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Stereospecific *N*-oxide-mediated monoprotection of *trans*-3,4-dihydroxypyrrolidine derivatives

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Abstract—We found that the syntheses of *O*-monosubstituted 1-*N*-alkyl-*trans*-3,4-dihydroxypyrrolidines, normally faces serious obstacles due to poorly reactive hydroxy groups as a consequence of the presence of a highly basic pyrrolidine nitrogen atom, but that they can be obtained easily in high yields by conversion of 1-*N*-alkyl-*trans*-3,4-dihydroxypyrrolidines into the corresponding *N*-oxides. *N*-Oxidation leads to the loss of the pyrrolidine nitrogen atom basicity and discrimination in the reactivity of the originally equivalent hydroxy groups by at least one order of magnitude. The reaction of *N*-oxide derivatives with DMTrCl or TBDPSCl then proceeds in an almost quantitative yield, rapidly, and stereospecifically on the hydroxy group which is in a *cis*-position to the *N*-oxide oxygen atom. In contrast to the TBDPS derivative, the DMTr derivative could be easily deoxygenated with triphenylphosphine in high yield. The structures of the products obtained were confirmed by 2D NMR experiments, and quantum-chemical calculations were performed to explain the reaction mechanism of the stereospecific course of the reaction.

1. Introduction

Enantiomeric *trans*-3,4-dihydroxypyrrolidines and their derivatives are important precursors for the stereospecific synthesis of biologically active compounds such as antitumor agents[1] and inhibitors of glycosidases,[2] anti-protozoa compounds,[3] or as building blocks for the synthesis of chiral catalysts.[4] The pyrrolidine ring has also been employed as a sugar mimic in analogues of nucleosides.[5–18]

The synthesis of *O*-monosubstituted 1-*N*-alkyl-*trans*-3,4-dihydroxypyrrolidines in high yields represent a serious problem due to the presence of equally reactive hydroxy groups. For instance, the silylation of 1-*N*-benzyl-*trans*-3,4-dihydroxypyrrolidine with TBDMSCl in DMF in the presence of imidazole afforded only 21% of the monosilylated product.[19] However, the alkylation of the same pyrrolidine derivative with chloromethyl-2-methoxyethyl ether in THF, using sodium hydride to generate the alkoxide, led to a 61% yield of the monoprotected derivative.[20] The benzoylation of 1-*N*-benzyl-*trans*-3,4-dihydroxypyrrolidine with benzoyl chloride in DMF, and in the presence of triethylamine gave, by recycling of unreacted dihydroxypyrrolidine and bis-benzoyl derivative, a final 90% yield of the monobenzoyl derivative, but the authors did not specify the number of cycles.[21]

An attempt to selectively protect one hydroxy group of (3*S*,4*S*)-*trans*-1-*N*-benzyl-3,4-dihydroxypyrrolidine **1a**[18,22,23] with DMTr (dimethoxytrityl) or TBDPS (*tert*-butyldiphenylsilyl) protecting groups under various conditions, has led to a moderate yield of the desired product which, in our hands, has never exceeded 55%.[18] The disubstituted derivative and the unreacted starting material were always present in the reaction mixture.

Based on the above-mentioned facts, the problem which we wanted to address in this paper concerned the influence of the *N*-oxide oxygen atom on the reactivity of the otherwise equally reactive hydroxy groups in *trans*-3,4-dihydroxypyrrolidine.

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2. Results and discussion

2.1. Synthesis

(3*S*,4S)-*N*-Benzyl-3,4-dihydroxypyrrolidine **1a**[18,22,23] was converted to its 1-*N*-oxido derivative **4a** by treatment with a mixture of 30% hydrogen peroxide and ethanol (1:1) overnight (Scheme 1). The *N*-oxide **4a** was reacted with DMTrCl or TBDPSCl, respectively, in pyridine. The reaction was left to proceed overnight (quantitative conversion), although the majority of starting material (~90%) was consumed, in contrast to the dimethoxytritylation of **1a**, within the first five minutes, as determined by HPLC (for the reaction profile see Fig. 1).

We also attempted the tosylation and benzoylation of compound **4a** to obtain the appropriate *mono*-derivative, but in this case the reaction gave a mixture of products.

An NMR study showed that only one diastereoisomeric dimethoxytrityl derivative, **5a**, was formed. It was subsequently silylated with TBDPSCl in pyridine to provide compound **6**, which in turn was detritylated with 80% aqueous acetic acid to give silyl derivative **9**. This compound was also obtained as the only product by the oxidation of **3** with hydrogen peroxide (Scheme 1). In this case, the oxidation proceeded with 100% stereoselectivity. The silyl derivative **7**, with the same stereochemistry as **5a** was obtained from **4a** and TBDPSCl. This compound was dimethoxytritylated to give the fully protected compound **8**. Both **8** and **9** served as compounds for assignment of the configuration on the nitrogen atom of the *N*-benzyl-*N*-oxido moiety. To confirm a more general validity of the described procedure and in order to avoid the influence of *N*-benzyl group on the stereochemical course of the

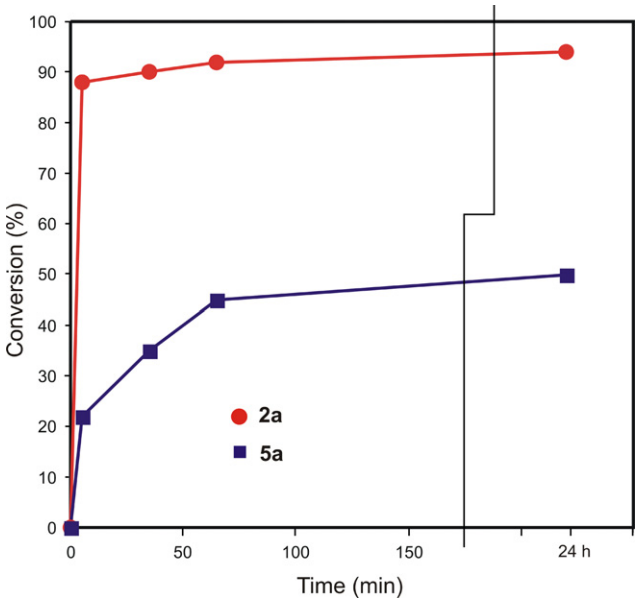
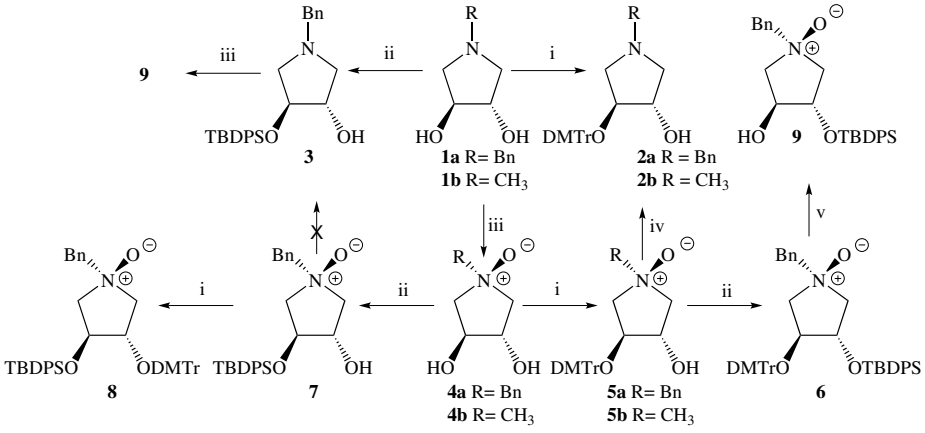


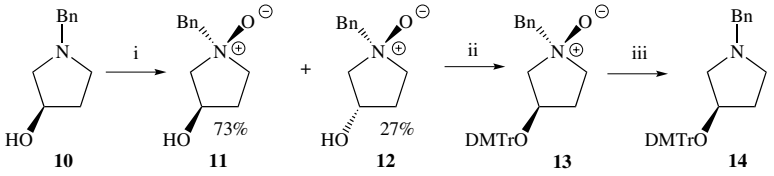
Figure 1. Kinetics of dimethoxytritylation of pyrrolidine **1a** and **4a** to monodimethoxytrityl derivatives **2a** and **5a**, respectively.

reaction, 1-*N*-methyl-3,4-dihydroxypyrrolidine[24] **1b** and its *N*-oxido derivative **4b** were prepared. Dimethoxytritylation of **4b** to **5b** proceeded in the same manner and with the same stereochemistry (only one diastereoisomer was formed), as in case of the 1-*N*-benzyl derivative **4a**.

In order to obtain more information about the reaction mechanism, we carried out an experiment with a diastereoisomeric mixture of (1*RS*,3*R*)-*N*-benzyl-3-hydroxypyrrolidine-*N*-oxides **11** and **12** (73:27) prepared by the oxidation of (3*S*)-*N*-benzyl-3-hydroxypyrrolidine **10**[7]



Scheme 1. Reagents: (i) DMTrCl, pyridine; (ii) TBDPSCl, pyridine; (iii) 30% H_2O_2/EtOH 1:1; (iv) Ph_3P, DCM; (v) 80% aq acetic acid.



Scheme 2. Reagents: (i) 30% H_2O_2/EtOH 1:1; (ii) DMTrCl, pyridine; (iii) Ph_3P, DCM.

(Scheme 2). Dimethoxytritylation of the mixture of **11** and **12** afforded only one diastereoisomeric DMTr derivative **13**, along with the unreacted compound **12**.

We also attempted to remove the *N*-oxide oxygen atom from *O*-DMTr derivatives **5a** and **13**, as well as from the *O*-TBDPS derivative **7**, using the reaction with triphenylphosphine.[25] Whereas the deoxygenation proceeded smoothly in case of the DMTr derivatives **5a** and **13**, the TBDPS derivative **7** was quite resistant; also the reduction of **7** with samarium diiodide[26] failed.

2.2. NMR analysis

The structure and purity of all the pyrrolidine derivatives were analyzed by means of ^{1}H and ^{13}C NMR spectra. The presence of an oxygen atom in the *N*-oxides can be detected indirectly by the low-field shifts (10–15 ppm) of carbon atoms bonded to nitrogen and also of the hydrogen atoms at vicinal positions (0.8–1.6 ppm) in comparison with analogous derivatives without oxygen. The largest low-field effect (ca. 85 ppm) can be observed in ^{15}N NMR as it is documented on a pair of compounds: **1b** (−337.9 ppm) and **4b** (−251.9 ppm).

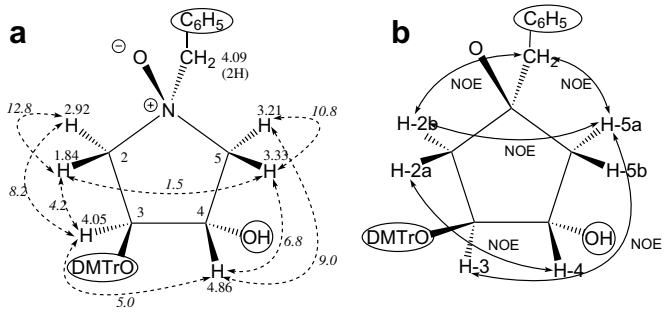


Figure 2. NMR structure analysis of compound **5a**: (a) Proton chemical shifts and coupling constants (indicated with dashed arrows); (b) selected non-trivial NOE's allowing for the stereochemical assignment of hydrogens at C-2, C-5 and determination of the relative configurations of *N*-benzyl group and substituents (OH, ODMTr).

A much more difficult task was encountered with the determination of the configuration at the nitrogen atom of the *N*-oxides due to the absence of relevant interproton coupling constants and the possible flexibility of the pyrrolidine ring. Therefore, we had to combine the observed endocyclic vicinal *J*(H,H) and NOE-contacts (from 2D-ROESY spectra) in order to determine first the relative (*cis*- and *trans*-) orientation of methylene hydrogen atoms at the 2- and 5-positions to the substituents at the 3- and 4-positions, as well as the conformational features of the pyrrolidine ring. Then we had to find the NOE contacts of methyl protons of the $N–CH_3$ group and/or methylene protons of the *N*-benzyl group to the hydrogen atoms at the 2- and 5-positions for the determination of configuration at the nitrogen atom. The NMR analysis for compound **5a** is illustrated in Figure 2. The coupling pattern observed in 2D-H,H-COSY spectrum and *J*(H,H) values (see Fig. 2a) leads to the assignment of the endocyclic protons in the 2-, 3-, 4-, and 5-positions. The observed NOE contacts H-4/H-2a, H-3/H-5a, and H-2b/H-5a indicate mutual *cis*-orientation of those pairs of protons and lead to the stereochemical assignment of methylene protons at C-2 and C-5. Then, the NOE contacts between the hydrogens of *N*-benzyl methylene group and the hydrogen atoms H-2b, H-5a define the configuration at the *N*-oxide nitrogen atom, as it is shown in Figure 2b.

A similar approach was used to establish the configuration of other *N*-oxides. No NOE contacts were observed

Table 1. ^{1}H NMR parameters of compounds **1**–**14** (coupling constants *J*(H,H) are given in italics)

Compound solvent	H-2	H-2′	H-3	H-4	H-5	H-5′
1a[a]	2.76 dd	2.32 dd	3.85 dd	3.85 dd	2.76 dd	2.32 dd
DMSO	*9.5*; *4.4*	*9.5*; *5.9*	*5.9*; *4.4*	*5.9*; *4.4*	*9.5*; *4.4*	*9.5*; *5.9*
1b[b]	2.70 dd	2.24 dd	3.82 dd	3.82 dd	2.70 dd	2.24 dd
DMSO	*9.6*; *6.0*	*9.6*; *4.0*	*6.0*; *4.0*	*6.0*; *4.0*	*9.6*; *6.0*	*9.6*; *4.0*
2a[c]	1.69 dd	1.56 dd	3.78 ddd	4.14 m	2.63 dd	2.23 dd
DMSO	*10.3*; *6.5*	*10.3*; *4.5*	*6.5*; *4.5*; *3.1*	*6.2*; *5.9*; *4.6*; *3.1*	*9.5*; *6.2*	*9.5*; *4.6*
2b[d]	1.80 dd	1.61 dd	3.82 ddd	4.12 m	2.67 dd	2.23 dd
DMSO	*10.3*; *6.4*	*10.3*; *4.1*	*6.4*; *4.1*; *2.8*	*6.1*; *4.5*; *2.8*	*9.6*; *6.1*	*9.6*; *4.5*
3[e]	2.57 dd	2.38 dd	4.08 ddd	4.10 m	2.36 dd	2.82 dd
DMSO	*9.8*; *5.7*	*9.8*; *4.1*	*5.7*; *4.1*; *2.4*	*6.0*; *5.2*; *3.8*; *2.4*	*9.8*; *3.8*	*9.8*; *6.0*
4a[f]	4.02 dd	3.35 dt	4.09 dt	4.33 dt	3.75 ddd	3.45 dd
DMSO	*12.3*; *6.6*	*12.3*; *2.3*; *1.9*	*6.6*; *2.4*; *2.3*	*2.4*; *6.3*; *6.1*	*11.8*; *6.3*; *1.9*	*11.8*; *6.1*
4b[g]	3.88 ddd	3.27 dd	4.38 ddd	3.94 dt	3.69 dd	3.25 ddd
DMSO	*11.8*; *6.6*; *2.1*	*11.8*; *4.4*	*6.6*; *4.4*; *1.0*	*4.4*; *1.0*; *0.9*	*11.2*; *4.4*	*11.2*; *2.1*; *0.9*
5a[h]	2.92 dd	1.84 dd	4.05 ddd	4.86 dq	3.33 dd	3.21 dd
DMSO	*12.8*; *8.2*	*12.8*; *4.2*	*8.2*; *5.0*; *4.2*	*9.0; 6.8*; *5.0*	*10.8*; *6.8*	*10.8*; *9.0*
5b[i]	3.26 dd	2.67 m	4.18 ddd	4.62 ddd	3.82 ddd	3.45 dd
DMSO, 50 °C	*12.9*; *7.0*	*12.9*; *2.8*; *1.4*	*7.0*; *3.6*; *2.8*	*6.7*; *5.9*; *3.6*	*11.7*; *5.9*; *1.4*	*11.7*; *6.7*
6[j]	2.98 dd	1.67 ddd	4.33 m	5.33 dt	3.14 td	2.52
DMSO	*12.3*; *8.6*	*12.3*; *4.5*; *1.5*	*8.6*; *6.0*; *4.5*	*9.7*; *6.0*; *6.0*	*10.0*; *9.7*; *1.5*	*10.0*; *6.0*
7[k]	3.70 dd	2.96 ddd	4.24 dt	4.67 m	3.30 br dd	3.20 ddd
DMSO	*12.1*; *7.9*	*12.1*; *4.2*; *1.3*	*7.9*; *4.2*; *4.0*	*7.3*; *6.2*; *4.0*	*10.9*; *7.3*	*10.9*; *6.2*; *1.3*

(*continued on next page*)

Table 1 (*continued*)

Compound solvent	H-2	H-2′	H-3	H-4	H-5	H-5′
8[l]	2.60 um	2.44 um	4.56 td	4.74 br q	3.26 dd	3.08 br dd
$CDCl_3$	*~12.0*; *6.6*	*~12.0*; *6.6*	*6.6*; *6.6*; *4.3*	*6.8*; *6.4*; *4.3*	*12.0*; *6.8*	*12.0*; *6.4*
9[m]	3.76 dd	3.06 dt	4.07 br d	4.49 ddt	3.43 dd	3.47 ddd
DMSO	*11.0*; *4.4*	*11.0*; *1.9*; *<1.5*	*4.4*; *<1.5*	*6.4*; *4.9*; *<1.5*; *<1.5*	*11.6*; *4.9*	*11.6*; *6.4*; *1.9*
10[n]	2.65 dd	2.28 dd	4.18 m	1.53 m	2.54 ddd	2.38 ddd
DMSO	*9.6*; *6.2*	*9.6*; *3.8*	*7.8*; *6.2*; *3.8*; *3.4*	*13.0; 7.8*; *5.6*; *3.4* 1.98 m *13.0*; *7.9*; *7.8*; *6.5*	*8.8*; *7.8*; *6.5*	*8.8*; *7.9*; *5.6*
11[o]	3.40 dd	3.00 dd	4.26 m	2.09 dddd	3.51 td	3.28 ddd
DMSO (73%)	*10.7*; *4.3*	*10.7*; *1.8*	*6.9*; *4.3*; *1.8; 0.9*	*13.6*; *9.2*; *8.0*; *0.9* 2.29 dddd *13.6*; *10.7*; *6.9*; *3.5*	*10.7*; *10.7*; *8.0*	*10.7*; *9.2*; *3.5*
12[p]	3.22 dd	3.19 dd	4.55 ddd	1.65 ddt	3.62 td	2.94 ddd
DMSO (27%)	*11.0*; *5.8*	*11.0*; *6.4*	*7.9*; *5.8*; *2.3*	*13.2*; *8.0*; *2.3*; *2.3* 2.54 ddt *13.2*; *10.5*; *7.9*; *7.9*	*10.5*; *10.5*; *8.0*	*10.5*; *7.9*; *2.3*
13[q]	3.18 dd	2.43 m	4.30 td	2.35 m	3.30 td	3.18 m
DMSO, 50 °C	*12.5*; *8.2*	*12.5*; *3.3*; *2.5*	*8.5*; *8.2; 6.5*	*12.6*; *11.4*; *7.8*; *6.5* 2.00 m *12.6*; *8.5*; *8.3*; *6.6*	*11.4*; *11.4*; *6.6*	*11.4*; *8.3* *7.8*; *2.5*
14[r]	2.17 dd	2.04 dd	4.03 m	1.42 m	2.37 ddd	2.24 ddd
DMSO	*9.9*; *6.8*	*9.9*; *4.9*	*8.1*; *6.8*; *4.9*; *4.3*	*13.4*; *8.1*; *5.7*; *4.3* 1.58 m *13.4*; *8.1*; *7.5*; *6.5*	*9.0*; *8.1*; *6.5*	*9.0*; *7.5*; *5.7*

Additional protons.
[a] NBn: 3.60 d (1H), 3.49 d (1H), 7.22–7.33 m (5H), OH: 4.56 b (2H).
[b] NCH_3: 2.17 s, OH: 4.80 b (2H).
[c] Bn: 3.31 d (1H), 3.26 d (1H), 7.25 m (2H), 7.19 m (1H), 7.10 m (2H), ODMTr: 6.83 m (2H), 6.84 m (2H), 7.19 m (1H), 7.26 m (2H), 7.28 m (2H), 7.29 m (2H), 3.71 s (3H), 3.715 s (3H).
[d] OH: 4.95 b (1H), ODMTr: 6.88 m (4H), 7.28 m (2H), 7.31 m (2H), 7.43 m (2H), 7.30 m (2H), 7.22 m (1H), 3.74 s (6H).
[e] NBn: 3.56 d (1H), 3.43 d (1H), 7.19–7.29 m (5H), OTBDPS: 1.01 s (9H), 7.36–7.46 m (6H), 7.59 m (2H), 7.65 m (2H), OH: 4.97 d (1H, $J = 5.2$).
[f] NBn: 4.64 d (1H), 4.67 d (1H), 7.36–7.42 m (3H), 7.57 m (2H).
[g] NCH_3: 3.15 s (3H).
[h] NBn: 4.09 br s (2H), 7.27 m (2H), 7.28 m (2H), 7.34 m (1H), ODMTr: 6.81 m (2H), 6.83 m (2H), 7.20 m (1H), 7.27 m (2H), 7.33 m (2H), 7.48 m (4H), 3.72 s (3H), 3.73 s (3H).
[i] NCH_3: 3.14 s (3H), ODMTr: 6.89 m (2H), 6.90 m (2H), 7.25 m (1H), 7.29 m (2H), 7.31 m (2H), 7.32 m (2H), 7.44 m (2H), 3.73 s (3H), 3.74 s (3H).
[j] NBn: 3.81 d (1H), 3.85 d (1H), 7.11 m (2H), 7.20 m (2H), 7.29 m (1H), OTBDPS: 7.81 m (2H), 7.67 m (2H), 7.55 m (1H), 7.50 m (1H), 7.48 m (2H), 7.42 m (2H), 1.09 s (9H), ODMTr: 6.75 m (2H), 6.79 m (2H), 7.24 m (2H), 7.29 m (2H), 7.20–7.45 m (5H), 3.73 s (3H), 3.71 s (3H).
[k] NBn: 4.21 d (1H), 4.18 d (1H), 7.37–7.46 m (2H), 7.28 m (2H), 7.34 m (1H), OTBDPS: 7.65 m (2H), 7.60 m (2H), 7.37–7.46 m (5H), 7.34 m (1H), 1.10 s (9H).
[l] NBn: 4.15 br d (1H), 3.98 br d (1H), 7.18–7.33 m (5H), OTBDPS: 7.74 m (2H), 7.67 m (2H), 7.48 m (1H), 7.45 m (1H), 7.38 m (2H), 7.37 m (2H), 1.10 s (9H), ODMTr: 6.76 m (2H), 6.74 m (2H), 7.29 m (2H), 7.32 m (2H), 7.18–7.45 m (5H), 3.755 s (3H), 3.765 s (3H).
[m] NBn: 4.42 s (2H), 7.36–7.53 m (5H), OTBDPS: 0.98 s (9H), 7.36–7.53 m (6H), 7.52 m (2H), 7.57 m (2H).
[n] NBn: 3.56 d (1H), 3.51 d (1H), 7.21–7.32 m (5H).
[o] NBn: 4.39 d (1H), 4.35 d (1H), 7.38 m (3H), 7.56 m (2H).
[p] NBn: 4.38 d (1H), 4.33 d (1H), 7.38 m (3H), 7.56 m (2H).
[q] NBn: 4.25 d (1H), 4.22 d (1H), 7.20–7.40 m (5H), ODMTr: 6.84 m (2H), 6.86 m (2H); 7.20–7.40 m (9H), 3.742 s (3H), 3.735 s (3H).
[r] NBn: 3.39 d, 3.36 d, 7.17–7.28 m (5H), ODMTr: 6.85 m (2H), 6.86 m (2H), 7.25 m (2H), 7.26 m (2H), 7.39 m (2H), 7.17–7.28 m (3H).

between the aromatic hydrogens of substituents and pyrrolidine protons, obviously due to the preferred orientation of the aromatic substituents out of the pyrrolidine ring. The ^1H and ^{13}C NMR data of compounds **1**–**14** are summarized in Tables 1 and 2.

2.3. Reaction mechanism and molecular modeling

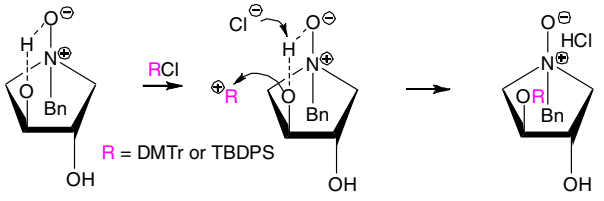
The NMR data clearly show that *N*-oxide oxygen atom in compounds **5a**, **5b**, **13**, and **7** is *cis*-oriented toward the hydroxyl function bearing the DMTr or TBDPS groups. The introduction of the *N*-oxide moiety into *N*-benzyl-3,4-dihydroxypyrrolidine **1a** completely changes the reactivity of both hydroxy groups which become chemically non-equivalent due to their *trans* and *cis* orientations to the *N*-oxide oxygen atom. The electron reach *N*-oxide oxygen atom could be involved in the intramolecular hydrogen bridge (Scheme 3) and thus influence the nucleophilicity of the hydroxy group which is *cis*-oriented toward *N*-oxide oxygen atom.

The analysis of electrostatic potentials, molecular HOMO orbitals, conformational energies, etc. of compounds **1b** and **4b** supported the proposed reaction mechanism. Firstly, comparison of electrostatic potentials clearly shows (Fig. 3) that all potential nucleophilic centers (the *N* atom

Table 2. Carbon-13 NMR chemical shifts of compounds **1**–**14**

Compound solvent	C-2	C-3	C-4	C-5	Other carbons
1a DMSO	60.92	77.69	77.69	60.92	NBn: 60.12, 138.98, 128.75(2), 128.29(2), 126.99
1b DMSO	62.72	77.65	77.65	62.72	NCH_3: 42.83
2a DMSO	59.01	80.60	76.79	60.29	NBn: 59.83, 138.66, 128.63(2), 128.09(2), 126.82; ODMTr: 158.26(2), 145.94, 136.94, 136.48, 130.16(2), 130.03(2), 128.09(2), 127.89(2), 126.72, 113.29(2), 113.25(2), 86.01, 55.19(2)
2b DMSO	61.38	81.06	77.25	62.44	NCH_3: 42.39; ODMTr: 158.29(2), 145.83, 136.84, 136.57, 130.15(2), 130.08(2), 128.18(2), 127.94(2), 126.83, 113.35(2), 113.32(2), 86.16, 55.23(2)
3 DMSO	60.68	80.28	77.86	60.82	Bn: 59.96, 139.07, 128.54(2), 128.24(2), 126.90; OTBDPS: 135.46(2), 135.36(2), 133.88, 133.49, 129.93, 129.92, 127.92(2), 127.89(2), 26.90(3), 18.96
4a DMSO	71.99	76.08	76.28	71.08	Bn: 69.92, 130.40, 128.47(2), 132.88(2), 129.66
4b DMSO	77.34	77.61	78.37	71.81	NCH_3: 56.79
5a DMSO	72.17	77.77	74.57	70.54	NBn: 71.29, 131.59, 127.59(2), 132.38(2), 128.64; ODMTr: 158.42, 158.39, 145.39, 136.40, 135.78, 130.29(2), 130.08(2), 128.11(2), 127.94(2), 126.86, 113.40(2), 113.33(2), 86.08, 55.20(2)
5b DMSO	73.38	77.91	74.80	71.44	NCH_3: 56.96; ODMTr: 158.52(2), 144.86, 135.84, 135.57, 130.14(2), 130.05(2), 128.12(4), 127.14, 113.58(2), 113.55(2), 86.72, 55.26(2)
6 DMSO	71.53	77.36	77.14	68.60	NBn: 71.53, 131.99(3), 128.07(2), 127.41; OTBDPS: 135.50(2), 135.47(2), 132.96, 132.87, 130.43, 130.28, 127.98(2), 127.87(2), 27.04(3), 18.88; ODMTr: 158.45, 158.43, 145.20, 136.16, 135.55, 130.20(2), 130.07(2), 128.07(4), 126.94, 113.32(2), 113.28(2), 86.16, 55.17, 55.16
7 DMSO	71.93*	77.83**	76.02**	71.84*	NBn: 74.90*, 131.90, 132.47, 127.99(2), 128.75; OTBDPS: 135.54(2), 135.36(2), 133.36, 132.95, 130.09, 130.01, 127.94(2), 127.74(2), 28.86(3), 18.88
8 $CDCl_3$	71.78	77.22	78.14	72.05	NBn: 73.56, 132.17(3), 128.00(2), 129.18; OTBDPS: 136.02(2), 135.87(2), 132.93, 132.85, 130.20, 129.97, 128.00(2), 127.89(2), 27.01(3), 19.16; ODMTr: 158.87, 158.82, 144.86, 136.07, 135.46, 130.16(2), 130.13(2), 128.28(2), 128.05(2), 127.09, 113.50(2), 113.43(2), 87.25, 55.19, 55.15
9 DMSO	68.90	77.64	79.77	75.12	NBn: 69.88, 131.50, 128.08(2), 132.39(2), 129.01; OTBDPS: 135.25(2), 135.23(2), 132.88, 132.75, 130.22, 130.18, 128.08(2), 128.04(2), 26.77(3), 18.75
10 DMSO	62.79	69.57	34.63	52.60	NBn: 59.93, 139.44, 128.65(2), 128.28(2), 126.90
11 D_2O (77%)	73.08	69.37	32.11	65.76	NBn: 70.26, 129.99, 132.41(2), 128.66(2), 129.81
12 D_2O (23%)	73.83	68.53	31.36	65.69	NBn: 70.85, 130.02, 132.51(2), 128.66(2), 129.87
13 DMSO	69.74	71.04	30.83	65.18	NBn: 71.87, 131.02, 132.34(2), 127.96(2), 129.07; ODMTr: 158.44, 158.40, 145.27, 136.17, 135.94, 129.91(2), 129.84(2), 128.11(2), 127.82(2), 126.97, 113.54(2), 113.47(2), 86.64, 55.24(2)
14 DMSO	60.46	73.15	32.79	52.29	NBn: 59.68, 139.00, 128.57(2), 128.18(2), 126.85; ODMTr: 158.25(2), 145.98, 136.84, 136.76, 129.90(2), 129.87(2), 127.98(2), 127.89(2), 126.73, 113.36(4), 86.15, 55.16(2)

*,** The signals with the same symbols may by mutually interchanged.



Scheme 3.

as well as the oxygen atoms of both hydroxy groups) are equally attractive for incoming cation in the case of the *N*-methylpyrrolidine molecule **1b**. They are situated on the bottom of the separated funnel-shaped craters of negative potential values. In contrast, in the case of highly polarized *N*-oxide **4b**, there is a negative potential spreading over the whole half-space involving the *N*-oxide oxygen atom and *cis*-oriented 'reactive' hydroxy group making them undoubtedly more accessible for a cation (to simplify the calculation, we used Me_3Si^+ cation instead of $TBDPSi^+$ or $DMTr^+$ cations). On the other hand, the *trans*-oriented, 'non-reactive' hydroxy group, encapsulated in the zero potential ellipsoid surrounded by positive values, does not seem to be attractive for a cation.

Electrostatic potential was 'painted' on the electron density isosurface. Red represents negative regions around the oxygen and nitrogen atoms and blue represents positive regions around the hydrogen atoms.

Visualization of HOMO orbitals and HOMO frontier densities shows (Fig. 4) that the most nucleophilic site in the methylpyrrolidine **1b** molecule is the nitrogen atom. In contrast, the HOMO orbitals in *N*-oxide **4b** are equally divided between the *N*-oxide and the *cis*-oriented hydroxy group.

Finally, conformational energies of the speculative complexes consisting of **1b** and Me_3Si^+ cation confirmed that the cation should be preferably localized at the nitrogen atom (Fig. 5). In contrast, the *cis*-oriented, 'reactive' hydroxy group in **4b** seemed to be the landing site. It should be noted that the hydrogen atom of this hydroxyl overjumped onto the *N*-oxide oxygen atom from where it could be removed by the chloride anion or pyridine.

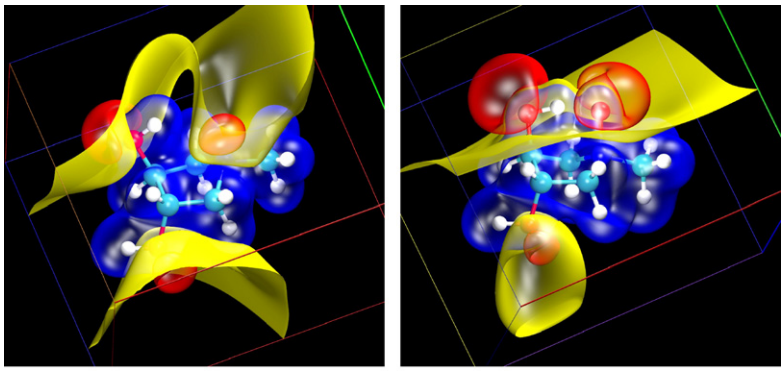


Figure 3. Electrostatic potential isosurfaces for compounds **1b** and **4b**—zero (yellow), positive (blue), negative (red).

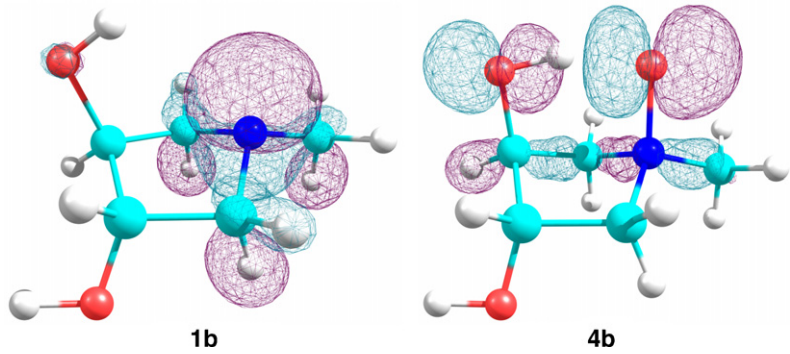


Figure 4. HOMO orbitals in the methylpyrrolidine **1b** and *N*-oxide **4b**.

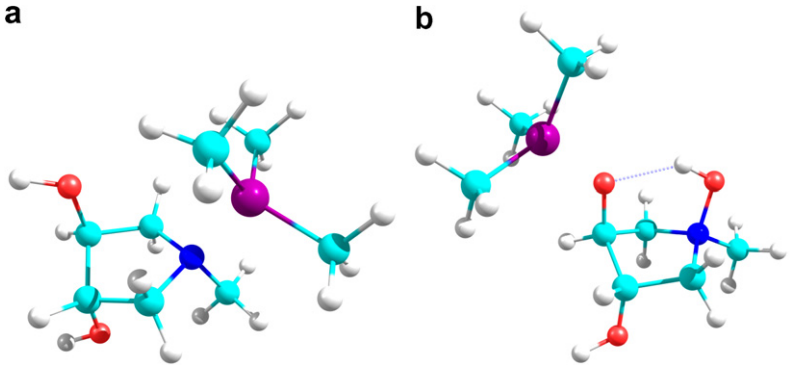


Figure 5. The lowest energy transition state intermediates [**1b**·Me_3Si^+] (a) and [**4b**·Me_3Si^+] (b).

In summary, the electrostatic potential analysis showed why the *trans*-oriented 'non-reactive' hydroxyl (*trans* to *N*-oxide oxygen atom) is neglected by cations in **4b**, and the conformational energies showed that an incoming cation would be connected to **4b** through the 'reactive' *cis*-hydroxy group, whereas the *N*-oxide oxygen atom would assist by temporary adopting the incoming proton. Moreover, the HOMO orbitals uncovered that the nitrogen atom, rather than both hydroxy groups, is the most nucleophilic site in **1b**, thus providing an explanation for a different reactivity toward electrophilic agents compared to **4b**.

3. Conclusion

We have found that the presence of an *N*-oxido moiety in 1-*N*-alkyl-*trans*-3,4-dihydroxypyrrolidine-*N*-oxides strongly enhances the reactivity of only one of the two hydroxy groups toward some of the electrophilic reagents, for example, DMTrCl and TBDPSCl. A detailed NMR study revealed that the hydroxy group, which is *cis*-oriented to the *N*-oxide oxygen atom, is the highly reactive one. The reaction mechanism was studied by ab initio calculation, and the data obtained are in full agreement with the

experimental data. These findings could be of practical use for an efficient monoprotection of *trans*-dihydroxypyrrolidines and their further synthetic exploitation. Additional studies on the reactivity enhancement caused by *N*-oxide oxygen atom in another type of the hydroxylated heterocyclic compounds are currently underway.

4. Experimental

4.1. Molecular modeling

Gas-phase quantum-mechanical calculations are a powerful tool for the investigation of *N*-oxide moieties.[27–29] Therefore, ab initio geometry optimizations of several model systems and subsequent calculations of electron densities, electrostatic potentials, molecular HOMO, LUMO, and natural orbitals were carried out at the HF level. The 6-31G(d) basis set was used. On this basis, the d-type functions referred to as polarization functions enable to describe precisely the geometry of the systems, in particular those involving bonds between the electronegative atoms, such as N–O. All calculations were performed with the GAUSSIAN03 quantum chemistry software package.[30] Results were visualized using VMD,[31] WEBMO,[32] and CHEMCRAFT[33] programs.

4.2. NMR spectroscopy

NMR spectra of the pyrrolidine derivatives were measured on Varian UNITY-500 and Bruker AVANCE-500 spectrometers (^{1}H at 500 MHz; ^{13}C at 125.7 MHz) in $CDCl_3$, DMSO, and/or D_2O. The chemical shifts are given in δ-scale [ppm] and the coupling constants in Hz. ^{1}H NMR spectra were referenced to tetramethylsilane (in $CDCl_3$) and/or residual signal of the solvent (δ(DMSO) = 2.50 and $\delta(D_2O) = 4.80$). ^{13}C NMR spectra were referenced either to the solvent peak (δ(DMSO) = 39.7 and $\delta(CDCl_3) = 77.0$) or DSS as secondary standard (in D_2O). Structural assignment of protons and carbon atoms was achieved using correlated homonuclear ^{1}H,^{1}H-2D-COSY and heteronuclear ^{1}H,^{13}C-2D-HMQC and ^{1}H,^{13}C-2D-HMBC spectra. The homonuclear ^{1}H,^{1}H-2D-ROESY spectra were used for determination of the spatially close hydrogen atoms and for the stereochemical assignment of methylene protons. The ^{15}N chemical shifts for compounds **1b** and **4b** were obtained from ^{1}H,^{15}N-2D-HMBC spectra in DMSO and referenced to CH_3NO_2 as the external standard (in capillary). Optical rotations were measured on polarimeter Autopol IV (Rudolph Res. Anal., USA) in ethanol at 589 nm.

4.3. Synthesis

Unless stated otherwise, all used solvents were anhydrous. Products were evaporated or lyophilized from dioxane, and dried over phosphorus pentoxide at 50–70 °C and 13 Pa. TLC was performed on silica gel pre-coated aluminum sheets UV 254 (Fluka). The compounds were detected by UV light (254 nm), by heating (detection of DMTr group; orange color), or by spraying with a 1% solution of ninhydrine to visualize pyrrolidines (they usually gave brown spots after heating). Preparative column chromatography was carried out on a silica gel (40–60 μm; Fluka) neutralized with triethylamine (1 mL/100 g), and the elution was performed at the flow rate of 40 mL/min. The following solvent systems were used for TLC and preparative chromatography: toluene–ethyl acetate 1:1 (T); chloroform–ethanol 9:1 (C1); ethyl acetate–acetone–ethanol–water 6:1:1:0.5 (H3). The concentrations of the solvent systems are provided in volume (v/v) percents. Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument, using FAB (ionization with Xe, accelerating voltage 8 kV). Glycerol and thioglycerol were used as matrices. IR spectra were measured in KBr tablets.

4.4. (3*S*,4*S*)-1-*N*-Benzyl-3-dimethoxytrityloxy-4-hydroxypyrrolidine 2a

4.4.1. Method A. Dimethoxytrityl chloride (2.2 g, 6.4 mmol) was added to a solution of **8a** (0.84 g, 4.3 mmol) in pyridine (50 mL). The reaction mixture was set aside at rt for 2 d. Anhydrous methanol (1 mL) was added, and the solution concentrated in vacuo. The product **2a** was obtained by chromatography on silica gel using a linear gradient of toluene in petroleum ether followed by a linear gradient of ethyl acetate in toluene in 52% yield (1.1 g, 2.23 mmol) as a yellow oil.

4.4.2. Method B. Compound **5a** (0.51 g, 1 mmol) was treated with triphenylphosphine (1.3 g, 5 mmol) in DCM (10 mL) at rt for 2 d. The product **2a** was obtained by purification on silica gel using a linear gradient of ethyl acetate in toluene in 75% yield (0.37 g, 0.75 mmol). HR-MS: $(M+H)^+$ calcd for $C_{32}H_{33}NO_4$, 495.2420; found, 495.2414. $[\alpha]_D^{20} = +35.8$ (*c* 0.396, ethanol).

4.5. (3*S*,4*S*)-1-*N*-Methyl-3-dimethoxytrityloxy-4-hydroxypyrrolidine 2b

A solution of compound **5b** (0.086 g, 0.2 mmol) and triphenylphosphine (0.52 g, 2 mmol) in DCM (2 mL) was set aside at rt for 2 d. The product **2b** was obtained by purification on silica gel using a linear gradient of ethyl acetate in toluene in 38% yield (0.032 g, 0.076 mmol) as a yellow oil. HR-MS: $(M+H)^+$ calcd for $C_{26}H_{30}NO_4$, 420.2169; found, 420.2173.

4.6. (3*S*,4*S*)-1-*N*-Benzyl-3-*tert*-butyldiphenylsilyloxy-4-hydroxypyrrolidine 3

1-*N*-Benzyl-3,4-dihydroxypyrrolidine[17,21,22] **1a** (2 g, 10.36 mmol) was treated with *tert*-butylchlorodiphenylsilane (2.91 mL, 12 mmol) and imidazole (0.82 g, 12 mmol) in pyridine (50 mL). The reaction mixture was stirred at rt overnight (TLC in T and C1), quenched with methanol (1 mL), and the solution was concentrated in vacuo. The desired product **3** was obtained by chromatography on silica gel using a linear gradient of ethyl acetate in toluene in 22% yield (0.93 g, 2.24 mmol) as a yellowish thick oil. HR-MS: (M+H) calcd for $C_{27}H_{34}NO_2Si$, 432.2359; found, 432.2350. $[\alpha]_D^{20} = +27.8$ (*c* 0.416, ethanol).

4.7. (3*S*,4*S*)-1-*N*-Benzyl-3,4-dihydroxy-1-*N*-oxidopyrrolidine 4a

1-*N*-Benzyl-3,4-dihydroxypyrrolidine[17,21,22] **1a** (5.3 g, 27.4 mmol) was treated with a 1:1 mixture of 30% hydrogen peroxide and ethanol (30 mL) at rt overnight. The mixture was diluted with water (100 mL) and applied onto a column of Dowex 50 (H^+, 50 mL). The resin was washed with water (400 mL), and the product was eluted with 3% aqueous ammonia. The desired compound was obtained after evaporation in 95% yield (5.47 g, 26.14 mmol) as a colorless oil. HR-MS: (M+H) calcd for $C_{11}H_{16}NO_3$, 210.1130; found, 210.1130.

4.8. (3*S*,4*S*)-3,4-Dihydroxy-1-*N*-methyl-1-*N*-oxidopyrrolidine 4b

A solution of iodine (5.4 g, 21 mmol) in THF (50 mL) was slowly added to a vigorously stirred mixture of (3*S*,4*S*)-3,4-dihydroxy-1-*N*-methylpyrrolidin-5,6-dione[34] (1.23 g, 8.4 mmol) and sodium borohydride (1.7 g, 43 mmol) in THF (150 mL) at 0 °C for 2 h. The reaction mixture was stirred at rt overnight, quenched by the slow addition of 3 M hydrochloric acid (20 mL) at 0 °C, diluted with water (200 mL) and applied onto a Dowex 50 (H^+, 150 mL) column. The resin was washed with water–ethanol mixture (1:1) followed with 3% aqueous ammonia to afford (3*S*,4*S*)-3,4-dihydroxy-1-*N*-methylpyrrolidine **1b**. This product was treated with a mixture of 30% hydrogen peroxide (10 mL) and ethanol (10 mL) at rt overnight. The *N*-oxide **4b** was obtained after desalting on Dowex 50 (H^+) in an 11% overall yield (0.125 g, 0.935 mmol) as a colorless oil. ν_{max}(KBr) 3413, 3096, 2721 (OH); 2914, 2852 (CH_2); 1438, 1412, 1352 (CH_3); 1024 (C–OH); 962, 947 (N–O). HR-MS: (M+H) calcd for $C_5H_{12}NO_3$, 134.0817; found, 134.0813.

4.9. (1*S*,3*S*,4*S*)-1-*N*-Benzyl-4-dimethoxytrityloxy-3-hydroxy-1-*N*-oxidopyrrolidine 5a

N-Oxide **4a** (0.748 g, 3.5 mmol) was treated with dimethoxytrityl chloride (1.35 g, 4 mmol) in pyridine (35 mL) at rt overnight. The reaction was quenched with methanol (1 mL), concentrated at low temperature, and the residue was subjected to column chromatography on silica gel using a linear gradient of H3 in ethyl acetate. Dimethoxytrityl derivative **5a** was obtained in 95% yield (1.7 g, 3.3 mmol) as an amorphous solid. ν_{max}(KBr) 3239, 2636 (OH); 2934, 1463, 1374 (CH_2); 1095 (COC); 1058 (C–OH); 927 (N–O); 3061, 3035, 3002, 2953, 2908, 2836, 1608, 1583, 1509, 1491, 1457, 1446, 1301, 1251, 1223, 1177, 1156, 1115, 1033, 1012, 1001, 912, 829, 756, 791, 727, 702, 618, 585, 528 (DMTr). HR-MS: (M+H) calcd for $C_{32}H_{34}NO_5$, 512. 2437; found, 512.2453. $[\alpha]_D^{20} = +31.4$ (*c* 0.419, ethanol).

4.10. (3*S*,4*S*)-3-Dimethoxytrityloxy-4-hydroxy-1-*N*-methyl-1-*N*-oxidopyrrolidine 5b

The title compound was prepared from *N*-oxide **4b** (0.12 g, 0.902 mmol) and dimethoxytrityl chloride (0.34 g, 1 mmol) in pyridine (10 mL) as described for the compound **5a**. Compound **5b** was obtained 0.344 g (0.79 mmol, 88%) in the form of a yellowish foam. ν_{max}(KBr) 3270 (OH); 2950 (CH_3); 1463 (CH_2); 1361 (N–CH_3); 1087 (C–OH); 937 (N–O); 3056, 3034, 3001, 1608, 1582, 1509, 1446, 1252, 1222, 1178, 1116, 1014, 829, 791, 727, 635, 528, 585, 1492, 1155, 1002, 911, 756, 704, 617, 2908, 2836, 1301, 1033 (DMTr). HR-MS: (M+H) calcd for $C_{26}H_{30}NO_5$, 436.2124; found, 436.2124.

4.11. (1*S*,3*S*,4*S*)-1-*N*-Benzyl-4-*tert*-butyldiphenylsilyloxy-3-dimethoxytrityloxy-1-*N*-oxidopyrrolidine 6

Dimethoxytrityl derivative **5a** (0.5 g, 0.98 mmol) was treated with *tert*-butylchlorodiphenylsilane (1.04 mL, 4 mmol) and imidazole (0.14 g, 2 mmol) in pyridine (10 mL) at rt overnight. The reaction was quenched with methanol (1 mL), concentrated at low temperature, and the desired product **6** was obtained by chromatography on silica gel using a linear gradient of ethanol in chloroform in 54% yield (0.4 g, 0.53 mmol) as a yellowish foam. HR-MS: (M+H) calcd for $C_{48}H_{52}NO_5Si$, 750.3615; found, 750.3589. $[\alpha]_D^{20} = +53.1$ (*c* 0.199, ethanol).

4.12. (1*S*,3*S*,4*S*)-1-*N*-Benzyl-3-*tert*-butyldiphenylsilyloxy-4-hydroxy-1-*N*-oxidopyrrolidine 7

The *N*-oxide **4a** (2 g, 10.36 mmol) was treated with *tert*-butylchlorodiphenylsilane (3.5 mL, 13.7 mmol) in pyridine (100 mL) at rt overnight. Methanol (1 mL) was added, the solvents were evaporated, and the residue was dissolved in 70% aqueous ethanol (100 mL), and applied onto a column of Dowex 50 (H^+, 50 mL). The resin was washed with 70% ethanol (400 mL), and the desired compound was eluted with a 3% aqueous ammonia–ethanol mixture (1:1). Compound **7** was obtained in 98% yield (4.53 g, 10.12 mmol) as a white foam. ν_{max}(KBr) 2931 (CH_2); 2857 (CH_2); 2800 (OH); 1085 (C–OH); 936 (N–O); 3088, 2030, 1605, 1495, 1457, 1159, 757, 622 (Bn); 3070, 3048, 2931, 2857, 1596, 1589, 1568, 1488, 1428, 1332, 1188, 1113, 1105, 1026, 998, 918, 857, 740, 688, 613, 507, 489 (TBDPS). HR-MS: (M+H) calcd for $C_{27}H_{34}NO_3Si$, 448.2308; found, 448.2228.

4.13. (1*R*,3*S*,4*S*)-1-*N*-Benzyl-4-*tert*-butyldiphenylsilyloxy-3-dimethoxytrityloxy-1-*N*-oxidopyrrolidine 8

The silyl derivative **7** (0.5 g, 1.12 mmol) was treated with dimethoxytrityl chloride (0.7 g, 2.07 mmol) in pyridine (10 mL) at rt for 5 d. The reaction was quenched with methanol (1 mL), solvents were evaporated, and product **8** was obtained by chromatography on silica gel using a linear gradient of ethanol in chloroform in 44% yield (0.367 g, 0.49 mmol) as a yellowish foam. HR-MS: (M+H) calcd for $C_{48}H_{52}NO_5Si$, 750.3615; found, 750.3589. $[\alpha]_D^{20} = +37.6$ (*c* 0.507, ethanol).

4.14. (1*R*,3*S*,4*S*)-1-*N*-Benzyl-3-*tert*-butyldiphenylsilyloxy-4-hydroxy-1-*N*-oxidopyrrolidine 9

4.14.1. Method A. Compound **6** (0.4 g, 0.53 mmol) was dissolved in 80% aqueous acetic acid (20 mL), the solution then set aside for 2 h, concentrated in vacuo, and the residue was co-evaporated with water and ethanol (3×). Product **9** was obtained by column chromatography on silica gel

using a linear gradient of ethanol in chloroform in 70% yield (0.16 g, 0.37 mmol) as a white foam.

4.14.2. Method B. Hydrogen peroxide (30%, 10 mL) was added to a solution of **3** (0.93 g, 2.16 mmol) in ethanol (20 mL). The solution was set aside at rt overnight, and then applied on the column of Dowex 50 (H^+, 50 mL). The resin was washed with 50% aq ethanol (200 mL) to remove hydrogen peroxide, and the desired product was eluted with 3% ammonium hydroxide in 50% aq ethanol (150 mL) to afford 95% yield (0.92 g, 2.051 mmol) of compound **9** as a white foam. HR-MS: (M+H) calcd for $C_{27}H_{34}NO_3Si$, 448.2308; found, 448.2228.

4.15. (1*RS*,3*S*)-1-*N*-Benzyl-3-hydroxy-1-*N*-oxidopyrrolidines 11 and 12

1-*N*-Benzyl-3-hydroxypyrrolidine **10** (1.5 g, 8.6 mmol) was treated with a mixture of 30% hydrogen peroxide (15 mL) and ethanol (15 mL) at rt overnight. The mixture was diluted with water (30 mL) and applied onto a column of Dowex 50 (H^+, 30 mL). The resin was washed with water (200 mL), and the desired compound was eluted with 3% aqueous ammonia. After evaporation, 1.5 g (7.8 mmol) of a mixture of *N*-oxides **11** and **12** were obtained in 90% yield (1.5 g, 7.8 mmol) as a colorless oil. HR-MS: (M+H) calcd for $C_{11}H_{16}NO_2$, 194.1181; found, 194.1166.

4.16. (1*R*,3*R*)-1-*N*-Benzyl-3-dimethoxytrityloxy-1-*N*-oxidopyrrolidine 13

The epimeric mixture of *N*-oxides **11** and **12** (0.24 g, 1.23 mmol) was treated with dimethoxytrityl chloride (0.46 g, 1.4 mmol) in a mixture of DMF (4 mL) and pyridine (20 mL) at rt for 1 h. The reaction was quenched with methanol (0.2 mL), the solvents evaporated, and the residue subjected to column chromatography on silica gel using a linear gradient of H3 in ethyl acetate. The desired product **13** was obtained in 74% yield (0.45 g, 0.91 mmol) as a yellow foam. ν_{max}(KBr) 928 (N–O); 2936, 1463, 1378 (CH_2); 3058, 3034, 3000, 2952, 2907, 2835, 1608, 1582, 1509, 1492, 1457, 1446, 1352, 1224, 1178, 1154, 1117, 1099, 1082, 1014, 1003, 913, 829, 791, 754, 727, 702, 613, 583, 523 (DMTr, Bn); HR-MS: (M+H) calcd for $C_{32}H_{34}NO_4$, 495.2410; found, 495.2408. $[\alpha]_D^{20} = -20.1$ (*c* 0.384, ethanol).

4.17. (3*R*)-1-*N*-Benzyl-3-dimethoxytrityloxypyrrolidine 14

A solution of compound **13** (0.1 g, 0.2 mmol) and triphenylphosphine (0.52 g, 2 mmol) in DCM (2 mL) was set aside at rt overnight. The product **14** was obtained by purification on silica gel using a linear gradient of ethyl acetate in toluene in 92% yield (0.088 g, 0.184 mmol) as a thick yellow oil. HR-MS: (M+H) calcd for $C_{32}H_{34}NO_3$, 480.2539; found, 480.2529.

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