TBAT-Mediated Nitrone Formation of ω-Mesyloxy-*O*-*tert*-butyldiphenylsilyloximes: Facile Synthesis of Cyclic Nitrones from Hemiacetals

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Abstract: Chiral and cyclic nitrones were synthesized by TBAT-mediated desilylative cyclization of ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloximes, readily prepared from sugar derivatives by a consecutive treatment with *O*-*tert*-butyldiphenylsilylhydroxylamine and with mesyl chloride. The method was applied to sequential nitrone formation and intramolecular cycloaddition.

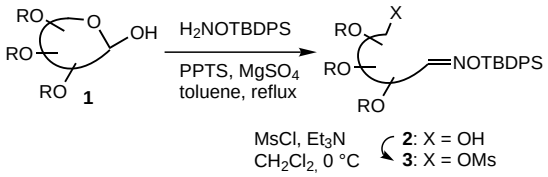
Key words: carbohydrate-derived ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloxime, TBAT, cyclization, nitrone, intramolecular cycloaddition

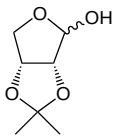
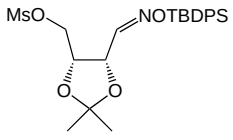
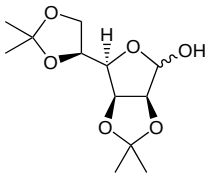
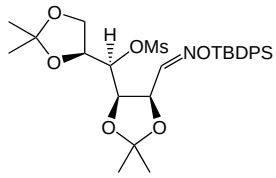
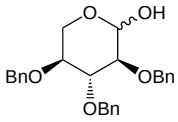
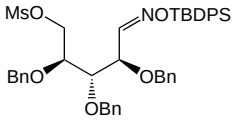
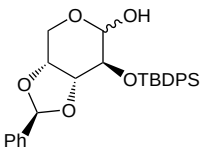
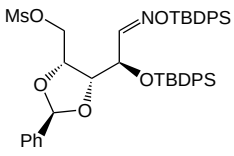
Chiral and cyclic nitrones are recognized as attractive synthetic intermediates, especially for optically active alkaloids and amino sugars.[1] Therefore, there have been intensive studies on the syntheses of such nitrones: oxidation of secondary amines or hydroxylamines,[1b,d,2] intramolecular condensation of aldehydes with hydroxylamines,[1i,j] intramolecular Michael addition of nitrogen-atom of oximes,[3] and intramolecular *N*-alkylation of oximes having leaving groups in the molecule.[1a,c,1e–g] Among them, the *N*-alkylation of oximes is the most attractive because of the regio- and stereospecificity. In this context, synthesis of (3*R*,4*S*)-3,4-isopropylidenedioxypyrroline 1-oxide from 3,4-isopropylidene-D-erythrose via 3,4-isopropylidene-4-mesyloxy-D-erythrose *O*-trimethylsilyloxime has recently been described.[4] This report prompted us to present results of our own work on a general method for synthesis of chiral and cyclic nitrones using TBAT-mediated cyclization of ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloximes, readily prepared from chiral hemiacetals such as sugars.[5]

Our investigation was initiated by preparation of intramolecular-alkylation precursors **3a**–**d** from the hemiacetals **1a**–**d** (Table 1). Treatment of lactol **1a**[6] derived from D-erythrose with *O*-*tert*-butyldiphenylsilylhydroxylamine (H_2NOTBDPS)[7] in boiling toluene in the presence of 0.05 equiv. of PPTS and excess $MgSO_4$ gave ω-hydroxyl-*O*-*tert*-butyldiphenylsilyloxime **2a**.[8] The latent hydroxyl group of the oxime group of **2a** is effectively differentiated from the primary ω-hydroxyl group, and hence the ω-hydroxyl group can be easily transformed into a leaving group. Thus, treatment of **2a** with mesyl chloride and Et_3N in CH_2Cl_2 at 0 °C afforded ω-mesyloxyoxime **3a** in 98% yield from **1a** (entry 1).[9] Similar reactions of lactols **1b**,[10] **1c**, and **1d** afforded ω-mesyloxyoximes **3b**, **3c**, and **3d** in 89%, 92%, and 59% yields, respectively.

With four mesylates **3a**–**d** in hand, a fluoride ion-mediated nitrone formation reaction was next examined (Table 2). When compound **3a** was treated with CsF in boiling THF, desilylative cyclization occurred to give nitrone **4a** in 42% yield (entry 1). The use of TBAF as a fluoride ion-source again gave low yields of **4a**, probably due to the instability of **4a** under the basic conditions arising from TBAF (entries 2 and 3). The most satisfactory result was obtained by employing tetrabutylammonium triphenyldifluorosiliconate (TBAT),[11] known as a non-basic fluoride

Table 1 Formation of ω-Mesyloxy-*O*-*tert*-butyldiphenylsilyl oximes **3**.



Entry	Sugar Derivative **1**	*O*-TBDPS Oxime **2**	Yield (%)
1	 **1a**	 **3a**	98
2	 **1b**	 **3b**	89
3	 **1c**	 **3c**	92
4	 **1d**	 **3d**	59

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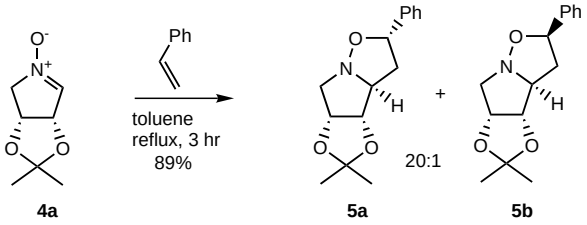
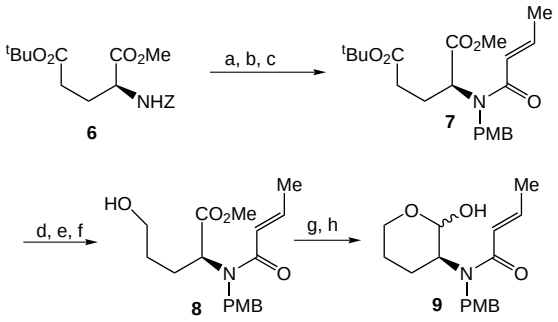
source. Thus, heating **3a** with TBAT (1.0–1.05 equiv) and MS 4Å in boiling THF rapidly caused desilylative cyclization to afford **4a** in 70% yield (entry 4).[12,13] Secondary mesylate **3b** and homologated mesylate **3c** also underwent nitrone-formation reactions under similar conditions to give α′-substituted nitrone **4b** and six-membered nitrone **4c** in 67% and 71% yields, respectively (entries 5 and 6). Since the present conditions are very mild, an *O*-TBDPS group can be compatible through the nitrone formation (entries 7 and 8).

The nitrones obtained here were found to be very useful. For example, nitrone **4a** underwent 1,3-dipolar cycloaddition with styrene to afford cycloadduct **5a** in a highly stereoselective manner, along with a small amount of **5b** (Scheme 1).

We next turned our attention to the application of the present nitrone-formation reaction to a sequential nitrone formation and intramolecular cycloaddition. The requisite

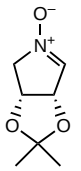
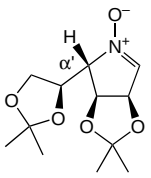
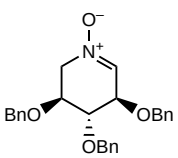
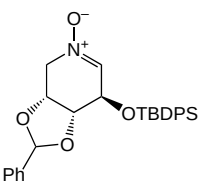


Scheme 1



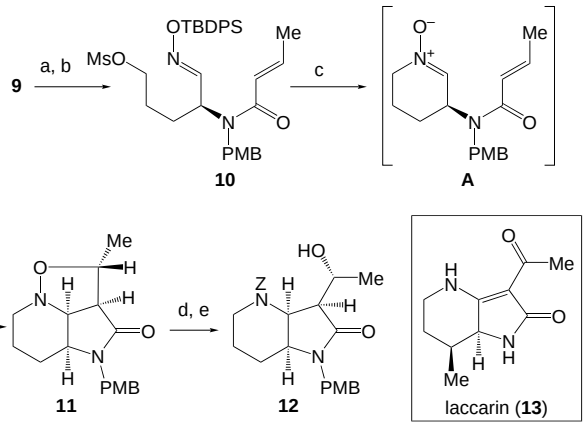
Scheme 2 a) 5% Pd/C, H_2, MeOH; b) *p*-anisaldehyde, $NaBH_3CN$, EtOH, AcOH, H_2O; c) (*E*)-ClCOCH=CHMe, aq $NaHCO_3$, CH_2Cl_2, 92% from **6**; d) TFA, CH_2Cl_2; e) *i*-BuOCOCl, Et_3N; f) $Zn(BH_4)_2$, THF, 78% from **7**; g) TsOH, benzene, reflux; h) DIBAL-H, Et_2O–CH_2Cl_2, –78 °C, 93% from **8**

Table 2 Desilylative Cyclization of ω-Mesyloxy-*O*-*tert*-butyldiphenylsilyloximes **3**.

Entry	Oxime	Conditions	Nitrone	Yield (%)
1	**3a**	CsF, THF, reflux, 7 min		42
2	**3a**	TBAF, THF, reflux, 7 min		37
3	**3a**	TBAF, benzene, reflux, 7 min		34
4	**3a**	TBAT, THF, reflux, 7 min	**4a**	70
5	**3b**	TBAT, THF, reflux, 5 min	 **4b**	67
6	**3c**	TBAT, THF, reflux, 5 min	 **4c**	71
7	**3d**	TBAT, THF, reflux, 5 min	 **4d**	13
8	**3d**	TBAT, benzene, reflux, 5 min		49

hemiacetal **9** was prepared from readily available L-glutamate derivative **6** in 67% overall yield (Scheme 2).

Hemiacetal **9** was treated with $NH_2OTBDPS$ in the presence of $MgSO_4$ and PPTS in boiling Et_2O followed by exposure to mesyl chloride and Et_3N to give mesylate **10** in 96% yield (Scheme 3). Treatment of **10** with TBAT in the presence of MS 4A in refluxing THF afforded cycloadduct **11** in 84% yield via desilylation and intramolecular cycloaddition of the resulting nitrone **A**. Hydrogenolysis of the *N*-*O* bond of cycloadduct **11** followed by treatment with benzyl chloroformate gave bicyclic alcohol **12.** The present sequence would be useful for synthesis of an alkaloid laccarin (**13**) possessing phosphodiesterase inhibitory activity.[14]



Scheme 3 a) $NH_2OTBDPS$, cat. PPTS, $MgSO_4$, Et_2O, reflux; b) MsCl, Et_3N, CH_2Cl_2, 96% from **9**; c) TBAT, MS 4A, THF, reflux, 30 min, 84%; d) $Pd(OH)_2$, H_2, MeOH; e) CbzCl, aq $NaHCO_3$, 91% from **11**

In conclusion, we have developed a general method for synthesis of chiral and cyclic nitrones from hemiacetals such as sugar derivatives using TBAT-mediated desilylative cyclization of ω-mesyloxy-*O*-*tert*-butyldiphenylsilyloximes. This synthetic sequence would be useful for polyhydroxylated alkaloids and aza-sugars.

Acknowledgement

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(8) When H_2NOTMS or H_2NOTBDMS was used, a mixture of the corresponding ω-hydroxy-*O*-silylated oxime and the desilylated oxime was obtained. Use of azeotropic removal of water instead of $MgSO_4$, again gave a similar mixture.

(9) In contrast, treatment of desilylated congener of **2a** with mesyl chloride (1 equiv) and Et_3N (2 equiv) gave an inseparable complex mixture.

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(12) The reaction required a prolonged reaction time without MS 4Å.

(13) Typical procedure. Preparation of **4a** from **1a**: A mixture of **1a** (500 mg, 3.12 mmol) and $MgSO_4$ (1.5 g) in toluene (5 mL) was heated at reflux for 5 min. To this mixture were added successively H_2NOTBDPS (2.54 g, 9.36 mmol) and PPTS (39.0 mg, 0.156 mmol) at the same temperature. After further heating for 15 min, $MgSO_4$ was filtered off, and the filtrate was washed successively with an aqueous saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with *n*-hexane–EtOAc (2:1) to give **2a**. Compound **2a** was dissolved in CH_2Cl_2 (8 mL). Mesyl chloride (0.73 mL, 9.26 mmol) and Et_3N (0.60 mL, 9.27 mmol) were added to the stirred solution at 0 °C. After stirring for 15 min, water was added to the mixture, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with *n*-hexane–EtOAc (3:1) to afford a 65:35 mixture of (*E*)-**3a** and (*Z*)-**3a** (1.51 g, 98% from **1a**). (*E*)-**3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (9 H, s), 1.36 (3 H, s), 1.53 (3 H, s), 2.97 (3 H, s), 4.16 (1 H, dd, *J* = 6.8, 11.2 Hz), 4.20 (1 H, dd, *J* = 4.5, 11.2 Hz), 4.46 (1 H, br dt, *J* = 4.5, 6.8 Hz), 4.79 (1 H, br t, *J* = 7.3 Hz), 7.39–7.41 (5 H, m), 7.64–7.69 (6 H, m). (*Z*)-**3a**: 1.11 (9 H, s), 1.31 (3 H, s), 1.49 (3 H, s), 2.86 (3 H, s), 4.08 (1 H, dd, *J* = 5.5, 11.0 Hz), 4.27 (1 H, dd, *J* = 2.8, 11.0 Hz), 4.76 (1 H, br dt, *J* = 2.8, 7.3 Hz), 5.44 (1 H, br dd, *J* = 3.7, 7.3 Hz), 7.19 (1 H, d, *J* = 3.7 Hz), 7.36–7.43 (5 H, m), 7.61–7.68 (5 H, m). To a boiling suspension of **3a** obtained above (603 mg, 1.23 mmol) and MS 4A (powder, 2.5 g) in THF (50 mL) was added a solution of TBAT (682 mg, 1.23 mmol) in THF (3 mL), and the mixture was further heated at the same temperature for 7 min. After cooling, MS 4A was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc–MeOH (1:0 to 8:1) to give **4a** (135 mg, 70%), mp 110–112 °C (diisopropyl ether), $[\alpha]_D^{26}$ –26.3 (*c* 0.50, CH_2Cl_2) [lit.[4] mp 110–111 °C, $[\alpha]_D^{20}$ –28.0 (*c* 0.46, CH_2Cl_2)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (3 H, s), 1.47 (3 H, s), 4.05 (1 H, br d, *J* = 15.1 Hz), 4.14 (1 H, br dd, *J* = 4.4, 15.1 Hz), 4.92 (1 H, br t, *J* = 6.4 Hz), 5.31 (1 H, br d, *J* = 5.9 Hz), 6.89 (1 H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 27.1, 67.9, 73.5, 79.8, 112.1, 132.5. The ^{1}H NMR spectral data are identical with those previously reported.[4]

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