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STEREOSELECTIVE SYNTHESIS OF β-AMINO ACIDS BY ALDOL-TYPE ADDITION

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This paper is dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday.

Abstract –A synthesis of α-oxygenated β-amino acid derivatives using an aldol-type addition is described. Depending on the enol equivalent different oxidation states of the oxygen substituent are accessible, while choosing a chiral imine allows to generate the aldol product in a stereoselective manner. This methodology has been applied to the synthesis of the biologically active compound Telaprevir, used in the traetment of hepatitis C.

β-Amino acids are a common building block in many biologically active compounds (Figure 1). Some well-known examples are the microtubule-stabilizing anti-cancer agent Taxol (**1**), the protease inhibitor Bestatin (**2**), used in the treatment of acute myeloid leukemia, and Telaprevir (**3**), developed for the treatment of hepatitis C.[1] Due to their importance, a lot of research groups have focused on their synthesis and applications, which has resulted in a large number of publications.

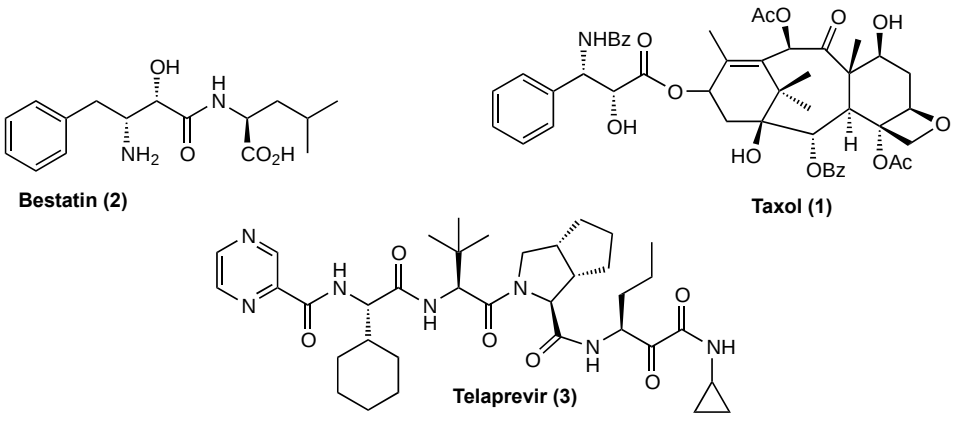
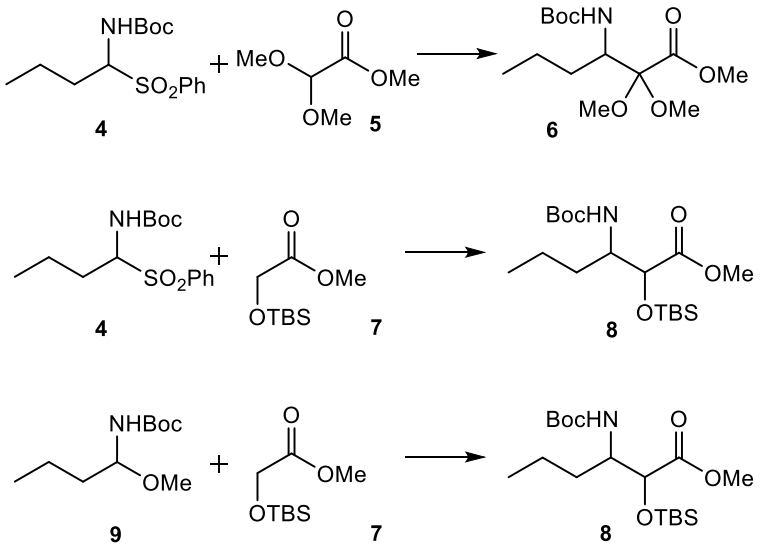


Figure 1

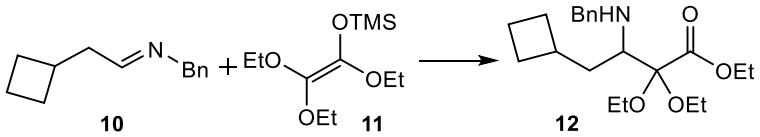
β-Amino acids are typically synthesized by ring opening of *β*-lactams, the Mannich reaction, conjugate additions, but also employing less well known methods such as the opening of aziridines.[2] Recent literature reports have illustrated the latter methods in organocatalytic format.[2] The Mannich reaction, where a silyl enol ether is reacted with an imine possessing a stereogenic centre to induce substrate control in the Mannich-type product, has received considerable attention as a method for the preparation of *α*-oxygenated *β*-amino acids. Here, pioneering work was done by Yamamoto, by using double stereodifferentiation to achieve satisfying diastereoselectivities.[3]

Herein we would like to report an extension of this methodology that provides a practical and straightforward method for the generation of *α*-oxygenated *β*-amino acids and which relies on substrate control by using a cheap auxiliary in the reaction of an imine with an enol equivalent.



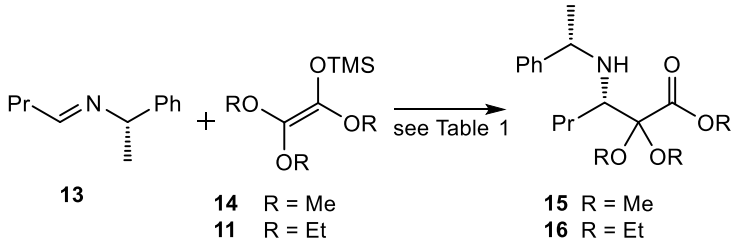
Scheme 1. Nucleophile addition using in situ generated, activated imines

In a model system an *α*-amido sulfone was used to generate an activated imine *in situ*, which was then reacted with a nucleophile (Scheme 1).[4] This was achieved in the presence of an ester by using lithium diisopropylamide (LDA), thus generating the two reactive species; the activated imine and the enolate, in a single step. The reaction of 2.5 equivalents of LDA with equimolar amounts of amido sulfone **4** and methyl dimethoxyacetate (**5**) in THF at -78 °C afforded the aldol product **6** in an excellent yield. When the nucleophile was generated from the glycolic ester derivative **7**, the aldol product **8** was formed as a diastereomeric mixture. The hemiaminal **9** could also be used to generate the activated imine under basic conditions. Unactivated imines like **10** can also be used as electrophiles; but lithium enolates are not suitable nucleophiles for such substrates For this reason, the enol equivalent was switched to the silyl enol ether **11**, resulting in the generation of the aldol product **12** in good yields (Scheme 2).



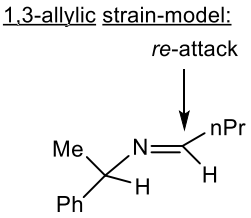
Scheme 2. Mukaiyama-type aldol addition with an imine

Now the major task was to introduce chirality by way of substrate control starting from the imine **13**. Imine **13** was prepared by condensation of butyraldehyde with the chiral amine (*S*)-phenylethylamine.[5] It was then reacted under Lewis acid catalysis with silyl enol ether **14** or **11**, which were in turn generated from the corresponding glyoxylate ester, to give the aldol products **15** and **16** in good yields and selectivities (Scheme 3).



Scheme 3. Asymmetric Mukaiyama-type aldol addition with chiral imine

The newly formed stereocenter is generated by *re*-attack on the imine in accordance with the 1,3-allylic strain model (Scheme 4). [6]



Scheme 4. *Re*-Attack on the imine

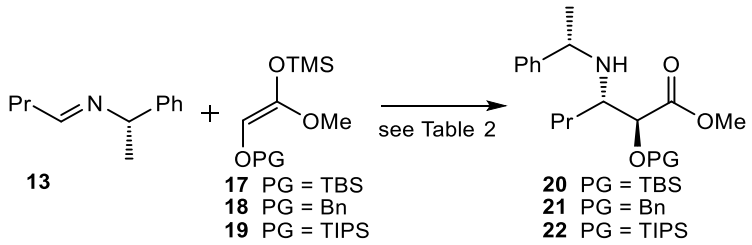
A series of Lewis acids (LA) were tested as catalysts (Table 1). The highest yields were observed with $HBF_4{\cdot}Et_2O$ and $AlCl_3$ (Table 1, entries 9 and 12), while $MgBr_2{\cdot}Et_2O$ provided the best diastereomeric ratios for the aldol products **15** and **16** (entries 1, 3 and 5). Other Lewis acids resulted in either lower yields, slower conversions or lower selectivities. To the best of our knowledge, this is the first time that an α-keto-β-amino acid has been synthesized directly without the need to oxidize the α-position.

Table 1. Diastereomeric ratio of aldol addition with chiral imines and glyoxyl ester derivatives

Entry	Enol	LA	Solvent	Yield (%)	dr (*syn*:*anti*)
1	14	$MgBr_2 \cdot Et_2O$	CH_2Cl_2	76%	7:2
2	14	B(OPh)·BINOL	CH_2Cl_2	64%	4:1
3	11	$MgBr_2 \cdot Et_2O$	CH_2Cl_2	86%	10:1
4	11	$MgBr_2 \cdot Et_2O$	toluene	54%[a]	6.5:1[c]
5	11	$MgBr_2 \cdot Et_2O$	THF	n.d.	10:1[c]
6	11	$BF_3 \cdot Et_2O$	THF	38%[a]	5.5:1[c]
7	11	$TiCl_4$	THF	19%[a]	4:1[d]
8	11	$ZnCl_2$	THF	38%[b]	4.6:1[d]
9	11	$AlCl_3$	THF	68%[a]	2.8:1[d]
10	11	$SnCl_2$	THF	38%[b]	4.5:1[d]
11	11	$FeCl_3$ (anhydr.)	THF	13%[b]	3:1[d]
12	11	$HBF_4 \cdot Et_2O$	THF	64%[a]	6.1:1[c]

[a] Isolated yield. [b] Yield determined by GC. [c] The reaction was carried out at 0 °C. [d] The reaction was carried out at room temperature

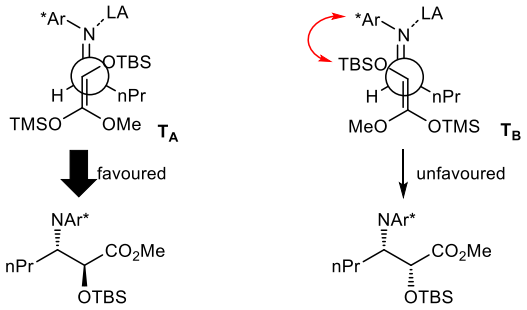
The reaction using glycolate ester derivatives as enol equivalents is more complex, as two new stereocenters can give rise to four different diastereoisomers (Scheme 5).



Scheme 5. Asymmetric Mukaiyama-type aldol addition with glycolate esters

The β-stereocenter is derived from the *re*-attack on the chiral imine in accordance with the 1,3-allylic strain model in a similar manner to the examples described earlier. Of the two possible open transition states resulting from the *re*-side attack, $\mathbf{T_A}$ leading to the *anti*-product exhibits less steric repulsion than $\mathbf{T_B}$ which leads to the *syn*-product (Scheme 6). This indicates that the bulk of the protecting group has an influence on the selectivity, which is reflected in the different dr of the aldol products **17**, **18** and **19**. As the steric bulk increases from benzyl (Bn) to *tert*-butyldimethylsilyl (TBS) and triisopropylsilyl (TIPS), slightly better selectivities are observed.

At first special care was taken to generate stereochemically pure silyl enol ethers to reduce the number of possible products. This was achieved by using an internal quench protocol with lithium tetramethylpiperidide (LiTMP) as base in the presence of trimethylchlorosilane (TMSCl).[7] However, it was found that using a 2:1 *E*:*Z* enol mixture resulted in the same dr as using pure *E* enol, (compare entries 1 and 2 in Table 2), which strongly supports the assumption of an open TS (Scheme 6).



Scheme 6. Open transition states T_A and T_B

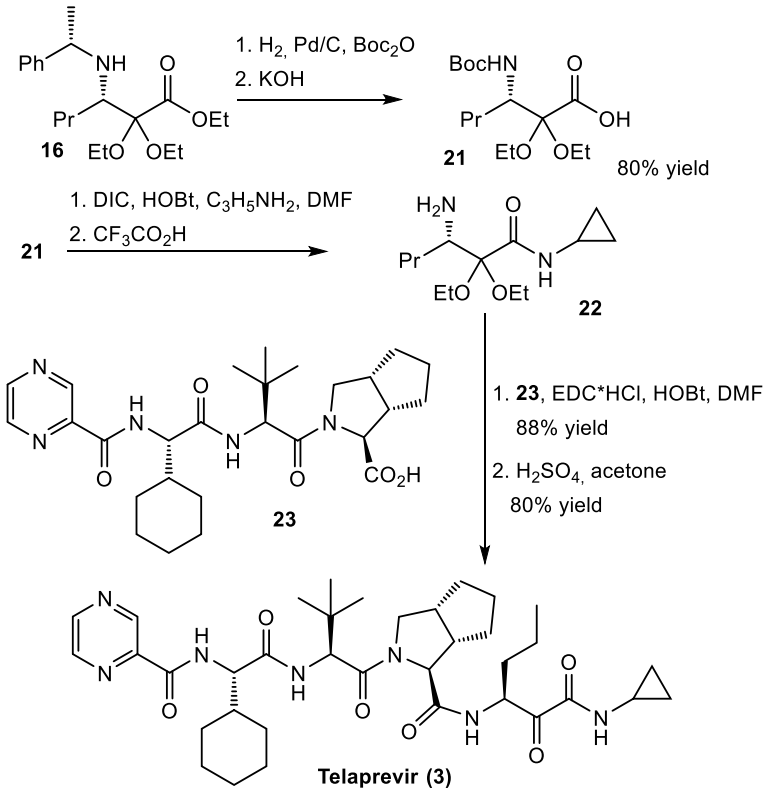
In all reactions it was found that one diastereoisomer was the predominant product,[8] Using Yamamoto's double stereodifferentiating protocol gave only a slight increase in stereoinduction (compare entries 1 and 2 with 5 and 6 with 7 in Table 2). Using a mild LA like $MgBr_2{\cdot}Et_2O$ and a bulky PG at 0 °C gave the most promising results.

Table 2. Diastereomeric ratio of aldol addition with chiral imines and glycolate esters

Entry	enol	LA	Solvent	dr[c]
1	17[a]	$MgBr_2{\cdot}Et_2O$	CH_2Cl_2	1:0.32:0.14:-
2	17[b]	$MgBr_2{\cdot}Et_2O$	CH_2Cl_2	1:0.30:0.13:-
3	17[a]	$TiCl_4$	CH_2Cl_2	1.1:0.4:1:0.2
4	17[a]	$BF_3{\cdot}Et_2O$	CH_2Cl_2	No rxn
5	17[a]	B(OPh)·BINOL	CH_2Cl_2	1:0.24:0.11:0.08
6	18[a]	$MgBr_2{\cdot}Et_2O$	CH_2Cl_2	1:0.5:0.2:-
7	18[a]	B(OPh)·BINOL	CH_2Cl_2	1:0.3:0.1:-
8	18[a]	$TiCl_4$	CH_2Cl_2	No rxn
9	19[a]	$MgBr_2{\cdot}Et_2O$	CH_2Cl_2	5:-:1:-
10	19[a]	$BF_3{\cdot}Et_2O$	CH_2Cl_2	10:-:1:-[d]

[a] *E*:*Z*>99:1; [b] *E*:*Z* = 2:1; [c] 2*S*, 3*S*: 2*R*, 3*S*: 2*R*,3*R*: 2*S*,3*R*. Assignment based on NOE studies of major product, enolate geometries and ^{1}H NMR analysis; [d] low yield

To illustrate the applicability of our synthetic strategy, the HCV drug Telaprevir (**3**) was chosen as an example. Aldol product **16** is a suitable building block of the terminal *β*-amino acid in Telaprevir (**3**). Thus, after protecting group manipulations, saponification and amidation led to the free *β*-amino amide **22** which was coupled with peptide **23**. Cleavage of the diethyl acetal under acidic conditions generated the drug Telaprevir (**3**). Both aldol products **16** and **19** respectively **20** are suitable building blocks for Telaprevir (**3**). Employing the aldol product **16** in which the *α*-keto center is already in place has the additional advantage of avoiding by-products arising from a final oxidation.



Scheme 7. Example for the use of aldol product **16**

CONCLUSIONS

We have shown that an aldol strategy is a viable method for generating *β*-amino acid derivatives, which can be used as suitable precursors for building blocks for the synthesis of natural products or a drug such as Telaprevir (**3**). Activated imines generated *in situ* from different precursors as well as benzylic imines are both suitable electrophilic substrates.

When an imine with a chiral center in the *α*-position to the nitrogen is used, stereochemical induction in the newly formed amine center is observed. Depending on the nature of the nucleophile, either amino alcohols or amino acetals can be generated.

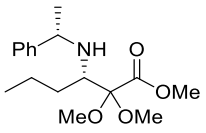
EXPERIMENTAL

The following procedures were used in all reactions unless otherwise noted. Reaction vessels were oven-dried and moisture sensitive reactions were performed under a slight nitrogen over-pressure. Sensitive liquids and solutions were transferred by double tipped needle or syringe through rubber septa. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel 60-F254 plates. Flash column chromatography was performed with silica gel (0.04-0.063 mm, 240-400 mesh) under pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All commercially available reagents were used without further purification unless stated otherwise. THF, Et_2O and CH_2Cl_2 were bought anhydrous in sure-seal bottles and kept under nitrogen over molecular sieves. All other solvents were HPLC grade. NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ or C_6D_6 solutions and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26 ppm, ^{13}C, δ = 77.00 ppm) and the residual C_6H_6 signal (^1H, δ = 7.16 ppm, ^{13}C, δ = 128.00 ppm). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, b = broad signal). Assignments of proton resonances were confirmed, when possible, by correlated spectroscopy.

General procedure to generate TMS silyl enol ethers:

To a solution of diisopropylamine (1.5 eq.) in THF (1.5M) at 0 °C under N_2 was added *n*BuLi (1.4 eq., 1.6 M in hexane) and the mixture was stirred for 20 min. The lithium diisopropylamide (LDA) was cooled to -80 °C and trimethylchlorosilane (TMSCl, 1.4 eq.) was added followed by the methyl ester (1 eq.). The reaction was allowed to reach 0 °C over 3 h, brought to room temperature and stirred for 30 min. Pentane was added and the white precipitate filtered off over celite. The solvent was removed under reduced pressure. Purification if necessary was performed by bulb-to-bulb distillation. All data in accordance with literature.

(*S*)-Methyl 2,2-dimethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate (15)



To imine (4 g, 22.8 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added $MgBr_2 \cdot Et_2O$ (8.84 g, 34,2 mmol) and the mixture was stirred for 15 min. The silyl enol ether (5 g, 24.2 mmol) in CH_2Cl_2 (15 mL) was added and the reaction was stirred at 0 °C for 4 h. Brine was added, layers separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and the solvent was removed under

reduced pressure. Purification by column chromatography on silicagel (cyclohexane:EtOAc 10:1 → 3:1) gave the aldol adduct.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.28 (m, 4H), 7.21 (m, 1H), 4.23 (q, J = 6.62 Hz, 1H), 3.82 (s, 3H), 3.27 (s, 3H), 3.19 (s, 3H), 2.73 (dd, J = 10.08, 2.52 Hz, 1H), 1.49 (m, 1H), 1.37 (m, 1H), 1.27 (d, J = 6.65 Hz, 3H), 1.09-0.97 (m, 2H), 0.67 (t, J = 8.23 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.25, 146.29, 128.09, 127.33, 126.68, 106.08, 56.22, 55.96, 52.15, 50.61, 49.75, 33.36, 24.86, 19.66, 13.84. HRMS (ESI^+) (m/z): $[M + H]^+$ for $C_{17}H_{28}NO_4$ calcd. 310.2013; found 310.2011.

(*S*)-Methyl 2,2-dimethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate (15)

With BF_3·OEt_2:

(S,E)-N-Butylidene-1-phenylethanamine (**13**, 10.0 g, 57.0 mmol) was dissolved in 250 mL 2-methyltetrahydrofuran and cooled to 0 °C. BF_3·OEt_2 (7.0 mL, 57.0 mmol) was added to the mixture followed by a solution of trimethyl((1,2,2-triethoxyvinyl)oxy)silane (**11**, 11.34 g, 45.6 mmol) in 80 mL 2-methyltetrahydrofuran, and the mixture was stirred at 0 °C. After 4 h, further imine (1.8 g, 10.2 mmol) and BF_3·OEt_2 (1.2 mL, 9.7 mmol) were added and the mixture was stirred at 0 °C for further 3 h. The volume of the mixture was halved by evaporation, water was added, the mixture was neutralized (pH = 7.2) with 2N NaOH, and the phases were separated. Removal of the solvent in vacuo yielded 19.1 g crude (*S*)-ethyl 2,2-diethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate as a 85:15 (*syn*:*anti*) diastereomeric mixture.

(*S*)-Methyl 2,2-dimethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate (15)

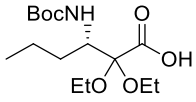
With HBF_4·OEt_2:

(S,E)-N-Butylidene-1-phenylethanamine (**13**, 10.0 g, 57.0 mmol) was dissolved in 250 mL 2-methyltetrahydrofuran and cooled to 0 °C. HBF_4·OEt_2 (9.24 g, 57.0 mmol) was added to the mixture followed by a solution of trimethyl((1,2,2-triethoxyvinyl)oxy)silane (**11**, 11.34 g, 45.6 mmol) in 80 mL 2-methyltetrahydrofuran, and the mixture was stirred at 0 °C for 3.25 h. Water (400 mL) was added to quench the reaction, the mixture was neutralized (pH = 7.6) with 10N NaOH, the phases were separated and the organic phase was extracted once more with further 400 mL water. Water (300 mL) and 2-methyltetrahydrofuran (50 mL) were added to the mixture, the pH was acidified (pH = 5.6) with 2N HCl and the phases were separated. The organic phase was extracted with further 300 mL water and 50 mL 2-methyltetrahydrofuran and the solvent of the organic phase was removed in vacuo to yield 17.1 g crude (*S*)-ethyl 2,2-diethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate as a 86:14 (*syn*:*anti*) diastereomeric mixture.

Diastereomer separation in (*S*)-ethyl 2,2-diethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate by extraction (representative procedure):

A diastereomeric mixture of (*S*)-ethyl 2,2-diethoxy-3-(((*S*)-1-phenylethyl)amino)hexanoate (6.4 g, d.r.: 85:15) was dissolved in 100 mL $^{i}Pr_2O$ and 2mL water were added. The mixture was acidified to pH = 2.21 with 50% H_2SO_4 and the resulting organic phase was concentrated to half its volume (50 mL). 1 mL Water was added, and the mixture was acidified again to pH = 2.22 with 50% H_2SO_4. The aqueous phase was combined with the aqueous phase from the previous extraction (V = 1.5 mL) and extracted with 11 mL $^{i}Pr_2O$ after adjusting the pH to 2.17 with 5M NaOH. The combined organic phases were concentrated (V = 40 mL), 1 mL water was added and the mixture was acidified to pH = 2.18 with 50% H_2SO_4. The organic phase was separated and the solvent was removed in vacuo to yield a 98:2 (*syn:anti*) mixture of diastereomers (37.5 mL solution, assay: 28%, 76% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.14 (m, 5H, HAr), 4.39-4.16 (m, 3H, $COOCH_2$ and $CH(CH_3)$), 3.58-3.31 (m, 5H, OCH_2CH_3 and CHNH), 2.69 (dd, J = 7.80 Hz, J = 2.37 Hz, 1H, NH), 1.47-1.12 (m, 19H, CH_3, CH_2, $COCH_2CH_3$ and OCH_2CH_3), 0.63 (t, J = 7.00 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.0, 146.4, 128.0, 127.5, 126.6, 105.4, 61.0, 59.0, 57.0, 56.8, 56.3, 33.6, 24.8, 19.6, 15.3, 15.2, 14.3, 13.8. HRMS (ESI^+) (*m/z*): $[M + H]^+$ for $C_{20}H_{34}NO_4$ calcd. 352.2482; found 352.2470.

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-2,2-diethoxyhexanoic acid (21)

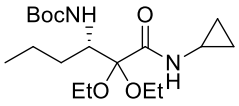


Step 1 – PG exchange: Boc_2O (9.19 g, 42.1 mmol) was added to a solution of **16** (8.1 g, 23 mmol) in 500 mL EtOH. The flask was flushed with nitrogen and a slurry of Pd/C (10 mol%, 10% w/w) in EtOH was added. Forming gas (95% N_2, 5% H_2) was bubbled through the mixture for 23 h at room temperature, after which the catalyst was filtered over a pressure strainer and washed with 20 mL EtOH. The solvent was removed *in vacuo* to give 9.9 g crude product, which was used without further purification in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.98 (d, J = 10.50 Hz, N*H*), 4.28-4.17 (m, 2H, $COOCH_2CH_3$), 4.00-3.95 (dt, J = 10.50 and 2.50 Hz, C*H*NH), 3.72-3.40 (m, 4H, OCH_2CH_3), 1.41-1.14 (m, 22H, BOC-CH_3, $COCH_2CH_3$ and OCH_2CH_3), 0.88 (t, J = 7.25 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 156.0, 146.7, 102.0, 85.1, 78.9, 61.4, 58.7, 58.6, 53.1, 33.3, 28.4, 27.4, 19.4, 15.3, 15.0, 14.2, 13.9.

Step 2 – saponification: A solution of KOH (6.95 g, 123.9 mmol) in 100 mL water was added to a solution of the ester (8.6 g, 24.6 mmol) in 100 mL EtOH. Further 100 mL EtOH were added to obtain a clear solution and the mixture was stirred at room temperature for 23 h. CH_2Cl_2 (200 mL) and water (200

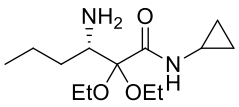
mL) were added, and the pH of the mixture was adjusted with conc. HCl from 12.5 to 2.5. The phases were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo* to yield 6.3 g of **21** (80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.13 (bs, 1H, COO*H*), 5.00 (d, J = 10.00 Hz, N*H*), 4.02 (t, J = 10.00 C*H*NH), 3.70-3.39 (m, 4H, OCH_2CH$_3$), 1.63-1.12 (m, 19H, BOC-CH_3 and OCH$_2$CH_3), 0.89 (t, J = 7.25 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.7, 156.4, 101.8, 79.3, 59.2, 58.6, 52.3, 32.4, 28.3, 26.9, 19.4, 14.9, 14.4, 13.8. HRMS (ESI$^+$) (*m*/*z*): $[M + H]^+$ for $C_{15}H_{30}NO_6$ calcd. 320.2068; found 320.2066.

(*S*)-*tert*-Butyl (1-(cyclopropylamino)-2,2-diethoxy-1-oxohexan-3-yl)carbamate



16 (8.03 g, 25.1 mmol) was dissolved under nitrogen in 400 mL DMF and hydroxybenzotriazole (4.10 g, 30.3 mmol), *N*,*N*'-diisopropylcarbodiimide (7.7 mL, 49.7 mmol) and cyclopropylamine (3.5 mL, 50.0 mmol) were added to the reaction mixture. After stirring for 24 h at room temperature, the mixture was quenched with 400 mL 5% NaCl and 800 mL EtOAc and the phases were separated. The aqueous phase was extracted with 100 mL EtOAc, the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (cyclohexane:EtOAc 10:1 → 3:1) yielded 8.56 g of the amide. (95% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.96 (bs, 1H, CON*H*), 5.70 (d, J = 9.78 Hz, 1H, N*H*), 3.91 (t, J = 10.55 Hz, C*H*NH), 3.63-3.26 (m, 4H, OCH_2CH$_3$), 2.68 (m, 1H, C*H*(CH$_2$)$_2$), 1.41 (s, 11H, BOC-CH_3 and CH_2), 1.21-1.12 (m, 8H, OCH$_2$CH_3 and CH_2), 0.88 (t, J = 7.06 Hz, 3H, CH_3), 0.81-0.78 (m, 2H, CH_2), 0.53-0.48 (m, 2H, CH$_2$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 157.0, 100.5, 78.5, 58.6, 56.8, 52.6, 32.5, 28.4, 22.0, 19.3, 15.4, 15.0, 14.0, 6.5, 6.4. HRMS (ESI$^+$) (*m*/*z*): $[M + H]^+$ for $C_{18}H_{35}N_2O_5$ calcd. 359.2540; found: 359.2533.

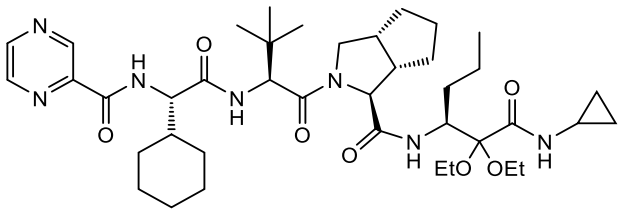
(*S*)-3-Amino-*N*-cyclopropyl-2,2-diethoxyhexanamide (22)



Trifluoroacetic acid (2.45 mL, 32.1 mmol) was added to a solution of (*S*)-*tert*-butyl (1-(cyclopropylamino)-2,2-diethoxy-1-oxohexan-3-yl)carbamate (2.3 g, 6.41 mmol) in 45 mL CH_2Cl_2 and the mixture was stirred at room temperature for 18 h. A saturated aqueous $NaHCO_3$ solution was carefully added to the mixture, the aqueous phase was extracted with CH_2Cl_2 (2x30 mL) and the

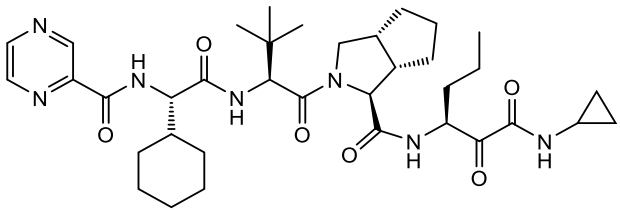
combined organic phases were dried over Na_2SO_4. Removal of the solvent *in vacuo* yielded 1.44 g **22** as a pale yellow oil. (87% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (bs, 1H, CONH), 3.61-3.39 (m, 4H, OCH_2CH_3), 3.08 (dd, J = 10.56 Hz, J = 2.64 Hz, 1H, $CHNH_2$), 2.79-2.70 (m, 3H, $CH(CH_2)_2$ and NH_2 (pH-dependent)),1.64-1.31 (m, 4H, CH_2), 1.22 (t, J = 7.04 Hz, 6H, OCH_2CH_3), 0.92 (t, J = 7.14 Hz, 3H, CH_3), 0.85-0.78 (m, 2H, CH_2), 0.55-0.52 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0 (CONH), 101.5 ($C(OEt)_2$), 58.7 (OCH_2CH_3), 57.0 (OCH_2CH_3), 54.4 ($CHNH_2$), 32.7 ($(CH_2)_2CH_3$), 22.0 ($CH(CH_2)_2$), 19.9 ($(CH_2)_2CH_3$), 15.4 (OCH_2CH_3), 15.1 (OCH_2CH_3), 14.0 ($(CH_2)_2CH_3$), 6.5 ($CH(CH_2)_2$), 6.5 ($CH(CH_2)_2$). HRMS (ESI$^+$) (m/z): $[M + H]^+$ for $C_{13}H_{27}NO_3$ calcd. 259.2016; found: 259.2012.

(1*S*,3a*R*,6a*S*)-2-((*S*)-2-((*S*)-2-Cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl-butanoyl)-*N*-((*S*)-1-(cyclopropylamino)-1-oxo-2,2'-diethoxyhexan-3-yl)octahydrocyclopenta-[*c*]pyrrole-1-carboxamide (Telaprevir diethyl ketal)



To a solution of the compound **23** (362 mg, 0.704 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (162 mg, 0.844 mmol) and hydroxybenzotriazole (119 mg, 0.844 mmol) in CH_2Cl_2 (10 mL) was added amine **22** (200 mg, 0.774 mmol) and the mixture was stirred at ambient temperature for 15 h. Water was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with an aqueous, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and the organic solvent was removed under reduced pressure to give 570 mg Telaprevir diethyl ketal. (88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (d, J = 1.26 Hz, 1H), 8.74 (d, J = 2.52 Hz, 1H), 8.55 (dd, J = 2.30, 1.48 Hz, 1H), 8.36 (d, J = 9.46 Hz, 1H), 7.11 (d, J = 9.46 Hz, 1H), 6.99 (d, J = 2.83 Hz, 1H), 6.47 (d, J = 9.46 Hz, 1H), 4.70 (d, J = 9.77 Hz, 1H), 4.46 (dd, J = 8.88, 6.55 Hz, 1H), 4.33 (d, J = 10.25 Hz, 1H), 4.21 (d, J = 4.10 Hz, 1H), 3.88 (dd, J = 10.40, 7.25 Hz, 1H), 3.72 (dd, J = 10.25, 2.68 Hz, 1H), 3.60 (m, 1H), 3.53 (m, 1H), 3.41 (m, 1H), 3.30 (m, 1H), 2.85 (m, 1H), 2.76 (m, 1H), 2.72 (m, 1H), 1.96-1.82 (m, 3H), 1.76-1.60 (m, 7H), 1.57 (bs, 6H), 1.45-1.35 (m, 3H), 1.33-1.22 (m, 2H), 1.20 (t, J = 6.93 Hz, 3H), 1.12 (t, J = 7.09 Hz, 3H), 1.08 (m, 2H), 1.01 (s, 9H), 0.86 (t, J = 7.25 Hz, 3H), 0.83 (m, 2H), 0.53 (m, 2H). HRMS (ESI$^+$) (m/z): $[M + H]^+$ for $C_{13}H_{27}NO_3$ calcd. 754.4862; found: 754.4855.

(1*S*,3a*R*,6a*S*)-2-((*S*)-2-((*S*)-2-Cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl-butanoyl)-*N*-((*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[*c*]pyrrole-1-carboxamide (3)



100 mg Telaprevir diethyl ketal was dissolved in 100 µL acetone, 0.5 mL water and 0.5 mL conc. H_2SO_4 at 0 °C. The mixture was stirred at room temperature for 17 h until complete conversion was observed. Water and CH_2Cl_2 was added, the organic phase was separated and solvent was reduced to dryness to yield 72mg (80% yield) of Telaprevir. All data is in accordance with literature.[9]

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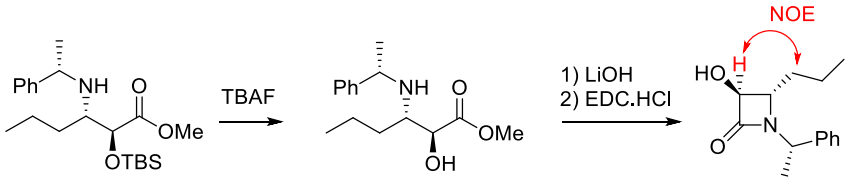
8. The relative configuration was proven by NOE-studies on the related β-lactam.



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