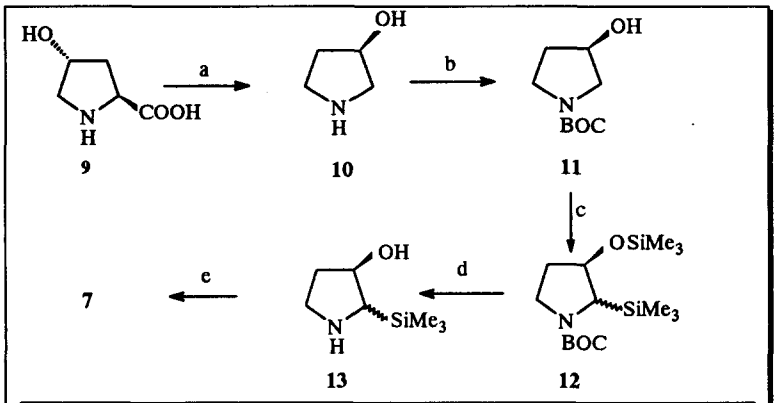


SCHEME- 2

As per our synthetic design precursor **7** was obtained from (R)-3-hydroxy pyrrolidine (**10**), easily obtainable[10] from commercially available *trans*-(R)-4-hydroxy-L-proline (**9**), through the sequences as outlined in **Scheme 3**. Metallation[11] 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 regiospecificity 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% yield[12].

PET cyclization of **7** was effected by irradiating (Pyrex filter light, λ >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 air[13] 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



Reagents and conditions:

a) cyclohexanol, 2-cyclohexen-1-one, 160°C, 4h b) BOC-N_3, Et_3N, dioxan, 8h
c) s-BuLi, TMEDA, THF, -78°C, 3.5h, TMSCl. d) TFA, DCM, 0°C, 30 min.
e) K_2CO_3, CH_3CN, 4-bromo-1-butene, 80°C, 3.5h

SCHEME- 3

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 data[14]. The stereochemistry of **8a** was established on the similar logic as reported[5,8] earlier by comparing the chemical shift values of $-CH_3$ in ^1H NMR (δ1.05) and ^{13}C NMR (δ14.17) with the minor isomer (δ1.10 and δ14.63 respectively) which indicated the 1,5- *cis* stereochemistry in **8a**. The optical rotation of **8a** ($[\alpha]_D^{29}$ = -90.8°, c = 0.033 EtOH) is also found comparable with the literature[15]($[\alpha]_D^{29}$ = -91.1°, 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 value[16].

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

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12. 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(M^++1), 196, 172, 140 (100%), 122, 73, 55.
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14. 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.
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