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LETTERS

A Convenient Access to (3*S*)-3-(Triisopropylsilyl)oxy-1-pyrroline *N*-Oxide, A Useful Intermediate for Polyfunctionalized Enantiopure Indolizidine and Pyrrolizidine Synthesis

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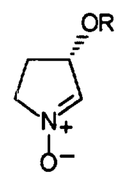
Abstract: Optimization of a strategy providing the enantiomerically pure nitrone **2** in five steps and 28% overall yield from L-malic acid has been achieved by the combined use of DIBAL-H as the reductant and triisopropylsilyl as the protecting group. The utility of nitrone **2** as synthetic intermediate is demonstrated by a ready access to polyhydroxylated indolizidines and pyrrolizidines via stereoselective 1,3-dipolar cycloaddition reactions.

Keywords: Nitrones; Indolizidines; Pyrrolizidines; Asymmetric synthesis

Five-membered cyclic nitrones have emerged as useful building blocks for the construction of nitrogen heterocycles, pyrrolizidine and indolizidine alkaloids and biologically active compounds.[1] Recent research has focused on the synthesis of optically active pyrroline *N*-oxides,[2] as precursors for such targets in enantiomerically pure form. In this context, we have recently reported the synthesis of enantiomerically pure TBDMS protected hydroxy nitrone **1** by a highly selective oxidation of the corresponding hydroxylamine **6**.[3] The synthesis of **1**, from readily available L-malic acid, required a lengthy protection-deprotection strategy (Scheme 1), since direct protection as the TBDMS ether proved unviable, probably due to silyl migration to the primary alcohol functionality after reduction of the ester groups of **7** (Scheme 2). An alternative synthesis of the same nitrone **1** reported successively by Murahashi and co-workers,[4] based on oxidation of the parent pyrrolidine, prompts us to disclose the optimization of our own route to a related silyl protected nitrone. The oxidation of a *N*-hydroxypyrrolidine to a nitrone occurs, in fact, with much higher yield, regioselectivity, and reproducibility than the corresponding pyrrolidine. Herein we report the direct and successful preparation of nitrone **2** making use of the triisopropylsilyl (TIPS) protection, as well as the application of this nitrone to the construction of highly functionalized indolizidine and pyrrolizidine skeleta by cycloaddition routes.



R = TBDMS **1**
R = TIPS **2**

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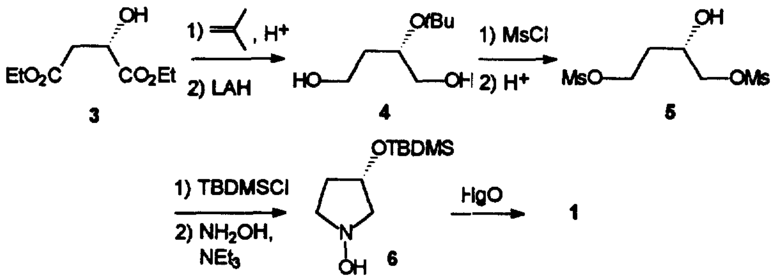
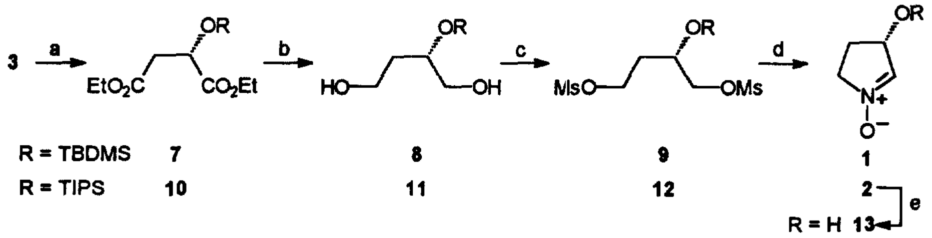
Scheme 1



To make our methodology efficient, a tuning of the reduction of the TBDMS substituted malate to the monoprotected triol was necessary. Use of DIBAL-H in CH_2Cl_2 at -20 °C met with partial success affording an encouraging 45% yield of the desired protected triol **8** (Scheme 2).[5] The combination of these conditions with the use of a bulkier triisopropylsilyl protecting group gave a rewarding 83% yield of the triol **11**,[5] suitable precursor of the silylated nitrone **2**. Mesylation under standard conditions gave the dimesylate **12**,[5] which was converted to the nitrone **2**[5,6] by the usual two-step procedure (double nucleophilic displacement with hydroxylamine followed by oxidation) without isolation of the intermediate cyclic hydroxylamine. The final oxidation, performed by means of yellow HgO, afforded the wanted nitrone with a 11:1 selectivity over its regioisomer, as expected on the basis of our previous results.[3,7] The major nitrone could be easily obtained pure by flash column chromatography. Nitrone **2**, then, can be prepared from L-malic acid in five steps and 28% overall yield and appropriate scale-up allowed its synthesis in multigram quantity. Nitrone **2** can be easily deprotected to the stable parent hydroxynitrone **13**[3] [mp 104-106 °C, $[\alpha]^{26}_{D}$ −145.6 (c 0.87, $CHCl_3$)] in almost quantitative yield with CsF in absolute EtOH (Scheme 2).

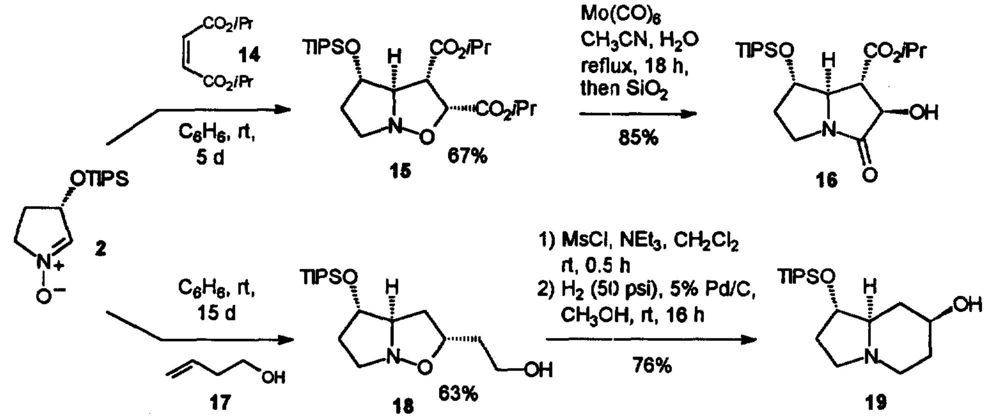
Scheme 2



a) R-Cl (2 equiv), imidazole (1 equiv), DMF, rt, 24 h, **7**, 76%, **10**, 83%; b) DIBAL-H (6 equiv), CH_2Cl_2, -20 °C, 3.5 h, **8**, 45%, **11**, 83%; c) MsCl (4.3 equiv), NEt_3 (6 equiv), CH_2Cl_2, rt, 1 h, **9**, 89%, **12**, 94%; d) i. $NH_2OH{\cdot}HCl$ (4.5 equiv), NEt_3, reflux, 2.5 h, ii. HgO (2.3 equiv), CH_2Cl_2, rt, 2 h, **1**, 59%, **2**, 50%; e) CsF (1.4 equiv), EtOH, rt, 3 d, 98%.

Enantiomerically pure 3-oxy substituted pyrroline *N*-oxides have already found applications as useful intermediates for the synthesis of the alkaloid (−)-hastanecine[8] and of pseudo imino disaccharides[9] and nitrone **1** itself has been converted to Geissman-Waiss lactone,[4] an important precursor for a series of pyrrolizidine alkaloids.[10] The applicability of nitrone **2** in similar protocols has been tested in two procedures able to warrant access to the pyrrolizidine and indolizidine nuclei, by means of cycloaddition reactions to maleic acid esters and to 3-butenol (Scheme 3), respectively.[1f] Both cycloadditions to diisopropyl maleate (**14**) and 3-butenol (**17**) gave, as expected,[2d,i,8] a major cycloadduct which derived from an approach of the dipolarophile from the face of nitrone opposite to the substituent in an *exo* fashion (*exo-anti* TS). Both adducts **15**[5] and **18**[5] were obtained with moderate selectivity,[11] but high yield (67% and 63%, respectively, after purification). The pyrroloisoxazolidines **15** and **18** were converted into the desired nitrogen bridgehead bicyclic heterocycles by known procedures. Treatment of **15** with $Mo(CO)_6$ in aqueous acetonitrile at reflux,[12] followed by overnight standing of the reaction mixture over silica gel[13] afforded the pyrrolizidinone **16** in 85% yield.[5,14] Adduct **18** gave the indolizidine **19**[5,15] by a two-step procedure, consisting of mesylation of the alcohol, directly followed by hydrogenation of the intermediate bridged salt. Products **16** and **19** are immediate precursors to pyrrolizidine and indolizidine alkaloids and their biologically active analogues.[2d,8]

Scheme 3



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5. All new compounds gave satisfactory spectroscopical and analytical data.
6. (3*S*)-3-(Triisopropylsilyl)oxy-1-pyrroline *N*-oxide (**2**): oil; $[\alpha]_D^{20} = -35.2$ (*c* 0.31, CH_2Cl_2); ^{1}H-NMR: δ 6.90 (d, *J* = 1.8 Hz, 1H), 5.10 (d, *J* = 5.3 Hz, 1H), 4.22-4.05 (m, 1H), 3.90-3.75 (m, 1H), 2.70-2.45 (m, 1H), 2.20-2.00 (m, 1H), 1.20-0.90 (m, 21H); ^{13}C-NMR: δ 136.0 (d), 72.3 (d), 61.2 (t), 31.2 (t), 17.8 (q, 6C), 11.9 (d, 3C); Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.35; H, 10.39; N, 5.32.
7. Selectivity achieved by Murahashi[2j,4] in the oxidation of the TBDMS-protected pyrrolidine with Na_2WO_4/H_2O_2 was only 6.8:1.
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10. See for example: Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 23.
11. In the crude reaction mixtures, adduct **15** was detected together its *endo-anti* and *exo-syn* diastereoisomers in a 6:1.5:1 ratio and adduct **18** was in a 7.5:1 ratio together its *exo-syn* diastereoisomer.
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14. (1*S*,2*R*,7*S*,7a*R*)-Hexahydro-7-(triisopropyl)oxy-2-hydroxy-1-isopropyloxycarbonylpyrrolizin-3-one (**16**): oil; $[\alpha]_D^{22} = +48.7$ (*c* 1.15, $CHCl_3$); ^{1}H-NMR: δ 5.08 (sept, *J* = 6.2 Hz, 1H), 4.76 (br d, *J* = 9.5 Hz, 1H), 4.23 (q, *J* = 5.1 Hz, 1H), 3.84 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.78 (dd, *J* = 13.2, 7.4 Hz, 1H), 3.45 (br s, 1H), 3.28-3.15 (m, 1H), 2.76 (dd, *J* = 9.5, 8.8 Hz, 1H), 2.09-1.90 (m, 2H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.22-0.88 (m, 3H), 1.05 (s, 18H); ^{13}C-NMR: δ 173.4 (s), 170.5 (s), 76.1 (d), 75.6 (d), 69.4 (d), 66.4 (d), 55.1 (d), 41.1 (t), 35.3 (t), 21.7 (q, 2C), 17.9 (q, 6C), 12.1 (d, 3C); Anal. Calcd for $C_{20}H_{37}NO_5Si$: C, 60.11; H, 9.33; N, 3.51. Found: C, 59.93; H, 9.39; N, 3.61.
15. (1*S*,7*S*,8a*R*)-Octahydro-1-(triisopropyl)oxy-7-hydroxyindolizine (**19**): white solid, mp 110-111°C; $[\alpha]_D^{16} = +47.8$ (*c* 0.43, $CHCl_3$); ^{1}H-NMR: δ 4.10-4.00 (m, 1H), 3.65 (ddt, *J* = 4.4, 4.3, 10.9 Hz, 1H), 3.02-2.92 (m, 2H), 2.42-1.85 (m, 7H), 1.69-1.43 (m, 2H), 1.20-0.90 (m, 21H); ^{13}C-NMR: δ 76.2 (d), 69.6 (d), 69.4 (d), 51.7 (t), 50.3 (t), 38.4 (t), 34.5 (t), 33.5 (t), 17.9 (q, 6C), 12.1 (d, 3C); Anal. Calcd for $C_{17}H_{35}NO_2Si$: C, 65.12; H, 11.25; N, 4.47. Found: C, 65.12; H, 11.56; N, 4.15.