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Stereoselective addition of organometallic reagents to a chiral acyclic nitrone derived from L-erythrulose

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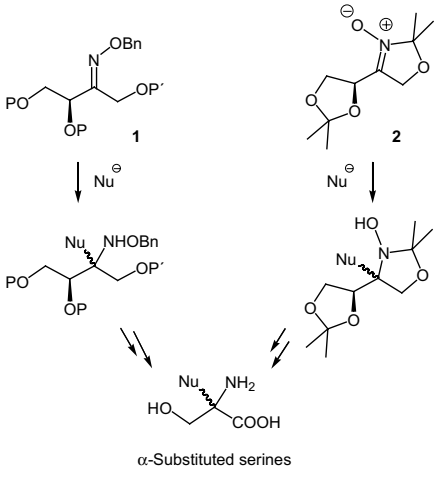
Abstract—The additions of various organolithium and organomagnesium reagents to a chiral nitrone prepared from L-erythrulose took place with variable diastereoselectivity. The degree and strength of the facial selectivity can be modified if the reaction is performed in the presence of Lewis acid additives: zinc bromide enhances the attack to the *Si* face of the C=N bond whereas diethyl aluminium chloride promotes attack to the *Re* face. The obtained adducts can be then transformed into protected *N*-hydroxy-α,α-disubstituted-α-amino acid derivatives as well as into the corresponding α,α-disubstituted α-amino acids.

1. Introduction

The addition of carbon nucleophiles to C=N bonds[1,2] is a synthetically important method of preparing many types of biologically relevant nitrogen-containing compounds, among them non-proteinogenic amino acids. These are used, for example, in the synthesis of non-natural peptides.[3] One important class of non-proteinogenic amino acids are α,α-disubstituted α-amino carboxylic acids.[4] Another class, also of interest as synthetic targets, are *N*-hydroxy amino acids.[5] In relation with these synthetic goals, we reported several years ago the stereoselective additions of organolithium reagents to the C=N bond of chiral *E* oximes **1** (P, P′ = protecting groups),[6] prepared from four-carbon monosaccharide L-erythrulose.[7] The obtained adducts were then transformed into various α-substituted serine derivatives (Scheme 1). As an alternative approach to the same targets, we later reported on the stereoselective additions of lithium and magnesium organometallics to the C=N bond of the homochiral keto nitrone[8] **2**, also prepared from L-erythrulose.[9]



Scheme 1. Nucleophillic additions to oximes **1** and nitrone **2**.

2. Results and discussion

2.1. Preparation of chiral nitrone 3 and its reactions with organometallic reagents

Even though organometallic additions to the C=N bond of both **1** and **2** took place with good diastereoselectivity (diastereomeric ratios, dr, were often >95:5), the overall efficiency of the process suffered from unsatisfactory yields in the preparation of the two chiral precursors.[10]

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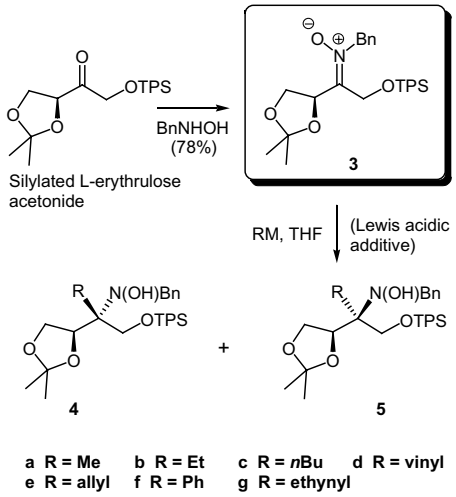
We thus looked for another chiral nitrone, which could not only be obtainable from L-erythrulose in good yield but also undergo stereoselective reactions with organometallic reagents. After some experimentation, we found that the reaction of a known silylated L-erythrulose derivative[7] with *N*-benzyl hydroxyl amine gave rise to nitrone **3** in good yield (Scheme 2, TPS = *t*-butyldiphenylsilyl). Compound **3** was an oil and thus not amenable to X-ray diffraction analysis but NOE measurements permitted us to assign the configuration of the C=N bond as *Z*.[11,12]



Scheme 2. Preparation of **3** and its reactions with organometallic reagents.

2.2. Determination of the configurations of the addition products

The reaction of nitrone **3** with several organometallic reagents yielded mixtures of diastereoisomeric adducts **4** and **5** (see Scheme 2 and Table 1). For adducts **4a**, **4c** and **4f** (Table 1, entries 3, 16 and 31), the configurations were established by means of chemical correlations as depicted in Scheme 3. Thus, reductive cleavage of the N–O bond with the zinc–copper couple was followed by acetonide hydrolysis, selective silylation of the primary hydroxyl group and ring closure to oxazolidinones **6a**, **6c** and **6f**. NOE measurements in the latter allowed the establishment of the relative configurations of the stereocentres.[13] Adducts **4b** and **4e** (Table 1, entries 9 and 28) could be obtained as crystals amenable to X-ray diffraction analysis.[14] Where mixtures of **4** and **5** were formed, their NMR spectra were compared with those of the pure adduct **4**. Finally, the configurations of the addition products **4d/5d** or **4g/5g** formed with vinyl or ethynyl magnesium bromide, respectively, were established by means of hydrogenation and spectral comparison with the product mixtures **4b/5b** generated from ethyl magnesium bromide.

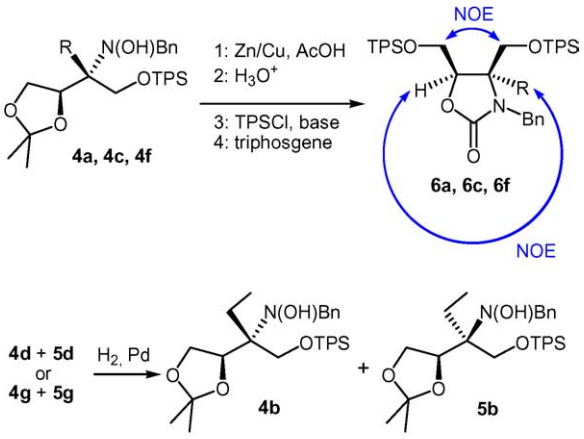
2.3. Mechanistic discussion

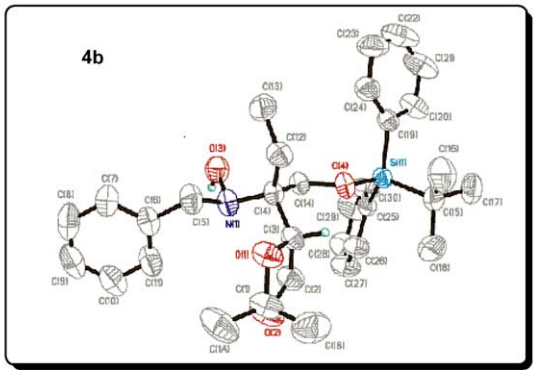
Inspection of Table 1 clearly shows that only the Grignard reagents give useful results in reactions with nitrone **3**. The addition of organolithium derivatives (entries 44–50) not only in general gave inferior yields but also show lower degrees of diastereoselectivity.

Table 1. Diastereomeric ratios (dr) in the reactions of nitrone **3** with organomagnesium and orgamolithium reagents[a]

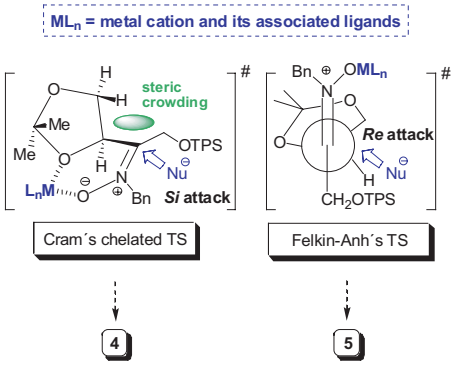
Entry	Organometallic reagent	Solvent	Additive	Yield % (dr)[b]
1	MeMgCl	THF	None	63 (85:15)
2	MeMgCl	Et_2O	None	65 (78:22)
3[b]	MeMgCl	THF	$ZnBr_2$	**72 (95:5)**
4	MeMgCl	Et_2O	$ZnBr_2$	78 (88:12)
5	MeMgCl	THF	Et_2AlCl	69 (54:46)
6[b]	MeMgCl	Et_2O	Et_2AlCl	66 (67:33)
7	EtMgBr	THF	None	74 (85:15)
8	EtMgBr	Et_2O	None	60 (85:15)
9	EtMgBr	THF	$ZnBr_2$	**79 (93:7)**
10	EtMgBr	Et_2O	$ZnBr_2$	75 (89:11)
11	EtMgBr	THF	Et_2AlCl	85 (47:53)
12[b]	EtMgBr	Et_2O	Et_2AlCl	55 (65:35)
13	*n*BuMgCl	THF	None	75 (83:17)
14	*n*BuMgCl	Et_2O	None	65 (87:13)
15[b]	*n*BuMgCl	THF	$ZnBr_2$	75 (88:12)
16	*n*BuMgCl	Et_2O	$ZnBr_2$	**72 (>95:5)**
17	*n*BuMgCl	THF	Et_2AlCl	74 (50:50)
18[b]	*n*BuMgCl	Et_2O	Et_2AlCl	78 (31:69)
19	CH_2=CHMgBr	THF	None	75 (80:20)
20	CH_2=CHMgBr	Et_2O	None	63 (55:45)
21[b]	CH_2=CHMgBr	THF	$ZnBr_2$	80 (85:15)
22	CH_2=CHMgBr	Et_2O	$ZnBr_2$	80 (64:36)
23	CH_2=CHMgBr	THF	Et_2AlCl	**78 (<5:95)**
24[b]	CH_2=CHMgBr	Et_2O	Et_2AlCl	**87 (<5:95)**
25	CH_2=$CHCH_2$MgBr	THF	None	**84 (<5:95)**
26	CH_2=$CHCH_2$MgBr	Et_2O	None	92 (50:50)
27[b]	CH_2=$CHCH_2$MgBr	THF	$ZnBr_2$	80 (80:20)
28	CH_2=$CHCH_2$MgBr	Et_2O	$ZnBr_2$	**86 (90:10)**
29	CH_2=$CHCH_2$MgBr	THF	Et_2AlCl	80 (15:85)
30[b]	CH_2=$CHCH_2$MgBr	Et_2O	Et_2AlCl	87 (20:80)
31	PhMgCl	THF	None	**90 (>95:5)**
32	PhMgCl	Et_2O	None	85 (85:15)
33[b]	PhMgCl	THF	$ZnBr_2$	**85 (>95:5)**
34	PhMgCl	Et_2O	$ZnBr_2$	82 (80:20)
35	PhMgCl	THF	Et_2AlCl	60 (30:70)
36[b]	PhMgCl	Et_2O	Et_2AlCl	67 (39:61)
37	HC≡CMgBr[c]	THF	None	82 (33:67)
38	HC≡CMgBr[c]	Et_2O	None	90 (40:60)
39[b]	HC≡CMgBr[c]	THF	$ZnBr_2$	80 (52:48)
40	HC≡CMgBr[c]	Et_2O	$ZnBr_2$	85 (40:60)
41	HC≡CMgBr[c]	THF	Et_2AlCl	75 (19:81)
42[b]	HC≡CMgBr[c]	Et_2O	Et_2AlCl	80 (28:72)
43	*t*BuMgCl	THF or Et_2O	None[d]	No reaction
44	MeLi	Et_2O[e]	None	55 (13:87)
45	MeLi	Et_2O[e]	$ZnBr_2$	**77 (10:90)**
46	MeLi	Et_2O[e]	Et_2AlCl	80 (13:87)
47[b]	*n*BuLi or *t*BuLi	Et_2O[e]	None[f]	Decomp.
48	PhLi	Et_2O[e]	None	63 (80:20)
49	PhLi	Et_2O[e]	$ZnBr_2$	65 (70:30)
50	PhLi	Et_2O[e]	Et_2AlCl	92 (23:77)

[a] For reaction conditions, see Experimental section.
[b] Dr's were measured by high-field ^1H and ^{13}C NMR. Values such as >95:5 or <5:95 indicate that the minor stereoisomer was not detected with this technique.
[c] The reaction was performed at 0 °C.
[d] With $ZnBr_2$ or Et_2AlCl as additives, no reaction was observed, either.
[e] In THF, decomposition was observed.
[f] With $ZnBr_2$ or Et_2AlCl as additives, decomposition was observed, as well.





Scheme 3. Determination of the configurations of adducts **4** and **5** via chemical correlations and ORTEP structure of **4b**.



Scheme 4. Mechanistic proposals for the reactions of keto nitrone **3** with organometallic reagents.

Furthermore, the high reactivity of these reagents cause decomposition in some cases (entry 47), most likely because of its extreme basicity. Grignard reagents, however, display an adequate level of reactivity except in cases of steric crowding (entry 43). The use of either Et_2O or THF as solvent gave comparable results in broad terms, even though the latter tends to perform somewhat better in both yield and dr. Further changes in either of these two features were observed when the reactions were carried out in the presence of the Lewis acid $ZnBr_2$ or Et_2AlCl.

Various mechanistic models have been proposed to explain the stereochemical outcome of the additions of organometallic reagents to the C=N bond of nitrones. In almost all cases, such reactions have been performed on functionalized nitrones derived from aldehydes.[15] As a matter of fact, the formation of either **4** or **5** can be rationalized within the mechanistic frame of Cram's α-chelated (→**4**) versus Felkin–Anh's non-chelated (→**5**) transition states (TS)[6a] (M = Mg or Li in Scheme 4). A β-chelated TS should also lead to stereoisomer **5**. However, our experience with organometallic additions to various types of erythrulose derivatives[6a,16] has led us to consider this mechanistic alternative less likely here (see also below). Very variable dr's were observed when no Lewis acidic additive was present, with only the additions of allyl and phenyl Grignard reagents being highly stereoselective (entries 25 and 31). Interestingly, whereas stereoisomer **4** was the almost exclusive adduct with phenylmagnesium bromide, **5** was the only isomer detected in the case of the allylmagnesium reagent. Whether this differential behaviour of the allyl reagent is related to a different aggregation state of the reagent, to an intrinsic preference for a non-chelated cyclic TS of the metallo-ene type[17] or to another cause is still unclear.

When the addition was performed in the presence of $ZnBr_2$ (1 equiv),[5d,15d,e,h] a visible increase in the proportion of **4** was observed, in several cases up to synthetically useful values (entries 3, 9 and 16). As commented above, the addition of the phenyl Grignard reagent is already very stereoselective without the Lewis acid additive (entry 31) and remains so after adding $ZnBr_2$ (entry 33). These results may be explained if we assume that the bidentate Lewis acid $ZnBr_2$ binds to the substrate as the chelating species ($ML_n = ZnBr_2$ in the left TS of Scheme 4) more tightly then the magnesium cation present in the reaction mixture.

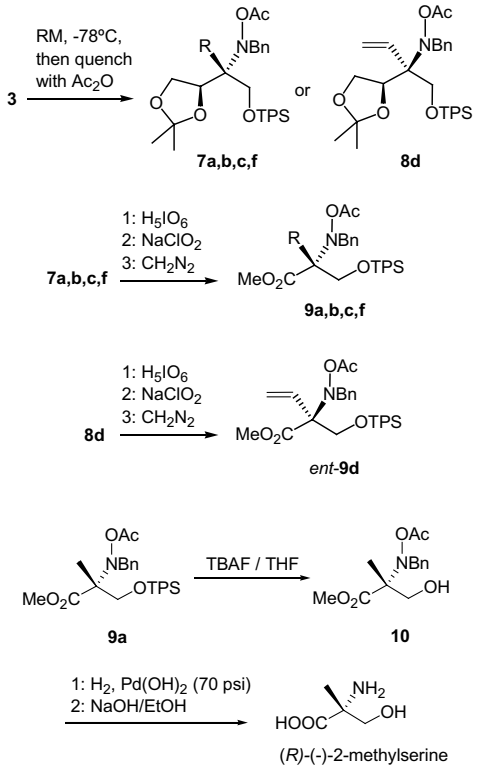
In contrast, the addition of Et_2AlCl (1 equiv) to the reaction mixture always caused a marked increase in the proportion of the Felkin–Anh isomer **5**. However, the stereochemical bias imposed by this Lewis acid was not strong enough to cause a complete reversal of the stereoselectivity[5d,15d,e,h,i] except in the case of vinyl magnesium bromide, which proved highly stereoselective in the presence of Et_2AlCl (entries 23 and 24) and yielded only **5**. Results of this type have previously been observed in the additions of organometallics to α-oxygenated nitrones.[5d,15] In order to explain such results, it has been proposed that Et_2AlCl acts as a monodentate Lewis acid, which coordinates only with the negatively charged oxygen atom of the nitrone, thus leading to a Felkin–Anh-type TS ($ML_n = AlClEt_2$ in the right part of Scheme 4). It is worth mentioning that Evans et al. have shown that Me_2AlCl and $MeAlCl_2$ are exceptionally strong chelating species if added in an excess of at least 2–2.5 equiv.[18] However, the results presented in Table 1 were essentially the same with either 1 or 2.5 equiv of Et_2AlCl added to the reaction mixture. This and the preferred formation of stereoisomer **5** do not lend support to the idea that chelates are formed here in the presence of this Lewis acid. Perhaps the negatively

charged oxygen atom of the nitrone displaces the chlorine atom and forms a $C{=}N^{+}$-$OAlEt_2$ species, where the aluminium atom is possibly not Lewis acidic enough to coordinate with one of the ketal oxygen atoms and close the chelate ring.

2.4. Synthesis of α,α-disubstituted α-amino acids

We have also investigated the conversion of the obtained adducts into derivatives of non-proteinogenic amino acids of the type mentioned in the introduction. For synthetic purposes, it proved much better to quench the reaction mixture with acetic anhydride at −78 °C instead of the aqueous work-up. In this way, we have obtained *N*-acetoxy derivatives **7a**, **7b**, **7c**, **7f** and **8d**, which were more stable than their deacetylated counterparts, as well as easier to purify by means of chromatography (Scheme 5). Subsequent functional manipulations transform **7** or **8** into the *N*-acetoxy α-amino esters **9** or *ent*-**9**, which are protected forms of *N*-hydroxy α-substituted α-amino acids.

The α,α-disubstituted α-amino acids themselves can also be made available by means of this methodology, as shown in Scheme 5 for the case of (*R*)-2-methylserine. Compound **9a** was first desilylated with TBAF in THF to hydroxy ester **10** and then subjected to hydrogenolysis in the presence of Pearlman's catalyst. This caused both debenzylation and reductive cleavage of the N–O bond to yield (*R*)-(−)-2-methyl serine methyl ester, which was then uneventfully hydrolyzed to (*R*)-(−)-2-methyl serine.[6b] Further amino acids with other α-substituents may also be prepared through desilylation of the TPS group and nucleophilic substitution of the hydroxyl function.



Scheme 5. Conversion of adducts into protected α-substituted *N*-hydroxy α-amino acids and synthesis of *R*-(−)-2-methylserine.

3. Conclusions

In summary, we have investigated the additions of several organometallic reagents to a chiral nitrone **3** derived from L-erythrulose. Under specific reaction conditions, these additions have turned out to be very stereoselective. The better overall yield in the preparation of the starting nitrone has led us to prefer its use to that of our previous chiral precursors **1** and **2**. We have also reported a convenient methodology for the synthesis of the enantiopure form of *N*-hydroxy α-substituted α-amino acids and α-substituted α-amino acids, two types of non-proteinogenic amino acids. This method can be further applied to the preparation of aminopolyols bearing *tert*-alkyl amine fragments, as well as of other nitrogenated natural products of pharmacological interest.

4. Experimental

4.1. General

NMR spectra were measured at 400 or 500 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centred at 77.00 ppm for ^{13}C NMR data). The multiplicities of the ^{13}C NMR signals were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or with the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR data are given only for compounds with relevant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into 5% aq $NaHCO_3$ (if the reaction was carried out in an acidic medium) or into satd aq NH_4Cl (if it was carried out in a basic medium), extracting with the indicated solvent, then washing again the organic layer with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent in vacuo. When the solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent, and the washing liquids incorporated to the main organic layer. The obtained material was then chromatographed on a silica gel column (60–200 μ) with the indicated eluent.

4.2. General reaction conditions for organometallic additions to nitrone 3 with aqueous work-up

The preparation and physical data of nitrone **3** have been previously described.[11] A solution of **3** (504 mg,

1 mmol) in the appropriate solvent (5 mL) was cooled under N_2 to −78°C and treated with the appropriate organometal reagent (5 mmol). After stirring for 5 h at the same temperature, the reaction mixture was worked-up (extraction with EtOAc). The organic layers were then dried over anhyd Na_2SO_4 and concentrated in vacuo. Column chromatography of the oily residue on a silica gel column (hexanes–EtOAc 4:1) afforded adducts **4/5** (for relative proportions and chemical yields, see Table 1). Additions in the presence of Lewis acid additives were performed in the same way except that the Lewis acid (1 mmol) was added to a ice-cooled solution of **3**; the solution was then stirred for 15 min and cooled to −78 °C, prior to addition of the organometal reagent. In the case of Et_2AlCl, the reactions were also performed in the presence of 2.5 equiv of the Lewis acid. The results, however, were essentially the same as with 1 equivalent of the Lewis acid. Physical and spectral data are given hereafter for compounds, which were only isolated in a pure state.

4.3. (1*R*)-*N*-Benzyl-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-1-methylethyl]-hydroxylamine, 4a

Oil, $[\alpha]_D$ = +17.8 (*c* 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (500 MHz, $CDCl_3$) 7.85–7.80 (4H, m), 7.50–7.30 (11H, m), 5.10 (1H, br s, OH), 4.75 (1H, t, *J* = 7 Hz), 4.30–4.10 (4H, m), 4.06, 3.97 (2H, AB system, *J* = 11 Hz), 1.48 (3H, s), 1.44 (3H, s), 1.18 (9H, s), 1.16 (3H, s); δ_C (125 MHz, $CDCl_3$) δ 139.5, 133.0, 132.7, 108.4, 66.0, 19.1 (C), 135.6, 135.5, 129.6, 129.5, 128.7, 128.1, 127.7, 127.6, 127.5, 126.8, 76.1 (CH), 66.0, 65.4, 58.0 (CH_2), 26.8 (×3), 26.2, 24.9, 13.7 (CH_3). HR FABMS *m*/*z* 520.2873 [M+H^+], calcd for $C_{31}H_{42}NO_4Si$, 520.2883.

4.4. (1*S*)-*N*-Benzyl-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-1-methylethyl]-hydroxylamine, 5a

Oil, $[\alpha]_D$ = −10.5 (*c* 0.9, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (400 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.30 (11H, m), 4.60 (1H, br s, OH), 4.49 (1H, dd, *J* = 8, 7 Hz), 4.15–4.05 (3H, m), 4.00 (1H, t, *J* = 8 Hz), 3.90, 3.87 (2H, AB system, *J* = 11 Hz), 1.42 (6H, s), 1.26 (3H, s), 1.17 (9H, s); δ_C (100 MHz, $CDCl_3$) δ 139.9, 133.2 (×2), 108.6, 65.7, 19.3 (C), 135.9, 135.8, 129.7, 129.1, 128.3, 128.2, 127.8, 127.6, 126.9, 78.5 (CH), 65.9, 65.4, 57.9 (CH_2), 27.0 (×3), 26.4, 25.4, 14.2 (CH_3).

4.5. (1*R*)-*N*-Benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-propyl]-hydroxylamine, 4b

Solid, mp 68–69 °C; $[\alpha]_D$ = −1.6 (*c* 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.30 (11H, m), 5.00 (1H, br s, OH), 4.73 (1H, t, *J* = 7.3 Hz), 4.35 (1H, t, *J* = 8 Hz), 4.25 (1H, d, *J* = 14 Hz), 4.10 (2H, m), 4.03, 4.00 (2H, AB system, *J* = 10.7 Hz), 1.90–1.75 (2H, m), 1.46 (3H, s), 1.44 (3H, s), 1.18 (9H, s), 1.02 (3H, t, *J* = 7.5 Hz); δ_C (125 MHz, $CDCl_3$) δ 139.6, 133.0, 132.8, 108.1, 66.2, 19.1 (C), 135.7, 135.6, 129.6, 129.5, 128.7, 128.1, 127.7, 127.6, 127.5, 126.8, 77.1 (CH), 65.6, 65.0, 57.8, 22.2 (CH_2), 26.9 (×3), 26.4, 25.0, 7.8 (CH_3). HR FABMS *m*/*z* 534.3044 [M+H^+], calcd for $C_{32}H_{44}NO_4Si$, 534.3039. Anal. Calcd for $C_{32}H_{43}NO_4Si$: C, 72.00; H, 8.12. Found, C, 72.01; H, 8.08.

4.6. (1*R*)-*N*-Benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-pentyl]-hydroxylamine, 4c

Oil, $[\alpha]_D$ = −4.1 (*c* 0.5, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.30 (11H, m), 5.00 (1H, br s, OH), 4.68 (1H, t, *J* = 7.5 Hz), 4.33 (1H, dd, *J* = 8, 7 Hz), 4.20 1H, d, *J* = 14 Hz), 4.09 (1H, dd, *J* = 8, 7 Hz), 4.03 (1H, d, *J* = 14 Hz), 4.00, 3.93 (2H, AB system, *J* = 10.7 Hz), 1.75–1.65 (2H, m), 1.42 (3H, s), 1.41 (3H, s), 1.45–1.25 (4H, m), 1.13 (9H, s), 0.92 (3H, t, *J* = 7.2 Hz); δ_C (100 MHz, $CDCl_3$) δ 139.6, 133.0, 132.8, 108.2, 66.3, 19.2 (C), 135.8, 135.7, 129.8, 129.6, 128.8, 128.3, 127.8, 127.7, 127.5, 126.8, 77.3 (CH), 65.7, 65.3, 57.9, 29.6, 25.2, 23.8 (CH_2), 27.0 (×3), 26.4, 25.0, 14.2 (CH_3). HR FABMS *m*/*z* 562.3364 [M+H^+], calcd for $C_{34}H_{48}NO_4Si$, 562.3352.

4.7. (1*S*)-*N*-Benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-allyl]-hydroxylamine, 5d

Oil, $[\alpha]_D$ = −13.2 (*c* 1, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (400 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.30 (11H, m), 6.10 (1H, dd, *J* = 17.7, 11.6 Hz), 5.50–5.40 (2H, m), 4.90 (1H, br s, OH), 4.65 (1H, t, *J* = 7.5 Hz), 4.18 (1H, d, *J* = 14 Hz), 4.15–4.05 (4H, m), 4.03 (1H, d, *J* = 14 Hz), 1.43 (3H, s), 1.41 (3H, s), 1.16 (9H, s); δ_C (100 MHz, $CDCl_3$) δ 139.8, 133.0, 132.9, 108.6, 68.8, 19.3 (C), 135.8 (×2), 135.3, 129.9, 128.9, 128.2, 127.8, 127.7, 126.8, 77.9 (CH), 118.6, 66.2, 63.6, 58.0 (CH_2), 27.0 (×3), 26.4, 25.3 (CH_3). HR FABMS *m*/*z* 532.2895 [M+H^+], calcd for $C_{32}H_{42}NO_4Si$, 532.2881.

4.8. (1*R*)-*N*-Benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-but-3-enyl]-hydroxylamine, 4e

Solid, mp 66–67 °C; $[\alpha]_D$ = −0.1 (*c* 0.4, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.30 (11H, m), 6.00 (1H, m), 5.10 (1H, br d, *J* = 17 Hz), 5.05 (1H, br d, *J* = 10 Hz), 4.80 (1H, br s, OH), 4.67 (1H, t, *J* = 7.5 Hz), 4.30 (2H, m), 4.10–4.00 (4H, m), 2.60 (1H, dd, *J* = 14.5, 6.5 Hz), 2.50 (1H, dd, *J* = 14.5, 7.5 Hz), 1.43 (3H, s), 1.39 (3H, s), 1.14 (9H, s); δ_C (125 MHz, $CDCl_3$) δ 139.6, 133.0, 132.8, 108.0, 65.3, 19.2 (C), 135.8, 135.7, 134.6, 129.9, 129.8, 128.8, 128.2, 127.8, 127.7, 126.8, 76.8 (CH), 117.2, 66.7, 65.6, 58.0, 33.9 (CH_2), 27.0 (×3), 26.4, 25.0 (CH_3). HR FABMS *m*/*z* 546.3048 [M+H^+], calcd for $C_{33}H_{44}NO_4Si$, 546.3039. Anal. Calcd for $C_{33}H_{43}NO_4Si$: C, 72.62; H, 7.94. Found, C, 72.57; H, 8.08.

4.9. (1*S*)-*N*-Benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-but-3-enyl]-hydroxylamine, 5e

Oil, $[\alpha]_D = -4.3$ (*c* 0.9, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.30 (11H, m), 6.03 (1H, m), 5.15 (1H, br d, $J = 17$ Hz), 5.09 (1H, br d, $J = 10$ Hz), 4.80 (1H, br s, OH), 4.50 (1H, t, $J = 7.5$ Hz), 4.16 (2H, m), 4.07-4.00 (3H, m), 3.90 (1H, d, $J = 10.5$ Hz), 2.65 (2H, br d, $J = 7$ Hz), 1.39 (3H, s), 1.37 (3H, s), 1.12 (9H, s); δ_C (125 MHz, $CDCl_3$) δ 139.6, 133.0, 132.8, 107.9, 63.8, 19.2 (C), 135.8, 135.7, 134.8, 129.8, 128.9 128.2, 127.8, 127.7, 126.8, 77.7 (CH), 117.3, 67.1, 65.8, 57.8, 34.6 (CH_2), 27.0 (×3), 26.4, 25.0 (CH_3).

4.10. (1*R*)-*N*-Benzyl-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-1-phenylethyl]-hydroxylamine, 4f

Solid, mp 53–54 °C, $[\alpha]_D = +4.2$ (*c* 0.6, $CHCl_3$); IR ν_{max} (cm^{-1}) 3410 (br, OH); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.40 (12H, m), 7.30–7.20 (4H, m), 6.10 (1H, br s, OH), 5.20 (1H, t, $J = 7$ Hz), 4.80 (1H, d, $J = 10.6$ Hz), 4.39 (1H, d, $J = 10.6$ Hz), 4.20–4.05 (4H, m), 1.36 (3H, s), 1.10 (9H, s), 0.80 (3H, s); δ_C (125 MHz, $CDCl_3$) δ 138.9, 138.2, 132.4, 132.1, 108.8, 69.3, 19.2 (C), 135.8, 135.7, 130.0, 129.9, 129.8, 128.8, 128.2, 127.8, 127.7, 126.9, 76.1 (CH), 66.6, 65.6, 58.5 (CH_2), 27.0 (×3), 25.6 (×2) (CH_3). HR FABMS *m*/*z* 582.3032 [$M+H^+$], calcd for $C_{36}H_{44}NO_4Si$, 582.3039. Anal. Calcd for $C_{36}H_{43}NO_4Si$: C, 74.32; H, 7.45. Found, C, 74.37; H, 7.59.

4.11. Determination of the configurations of adducts 4 via chemical correlations

4.11.1. Reductive cleavage of the N–O bond. Activated Zn powder (654 mg, 10 mmol) was added under an inert atmosphere to a solution of $Cu(OAc)_2$ (36 mg, 0.2 mmol) in acetic acid (3 mL). The mixture was then stirred at room temperature for 15 min followed by the addition of a solution of adduct **4** (2 mmol) in acetic acid (3 mL). The reaction mixture was stirred at 70 °C (bath temp) for 35 min. After this time, the mixture was cooled to room temperature and treated with tetrasodium ethylendiamintetraacetate (Na_4EDTA, 2 g, 5.3 mmol) followed by stirring for 10 min. The solution was then treated with 3 M NaOH until its pH value was above 10, followed by a threefold extraction with EtOAc. The organic layers were washed once again with Na_4EDTA and brine, dried over anhyd Na_2SO_4, filtered and concentrated in vacuo. The oily residue was subjected to column chromatography on silica gel (hexanes–EtOAc 9:1) to yield the corresponding *tert*-alkyl *N*-benzylamine. Chemical yields: 70% (R = Me), 69% (R = *n*Bu), 72% (R = Ph).

4.11.2. Acetonide hydrolysis. The product from the previous reaction was dissolved in MeOH (10 mL), and treated with 2 M HCl (10 mL). The mixture was then heated at reflux for 30 min and then for a further 30 min at room temperature, after which it was diluted with MeOH (20 mL) and treated carefully with solid Na_2CO_3 until evolution of CO_2 ceased. The reaction mixture was then filtered through Celite, evaporated in vacuo and chromatographed on silica gel (hexanes–EtOAc 1:1) to afford the corresponding aminopolyol. Chemical yields: 80% (R = Me), 82% (R = *n*Bu), 85% (R = Ph).

4.11.3. Selective silylation. A solution of the amino alcohol from above, triethyl amine (182 μL, 1.3 mmol) and *N*,*N*-dimethylaminopyridine (6 mg, 0.05 mmol) in dry CH_2Cl_2 (3 mL) was treated dropwise under an inert atmosphere with TPS chloride (260 μL, 1 mmol). The reaction mixture was stirred overnight at room temperature and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes–EtOAc 9:1) gave rise to the desired silyl derivative. Chemical yields: 66% (R = Me), 72% (R = *n*Bu), 65% (R = Ph).

4.11.4. Oxazolidinone formation. The silylated compound from above was dissolved under an inert atmosphere in dry CH_2Cl_2 (4 mL) and treated sequentially with triethyl amine (280 μL, 2 mmol) and triphosgene (296 mg, 1 mmol). The reaction mixture was then stirred at room temperature for 2 d. Work-up (extraction with CH_2Cl_2) followed by column chromatography on silica gel (hexanes–EtOAc 9:1) yielded the desired oxazolidinones **6**. Chemical yields: **6a**, 73%; **6c**, 78%; **6f**, 70%.

4.12. (4*R*,5*R*)-3-Benzyl-4,5-bis-(*tert*-butyldiphenylsilyloxymethyl)-4-methyloxazolidin-2-one, 6a

Oil, $[\alpha]_D = -43$ (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}) 1756 (C=O); δ_H (400 MHz, $CDCl_3$) 7.70–7.65 (6H, m), 7.55 (2H, m), 7.50–7.35 (12H, m), 7.25 (3H, m), 7.15 (2H, m), 4.58 (1H, d, $J = 16$ Hz), 4.28 (1H, t, $J = 6$ Hz), 4.18 (2H, m), 3.75 (1H, d, $J = 11.5$ Hz), 3.60 (1H, d, $J = 11.5$ Hz), 3.48 (1H, d, $J = 16$ Hz), 1.07 (9H, s), 1.04 (9H, s), 0.95 (3H, s); δ_C (100 MHz, $CDCl_3$) δ 158.3, 133.0, 132.8, 132.6, 132.3, 63.9, 19.1, 19.0 (C), 136.1, 135.8, 135.5, 130.2, 130.0, 128.4, 128.0, 127.9, 127.8, 127.5, 127.3, 82.9 (CH), 63.4, 61.9, 44.1 (CH_2), 26.9 (×3), 26.8 (×3), 21.8 (CH_3). HR FABMS *m*/*z* 728.3623 [$M+H^+$], calcd for $C_{45}H_{54}NO_4Si_2$, 728.3591.

4.13. (4*R*,5*R*)-3-Benzyl-4-butyl-4,5-bis-(*tert*-butyldiphenylsilyloxymethyl)-oxazolidin-2-one, 6c

Oil, $[\alpha]_D = -14.6$ (*c* 0.2, $CHCl_3$); IR ν_{max} (cm^{-1}) 1755 (C=O); δ_H (400 MHz, $CDCl_3$) 7.70–7.65 (6H, m), 7.55 (2H, m), 7.50–7.35 (12H, m), 7.25 (3H, m), 7.15 (2H, m), 4.50 (1H, d, $J = 15.7$ Hz), 4.32 (1H, t, $J = 6$ Hz), 4.13 (1H, dd, $J = 11.3$, 6 Hz), 4.08 (1H, dd, $J = 11.3$, 6 Hz), 3.72 (1H, d, $J = 11.5$ Hz), 3.59 (1H, d, $J = 11.5$ Hz), 3.49 (1H, d, $J = 15.7$ Hz), 1.25 (2H, m), 1.04 (9H, s), 1.01 (9H, s), 1.00–0.70 (4H, m), 0.60 (3H, t, $J = 6.5$ Hz); δ_C (100 MHz, $CDCl_3$) δ 158.8, 133.0, 132.8, 132.6, 132.3, 66.6, 19.1, 19.0 (C), 136.1, 135.8, 135.5, 130.2, 130.0, 128.4, 128.0, 127.9, 127.8, 127.5, 127.3, 79.5 (CH), 63.5, 62.5, 44.5, 33.3, 24.7, 22.7 (CH_2), 26.9 (×3), 26.8 (×3), 13.6 (CH_3). HR FABMS *m*/*z* 770.4094 [$M+H^+$], calcd for $C_{48}H_{60}NO_4Si_2$, 770.4060.

4.14. (4*R*,5*R*)-3-Benzyl-4,5-bis-(*tert*-butyldiphenylsilyloxymethyl)-4-phenyloxazolidin-2-one, 6f

Oil, $[\alpha]_D = -7.5$ (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}) 1756 (C=O); δ_H (500 MHz, $CDCl_3$) 7.65 (2H, m), 7.55 (2H, m), 7.45 (2H, m), 7.45–7.30 (16H, m), 7.20–7.10 (5H, m), 7.00 (3H, m), 4.50 (3H, m), 4.19 (1H, d, $J = 11$ Hz), 4.10 (2H, m), 3.59 (1H, d, $J = 15.5$ Hz), 1.02 (9H, s), 0.87 (9H, s); δ_C (125 MHz, $CDCl_3$) δ 158.9, 138.6, 137.5, 132.7, 132.6, 132.4, 132.1, 69.1, 19.0 (×2) (C), 136.2, 135.8, 130.2, 129.9, 129.8, 128.8, 128.2, 127.8, 127.7, 126.9, 84.5 (CH), 62.0, 61.9, 45.7 (CH_2), 26.8 (×3), 26.6 (×3) (CH_3). HR FABMS *m*/*z* 790.3745 [M+H$^+$], calcd for $C_{50}H_{56}NO_4Si_2$, 790.3748.

4.15. General reaction conditions for organometallic additions to nitrone 3 with acetylation quench

For the preparation of amino acid derivatives, the reaction was performed as described in Paragraph 4.2 except that acetic anhydride (190 μL, 2 mmol) was added at −78 °C to the reaction mixture. The cooling bath was removed and the mixture stirred for 30 min at room temperature. After quenching with satd aq NH_4Cl (2 mL), the reaction mixture was stirred for a further 15 min, poured into brine, worked-up and chromatographed on silica gel (hexanes–EtOAc 9:1). Chemical yields: **7a**, 74%; **7b**, 70%; **7c**, 80%; **7f**, 96%; **8d**, 65%.

4.16. (1*R*)-*N*-Acetoxy-*N*-benzyl-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-1-methylethyl]amine, 7a

Oil, $[\alpha]_D = +10.5$ (*c* 5.7, $CHCl_3$); IR ν_{max} (cm^{-1}) 1765 (C=O); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (4H, m), 7.50–7.25 (11H, m), 4.44 (1H, br d, $J = 14$ Hz), 4.35–4.30 (2H, m), 4.21 (1H, br t, $J = 7.5$ Hz), 4.06 (1H, dd, $J = 8.5$, 7 Hz), 4.00 (1H, m), 3.91 (1H, m), 1.70 (3H, s), 1.40 (3H, s), 1.31 (3H, s), 1.18 (3H, s), 1.12 (9H, s); δ_C (125 MHz, $CDCl_3$) δ 169.6 (br), 137.6, 133.2, 133.1, 108.8, 67.1, 19.3 (C), 135.9, 135.7, 129.8, 129.7, 129.4, 128.1, 127.7, 127.6, 127.3, 75.9 (CH), 65.7, 64.9, 58.3 (CH_2), 26.9 (×3), 26.2, 24.8, 19.0, 14.3 (CH_3). HR FABMS *m*/*z* 562.3006 [M+H$^+$], calcd for $C_{33}H_{44}NO_5Si$, 562.2989.

4.17. (1*R*)-*N*-Acetoxy-*N*-benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-propyl]amine, 7b

Oil; $[\alpha]_D = +9.7$ (*c* 1.1, $CHCl_3$); IR ν_{max} (cm^{-1}) 1766 (C=O); δ_H (400 MHz, $CDCl_3$) 7.75–7.65 (4H, m), 7.45–7.20 (11H, m), 4.59 (1H, t, $J = 7.5$ Hz), 4.43 (1H, br d, $J = 14$ Hz), 4.16 (1H, d, $J = 14$ Hz), 4.05–3.95 (3H, m), 3.77 (1H, d, $J = 11$ Hz), 1.90 (1H, m), 1.61 (3H, s), 1.60 (1H, m), 1.34 (3H, s), 1.30 (3H, s), 1.09 (9H, s), 1.00 (3H, t, $J = 7.5$ Hz); δ_C (100 MHz, $CDCl_3$) δ 169.5 (br), 137.6, 133.0, 132.9, 108.3, 67.8, 19.3 (C), 135.8, 135.7, 129.9, 129.8, 129.4, 128.1, 127.8, 127.7, 127.3, 77.3 (CH), 65.5, 63.3, 57.9, 23.0 (CH_2), 27.0 (×3), 26.4, 24.9, 19.1, 7.7 (CH_3). HR FABMS *m*/*z* 576.3133 [M+H$^+$], calcd for $C_{34}H_{46}NO_5Si$, 576.3145.

4.18. (1*R*)-*N*-Acetoxy-*N*-benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-pentyl]amine, 7c

Oil, $[\alpha]_D = +7.5$ (*c* 1.3, $CHCl_3$); IR ν_{max} (cm^{-1}) 1769 (C=O); δ_H (500 MHz, $CDCl_3$) 7.75–7.70 (4H, m), 7.50–7.25 (11H, m), 4.58 (1H, t, $J = 7.5$ Hz), 4.44 (1H, br d, $J = 14.4$ Hz), 4.18 (1H, br d, $J = 14.4$ Hz), 4.04 (2H, m), 3.95 (1H, dd, $J = 8$, 7.5 Hz), 3.77 (1H, d, $J = 11$ Hz), 1.85 (1H, m), 1.59 (3H, s), 1.55–1.45 (3H, m), 1.33 (3H, s), 1.29 (3H, s), 1.30–1.20 (2H, m), 1.09 (9H, s), 0.88 (3H, t, $J = 7.2$ Hz); δ_C (125 MHz, $CDCl_3$) δ 169.5 (br), 137.7, 133.1, 133.0, 108.3, 68.0, 19.3 (C), 135.9, 135.8, 129.9, 129.8, 129.4, 128.1, 127.9, 127.7, 127.3, 77.7 (CH), 65.6, 63.5, 58.0, 30.2, 24.9, 23.7 (CH_2), 27.0 (×3), 26.4, 24.8, 19.0, 13.9 (CH_3). HR FABMS *m*/*z* 604.3438 [M+H$^+$], calcd for $C_{36}H_{50}NO_5Si$, 604.3458.

4.19. (1*R*)-*N*-Acetoxy-*N*-Benzyl-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-1-phenylethyl]amine, 7f

Solid, 104–105 °C, $[\alpha]_D = +0.2$ (*c* 0.6, $CHCl_3$); IR ν_{max} (cm^{-1}) 1767 (C=O); δ_H (500 MHz, $CDCl_3$) 7.80–7.75 (6H, m), 7.50–7.20 (14H, m), 4.79 (2H, m), 4.30 (1H, d, $J = 15$ Hz), 4.26 (1H, d, $J = 11.7$ Hz), 4.18 (1H, d, $J = 15$ Hz), 3.62 (1H, m), 3.42 (1H, m), 1.75 (3H, s), 1.22 (3H, s), 1.10 (9H, s), 1.08 (3H, s); δ_C (125 MHz, $CDCl_3$) δ 169.4 (br), 138.1, 137.9, 133.0, 132.9, 109.2, 71.6, 19.2 (C), 135.9, 135.8, 129.9, 129.8, 128.7, 128.4, 128.0, 127.9, 127.7, 127.0, 79.9 (CH), 66.4, 61.4, 58.5 (CH_2), 27.0 (×3), 25.9, 24.9, 19.1 (CH_3). HR FABMS *m*/*z* 624.3169 [M+H$^+$], calcd for $C_{38}H_{46}NO_5Si$, 624.3145. Anal. Calcd for $C_{38}H_{45}NO_5Si$: C, 73.16; H, 7.27. Found, C, 73.30; H, 7.39.

4.20. (1*S*)-*N*-Acetoxy-*N*-Benzyl-*N*-[1-(*tert*-butyldiphenylsilyloxymethyl)-1-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-allyl]amine, 8d

Oil, $[\alpha]_D = -17.4$ (*c* 0.3, $CHCl_3$); IR ν_{max} (cm^{-1}) 1766 (C=O); δ_H (500 MHz, $CDCl_3$) 7.70–7.65 (4H, m), 7.50–7.20 (11H, m), 6.05 (1H, dd, $J = 18$, 11.2 Hz), 5.45–5.40 (2H, m), 4.15 (1H, m), 4.10–3.90 (6H, m), 1.60 (3H, s), 1.31 (3H, s), 1.28 (3H, s), 1.09 (9H, s); δ_C (125 MHz, $CDCl_3$) δ 169.5 (br), 137.5, 134.6, 132.9, 132.8, 108.6, 70.0, 19.3 (C), 135.9, 135.8, 130.0, 129.8, 129.5, 128.0, 127.9, 127.7, 127.4, 77.5 (CH), 119.1, 66.0, 63.4, 58.2 (CH_2), 27.0 (×3), 26.2, 24.8, 19.2 (CH_3). HR FABMS *m*/*z* 574.2975 [M+H$^+$], calcd for $C_{34}H_{44}NO_5Si$, 574.2989.

4.21. General procedure for the conversion of adducts 7 and 8 into *N*-hydroxy α,α-disubstituted amino acid derivatives 9 and *ent*-9

Compound **7** or **8** (1.5 mmol) was dissolved in Et_2O (10 mL)[19] and treated with H_5IO_6 (800 mg, ca. 3.5 mmol). The reaction mixture was stirred under Ar at room temperature until consumption of the starting material (ca. 4 h, TLC monitoring). After this time, the mixture was filtered through a pad of Celite. The

organic layers were then concentrated in vacuo to yield a crude aldehyde, which was used directly in the next reaction.

The crude product of the previous reaction was dissolved in acetonitrile (5 mL) and treated dropwise with an aqueous solution of $NaClO_2$ (2.5 mmol). The mixture was cooled in an ice bath and treated with a phosphate buffer solution (prepared dissolving 50 mg of NaH_2PO_4 in 2 mL of water) and 30% aqueous hydrogen peroxide (0.2 mL, 1.75 mmol). The reaction mixture was then stirred for 4 h while maintaining the temperature below 10 °C. After this time, sodium sulfite (15 mg, 0.12 mmol) was added, followed by 10% aqueous HCl until a pH ≈ 3. The reaction mixture was then extracted with CH_2Cl_2, and the organic layer dried over anhyd Na_2SO_4 and concentrated in vacuo to yield a crude carboxylic acid, which was dissolved in Et_2O and treated with excess diazomethane. Elimination of all volatiles in vacuo and column chromatography of the residue on silica gel (elution with hexanes–EtOAc 9:1) afforded the protected *N*-hydroxy aminoester **9**. Overall chemical yields: **9a**, 70%; **9b**, 62%; **9c**, 63%; **9f**, 60%; *ent*-**9d**, 60%.

4.22. Methyl (2*R*)-2-(*N*-acetoxy-*N*-benzylamino)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropionate, 9a

Oil, $[\alpha]_D = -2$ (*c* 0.4, $CHCl_3$); IR ν_{max} (cm^{-1}) 1774, 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 7.65 (4H, m), 7.50–7.25 (11H, m), 4.21 (1H, d, *J* = 13.8 Hz), 4.11 (1H, d, *J* = 9.7 Hz), 4.02 (1H, br d, *J* = 13.8 Hz), 3.78 (1H, d, *J* = 9.7 Hz), 3.75 (3H, s), 1.64 (3H, s), 1.56 (3H, s), 1.04 (9H, s); δ_C (100 MHz, $CDCl_3$) δ 171.5, 169.6 (br), 136.4, 132.9, 132.8, 72.1, 19.2 (C), 135.7, 135.6, 129.8, 129.7, 128.1, 127.7, 127.6, 127.5 (CH), 66.9, 58.2 (CH_2), 52.0, 26.8 (×3), 18.7, 17.3 (CH_3). HR FABMS *m*/*z* 520.2507 [M+H$^+$], calcd for $C_{30}H_{38}NO_5Si$, 520.2519.

4.23. Methyl (2*R*)-2-(*N*-acetoxy-*N*-benzylamino)-2-(*tert*-butyldiphenylsilyloxymethyl)butyrate, 9b

Oil; $[\alpha]_D = -4.3$ (*c* 1.5, $CHCl_3$); IR ν_{max} (cm^{-1}) 1769, 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 7.70–7.65 (4H, m), 7.45–7.20 (11H, m), 4.29 (1H, d, *J* = 14 Hz), 4.10–4.00 (3H, m), 3.72 (3H, s), 2.15–1.95 (2H, m), 1.61 (3H, s), 1.06 (9H, s), 0.97 (3H, t, *J* = 7.4 Hz); δ_C (100 MHz, $CDCl_3$) δ 171.5, 169.5 (br), 136.8, 132.9, 132.8, 74.4, 19.3 (C), 135.7, 135.6, 129.8, 129.7, 129.5, 128.1, 127.7, 127.6, 127.4 (CH), 62.6, 58.0, 24.1 (CH_2), 51.8, 26.8 (×3), 18.7, 8.0 (CH_3). HR FABMS *m*/*z* 534.2683 [M+H$^+$], calcd for $C_{31}H_{40}NO_5Si$, 534.2675.

4.24. Methyl (2*R*)-2-(*N*-acetoxy-*N*-benzylamino)-2-(*tert*-butyldiphenylsilyloxymethyl)hexanoate, 9c

Oil, $[\alpha]_D = -3.6$ (*c* 0.4, $CHCl_3$); IR ν_{max} (cm^{-1}) 1775, 1734 (C=O); δ_H (500 MHz, $CDCl_3$) 7.70–7.65 (4H, m), 7.45–7.20 (11H, m), 4.30 (1H, d, *J* = 14 Hz), 4.10–4.00 (3H, m), 3.71 (3H, s), 2.10–1.90 (2H, m), 1.61 (3H, s), 1.45 (1H, m), 1.35–1.20 (3H, m), 1.07 (9H, s), 0.90 (3H, t, *J* = 7.4 Hz); δ_C (125 MHz, $CDCl_3$) δ 171.5, 169.5 (br), 136.9, 133.1, 133.0, 74.3, 19.3 (C), 135.8, 135.7, 129.9, 129.8, 129.5, 128.1, 127.9, 127.7, 127.5 (CH), 63.1, 58.0, 31.0, 25.4, 23.3 (CH_2), 51.7, 27.0 (×3), 18.7, 14.0 (CH_3). HR FABMS *m*/*z* 562.2998 [M+H$^+$], calcd for $C_{33}H_{44}NO_5Si$, 562.2988.

4.25. Methyl (2*R*)-2-(*N*-acetoxy-*N*-benzylamino)-3-(*tert*-butyldiphenylsilyloxy)-2-phenylpropionate, 9f

Oil, $[\alpha]_D = +12.3$ (*c* 1.3, $CHCl_3$); IR ν_{max} (cm^{-1}) 1770, 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 7.65–7.55 (4H, m), 7.45–7.20 (16H, m), 4.48 (1H, d, *J* = 10 Hz), 4.29 (1H, d, *J* = 14.5 Hz), 4.24 (1H, br d, *J* = 10 Hz), 4.17 (1H, br d, *J* = 14.5 Hz), 3.83 (3H, s), 1.54 (3H, s), 0.97 (9H, s); δ_C (100 MHz, $CDCl_3$) δ 170.0, 169.4 (br), 137.6, 137.1, 133.0, 132.9, 78.1, 19.2 (C), 135.7, 135.6, 129.9, 129.8, 128.7, 128.4, 128.0, 127.9, 127.7, 127.0 (CH), 67.1, 58.6 (CH_2), 51.8, 26.8 (×3), 18.7 (CH_3). HR FABMS *m*/*z* 582.2672 [M+H$^+$], calcd for $C_{35}H_{40}NO_5Si$, 582.2676.

4.26. Methyl (2*S*)-2-(*N*-acetoxy-*N*-benzylamino)-2-(*tert*-butyldiphenylsilyloxymethyl)-but-3-enoate, ent-9d

Oil, $[\alpha]_D = +0.7$ (*c* 0.2, $CHCl_3$); IR ν_{max} (cm^{-1}) 1763, 1740 (C=O); δ_H (500 MHz, $CDCl_3$) 7.70–7.65 (4H, m), 7.50–7.20 (11H, m), 6.15 (1H, dd, *J* = 17.7, 11.2 Hz), 5.50 (1H, br d, *J* = 17.7 Hz), 5.43 (1H, br d, *J* = 11.2 Hz), 4.29 (1H, d, *J* = 14 Hz), 4.20 (1H, br d, *J* = 10 Hz), 4.15 (1H, br d, *J* = 14 Hz), 4.04 (1H, d, *J* = 10 Hz), 3.76 (3H, s), 1.63 (3H, s), 1.02 (9H, s); δ_C (125 MHz, $CDCl_3$) δ 170.1, 169.0 (br), 136.8, 133.0, 132.9, 75.8, 19.3 (C), 135.8, 135.7, 134.2, 129.8, 129.6, 128.2, 127.7, 127.5 (CH), 119.3, 66.3, 58.6 (CH_2), 52.0, 26.8 (×3), 18.9 (CH_3). HR FABMS *m*/*z* 532.2532 [M+H$^+$], calcd for $C_{31}H_{38}NO_5Si$, 532.2519.

4.27. Conversion of 9a into (*R*)-(−)-2-methylserine

Compound **9a** (230 mg, 0.6 mmol) was dissolved in dry THF (5 mL) and treated with tetra-*n*-butylammonium fluoride trihydrate (189 mg, 0.6 mmol). The reaction mixture was then stirred under Ar for 1 h. After this time, the reaction mixture was quenched into satd aq NH_4Cl (10 mL), stirred for 5 min and extracted with CH_2Cl_2. The organic layer was dried over anhyd Na_2SO_4, evaporated in vacuo and chromatographed on silica gel (elution with hexanes–EtOAc 7:3) to yield β-hydroxy ester **10** (160 mg, 87%): oil, δ_H (500 MHz, $CDCl_3$) 7.30–7.25 (5H, m), 5.70 (1H, br s, OH), 4.78 (1H, d, *J* = 11.5 Hz), 4.22 (1H, d, *J* = 11.5 Hz), 4.01 (2H, AB system, *J* = 14 Hz), 3.79 (3H, s), 2.12 (3H, s), 1.45 (3H, s); δ_C (125 MHz, $CDCl_3$) δ 172.2, 171.5, 138.8, 69.1 (C), 128.5, 128.2, 127.0 (CH), 66.1, 56.8 (CH_2), 52.0, 20.9, 17.8 (CH_3).

Compound **10** obtained above and Pearlman's catalyst (31 mg) were dissolved in MeOH (10 mL) and stirred at room temperature under an H_2 atmosphere (70 psi) for 5 d. The mixture was then filtered, concentrated in vacuo, dissolved in EtOH (5 mL) and treated with an aqueous solution of NaOH 2 M (5 mL). The mixture was then stirred at room temperature for 1 h. The pH value was then adjusted to 1 by adding 1 M HCl. After

solvent removal, the remaining residue was purified via ion interchange chromatography with Dowex 50WX8-400 (the resin was previously washed with water, 1 M HCl and again with water until neutral pH). *R*-(−)-2-methylserine (40 mg, 64% overall yield)[6b] was eluted with aqueous ammonia, first 0.02 M and then 0.1 M.

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13. An exception was oxazolidinone **6f**, where unequivocal NOE measurements were not possible due to overlapping of the key signals. In this case, however, the configuration was unequivocally determined by means of X-ray diffraction analysis of product **7f**.
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