New Approaches to Branched β-Amino α-Hydroxy Acids, Taxol Side-chain Analogs

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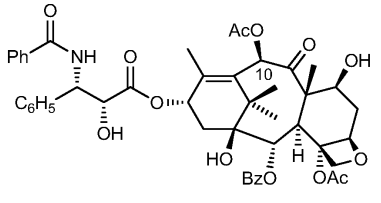
Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

The phenylisothreonine derivatives, taxol side-chain analogs, were synthesized by two routes, one based on the highly stereoselective addition of a phenyl Grignard reagent to the L-threose-derived nitrone **7**, and the other using asymmetric α-alkoxyallylation of the ketimine **20** with chiral allyl boron reagents.

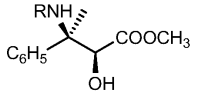
Key words: Phenylisothreonine, Taxol Side-chain, Diastereoselective Grignard Addition, Keto-Nitrone, α-Alkoxyallylation of Imines

Introduction

The stereoselective synthesis of β-amino acids and their derivatives has been an active area of research, due to the importance of β-amino acids in various fields [1]. In particular, non-proteinogenic β-amino α-hydroxy acids are found in many natural products and drugs, for example *N*-benzoyl-3-phenylisoserine as a side-chain of taxol which has been approved for treatment of ovarian and breast cancer by the FDA [2] (Fig. 1).



Taxol **1**



2: R = H; **3:** R = Boc

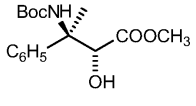


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Fig. 1. Structure of taxol and taxol side-chain analogs.

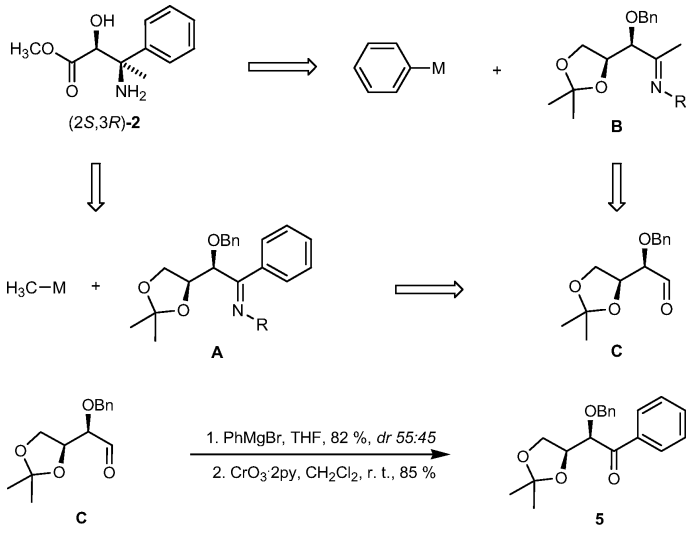
Structure-activity relationship studies have revealed that the side-chain is essential for the antitumor activity [3]. Thus, in the last 20 years efficient syntheses of phenylisoserine and its analogs have attracted much attention from academic groups as well as from industry [4]. In this article, we first report on a highly diastereoselective addition of a phenyl Grignard reagent to the L-threose-derived nitrone **7**, leading to a key intermediate **8** of (2*S*, 3*R*)-phenylisothreonine methyl ester **2** ("*threo*") in excellent diastereoselectivity ($dr >$ 95 : 5). Secondly, the syntheses of *N*-Boc-protected phenylisothreonine derivatives **3** and **4** using different chiral boron reagents **16** and **18** are outlined.

Results and Discussion

Diastereoselective Grignard addition to a chiral, threose-derived keto-nitrone

Up-to-date, with a large number of diverse syntheses of phenylisoserine and derivatives published [4], it is surprising that only two examples of branched phenylisoserines have been reported [5]. Galeazzi's group [5a] developed an approach to branched phenylisoserines by stereoselective iodocyclization of respective amides obtained from Baylis-Hillman adducts. Greene and coworkers [5b] disclosed the first synthesis of β-methyl-branched phenylisoserine as a side-chain of taxol *via* a β-lactam.

Owing to the importance of this class of β-amino acids, in our group new approaches for an access to β-methyl-branched phenylisoserine derivatives were explored. Previously variously substituted 1,2-amino-alcohols had been prepared by several methods [6]. For



Scheme 1. Initial plan for the synthesis of (2*S*,3*R*)-phenylisothreonine methyl ester **2**.

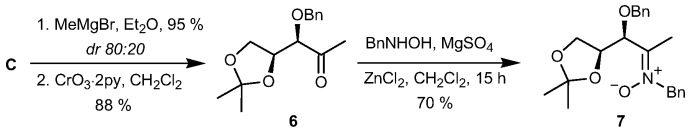
Scheme 2. Preparation of the ketone **5** as precursor of type **A** imines.

example, highly stereoselective additions to α-alkoxyimines or derivatives had provided efficient and versatile access to 1,2-aminoalcohols with the amino group attached to a secondary alkyl group [6, 7], and we have shown the viability of this approach by straightforward and versatile syntheses of such amino hydroxy acids, notably of the statine family (norstatine, statine, homostatine, 'silastatine', isonorstatine) and of phenylisoserine [1, 6a – d]. In other approaches, isoxazolinium salts [6e] or epoxypentenols (from the asymmetric epoxidation of divinylcarbinol) [6f] served as key intermediates for elaboration of variously substituted, optically active amino hydroxy acids. Therefore, in principle, such *tert*-alkylamino alcohols should be accessible from ketimines or equivalent derivatives by selective addition of organometallic reagents. The addition of Grignard and lithium reagents to the C=N double bond of the *N*,*O*-dibenzylthreose derivative [6a, 8] had been found to proceed with high *threo* selectivity. Consequently, we envisioned that (2*S*, 3*R*)-phenylisothreonine methyl ester **2** could be dealt with in this manner. The initial plan is outlined in Scheme 1.

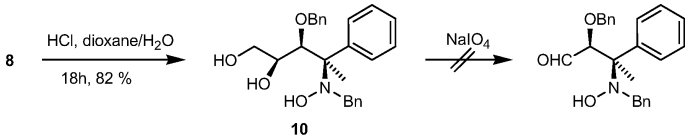
Based on the analysis presented above, the C=N double bond formation is essential for this route. This might be effected by condensation of a ketone with various amino derivatives such as benzylamine, (*R*)-1-phenylethylamine or *O*-benzylhydroxylamine. Thus, the synthesis of the ketone **5** as a precursor of the **A** type imine species was achieved as shown in Scheme 2. The starting material, crystalline 2-*O*-benzyl-3,4-*O*-isopropylidene-L-threose **C**, is easily available in four steps from diethyl L-tartrate *via* 2-*O*-benzyl-L-threitol, according to lit. [8b – d] (50 % overall yield). The aldehyde **C** was treated with phenylmagnesium bromide in THF at 0 °C to give the alcohol intermediate (*dr* 55 : 45) which was oxidized using Collins' reagent [8c] to provide the ketone **5** in 69 % overall yield (Scheme 2).

With the ketone **5** at hand, ketimine formation was tested under different conditions ($BnNH_2$, Al_2O_3, CH_2Cl_2, $BnNH_2$, $TiCl_4$, Et_3N, CH_2Cl_2), but all proved unsuccessful. Therefore, we shifted our attention to prepare a suitable nitrone derivative. Treatment of the ketone **5** with *O*-benzylhydroxylamine in dichloromethane in the presence of magnesium sulfate [9], however, did not afford the expected product (even with the Lewis acid zinc chloride as an additive). This failure might result from the structure of the ketone **5**, because the phenyl group could reduce the activity of the carbonyl group. Accordingly, formation of imines of Type **B** was considered. The ketone **6** was prepared in the same way as described in Scheme 2. The aldehyde **C** reacted with methylmagnesium bromide at 0 °C to provide the corresponding alcohol (*dr* 80 : 20); this was followed by oxidation leading to the ketone **6**. Condensation of the ketone **6** with *N*-benzylhydroxylamine in the presence of magnesium sulfate after 2 d provided the required nitrone **7** in a mere 38 % yield [9]. To our delight, this could be improved to 70 % by addition of zinc chloride with shorter reaction time (Scheme 3); 20 % of the starting material **6** was recovered.

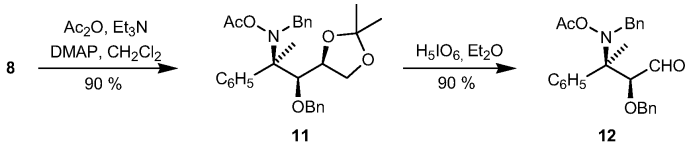
With the nitrone **7** at hand, the addition of Grignard reagents [10] was investigated. In order to



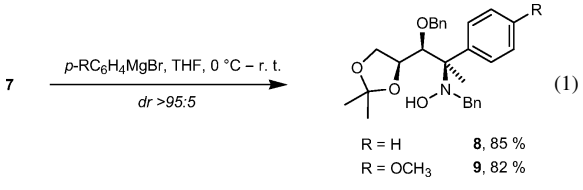
Scheme 3. Preparation of the **B** type nitrone **7**.



Scheme 4. Unsuccessful attempt to cleave the free hydroxylamino diol **10**.



Scheme 5. Synthesis of (2*S*,3*R*)-phenylisothreonine methyl ester (**2**).



access phenylisothreonine derivatives, phenylmagnesium and *p*-anisylmagnesium bromide were employed for additions. Gratifyingly, the reactions proceeded smoothly in 82 – 85 % yield with high diastereoselectivity (*dr* 95 : 5) in both cases (Eq. 1), to afford the hydroxylamino-triol derivatives **8** and **9**.

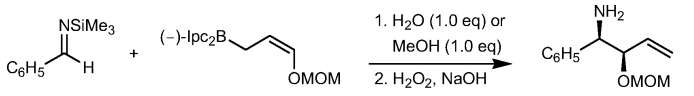
The key intermediate **8** was elaborated to attain the target structure **2**. Attempts to carry out both diol deprotection and cleavage with **8**, bearing the free hydroxylamino function, with periodic acid proved unsuccessful leading to decomposition. Moreover, acidic hydrolysis of the acetonide moiety of **8** yielded the free diol **10**, but subsequent cleavage of the diol with sodium metaperiodate again failed (Scheme 4).

After protection of the *N*-hydroxy group in **8** with acetic anhydride [11], the acetyl derivative, however, underwent oxidative cleavage with periodic acid in diethyl ether cleanly to give the aldehyde **12** [12]. This was oxidized to the carboxylic acid **13** using sodium chlorite [13], followed by esterification with diazomethane or with the two-step procedure [14] shown in Scheme 5.

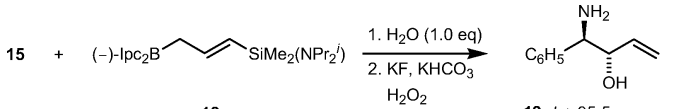
The resulting *N*,*O*,*O*-protected ester **14** was catalytically reduced (Pd/C, 10 %, H_2, 3 bar) to afford (2*S*,3*R*)-phenylisothreonine methyl ester (**2**) as colorless crystals in 92 % yield (Scheme 5). Unexpectedly, an attempted one-pot conversion of the aldehyde **12** into its methyl ester by bromine oxidation of the hemiacetal intermediate in methanol using Lichtenthaler's method [15] did not succeed. Finally, the configuration at the quartenary center of C-3 was established by an X-ray crystal structure analysis of **2** [16].

Enantioselective, α,α'-stereogenic α-alkoxyallylation of imines with chiral allylboranes

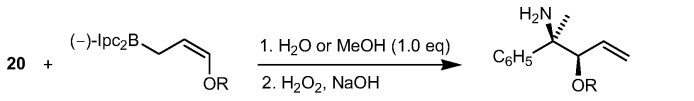
Next, the syntheses of *N*-protected (2*S*,3*R*/2*R*,3*S*)-phenylisothreonine methyl ester **3** ("*threo*") and (2*R*,3*S*/2*S*,3*R*)-phenylisothreonine **4** ("*erythro*") were envisaged utilizing α-alkoxyallylation of a ketimine with chiral allylboranes. The alkoxyallylation of aldehydes with such chiral boron reagents has well been documented [17]. However, the α-alkoxyallylation of ketimines so far has not been addressed. Ramachandran and Burghardt gave a first report on the alkoxyallylation of *N*-silyl- and *N*-alumino-aldimines using the corresponding boron "ate" complex obtained by reaction of allylic anions with *B*-methoxy-diisopino-



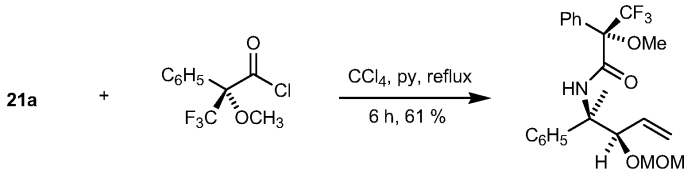
15 **16a** **17** *dr >95:5*; *er 93:7* (*ee* 86 %) (2)



18 **19** *dr >95:5*; *er 88:12* (*ee* 76 %) (3)



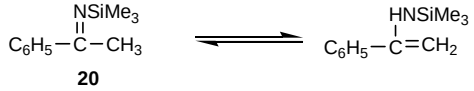
16a R = CH_2OCH_3 59 % **21a** *dr >95 : 5*; *er 69 : 31* (*ee* 38 %) (4)
16b R = CH_3 46 % **21b** *dr >95:5*; *er 60 : 40* (*ee* 20 %)



25 **26** (5)

camphenyl borane [18]. In order to develop new approaches to the taxol side-chain analogs, we have undertaken a systematic investigation of the alkoxyallylation of imines. Firstly, the alkoxyallylation of benzaldehyde *N*-trimethylsilylimine (**15**) using two kinds of chiral boron reagents, **16a** [18e] and **18** [18f], was studied (Eqs. 2, 3).

The silylimine **15**, prepared *in situ* [19], was added to each of the two boron reagents **16a** and **18** (Eqs. 2, 3), followed by addition of one equivalent of water or methanol to form the intermediate corresponding aldimine. After 3 h at this temperature, the reaction was worked up with alkaline hydrogen peroxide to provide the amino-hydroxy-alkenes **17** (*threo*, "*syn*") and **19** (*erythro*, "*anti*"), respectively. In both reactions, the diastereoselectivity was excellent (*dr* 95 : 5) according to ^{1}H NMR analysis; the enantiomeric excess amounted to 86 and 76 %, respectively. The determination of *er* values is discussed below. In view of obtaining the β-methyl-branched β-amino α-hydroxy acid as a taxol side-chain analog, the ketimine **20** was prepared from benzonitrile and methyl lithium and ensuing silylation according to a known protocol [20]. In fact, the product consisted of an equilibrium mixture of the ketimine **20** and its enamine tautomer (Scheme 6).



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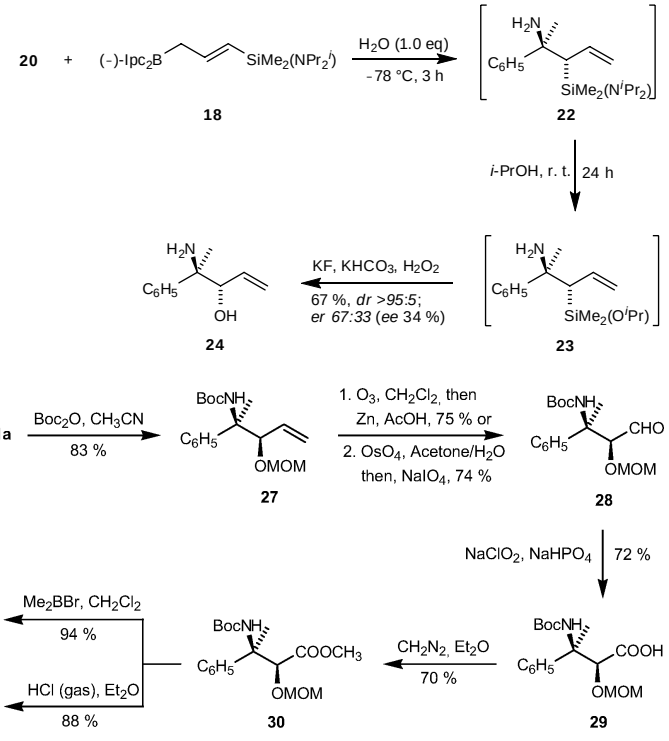
Scheme 6. Equilibrium of the ketimine **20**.

The imine **20** was treated with the allylboration reagents **16a** and **16b**, derived from methoxymethyl and methoxyallyl ether, respectively [18]. After the usual work-up as described above, the addition products **21a** and **21b** were obtained in moderate yield (Eq. 4).

Though the *threo*-diastereoselectivities in both cases were very high, the enantioselectivities with ratios of 69 : 31 and 60 : 40 were much lower (only the major enantiomer is depicted in the formula of **21**).

When the imine **20** was allowed to react with the chiral silylallyl boron reagent **18**, followed by addition of water, and worked up in the usual way (KF, H_2O_2, $NaHCO_3$) [21], a complex mixture resulted. This may have been due to the highly demanding steric situation for the oxidation of the silicon-carbon bond in the diisopropylaminosilane **22**.

Thus, the aminosilane **22** was transformed to the isopropyl silyl ether **23**, in view of the compatibility of the (*i*-PrO)Me_2Si group with the usual, mild hydrolytic work-up. By this way, the amino hydroxy olefin **24**



Scheme 7. Synthesis of the *erythro*-amino-hydroxybutene **24**.

Scheme 8. Syntheses of amino hydroxy esters **2** and **3**.

Table 1. Enantiomeric ratios of several amines (amino alcohols) as determined on their Mosher derivatives.

Entry	Amine	*dr*	*er*
1	**17**	> 95 : 5	93 : 7
2	**19**	> 95 : 5	88 : 12
3	**21a**	> 95 : 5	69 : 31
4	**21b**	> 95 : 5	60 : 40
5	**24**[a]	> 95 : 5	67 : 33

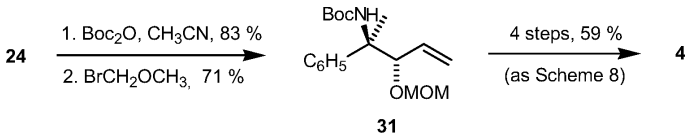
[a] The *er* was determined by GC using a chiral stationary phase.

could easily be isolated in good yield with very high *erythro*-selectivity, but on the other hand, again, with low enantioselectivity (*dr* 67 : 33) (Scheme 7).

The ratio of enantiomers was determined by conversion of the unsaturated amino alcohols into the corresponding Mosher amides using (+)-(*R*)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (**25**) (Eq. 5) [22]. Thus, the amine **21a** was treated with the acid chloride, prepared from Mosher's acid and thionyl chloride, to give the amide derivative **26** [22].

The enantiomeric ratios of the amino alcohols were determined by ^{1}H NMR integration and are given in Table 1. With both silyl imines, derived from benzaldehyde and acetophenone, very high diastereoselectivities were found in the formation of *threo* as well as *erythro* products. While the enantioselectivity of *threo* and likewise *erythro* formation with the benzaldimine is excellent (93 : 7 and 88 : 12), the results with the ketimine are not satisfying. However, to the best of our knowledge, this constitutes the first attempt of enantioselective α-alkoxyallylation of ketimines with chiral boron reagents.

With the unsaturated aminoalcohols **21a** and **24** at hand, the syntheses of the taxol side-chain analogs could be completed. After protection of the amino group with di-*t*-butyl dicarbonate in acetonitrile (83 %) [23], the double bond of **27** was oxidatively cleaved to afford the aldehyde **28**, which proceeded well with ozone [24] (75 %) and by dihydroxylation with osmium tetroxide followed by diol cleavage with sodium metaperiodate (74 %). The aldehyde **28** was transformed into the corresponding ester **30** in a two-step sequence: (*i*) oxidation with sodium chlorite to the acid **29** (72 %) and (*ii*) esterification with diazomethane (70 %) (Scheme 8). Selective removal of the methoxymethyl protecting group with bromo dimethylborane (Me_2BBr) [25] at low temperature (−78 °C) furnished the *N*-Boc-protected β-amino α-hydroxy methyl ester **3** in 94 % yield. On the other hand, *N*,*O*-deprotection occurred when the β-amino ester was treated with hydrogen chloride in diethyl



Scheme 9. Synthesis of the amino hydroxy ester **4**.

ether, providing the free β-amino α-hydroxy ester **2** in 88 % yield.

Finally, as a remaining problem, the configuration of **2** had to be elucidated. The relative configuration was established as *threo* by an X-ray crystal structure analysis of the precursor **29** [26]. The absolute configuration of the major enantiomer of phenylisothreonine **2** was assigned as (2*S*,3*R*) by comparison with the sample of compound **2** obtained from the first route (see Scheme 5). The amino ester **2** obtained now (Scheme 8) had NMR data identical with those of compound **2** as prepared in Scheme 5. The value of the optical rotation of compound **2** from the oxyallylation route (+27.5, c = 0.200, $CHCl_3$) was approximately half of that of the pure sample of (2*S*,3*R*)-phenylisothreonine methyl ester **2** (+58.2, c = 0.400, $CHCl_3$).

In the *erthro* series, the β-amino α-hydroxy olefin **24** was transformed into the corresponding *N*-protected amino hydroxy ester **4**. After protection of the amino group in **24** with di-*t*-butyl dicarbonate (83 %) and of the hydroxy group with methoxymethyl bromide (71 %), the *N*,*O*-protected aminobutenol **31** was obtained as a colorless oil (Scheme 9). Using the same strategy as described in Scheme 8, the *N*-Boc-protected methyl ester **4** was obtained in 59 % overall yield after four steps from the olefin **31**. The relative configuration of **4** had been established by an X-ray diffraction analysis of the preceding intermediate **24** [26].

Conclusion

We have elaborated two different routes to optically active diastereomers of phenylisothreonines as promising taxol side-chain analogs. One way focused on the diastereoselective addition of phenylmagnesium bromide to the threose-derived nitrone **7**; the other one concentrated on the enantioselective α-alkoxyallylation of achiral imines with chiral alkoxy or silyl allylboranes with an isopinocamphenyl auxiliary. While the diastereoselectivities of additions to the imines were excellent in both approaches, the crucial step of the latter route proceeded with low enantioselectivity only. The preparation of new taxol analogs by attaching the above and related β-branched β-amino α-hydroxy acids to baccatin, will be reported separately [27]. An extension of this study will also address a new approach towards derivatives of omuralide (essential constituent of the proteasome inhibitor lactacystin) [28].

Experimental Section

^{1}H NMR spectra were recorded with Bruker ARX 300 and 500 (300.1 and 500.1 MHz) instruments, ^{13}C NMR spectra were recorded with the same instruments (75.5 and 125.8 MHz). NMR shifts are reported relative to TMS as internal standard. FT-IR spectra were obtained on a Bruker (IFS 28) spectrophotometer. GC analysis was performed using a gas chromatograph with a FID detector. Melting points were measured with a Fisher-Johns heating apparatus and are uncorrected. Angles of rotation were measured with a polarimeter 241 MC of Perkin-Elmer. The optical rotations were calculated from the Na_D absorption. For the X-ray structure analyses a Nicolet P3 diffractometer with graphite monochromator was used. The measurements were done with Mo-K_α radiation. Crystal data and numbers pertinent to data collection and structure refinement of **2**, **24** and **29** are given in Table 2. CCDC 678061 (**2**), 678062 (**24**), 678063 (**29**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. Thin layer chromatography (TLC) was performed on precoated aluminium sheets (silical gel 60 F254) purchased from E. Merck (layer thickness 0.2 mm), and flash chromatography employed silica gel 60 with mesh size 40 – 62 μm (E. Merck). Tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium-benzophenone, methanol (MeOH) from magnesium and a catalytic amount of iodine. All other chemicals were purchased and used as received without further purification.

*(2S,3R)-3-Benzyloxy-1,2-isopropylidenedioxy-4-phenylbutanone (**5**)*

a) Preparation of the alcohol by addition of PhMgBr: A 50-mL two-necked round-bottom flask with a refluxing condenser was charged with Mg (38 mg, 1.56 mmol) in absolute THF (5 mL). A small amount of bromobenzene was added to initiate the reaction. The rest of bromobenzene (236 mg, 1.5 mmol) in THF (4 mL) was added dropwise within 5 min. The mixture was heated to reflux for 20 min and cooled to 0 °C. The aldehyde **C** (150 mg, 0.6 mmol) in THF (4 mL) was added dropwise, and the reaction mixture was stirred at

Table 2. Crystal structure data for **2**, **24**, **29**.

	2	**24**	**29**
Empirical formula	$C_{11}H_{15}NO_3$	$C_{11}H_{15}NO$	$C_{17}H_{25}NO_6$
Formula weight	209.24	177.24	339.38
Temperature, K	293(2)	293(2)	293(2)
Cryst. size, mm^3	$1.0 \times 0.4 \times 0.15$	$1.2 \times 0.6 \times 0.5$	$0.25 \times 0.25 \times 0.20$
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	$P2_12_12_1$	$P2_1/n$	$P2_1/n$
a, Å	5.5816(3)	11.169(3)	11.2371(11)
b, Å	8.0072(6)	13.308(4)	7.7596(6)
c, Å	24.7417(19)	14.479(3)	21.0307(15)
α, deg	90	90	90
β, deg	90	100.951(16)	102.725(8)
γ, deg	90	90	90
Volume, Å^3	1105.78(13)	2112.9(8)	1788.7(3)
Z	4	8	4
D_{calcd}, g·cm^{-3}	1.257	1.114	1.260
λ, Å	1.54178 (Cu)	0.71073 (Mo)	1.54178 (Cu)
μ(MoK_α), mm^{-1}	0.754	0.071	0.792
F(000), e	448	768	728
θ Range, deg	3.57 – 67.97	2.10 – 27.50	4.12 – 67.96
Index range h,k,l	$\pm6, \pm8, \pm29$	$+14, +17, \pm18$	$+13, +9, -25 \rightarrow +24$
Reflections collected	2020	5105	3213
Independent reflections	1670 [R(int) = 0.0313]	4861 [R(int) = 0.0124]	3036 [R(int) = 0.0469]
Completeness to θ_{max}, %	91.0	100.0	93.2
Data/parameters	1670 / 185	4861 / 260	3036 / 226
Goodness-of-fit on F^2	1.110	1.062	1.043
Final $R1/wR2$ [$I \geq 2\sigma(I)$]	0.0529, 0.1457	0.0613, 0.1552	0.0602, 0.1519
Final $R1/wR2$ (all data)	0.0552, 0.1493	0.0919, 01704	0.0898, 0.1874
Largest diff. peak and hole, e Å^{-3}	0.230 / −0.200	0.286 / −0.298	0.208 / −0.247

r. t. for 2 h. The reaction was quenched with sat. aq. NH_4Cl (2.5 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to provide a yellowish oil which was purified by flash chromatography on silica (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 5 : 1) to afford the alcohol (162 mg, 82 %) as a colorless, analytically pure oil; *dr* 55 : 45 from ^{13}C NMR spectrum. – Major isomer: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.49, 26.2 [2 q, C(CH_3)$_2$], 66.1 (t, C-1), 73.5 (d, C-4), 74.9 (d, C-2), 77.0 (t, OCH_2Ph), 83.4 (d, C-3), 109.27 [s, $C(CH_3)_2$], 126.4, 126.7, 127.96, 128.1, 128.2, 128.4 (6 d, 2 C_6H_5), 137.82, 141.12 (2 s, *i*-C of C_6H_5). – Minor isomer: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.44, 26.5 [2 s, C(CH_3)$_2$], 66.0 (t, C-1), 73.1 (d, C-4), 74.0 (d, C-2), 75.9 (t, OCH_2Ph), 81.3 (d, C-3), 109.33 [s, $C(CH_3)_2$], 137.82, 141.05 (2 s, *i*-C of C_6H_5); some signals not assigned due to overlap with those of the major isomer. – $C_{20}H_{24}O_4$ (328.4): calcd. C 73.15, H 7.36; found C 72.98, H 7.37.

b) Preparation of the ketone **5**: To a solution of pyridine (790 mg, 10.0 mmol) in dry CH_2Cl_2 (15 mL) was added CrO_3 (500 mg, 5.00 mmol) with stirring within 5 min. The mixture was stirred for an additional hour, then the alcohol prepared above (162 mg, 0.493 mmol) was added in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 4 h at r. t. For work-up, the organic phase was washed with sat. $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL), and 4 M HCl (2 × 10 mL). The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* (40 °C/660 mbar). The residue, a brown oil, was purified by flash chromatography on silica gel (6 g, column 3 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to afford the ketone **5** (137 mg, 85 %) as a colorless, analytically pure powder. – M. p. 105−106 °C. – $[\alpha]_D^{20}$ = 46.5 (c = 1.18, $CHCl_3$). – IR (neat): ν = 2986 (b), 1694 (C=O), 1371, 1262, 1227, 1207, 1147, 1059, 1030, 998, 967, 924, 897, 829, 777, 727, 691 cm^{-1}. – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.31, 1.33 [2 s, 6 H, C(CH_3)$_2$], 3.87 (dd, $^2J_{1a,1b}$ = 8.7, $^3J_{1a,2}$ = 6.3 Hz, 1 H, 1-H_a), 4.02 (dd, $^2J_{1a,1b}$ = 8.7, $^3J_{1b,2}$ = 6.6 Hz, 1 H, 1-H_b), 4.52 (A of AB, ^2J = 11.7 Hz, 1 H, OC$H_a$$H_b$Ph), 4.57 (m, 1 H, 2-H), 4.66 (d, $^3J_{2,3}$ = 6.0 Hz, 3-H), 4.72 (B of AB, ^2J = 11.7 Hz, 1 H, OCH_aH_bPh), 7.25 – 8.05 (m, 10 H, 2 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.2, 26.2 [2 q, C(CH_3)$_2$], 65.7 (t, C-1), 72.5 (t, OCH_2Ph), 76.4 (d, C-2), 82.4 (d, C-3), 109.9 [s, $C(CH_3)_2$], 128.0, 128.2, 128.4, 128.5, 129.3, 133.6 (6 d, 2 C_6H_5), 135.9, 137.1 (2 s, *i*-C of 2 C_6H_5), 199.0 (s, C-4). – $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.26, H 6.89.

(2S,3R)-3-Benzyloxy-1,2-isopropylidenedioxy-4-pentanone ***(6)***

a) Preparation of the alcohol by addition of H_3CMgBr: To a solution of the aldehyde **C** (750 mg, 3.0 mmol) in dry Et_2O (20 mL) was added CH_3MgBr (3 M in Et_2O, 2.5 mL,

7.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h and then quenched with sat. NH_4Cl (4 mL) solution. The mixture was extracted with Et_2O (3 × 25 mL), and the combined organic extracts were dried ($MgSO_4$). After concentration, the crude product was purified by flash chromatography over silica (20 g, column 7 cm × 3 cm, petroleum ether/EtOAc 5 : 1) to afford the alcohol (758 mg, 95 %) as a colorless oil which was directly used for the next step; *dr* 80 : 20 from ^{13}C NMR. – Major isomer: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.3 (q, C-5), 25.5, 26.6 [2 q, C(CH_3)$_2$], 66.0 (t, C-1), 67.7 (d, C-4), 74.5 (t, OCH_2Ph), 77.3 (d, C-2), 82.8 (d, C-3), 109.2 [s, $C(CH_3)_2$], 127.8, 127.2, 128.4 (3 d, C_6H_5), 138.3 (s, *i*-C of C_6H_5). – Minor isomer: ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.2 (q, C-5), 25.5, 26.4 [2 q, C(CH_3)$_2$], 65.9 (t, C-1), 67.4 (d, C-4), 73.7 (t, OCH_2Ph), 76.9 (d, C-2), 82.2 (d, C-3), 109.2 [s, $C(CH_3)_2$], 138.3 (s, *i*-C of C_6H_5); some signals could not be assigned due to overlap with those of the major isomer.

b) Preparation of the ketone **6**: Following the oxidation procedure as decribed for the synthesis of **5**, with pyridine (2.53 g, 32.0 mmol) in dry CH_2Cl_2 (50 mL), CrO_3 (1.6 g, 16 mmol) and the alcohol obtained above (532 mg, 2.0 mmol), the ketone **6** (464 mg, 88 %) was obtained as an analytically pure, colorless oil. – $[\alpha]_D^{20}$ = 67.9 (*c* = 1.60, $CHCl_3$). – IR (neat): ν = 2986, 2882, 1713, 1497, 1455, 1371, 1354, 1255, 1211, 1072, 1027, 844, 737, 697 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$,): δ = 1.34, 1.43 [2 s, 6 H, C(CH_3)$_2$], 2.22 (s, 3 H, 5-H), 3.78 (d, $^3J_{2,3}$ = 5.1 Hz, 1 H, 3-H), 3.87 (dd, $^2J_{1a,1b}$ = 8.5, $^3J_{1a,2}$ = 6.6 Hz, 1 H, 1-H_a), 4.01 (dd, $^2J_{1a,1b}$ = 8.5, $^3J_{1b,2}$ = 6.7 Hz, 1 H, 1-H_b), 4.31 (m, 1 H, 2-H), 4.57, 4.72 (A, B of AB, ^2J = 11.1 Hz, 2 H, OCH_2Ph), 7.31 – 7.37 (m, 5 H, C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.4, 26.2 [2 q, C(CH_3)$_2$], 27.6 (q, C-5), 65.7 (t, C-1), 73.4 (t, OCH_2Ph), 76.2 (d, C-2), 84.6 (d, C-3), 109.8 [s, $C(CH_3)_2$], 128.0, 128.1, 128.5 (3 d, C_6H_5), 137.1 (s, *i*-C of C_6H_5), 209.7 (s, C-4). – $C_{15}H_{20}O_4$ (264.3): calcd. C 68.16, H 7.63; found C 68.03, H 7.61.

*(2S,3R)-3-Benzyloxy-1,2-isopropylidenedioxy-4-pentanone N-benzylnitrone (threo) (**7**)*

To a well-stirred solution of the ketone **6** (792 mg, 3.00 mmol) in CH_2Cl_2 (25 mL) were added anhydrous $ZnCl_2$ (408 mg, 3.00 mmol), *N*-benzylhydroxylamine (443 mg, 3.60 mmol) and $MgSO_4$ (432 mg, 3.60 mmol). The resulting mixture was stirred at r. t. for 15 h. The solids were filtered off, and the filtrate was evaporated. The residue, a light-yellow oil, was purified by flash chromatography on silica (25 g, column 2.5 cm × 10 cm, petroleum ether/EtOAc 3 : 1 to pure EtOAc) to give the ketonitrone **7** (775 mg, 70 %) as a colorless, spectroscopically pure oil. The nitrone **7** was not stable, thus, after analysis by NMR spectroscopy, it was directly used for the next step. – IR (neat): ν = 3030, 2984, 2872, 1580, 1496, 1454, 1369, 1254, 1210, 1152, 1056, 1027, 921, 888, 841, 735, 696, 623 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.32, 1.43 [2 s, 6 H, C(CH_3)$_2$], 2.03 (s, 3 H, 5-H), 3.97 (m, 2 H, 1-H), 4.47 – 4.54 (m, 3 H, 2-H, NCH_2Ph), 5.01, 5.02 (A, B of AB, ^2J = 14.2 Hz, 2 H, OCH_2Ph), 5.08 (d, $^3J_{2,3}$ = 3.6 Hz, 1 H, 3-H), 7.27 – 7.36 (m, 10 H, 2 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8 (q, C-5), 25.6, 26.1 [2 q, C(CH_3)$_2$], 65.0 (t, NCH_2Ph), 65.3 (t, C-1), 73.1 (t, OCH_2Ph), 75.0 (d, C-2), 75.7 (d, C-3), 109.7 [s, $C(CH_3)_2$], 127.7, 127.8, 127.9, 128.3, 128.4, 128.9 (6 d, 2 C_6H_5), 133.2, 137.4 (2 s, *i*-C of 2 C_6H_5), 147.7 (s, C-4).

*(2S,3S,4R)-3-O-Benzyl-4-(N-benzylhydroxylamino)-1,2-O-isopropylidene-4-phenylpentane-1,2,3-triol (D-xylo) (**8**)*

According to the procedure given in lit. [10f], a 100-mL two-necked round-bottom flask with a reflux condenser was charged with Mg (224 mg, 9.3 mmol) in absolute THF (10 mL). At the beginning, a small amount of bromobenzene was added to initiate the reaction; the rest (1.37 g, 7.50 mmol) in THF (10 mL) was added dropwise over a period of 15 min. The mixture was heated to reflux for 20 min, cooled to 0 °C, then the nitrone **7** (369 mg, 0.54 mmol) in THF (8 mL) was added. After stirring for 6 h at r. t., the reaction was quenched with sat. aq. NH_4Cl (2 mL), and the mixture was poured into brine (10 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* (40 °C/220 mbar). The crude product was purified by flash chromatography on silica (15 g, column 6 cm × 2.5 cm, petroleum ether/EtOAc 8 : 1) to afford the hydroxylamine **8** (570 mg, 85 %) as a colorless, analytically pure oil; *dr* > 95 : 5. – $[\alpha]_D^{20}$ = 28.3 (*c* = 1.25, $CHCl_3$): – IR (neat). ν = 3410 (OH), 3028, 2983, 1602, 1495, 1453, 1369, 1212, 1158, 1071, 1047, 1028, 941, 912, 853, 735, 692 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.25, 1.37 [2 s, 6 H, C(CH_3)$_2$], 1.71 (s, 3 H, 5-H), 3.57 – 3.73 (m, 3 H, 1-H_a, NCH_2Ph), 3.83 ("t", $^2J_{1a,1b}$ = 8.0 Hz, $^3J_{1b,2}$ = 7.8 Hz, 1 H, 1-H_b), 3.92 (m, 1 H, 2-H), 4.10 (d, $^3J_{2,3}$ = 7.1 Hz, 1 H, 3-H), 4.66, 5.03 (A, B of AB, ^2J = 11.6 Hz, 2 H, OCH_2Ph), 4.70 (s, 1 H, OH), 7.21 – 7.55 (m, 15 H, 3 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.3 (q, C-5), 26.0, 26.7 [2 q, C(CH_3)$_2$], 57.5 (t, NCH_2Ph), 67.2 (t, C-1), 70.2 (s, C-4), 75.6 (t, OCH_2Ph), 78.5 (d, C-2), 84.5 (d, C-3), 107.7 [s, $C(CH_3)_2$], 127.3, 127.4, 127.6, 127.9, 128.0, 128.2, 128.4, 128.7, 129.6 (9 d, 3 C_6H_5), 139.0, 139.1, 140.8 (3 s, *i*-C of 3 C_6H_5). – $C_{28}H_{33}NO_4$ (447.6): calcd. C 75.14, H 7.43, N 3.13; found C 75.36, H 7.43, N 2.93.

*(2S,3S,4R)-3-O-Benzyl-4-(N-benzylhydroxylamino)-1,2-isopropylidene-4-(4-methoxyphenyl)-pentane-1,2,3-triol (D-xylo) (**9**)*

Following the procedure for the synthesis of **8**, from Mg (81 mg, 3.4 mmol), 4-bromo-anisole (506 mg, 2.71 mmol) in THF (6 + 15 mL), and the nitrone **7** (200 mg, 0.540 mmol) after chromatography (silica, 8 g, column 4 cm × 2 cm,

petroleum ether/EtOAc 7 : 1) the hydroxylamino triol **9** was obtained as a colorless, analytically pure oil (211 mg, 82 %, *dr* 95 : 5). – $[\alpha]_D^{20}$ = 29.2 (*c* = 1.20, $CHCl_3$). – IR (neat): ν = 3434 (OH), 2984, 1608, 1509, 1454, 1368, 1298, 1246, 1179, 1158, 1099, 1071, 1028, 938, 912, 839, 795, 735, 695 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.28, 1.38 [2 s, 6 H, $C(CH_3)_2$], 1.69 (s, 3 H, 5-H), 3.52 (b, 1 H, 1-H_a), 3.63, 3.66 (A, B of AB, ^2J = 13.9 Hz, 2 H, NCH_2Ph), 3.78 – 3.81 (m, 4 H, OCH_3, 1- H_b), 3.96 (m, 1 H, 2-H), 4.08 (d, $^3J_{2,3}$ = 7.8 Hz, 1 H, 3-H), 4.59 (b, 1 H, OH), 4.67, 5.03 (A, B of AB, ^2J = 11.6 Hz, 2 H, OCH_2Ph), 6.86 – 7.40 (m, 14 H, 2 C_6H_5, C_6H_4). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.3 (q, C-5), 26.0, 26.8 [2 q, $C(CH_3)_2$], 55.2 (q, OCH_3), 57.4 (t, NCH_2Ph), 67.3 (t, C-1), 69.7 (s, C-4), 75.9 (t, OCH_2Ph), 78.5 (d, C-2), 84.7 (d, C-3), 107.7 [s, $C(CH_3)_2$)], 113.3, 127.0, 127.3, 127.6, 128.2, 128.4, 128.5, 128.7, 128.9 (9 d, 2 C_6H_5 and C_6H_4), 132.7, 139.0, 139.1, 158.8 (4 s, *i*-C of 2 C_6H_5, C_6H_4). – $C_{29}H_{35}NO_5$ (477.6): calcd. C 72.93, H 7.39, N 2.93; found C 72.83, H 7.57, N 2.79.

*(2S,3S,4R)-3-O-Benzyl-4-(N-benzylhydroxylamino)-4-phenylpentane-1,2,3-triol (**10**)*

The hydroxylamine **8** (66 mg, 0.15 mmol) was dissolved in dioxane/H_2O (3.5 mL, 1 : 1), then concentrated HCl (4 drops) was added. The reaction mixture was stirred at 50 °C for 18 h. The solvent was evaporated under reduced pressure (40 °C/60 mbar). The residue was dissolved in saturated $NaHCO_3$ (3 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to furnish a colorless oil which was purified by flash chromatography on silica (4 g, column 4 cm × 1 cm, petroleum ether/EtOAc 2 : 1) to afford the free diol **10** (50 mg, 82 %) as an analytically pure, colorless powder. – M. p. 138 – 139 °C. – $[\alpha]_D^{20}$ = 48.5 (*c* = 1.20, $CHCl_3$). – IR (solid): ν = 3370 (OH), 3028, 2938, 1602, 1495, 1454, 1372, 1242, 1157, 1067, 1045, 1027, 913, 866, 731, 696 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.75 (s, 3 H, 5-H), 3.53 (dd, $^2J_{1a,1b}$ = 10.8 Hz, $^3J_{1a,2}$ = 5.2 Hz, 1 H, 1-H_a), 3.72 (s, 2 H, NCH_2Ph), 3.83 (dd, $^2J_{1a,1b}$ = 10.8 Hz, $^3J_{1b,2}$ = 5.4 Hz, 1 H, 1-H_b), 3.98 (m, 1 H, 2-H), 4.08 (d, $^3J_{2,3}$ = 3.6 Hz, 1 H, 3-H), 4.68, 4.77 (A, B of AB, ^2J = 11.4 Hz, 2 H, OCH_2Ph), 7.23 – 7.62 (m, 15 H, 3 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.8 (q, C-5), 56.8 (t, NCH_2Ph), 66.1 (t, C-1), 69.2 (d, C-2), 70.2 (s, C-4), 76.1 (t, OCH_2Ph), 82.2 (d, C-3), 127.3, 127.5, 127.8, 127.9, 128.0, 128.4, 128.5, 128.5, 128.7 (9 d, 3 C_6H_5), 137.8, 139.2, 140.7 (3 s, *i*-C of 3 C_6H_5). – $C_{25}H_{29}NO_4$ (407.5): calcd. C 73.68, H 7.17, N 3.44; found C 73.65, H 7.12, N 3.36.

*(2S,3S,4R)-4-(N-Acetoxy-N-benzylamino)-3-O-benzyl-1,2-O-isopropylidene-4-phenyl- pentane-1,2,3-triol (**11**)*

Following lit. [11], to a solution of the hydroxylamine **8** (320 mg, 0.716 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added DMAP (10 mg, 0.081 mmol), Et_3N (145 mg, 1.43 mmol), and acetic anhydride (139 mg, 1.36 mmol) dropwise. The reaction mixture was stirred for 3.5 h at r. t. and quenched by slow addition of aqueous HCl (5 %) at 0 °C until a pH of 7 was reached. The reaction mixture was diluted with Et_2O (20 mL) and washed with water (10 mL), sat. aq. $NaHCO_3$ (2 × 10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* (40 °C/700 mbar). The crude product was purified by flash chromatography on silca gel (10 g, column 5 cm × 2 cm, petroleum ether/EtOAc 7 : 1) to yield the protected hydroxylamine **11** (315 mg, 90 %) as an analytically pure, colorless oil. – $[\alpha]_D^{20}$ = 10.6 (*c* = 1.20, $CHCl_3$). – IR (neat): ν = 2984, 1761 (C=O), 1496, 1454, 1368, 1240, 1195, 1049, 1029, 994, 913, 863, 771, 735, 697 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.19, 1.31 [2 s, 6 H, $C(CH_3)_2$], 1.32 (s, 3 H, 5-H), 1.84 (s, 3 H, $OCOCH_3$), 2.66 ("t", $^2J_{1a,1b}$ = 6.9 Hz, $^3J_{1a,2}$ = 6.9 Hz, 1 H, 1-H_a), 3.21 ("t", $^2J_{1a,1b}$ = 8.3 Hz, $^3J_{1b,2}$ = 8.3 Hz, 1 H, 1-H_b), 3.70, 3.72 (A, B of AB, ^2J = 13.7 Hz, 2 H, NCH_2Ph), 3.90 (m, 1 H, 2-H), 4.15 (d, $^3J_{2,3}$ = 6.9 Hz, 1 H, 3-H), 4.48, 5.11 (A, B of AB, ^2J = 11.5 Hz, 2 H, OCH_2Ph), 7.18 – 7.70 (m, 15 H, 3 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.2 (q, C-5), 19.5 (q, $OCOCH_3$), 26.0, 26.9, [2 q, $C(CH_3)_2$], 58.0 (t, NCH_2Ph), 68.3 (t, C-1), 71.6 (s, C-4), 74.5 (t, OCH_2Ph), 77.9 (d, C-2), 85.9 (d, C-3), 108.5 [s, $C(CH_3)_2$], 127.4, 127.5, 128.4, 128.5, 128.6, 128.9, 129.9 (7 d, 3 C_6H_5), 137.6, 139.6, 141.5 (3 s, *i*-C of 3 C_6H_5), 171.4 (s, $OCOCH_3$). – $C_{30}H_{35}NO_5$ (489.6): calcd. C 73.59, H 7.21, N 2.86; found C 73.24, H 7.35, N 2.70.

*(2S,3R)-3-(N-Acetoxy-N-benzylamino)-2-benzyloxy-3-phenylbutanal (**12**)*

In analogy to lit. [12], H_5IO_6 (378 mg, 1.65 mmol) was added to a solution of the acetonide **11** (324 mg, 0.66 mmol) in Et_2O (10 mL), and the resulting mixture was stirred under N_2 for 5.5 h. The solid was filtered off, and aq. $Na_2S_2O_3$ (2 M, 3.0 mL) was added. The mixture was extracted with Et_2O (3 × 30 mL), and the organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the aldehyde **12** (248 mg, 90 %) as a colorless oil, used directly for the next step.

*(2S,3R)-3-(N-Acetoxy-N-benzylamino)-2-benzyloxy-3-phenylbutanoic acid (**13**)*

The aldehyde **12** (248 mg, 0.59 mmol) was dissolved in *t*-BuOH (6.0 mL) and 2-methyl-2-butene (2.5 mL), then $NaClO_2$ (90 mg, 0.99 mmol) and NaH_2PO_4 (119 mg, 0.99 mmol) were added. After stirring for 90 min, the same amount of $NaClO_2$ and NaH_2PO_4 was added again. After 1 h, NaOH solution (4 M, 2.5 mL) was added, and the solvent was removed under reduced pressure (40 °C/50 mbar). The residue, a colorless powder, was dissolved in water (6.0 mL), then 6 M HCl was added dropwise until a pH

of 3 – 4 was obtained. The mixture was extracted with EtOAc (4 × 30 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the acid **13** (225 mg, 88 %) as a colorless oil, used directly for the next step.

*Methyl (2S,3R)-3-(N-acetoxybenzylamino)-2-benzyloxy-3-phenylbutanoate (threo) (**14**)*

Without purification, the acid **13** was treated with a solution of excess ethereal CH_2N_2. After stirring for 10 min, the solvent was evaporated, and the yellow oil was purified by flash chromatography on silica (8 g, column 4 cm × 2 cm, petroleum ether/EtOAc 4 : 1). Thus, the ester **14** (196 mg, 85 %) was obtained as a colorless, analytically pure oil. – $[\alpha]_D^{20}$ = 74.6 (*c* = 1.50, $CHCl_3$). – IR (neat): ν = 3030, 2949, 1759 (C=O), 1740 (C=O), 1495, 1454, 1399, 1362, 1306, 1241, 1199, 1109, 1073, 1027, 997, 916, 833, 736, 694 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.43 (s, 3 H, 4-H), 1.92 (s, 3 H, $OCOCH_3$), 3.14 (s, 3 H, OCH_3), 3.72 (s, 2 H, NCH_2Ph), 4.24, 4.33 (A, B of AB, ^2J = 11.0 Hz, 2 H, OCH_2Ph), 4.80 (s, 1 H, 2-H), 7.18 – 7.36 (m, 15 H, 3 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.0, (q, C-4), 19.7 (q, $OCOCH_3$), 51.7 (q, OCH_3), 56.9 (q, NCH_2Ph), 71.0 (t, OCH_2Ph), 72.4 (s, C-3), 86.7 (d, C-2), 127.7, 128.0, 128.1, 128.3, 128.6, 128.7, 128.8, 129.3 (8 d, 3 C_6H_5), 137.9, 138.1, 140.8 (3 s, *i*-C of 3 C_6H_5), 171.2 (s, C-1, $OCOCH_3$). – $C_{27}H_{29}NO_5$ (447.5): calcd. C 72.46, H 6.53, N 3.13; found C 72.08, H 6.63, N 2.94.

*(2S,3R)-Phenylisothreonine methyl ester (**2**)*

The ester **14** (70 mg, 0.16 mmol) was dissolved in MeOH (6 mL), followed by addition of Pd/C (10 %, 33 mg). The mixture was hydrogenated (3 bar) at r. t. for 40 h. The catalyst was then filtered off, and the filtrate was concentrated *in vacuo* (40 °C/300 mbar). The crude product was crystallized from a mixture of Et_2O and CH_2Cl_2 (6 mL, 10 : 1) to provide the amino hydroxy ester **2** (31 mg, 92 %) as analytically pure, colorless crystals. – M. p. 125 °C. – $[\alpha]_D^{20}$ = 58.2 (*c* = 0.40, $CHCl_3$). – IR (neat): ν = 3303 – 2760 (b), 1736 (C=O), 1595, 1496, 1436, 1378, 1358, 1216, 1173, 1124, 1106, 1078, 1026, 971, 929, 906, 866, 764, 734, 694 cm^{-1}. – ^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.56 (s, 3 H, 4-H), 2.58 (b, 3 H, OH and NH_2), 3.69 (s, 3 H, OCH_3), 4.31 (s, 1 H, 2-H), 7.26 – 7.49 (m, 5 H, C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.7 (q, C-4), 52.2 (q, OCH_3), 58.0 (s, C-3), 78.2 (d, C-2), 125.5, 127.2, 128.3 (3 d, C_6H_5), 144.6 (s, *i*-C of C_6H_5), 173.4 (s, C-1). – $C_{11}H_{15}NO_3$ (209.2): calcd. C 63.14, H 7.23, N 6.69; found C 62.89, H 7.19, N 6.41.

*(1R,2R/1S,2S)-1-Amino-2-(methoxymethoxy)-1-phenyl-3-butene (threo) (**17**)*

a) Preparation of *N*-trimethylsilyl-imine **15** [19]: To a suspension of $(Me_3Si)_2NLi$ (2.55 g, 15.3 mmol) in Et_2O (18 mL) at 0 °C benzaldehyde (1.27 g, 12.0 mmol) was added dropwise, and the reaction mixture was stirred for 0.5 h at 0 °C. The imine **15** generated *in situ*, was directly used for the next step.

b) Preparation of the olefin **17**: According to lit. [17e], to a stirred solution of methoxymethyl allyl ether (1.17 g, 11.4 mmol) in THF (5 mL) was added *sec*-BuLi (1.4 M in cyclohexane, 7.50 mL, 10.5 mmol) at −78 °C over a period of 10 min. The mixture was stirred at −78 °C for 0.5 h, after which (–)-*B*-methoxydiisopinocampheyl borane (4.20 g, 13.3 mmol) in THF (7 mL) was added dropwise for formation of **16a**. After stirring for 1 h at −78 °C, $BF_3{\cdot}Et_2O$ (1.67 g, 11.8 mmol), the solution of the *N*-trimethylsilyl imine **15** and H_2O (220 mg, 12.2 mmol) in THF (2 mL) were added successively. The reaction mixture was stirred at −78 °C for 3 h, then warmed slowly to r. t. within 2 h at 0 °C, and an aqueous solution of a mixture of H_2O_2 (30 %, 3.3 mL, 29 mmol), and aqueous NaOH (3.0 M, 9.0 mL, 26 mmol) was added dropwise. The resulting mixture was stirred at r. t. for 3 h and heated to reflux for 1 h. Then most of the THF was distilled off, and H_2O (10 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL), the combined extracts were washed with brine (10 mL) and dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash chromatography (30 g, petroleum ether/EtOAc 1 : 1) to give the olefin **17** (1.59 g, 73 %) as a colorless analytically pure oil. According to ^1H NMR analysis, only one diastereoisomer was formed, *i. e.* *dr* > 95 : 5. A ^1H NMR spectrum of the corresponding Mosher derivative indicated a ratio of 93 : 7 of the two enantiomers. – $[\alpha]_D^{20}$ = −97.3 (*c* = 1.06, CH_2Cl_2). – IR (neat): ν = 3370, 3300, 3042, 2930, 2865, 1590, 1480, 1440, 1136, 1080, 1020, 900, 742 cm^{-1}. – ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.85 (s, 2 H, NH_2), 3.31 (s, 3 H, OCH_3), 4.06 (d, $J_{1,2}$ = 6.4 Hz, 1 H, 1-H), 4.21 (t, $J_{1,2} = J_{2,3}$ = 6.7 Hz, 1 H, 2-H), 4.58, 4.77 (A, B of AB, $J_{a,b}$ = 6.6 Hz, 1 H, OCH_2O), 5.20 (d, $J_{1,2a}$ = 17.0 Hz, 1 H, 4-H_a), 5.25 (d, $J_{1,2b}$ = 9.3 Hz, 1 H, 4-H_b), 5.67 – 5.74 (ddd, $J_{2,3}$ = 7.0, $J_{1,2a}$ = 17.2, $J_{1,2b}$ = 10.0 Hz, 1 H, 3-H), 7.30 – 7.45 (m, 5 H, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 55.6 (q, OCH_3), 59.9 (d, C-1), 82.0 (d, C-2), 94.2 (t, OCH_2O), 118.8 (t, C-4), 127.4, 127.6, 128.2 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 135.6 (d, C-3), 142.4 (s, *i*-C of C_6H_5). – $C_{12}H_{17}O_2N$ (207.3): calcd. C 69.54, H 8.27, N 6.76; found C 69.52, H 8.35, N 6.55.

*(1R,2S/1S,2R)-1-Amino-1-phenyl-3-buten-2-ol (**19**)*

In analogy to lit. [18f], to a solution of allyl-diisopropylamino-dimethylsilane (2.45 g, 12.3 mmol) in Et_2O (10 mL) was added *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA, 1.37 g, 11.8 mmol) and *n*-BuLi (1.6 M in cyclohexane, 7.5 mL, 12 mmol) at 0 °C. The solution was kept at 0 °C for 4 h, then cooled to −78 °C and treated with (–)-*B*-methoxy-diisopinocampheyl borane

(4.34 g, 13.7 mmol) in Et_2O (5 mL) for formation of **18**. The reaction mixture was kept at −78 °C for 2 h, then successively $BF_3{\cdot}Et_2O$ (2.15 g, 15.1 mmol), *N*-trimethylsilylimine **15** (from 1.27 g 12.0 mmol benzaldehyde, see preparation of **17**), and H_2O (220 mg, 12.2 mmol) in THF (2 mL) were added. The mixture was stirred at −78 °C for 3 h and then warmed slowly to r. t. After stirring for 5 h and addition of THF/MeOH (24 mL, 1 : 1), the mixture was treated with H_2O_2 (30 %, 30 mL, 268 mmol) in the presence of KF (1.62 g, 28.0 mmol) and $NaHCO_3$ (2.40 g, 28.6 mmol). The mixture was stirred at r. t. for further 12 h and filtered through celite. The celite pad was washed with EtOAc (160 mL), and the organic solute was dried ($MgSO_4$). After concentration under reduced pressure, the residue was purified by flash chromatography on silica (33 g, petroleum ether/EtOAc 3 : 1) to yield the amino alcohol **19** (810 mg, 54 %) as a colorless, analytically pure oil. According to ^{1}H NMR analysis, only one diastereoisomer was formed ($dr > 95 : 5$). The ^{1}H NMR analysis of the corresponding Mosher derivative indicated an 88 : 12 ratio of the two enantiomers. – $[\alpha]_D^{20} = -67$ (c = 1.0, $CHCl_3$). – IR (neat): ν = 3356, 2897, 1601, 1494, 1426, 1122, 1028, 764 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 2.33 (b, 3 H, NH_2, OH), 4.00 (d, $J_{1,2}$ = 5.3 Hz, 1 H, 1-H), 4.25 (t, $J_{1,2} = J_{2,3}$= 5.4 Hz, 1 H, 2-H), 5.19 (d, $J_{1,2a}$ = 10.7 Hz, 1 H, 4-H_a), 5.27 (d, $J_{1,2b}$ = 17.1 Hz, 1 H, 4-H_b), 5.64 – 5.71 (ddd, $J_{2,3}$= 5.8, $J_{1,2a}$ = 10.8, $J_{1,2b}$ = 17.2 Hz, 1 H, 3-H), 7.25 – 7.35 (m, 5 H, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 59.9 (d, C-1), 76.3 (d, C-2), 117.4 (t, C-4), 127.3, 127.6, 128.5 (3 d, *o*-, *m*-, *p*-C of C_6H_5),136.7 (d, C-3), 141.5 (s, *i*-C of C_6H_5). – $C_{10}H_{13}NO$ (163.2): calcd. C 73.59, H 8.03, N 8.58; found C 73.52, H 8.35, N 8.55.

*(2R,3R/2S,3S)-2-Amino-3-methoxymethoxy-2-phenyl-4-pentene (**21a**)*

a) Preparation of the *N*-trimethylsilyl imine **20**: To a stirred solution of benzonitrile (2.58 g, 25.0 mmol) in THF (50 mL) at −78 °C was added dropwise a methyllithium solution in diethyl ether (5 %, 17.3 mL, 27.5 mmol) over a perion of 20 min. After stirring for 2 h at −78 °C, the solution was allowed to warm to r. t., followed by addition of trimethylsilyl chloride (4.08 g, 37.6 mmol), and stirring was continued for 15 h. The *N*-trimethylsilyl imine **20** was used directly for the next step.

b) Preparation of **21a**: To a strirred solution of methoxymethyl allyl ether (2.54 g, 24.0 mmol) in THF (10 mL) was added *sec*-BuLi in cyclohexane (1.3 M, 18.5 mL, 24.0 mmol) at −78 °C over a period of 10 min. The mixture was stirred at −78 °C for an additional 30 min, then (–)-*B*-methoxydiisopinocamphenyl borane (10.6 g, 20.0 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h, then boron trifluoride etherate (3.78 g, 26.6 mmol) was added dropwise at this temperature. The mixture was immediately treated with the *N*-trimethylsilyl imine **20** and methanol (0.64 g, 11.7 mmol) in THF (2 mL), then stirred at −78 °C for 3 h and slowly warmed to r. t. over 2 h. After cooling to 0 °C, an aqueous solution of hydrogen peroxide and sodium hydroxide (2.00 g NaOH, 28.0 mmol; 14.3 mL H_2O; 5.7 mL H_2O_2, 30 %) was added dropwise. The mixture was stirred at r. t. for 3 h, and most of the solvent was removed *in vacuo*. Water (10 mL) was added, and the mixture was extracted with diethyl ether (3 × 40 mL). The combined ether phases were washed with brine (10 mL) and dried over $MgSO_4$. After concentration (40 °C), the crude product was purified by flash column chromatography (silica, 35 g, EtOAc/MeOH 10 : 1) to afford the amino ether **21a** as a colorless, analytically pure liquid (2.50 g, 58 %). According to ^{1}H NMR analysis, only one diastereomer was formed, *i. e.* $dr > 95 : 5$. The ^{1}H NMR spectrum of the corresponding Mosher derivative indicated a 70 : 30 ratio of the two diastereomers. – $[\alpha]_D^{20}$ = −28.7 (c = 1.41, $CHCl_3$). – IR (neat): ν = 3375, 2931, 2887, 1601, 1495, 1445, 1421, 1373, 1192, 1096, 1028, 920, 759, 699 cm^{-1}. – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, 1-H), 1.74 (b, 2 H, NH_2), 2.87 (s, 3 H, OCH_3), 4.17 (d, $J_{2,3}$ = 7.5 Hz, 1 H, 3-H), 4.32, 4.58 (A, B of AB, $J_{a,b}$ = 6.8 Hz, 2 H, OCH_2O), 5.25 (dd, $J_{1,2a}$ = 17.3, $J_{a,b}$ = 1.8 Hz, 1 H, 5-H_a), 5.33 (dd, $J_{1,2b}$ = 10.7, $J_{a,b}$ = 1.8 Hz, 1 H, 5-H_b), 5.71 (m, 1H, 4-H), 7.21 – 7.53 (m, 5H, C_6H_5). – ^{13}C NMR (75.5 MHz, CDCl3): δ = 27.1 (q, C-1), 55.2 (s, C-2), 57.6 (q, CH_2OCH_3), 84.2 (d, C-3), 93.7 (t, OCH_2O), 120.2 (t, C-5), 125.9, 126.3, 127.8 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 134.3 (d, C-4), 147.1 (s, *i*-C of C_6H_5). – $C_{13}H_{19}NO_2$ (221.3): calcd. C 70.56, H 8.65, N 6.33; found C 70.49, H 8.72, N 6.27.

*(2R,3R)-2-Amino-3-methoxy-2-phenyl-4-pentene (**21b**)*

Following the procedure used for the synthesis of compound **21a**, the amine **21b** was obtained as a colorless, analytically pure oil [0.82 g, 46 %; from 0.95 g (9.25 mmol) of benzonitrile]. According to ^{1}H NMR analysis, only one diastereoisomer was formed. The ^{1}H NMR spectrum of the corresponding Mosher amide indicated a ratio of the two enantiomers of 60 : 40. – $[\alpha]_D^{20} = -2.7$ (c = 1.0, $CHCl_3$). – IR (neat): ν = 3023 – 3375 (b), 2977, 2931, 2820, 1601 (C=C), 1494, 1372, 1090, 995, 928, 848, 772, 699 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, C-1), 1.75 (s, 2 H, NH_2), 3.21 (s, 3 H, OCH_3), 3.65 (d, $J_{2,3}$ = 7.2 Hz, 1 H, 3-H), 5.18 (dd, $J_{4,5a}$ = 18.4, $J_{a,b}$ = 1.4 Hz, 1 H, 5-H_a), 5.26 (dd, $J_{1,2b}$ = 10.3, $J_{a,b}$ = 1.6 Hz, 1 H, 4-H_b), 5.56 – 5.62 (ddd, $J_{3,4}$ = 7.3, $J_{1a,5}$ = 17.2, $J_{1b,5}$ = 10.4 Hz, 1 H, 3-H), 7.22 – 7.50 (m, 5 H, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.6 (q, C-1), 57.5 (q, OCH_3), 58.1 (s, C-2), 90.7 (d, C-3), 119.7 (t, C-5), 126.5, 126.7, 128.2 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 135.0 (d, C-4), 147.0 (s, *i*-C of C_6H_5). – $C_{12}H_{17}NO$ (191.3): calcd. C 75.35, H 8.96, N 7.32; found C 74.96, H 8.74, N 7.08.

*Mosher derivative of **21b***

Following the procedure given for the synthesis of compound **26**, the Mosher amide of **21b** was obtained as a light yellow oil; a diastereomeric ratio of 60 : 40 was observed from ^{1}H NMR analysis. – Major isomer: ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, C-1′), 3.22, 3.58 (2 s, 6 H, 2 OCH_3), 3.78 (m, 1 H, 3′-H), 5.05 (m, 2 H, 5′-H), 5.47 (m, 1 H, 4′-H), 7.19 – 7.77 (m, 10 H, C_6H_5). – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 19.5 (q, C-1), 57.6 (q, 2 OCH_3), 61.7 (s, C-2′), 89.1 (d, C-3′), 120.9 (t, C-5′), 126.4, 127.4, 127.9, 128.3, 128.8, 129.6 (6 d, 2 C_6H_5), 132.7 (d, C-4′), 142.9 (s, *i*-C of C_6H_5), 165.1 (s, C-1).

*(3S,4R/3R,4S)-2-Amino-2-phenyl-4-penten-3-ol (**24**)*

To a solution of (allyl)(diisopropylamino)dimethylsilane (3.99 g, 20.0 mmol) and TMEDA (2.32 g, 20 mmol) in diethyl ether (20 mL) was added dropwise *n*-BuLi (15 % in hexane, 7.98 mL, 18.7 mmol). The solution was stirred at 0 °C for 4 h and then cooled to −78 °C. After addition of (–)-*B*-methoxydiisopinocamphenyl borane (12.9 g, 24 mmol) in THF (5 mL), the solution was stirred at this temperature for 2 h, then succesively boron trifluoride etherate (3.77 g, 26.6 mmol), *N*-trimethylsilyl imine **20** (from benzonitrile, 2.58 g, 25.0 mmol; see preparation of **21a**) and methanol (0.64 g, 20.0 mmol) in THF (2 mL) were added. The mixture was stirred at −78 °C for 3 h, then warmed slowly to r. t. and stirred for 5 h. After that, 2-propanol (5.43 g, 91.6 mmol) was added, and the mixture was stirred at r. t. for 8 h. For work-up, a solution of alkaline hydrogen peroxide (THF 24 mL; MeOH 24 mL; KF 3.24 g 56.0 mmol; $NaHCO_3$ 4.80 g, 57.2 mmol; 30 % H_2O_2, 13.2 g, 110 mmol) was added. After stirring at r. t. for 24 h, the mixture was filtered through celite and washed with EtOAc (150 mL). The organic solution was dried ($MgSO_4$), concentrated under reduced pressure (40 °C/ 150 mbar) and the residue purified using column chromatography (silica, 40 g, EtOAc/MeOH 10 : 1) to yield the *anti*-diol **24** (2.07 g, 63 %) as a colorless, analytically pure oil, which slowely solidified. According to ^{1}H NMR analysis, only one diastereomer was formed, *i. e.* *dr* > 95 : 5. GC on chiral stationary column [Finnigan chromatograph MFC 800, FID detector, Bondex polysiloxane with 5.5 % of permethyl-β-cyclodextrin [29], 20 m capillary column, temp. 60 °C to 120 °C with 1 °C/min; retention time 54.7 (minor) and 55.4 (major) min] indicated a ratio of enantiomers of 67 : 33. – M. p. 106 – 108 °C. – $[\alpha]_D^{20}$ = 9.3 (*c* = 1.01, $CHCl_3$). – IR (KBr): ν = 3345 – 3058 (w, b, NH_2, OH), 2976, 2854, 1605, 1495, 1444, 1022, 758, 697 cm^{-1}. – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, 5-H), 2.44 (s, 3 H, OH, NH_2), 4.25 (dd, $J_{2,3}$ = 5.0, $J_{3,OH}$ = 1.4 Hz, 1 H, 3-H), 5.09 (dd, $^2J_{1a,1b}$ = 1.7, $J_{1a,2}$ = 10.5 Hz, 1 H, 1-H_a), 5.29 (dd, $^2J_{1a,1b}$ = 1.7, $J_{1b,2}$ = 17.2 Hz, 1 H, 1-H_b), 5.45 (ddd, $J_{1a,2}$ = 10.3, $J_{1b,2}$ = 17.3, $J_{2,3}$ = 5.1 Hz, 1 H, 2-H), 7.26 – 7.42 (m, 5 H, C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.8 (q, C-5), 58.3 (s, C-4), 78.5 (d, C-3), 116.7 (t, C-1), 125.5, 126.8, 128.2 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 137.0 (d, C-2), 145.9 (s, *i*-C of C_6H_5). – $C_{11}H_{15}NO$ (177.2): calcd. C 74.29, H 8.53, N 7.90; found C 74.45, H 8.49, N 7.83.

*(2R)-3,3,3-Trifluoro-2-methoxy-N-[(1R,2′R)-2′-methoxymethoxy-1′-methyl-1′-phenyl-but-3′-enyl]-2-phenylpropionamide (**26**), Mosher amide of **21a***

R-(+)-Mosher acid [22] (92 mg, 0.39 mmol) was slowly added to $SOCl_2$ (2 mL). After 50 h of reflux under N_2, excessive $SOCl_2$ was distilled off to provide the Mosher acid chloride **25**, to which was successively added dry CCl_4 (2 mL), pyridine (400 mg, 5.60 mmol) and the *O*-MOM-protected amino alcohol **21a** (60 mg, 0.29 mmol). The reaction mixture was heated to reflux for another 6 h. After removal of the solvent, the crude product was purified by flash chromatography on silica (EtOAc/petroleum ether 1 : 3) to furnish the Mosher derivative **26** (80 mg, 62 %, impure sample) as a light yellow oil with *dr* 70 : 30 from ^{1}H NMR data. – Major isomer: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.83 (s, CCH_3), 3.09, 3.47 (s, 2 OCH_3), 4.06 (d, $J_{2',3'}$ = 6.8 Hz, 1 H, 2′-H), 4.41 – 4.60 (m, OCH_2O), 5.10 (m, 4′-H), 5.47 (m, 3′-H), 7.18 – 7.60 (m, 2 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.2 (q, CCH_3), 55.3, 55.7 (2 q, 2 OCH_3), 61.0 (s, C-1′), 84.0 (d, C-2′), 104.3 (d, OCH_2O), 120.6 (t, C-4′), 125.8, 126.1, 127.70, 127.72, 128.0, 128.3, 128.5, 128.6, 128.8, 128.9, 129.3, 129.7 (12 d, *o*-, *m*-, *p*-C of 2 C_6H_5 of both diastereomers), 139. 3 (d, C-3′), 142.5 (s, *i*-C of C_6H_5), 165.0 (s, C-1). – Minor isomer: ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.76 (s, CCH_3), 3.01, 3.57 (2 s, 2 OCH_3), 4.17 (d, $J_{2',3'}$ = 6.8 Hz, 2′-H), 7.18 – 7.60 (m, 2 C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.5 (q, CCH_3), 55.1, 55.5 (2 q, 2 OCH_3), 61.2 (s, C-1′), 84.0 (d, C-2′), 94.3 (d, OCH_2O), 120.4 (t, C-4′), 137. 9 (d, C-3′), 142.6 (s, *i*-C of C_6H_5), 164.8 (s, C-1). Some peaks overlapped with those of the major isomer and could not be assigned.

*(2R,3R/2S,3S)-2-tert-Butoxycarbonylamino-3-methoxymethoxy-2-phenyl-4-pentene (**27**)*

In analogy to lit. [23], to a solution of the amine **21a** (600 mg, 2.64 mmol) in CH_3CN (10 mL) was added $(Boc)_2O$ (634 mg, 2.90 mmol) at 0 °C. After 30 min, the mixture was warmed to r. t. and stirred for 8 h. The reaction mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). After concentration *in vacuo*, the crude product was purified by flash chromatography on silica gel (petroleum ether / EtOAc 3 : 1) to provide the urethane **27** (730 mg, 83 %) as a colorless, analytically pure oil. – $[\alpha]_D^{20}$ = −18.0 (*c* = 1.14, $CHCl_3$). – IR (film): ν = 3432, 2977, 1721, 1702, 1489, 1446, 1365, 1246, 1172, 1018, 698 cm^{-1}. –

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, 3 CH_3), 1.73 (s, 3 H, CCH_3), 2.93 (s, 3 H, OCH_3), 4.01 (d, $^2J_{a,b}$ = 6.5 Hz, 1 H, OCH_aH$_b$O), 4.37 (s, 1 H, 2-H), 4.57 (d, $^2J_{a,b}$ = 6.5 Hz, 1 H, OCH$_a$$H_b$O), 5.27 (m, 2 H, 4-H), 5.65 (m, 1 H, 3-H), 7.17 – 7.32 (m, 5 H, C_6H_5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.2 (q, CCH_3), 28.4 (q, 3 CH_3), 55.5 (s, C-1), 60.3 (q, OCH_3), 79.0 [s, $C(CH_3)_3$], 84.7 (d, C-2), 94.0 (t, OCH_2O), 120.6 (t, C-4), 126.1, 126.6, 127.9 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 132.9 (d, C-3), 144.4 (s, *i*-C of C_6H_5), 155.2 (s, COO). – $C_{18}H_{27}NO_4$ (321.4): calcd. C 67.26, H 8.47, N 4.36; found C 67.11, H 8.47, N 4.29.

*(2S,3R/2R,3S)-3-tert-Butoxycarbonylamino-2-methoxymethoxy-3-phenylbutanal (**28**)*

A solution of the protected amine **27** (0.51 g, 1.66 mmol) in CH_2Cl_2 (20 mL) was treated at −78 °C with a stream of ozone for 10 min, followed by a stream of dried oxygen for 30 min. Then zinc powder (0.42 g, 6.4 mmol) and an aqueous solution of acetic acid (25 mmol, 3.0 mL, 50 %) were added. The reaction mixture was allowed to warm up to r. t. and stirred further for 12 h. The mixture was filtered through celite and washed with EtOAc (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the aldehyde **28** (340 mg, 63 %) as a yellow oil which was directly used for the next step. – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.37 (s, 9 H, 3 CH_3), 1.88 (s, 3 H, CCH_3), 3.14 (s, 3 H, OCH_3), 4.10 (s, 1 H, 2-H), 4.46 (d, $^2J_{a,b}$ = 6.8 Hz, 1 H, OCH_aH$_b$O), 4.56 (d, $^2J_{a,b}$ = 6.8 Hz, 1 H, OCH$_a$$H_b$O), 7.22 – 7.41 (m, 5 H, C_6H_5), 9.53 (s, 1 H, CHO). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (q, CH_3), 28.2 (q, 3 CH_3), 56.0 (s, C-1), 59.8 (q, OCH_3), 79.6 [s, $C(CH_3)_3$], 86.8 (d, C-2), 96.8 (t, OCH_2O), 125.8, 127.3, 128.4 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 142.5 (s, *i*-C of C_6H_5), 155.4 (s, NHCO), 201.3 (d, C-3).

*(2S,3R/2R,3S)-3-tert-Butoxycarbonylamino-2-methoxymethoxy-3-phenylbutanoic acid (**29**)*

To a solution of the aldehyde **28** (190 mg, 0.58 mmol) in *t*-BuOH (10 mL) and 2-methyl-2-butene (5.0 mL) were added $NaClO_2$ (79 mg, 0.87 mmol) and NaH_2PO_4 (105 mg, 0.87 mmol) in water (1.0 mL) at r. t. The resulting mixture was stirred at r. t. for 16 h, then the pH value of the solution was adjusted to 10 by adding a solution of NaOH (6 M). After removal of the solvent *in vacuo*, the residue was dissolved in water (30 mL) and acidified to pH < 3 by addition of aqueous hydrochloric acid (10 %). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). After removal of the solvent, crystallization from CH_2Cl_2 provided the acid **29** (140 mg, 72 %) as colorless crystals. – M. p. 156 – 157 °C. – IR (neat): ν = 3419, 2986, 1734 (C=O), 1635, 1422, 1326, 1149, 1044, 988, 879, 761, 698 cm^{-1}. – ^{1}H NMR (300.1 MHz, CD_3OD): δ = 1.41 (s, 9 H, 3 CH_3), 1.86 (s, 3 H, 4-H), 2.92 (s, 3 H, OCH_3), 4.08 (s, 1 H, 2-H), 4.34 (d, $^2J_{a,b}$ = 6.7 Hz, 1 H, OCH_aH$_b$O), 4.47 (d, $^2J_{a,b}$ = 6.9 Hz, 1 H, OCH$_a$$H_b$O), 7.20 – 7.41 (m, 5 H, C_6H_5). – ^{13}C NMR (75.5 MHz, CD_3OD): δ = 22.9 (q, C-4), 28.7 (q, 3 CH_3), 56.2 (s, C-3), 60.8 (q, OCH_3), 80.3 [s, $C(CH_3)_3$], 82.9 (d, C-2), 97.3 (t, OCH_2O), 127.5, 127.9, 129.0 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 143.5 (s, *i*-C of C_6H_5), 156.2 (s, COO), 173.2 (s, COOH).

*Methyl (2S,3R/2R,3S)-3-tert-butoxycarbonylamino-2-methoxymethoxy-3-phenyl-butyrate (**30**)*

The acid **29** (200 mg, 0.59 mmol) was treated with CH_2N_2 in Et_2O (excess) at r. t. After 15 min of stirring, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 5 : 1) to provide the ester **30** (200 mg, 96 %) as a colorless, analytically pure powder. – M. p. 65 – 66 °C. – $[\alpha]_D^{20}$ = −8.9 (*c* = 1.3, $CHCl_3$). – IR (solid): ν = 3430, 2975, 1723 (C=O), 1497, 1363, 1252, 1169, 1042, 920, 862, 778, 700 cm^{-1}. – ^{1}H NMR (300.1 MHz, CD_3OD): δ =1.39 [s, 9 H, $C(CH_3)_3$], 1.85 (s, 3 H, 4-H), 2.96 (s, 3 H, OCH_3), 3.69 (s, 3 H, $COOCH_3$), 4.08 (s, 1 H, 2-H), 4.34, 4.47 (A, B of AB, ^2J = 6.7 Hz, 2 H, OCH_2O), 5.84 (b, 1 H, NH), 7.18 – 7.37 (m, 5 H, C_6H_5). – ^{13}C NMR (75 MHz, CD_3OD): δ = 22.1 (q, C-4), 28.3 [q, $C(CH_3)_3$], 52.0 (q, $COOCH_3$), 55.9 (s, C-3), 60.4 (q, OCH_3), 79.3 [s, $C(CH_3)_3$], 82.2 (d, C-2), 96.2 (t, OCH_2O), 126.0, 127.0, 128.0 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 142.9 (s, *i*-C of C_6H_5), 154.6 (s, NCOO), 170.5 (s, C-1). – $C_{18}H_{27}NO_4$ (321.4): calcd. C 61.17, H 7.70, N 3.96; found C 61.36, H 7.75, N 3.83.

*(2S,3R/2R,3S)-3-tert-Butoxycarbonylamino-phenylisothreonine methyl ester (threo) (**3**)*

To a stirred solution of the ester **30** (61 mg, 0.17 mmol) in dry CH_2Cl_2 (6.0 mL) at −78 °C was slowly added a solution of Me_2BBr (30 % in CH_2Cl_2, 62 mg, 0.51 mmol). The mixture was stirred at −78 °C for 1 h and then was poured into a solution of THF (6.0 mL) and saturated aqueous $NaHCO_3$ (2.0 mL). After stirring for 5 min, the mixture was diluted with Et_2O (10 mL), the organic layer was separated and washed successively with water (3 mL), $NaHSO_4$ (3 mL, 10 %), and brine. The aqueous layer was extracted with Et_2O (2 × 10 mL), the combined organic phases were dried over $MgSO_4$. Removal of the solvent *in vacuo* and purification by flash chromatography (petroleum ether/EtOAc 4 : 1) afforded the *N*-Boc-amino hydroxy ester **3** (50 mg, 94 %) as a colorless, analytically pure powder. – M. p. 75 – 76 °C. – $[\alpha]_D^{20}$ = 3.9 (*c* = 1.0, $CHCl_3$). – IR (solid): ν = 3306, 2987, 1729, 1678, 1539, 1496,1446, 1368, 1291, 1257, 1165, 1051, 1015, 891, 759, 696 cm^{-1}. – ^{1}H NMR (500.1 MHz, CD_3Cl): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 1.72 (s, 3 H, 4-H), 3.69

(s, 3 H, $COOCH_3$), 4.56 (s, 2-H), 4.72, 5.40 (2 b, 2 H, NH, OH), 7.26 – 7.36 (m, 5 H, C_6H_5). – ^{13}C NMR (125 MHz, CD_3OD): δ = 28.3 [q, 4 C(CH_3)$_3$, C-4], 52.3 (q, $COOCH_3$), 61.5 (s, C-3), 78.0 [s, $C(CH_3)_3$], 80.4 (d, C-2), 126.0, 127.0, 128.0 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 142.0 (s, *i*-C of C_6H_5), 155.8 (s, NCOO), 172.4 (s, C-1). – $C_{18}H_{27}NO_4$ (321.4): calcd. C 62.12, H 7.49, N 4.53; found C 62.15, H 7.57, N 4.36.

*(2S,3R/2R,3S)-Phenylisothreonine methyl ester (threo) (**2**)*

To a stirred solution of the ester **30** (14 mg, 0.045 mmol) in Et_2O (2 mL) was added HCl in Et_2O (18 M, 0.6 mL) at 0 °C. The resulting mixture was stirred at r. t. for 12 h and then poured into aqueous NH_3 (25 %, 1.0 mL), followed by extraction with CH_2Cl_2 (4 × 5 mL). The organic extracts were dried over $MgSO_4$. After removal of the solvent *in vacuo*, the colorless powder obtained was recrystallized from Et_2O/CH_2Cl_2 (2.5 mL, 8 : 1) to give the amino hydroxy ester **2** (7.0 mg, 76 %) as a colorless powder. – M. p. 122 – 123 °C. – $[\alpha]_D^{20}$ = 27.5 (*c* = 0.20, $CHCl_3$); *cf.* enantiomerically pure **2** from the first route: $[\alpha]_D^{20}$ = 58.2 (*c* = 0.40, $CHCl_3$). – IR, ^{1}H and ^{13}C NMR data in complete agreement with those given above.

*(2R,3S/2S,3R)-2-tert-Butoxycarbonylamino-3-methoxymethoxy-2-phenyl-4-pentene (**31**)*

The amine **24** (500 mg, 2.80 mmol) was dissolved in CH_3CN (10 mL) to which $(Boc)_2O$ (740 mg, 3.30 mmol) was added at 0 °C. The reaction mixture was stirred for 30 min at the same temperature and then warmed to r. t. After 8 h of stirring, the solvent was removed under reduced pressure to give the *N*-protected amino alcohol as a colorless oil. This was dissolved in Et_2O (25 mL), followed by addition of CH_3OCH_2Br (410 mg, 3.10 mmol) and *N*-ethyldiisopropylamine (380 mg, 2.95 mmol) at 0 °C. The reaction mixture was stirred for 4 h at r. t., then H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), the combined extracts were washed with brine (10 mL) and dried ($MgSO_4$). After evaporation, the residue was purified by flash chromatography over silica gel (petroleum ether/EtOAc 14 : 1) to afford the *N*,*O*-protected olefin **31** (520 mg, 58 %) as a colorless, analytically pure oil. – $[\alpha]_D^{20}$ = –3.1 (*c* = 1.43, $CHCl_3$). – IR (neat): ν = 3432, 2977, 1728, 1697, 1491, 1448, 1345, 1247, 1149, 1053, 1022, 891, 698 cm^{-1}. – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.28 [s, 9 H, C(CH_3)$_3$], 1.82 (s, 3 H, 1-H), 3.25 (s, 3 H, OCH_3), 4.04 (d, 1 H, 3-H), 4.46, 4.60 (A, B of AB, $^2J_{a,b}$ = 5.7 Hz, 2 H, OCH_2O), 5.20 – 5.46 (m, 3 H, 4-H, 5-H), 7.17 – 7.29 (m, 5 H, C_6H_5). – ^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 22.2 [q, C(CH_3)$_3$], 28.3 (q, C-1), 55.9 (q, OCH_3), 59.8 (s,C-2), 77.2 [s, $C(CH_3)_3$], 84.1 (d, C-3), 94.2 (t, OCH_2O), 120.9 (t, C-5), 126.6, 126.7, 127.6 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 133.4 (d, C-4), 145.1 (s, *i*-C of C_6H_5), 154.6 (s, COO). – $C_{18}H_{27}NO_4$ (321.4): calcd. C 67.26, H 8.47, N 4.36; found C 67.27, H 8.51, N 4.40.

*(2R,3R/2S,3S)-3-tert-Butoxycarbonylamino-phenylisothreonine methyl ester (erythro) (**4**)*

Following the procedure used for the synthesis of **3** from **21a**, the ester **4** (94 %) was obtained as a colorless, spectroscopically pure oil. – $[\alpha]_D^{20}$ = 4.4 (*c* = 0.50, $CHCl_3$). – IR (neat): ν = 3409, 2977, 1726 (C=O), 1694 (C=O), 1495,1447, 1365, 1248, 1165, 1054, 1029, 761, 699 cm^{-1}. – ^{1}H NMR (300.1 MHz, CD_3Cl): δ = 1.35 [s, 9 H, C(CH_3)$_3$], 1.90 (s, 3 H, 4-H), 3.64 (s, 3 H, $COOCH_3$), 4.34 (s, 1 H, 2-H), 3.38, 5.74 (2 b, 2 H, NH, OH), 7.23 – 7.30 (m, 5 H, C_6H_5). – ^{13}C NMR (75 MHz, CD_3Cl): δ = 22.3 (q, C-4), 29.7 [q, C(CH_3)$_3$], 52.5 (q, $COOCH_3$), 60.4 (s, C-3), 77.2 [s, $C(CH_3)_3$], 79.8 (d, C-2), 125.7, 127.4, 128.3 (3 d, *o*-, *m*-, *p*-C of C_6H_5), 142.0 (s, *i*-C of C_6H_5), 154.9 (s, NCOO), 172.2(s, C-1). – $C_{16}H_{23}NO_5$ (309.4): calcd. C 62.12, H 7.49, N 4.53; found C 62.79, H 7.61, N 4.24. – HRMS (ESI, M^+ + Na): (*m/z*) = 332.1460 (calcd. 332.1468 for $C_{16}H_{23}NO_5Na$).

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