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Racemic *N*-sulfonyloxaziridines as highly diastereoselective enolate hydroxylating agents: enantioselective synthesis of (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide

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ABSTRACT

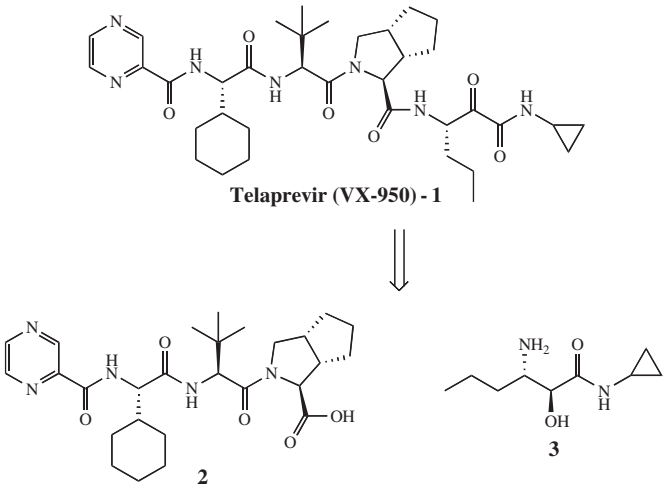
A new, highly enantioselective synthesis of (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide, a synthetic fragment of the experimental hepatitis C drug Telaprevir, has been described. Conjugate addition of the enantiomerically pure Davies lithium amide followed by hydroxylation of the in situ generated β-amino enolate was employed for the formation of the required stereogenic centres. Importantly, very high diastereoselectivities can still be achieved in the key-step when the relatively expensive and enantiopure (camphorsulfonyl)oxaziridine hydroxylating agent is replaced by racemic *trans*-*N*-sulfonyloxaziridines. Among the tested *N*-sulfonyloxaziridines the *iso*-propyl substituted analogue proved to be the ideal choice from an economic viewpoint.

1. Introduction

Telaprevir **1**, also known as VX-950, is an investigational drug for the treatment of hepatitis C.[1] This NS3/4A protease inhibitor acts as a covalent serine trap by virtue of its α-ketoamide part.[2] Based upon currently applied synthetic procedures, VX-950 is typically produced by the union of acid **2** with the precursor of the active site binding fragment, (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide **3** (Scheme 1).[3] Encouraged by the results of the clinical trials, we became interested in further synthetic developments of this particular subunit.

Originally, the (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide portion **3** was prepared via ring opening of the corresponding racemic *trans*-epoxide **4** followed by kinetic resolution (Scheme 2).[4] Since the separation of enantiomers at the end of the synthesis is clearly disadvantageous from a synthetic and economic point of view, the use of optically enriched epoxide has been proposed.

Although similar epoxides have been prepared in high enantiopurities by Shibazaki and co-workers using their asymmetric epoxidation strategy,[5] we decided to evaluate several alternative routes towards **3** that would be easy to scale up and economically viable.



Scheme 1. Retrosynthetic analysis.

In this article, we wish to present our results on the efficient assembly of **3** by an approach in which the required stereogenic centres are formed by the conjugate addition of an enantiomerically pure lithium amide, as described by Davies, followed by

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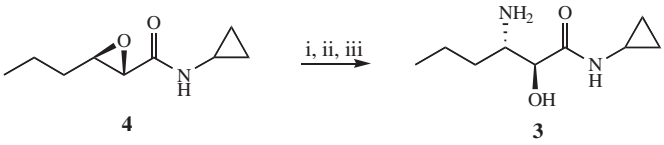


i. NaN_3, $MgSO_4$, MeOH; ii. H_2, Pd/C, MeOH; iii. resolution

Scheme 2. Enentioselective approach of Shibazaki.

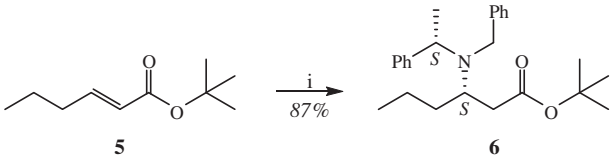
stereoselective hydroxylation of the in situ generated β-amino enolate by a racemic *trans*-*N*-sulfonyloxaziridine.

2. Results and discussion

Some time ago, Davies et al. established a general protocol for the synthesis of optically active β-amino carboxylic acid derivatives via the highly diastereoselective conjugate addition of the enantiomerically pure lithium *N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters and amides.[6] Furthermore, they demonstrated that subsequent hydroxylation of the corresponding β-amino enolates with (*R*) or (*S*)-(camphorsulfonyl)oxaziridine can occur with excellent levels of asymmetric induction, favouring the formation of the *anti* diastereoisomer.[7] Since then, this method has been applied to the synthesis of several biologically active compounds.[8]

We became interested in applying this elegant method to the synthesis of (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide **3**. Additionally, we wanted to test if cheaper achiral or racemic hydroxylating agents could replace the enantiopure (camphorsulfonyl) oxaziridine.[9] We expected that this modification would not decrease considerably the diastereoselectivity of the reaction, since it was claimed that the 1,2-asymmetric induction of the hydroxylation step was highly substrate controlled and that, in most cases, the diastereoselectivity remained high even under mismatched conditions.[7]

Following the literature protocol, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to (*E*)-*tert*-butyl-2-hexenoate resulted in the formation of **6** as a single diastereoisomer (Scheme 3). The predicted stereochemical assignment of the newly formed chiral centre was confirmed later on, at the end of the reaction sequence by comparison with an authentic sample of **3**. It is also important to note that, in order to avoid concomitant 1,2-addition, a *tert*-butyl ester should be employed rather than a methyl or ethyl ester.

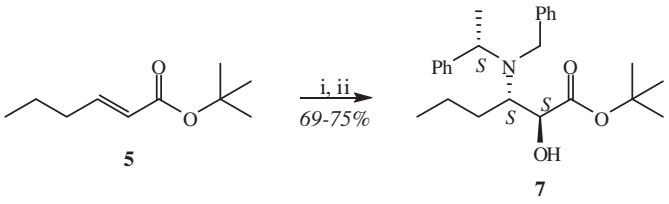


i. Lithium *(S)*-*N*-benzyl-*N*-*a*-methylbenzylamide, THF, -78°C, then $NH_4Cl_{(aq.)}$

Scheme 3. Controlling the selectivity of the addition.

Subsequently, in situ hydroxylation of the lithium enolate intermediate with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine or with (+)-(8,8-dichlorocamphorsulfonyl)oxaziridine gave the *anti*-β-amino-α-hydroxy ester **7** in 75% and 69% isolated yields, respectively, on a 1 mmol scale (Scheme 4). Formation of the corresponding *syn* diastereoisomer **8** was not observed by NMR spectroscopy.

At this point, we turned our attention to the replacement of the relatively expensive and enantiopure hydroxylating agent (Table 1). Simply bubbling oxygen gas through the solution of the enolate resulted in the formation of the *anti* and *syn* diastereoisomers **7** and **8** in a 2:1 ratio and in moderate yield (entry 1). Using racemic *trans*-



i. Lithium *(S)*-*N*-benzyl-*N*-*a*-methylbenzylamide, THF, -78°C;
ii. (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine, -78°C to 0°C or
(+)-(8, 8-dichlorocamphorsulfonyl)oxaziridine, -78°C to 0°C.

Scheme 4. Combining addition and hydroxylation.

N-*p*-toluenesulfonyl-3-phenyloxaziridine **9a**, a somewhat higher diastereomeric ratio of 4:1 could be obtained (entry 2). Encouraged by this last result, we decided to test similar racemic oxaziridines in which the rather flat phenyl substituent is replaced by sterically more demanding alkyl groups. The novel *N*-sulfonyloxaziridines **9b**–**e** were easily prepared via diastereoselective synthesis of the corresponding *trans*-imines **10b**–**e** followed by the subsequent oxidation of these intermediates by Oxone.[10]

We were gratified to find that replacing the phenyl substituent of the oxaziridine ring by various alkyl groups considerably increased the diastereoselectivity and the yield of the hydroxylation reaction. Previous isolation and characterization of the minor *syn* diastereoisomer **8** enabled us to determine the diastereomeric ratio of these reactions from the NMR spectra of the crude products. Whilst the linear *N*-propyl substituent gave already a higher diastereomeric ratio (8:1), α-branched alkyl groups, such as *iso*-propyl, *sec*-butyl or cyclohexyl led to an even further increase in the diastereoselectivity of the hydroxylation step (entries 3–6). In these latter cases, only traces of the *syn* product **8** can be detected by NMR spectroscopy and the *anti* diastereoisomer **7** is easily isolated and purified from the crude reaction mixture.

It is interesting to note that high diastereoselectivity has even been achieved using the *sec*-butyl substituted oxaziridine **9d**, which was formed and used as a 2:1 mixture of diastereoisomers.

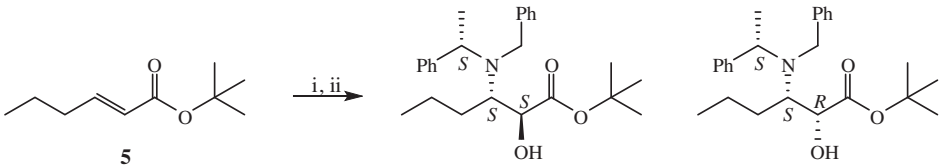
Additionally, it has to be pointed out that increasing further the size of the alkyl substituent decreased the reactivity of the oxaziridine. Therefore, the *iso*-propyl substituted oxaziridine **9c** proved to be the ideal choice, in terms of diastereoselectivity and reactivity, among the tested *N*-sulfonyloxaziridines.

Scaling up the reaction mixture to 5 mmol, using the optimized hydroxylating agent **9c**, led to an increase in the isolated yield of **7** without altering the diastereoselectivity of the reaction. Hydrolysis of the ester function, formation of the cyclopropylamide derivative and subsequent debenzylation by hydrogenolysis resulted in the formation of the required product **3** in a good overall yield (Scheme 5). The predicted relative and absolute stereochemistry was confirmed by comparison of the NMR spectroscopic data and optical rotation values of the synthetic product with those of an authentic sample of **3**.

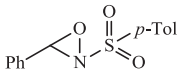
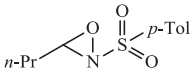
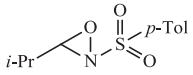
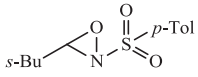
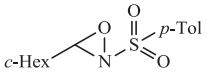
3. Conclusions

In conclusion, we have described a novel approach for the enantioselective synthesis of (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide **3**, a key-fragment of Telaprevir. Our route embodies the conjugate addition of an enantiomerically pure lithium amide to the α,β-unsaturated ester **5** followed by hydroxylation of the in situ generated β-amino enolate by a simple oxaziridine. Importantly, we have demonstrated that high diastereoselectivities can be reached in the hydroxylation step when the enantiopure (camphorsulfonyl)oxaziridine is replaced by much cheaper and racemic *trans*-*N*-sulfonyloxaziridines. Among the various oxaziridines

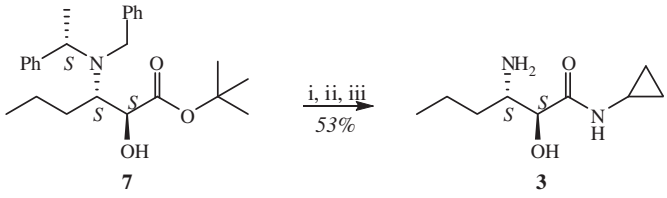
Table 1
Tandem facial-selective addition/facial-selective hydroxylation with racemic oxidants



i. Lithium *(S)*-*N*-benzyl-*N*-α-methylbenzylamide, THF, -78°C; ii. oxidizing agent, -78°C to 0°C

Entry	Oxidizing agent	Ratio of **7**/**8**[a]	Isolated yield of **7** (%)
1	O_2	2:1	35
2	 (+ −) **9a**	4:1	43
3	 (+ −) **9b**	8:1	79
4	 (+ −) **9c**	>10:1	76 (81)[b]
5	 **9d** ~2:1 ratio of diastereomers	>10:1	72
6	 (+ −) **9e**	>10:1	63

[a] Determined from the ^{1}H NMR spectra of the crude products.
[b] The reaction mixture was scaled up from 0.5 mmol to 5 mmol.



i. TFA, RT then $HCl_{(aq.)}$; ii. cyclopropylamine, Et_3N, PyBOP, DCM, RT; iii. Pd/C, H_2, AcOH, RT.

Scheme 5. Completing the synthesis of **3**.

studied in this reaction, the *iso*-propyl substituted reagent **9c** proved to be the ideal choice for an efficient and economic synthesis.

4. Experimental part

4.1. General information

Reactions involving organometallic or other moisture sensitive reagents were performed in flame-dried flask under an argon atmosphere. Commercially available reagents and starting materials were used as received unless otherwise stated. THF was distilled over sodium/benzophenone under an argon atmosphere. Analytical grade toluene, pentane and dichloromethane were used as received. Technical grade petroleum ether and ethyl acetate were distilled prior to use. Flash chromatographies were performed using Merck Silica Gel 60 (230–400 mesh) under pressure with the stated solvents. Nuclear magnetic resonance (NMR) spectra were recorded on BRUKER AC-300 Avance II (^{1}H: 300 MHz and ^{13}C 75 MHz) and on BRUKER AM-500 (^{1}H: 500 MHz and ^{13}C 125 MHz) in deuterated solvents. Infrared (IR) spectra were recorded on a SHIMADZU FTIR-8400S spectrometer. Low-resolution mass spectra were recorded on a FINNIGAN MAT-LCQ and high resolution mass spectra on a WATERS LCT PREMIER XE spectrometer.

4.2. Oxaziridines

(1*S*)-(+)-(10-Camphorsulfonyl)oxaziridine and (+)-(8,8-dichlorocamphorsulfonyl)oxaziridine were purchased from Aldrich. Racemic *trans*-*N*-*p*-toluenesulfonyl-3-phenyloxaziridine **9a** was easily prepared following a literature procedure involving the diastereoselective synthesis of the corresponding *trans*-imine and the subsequent oxidation of this intermediate by Oxone.[10] The same procedure was employed for the preparation of the other, previously unknown, racemic *trans*-*N*-sulfonyloxaziridines, as described below.

*4.2.1. General procedure for the formation of trans-imines **10a**–**e**.* *p*-Toluenesulfonamide (5.14 g, 30 mmol) and sodium benzenesulfinate (5.42 g, 33 mmol) were dissolved in a 1:1 mixture of formic acid and water (90 mL). The corresponding, freshly distilled aldehyde (30 mmol) was added and the mixture was stirred overnight

at room temperature. The resulting white precipitate was filtered off, washed with water (20 mL) and pentane (15 mL) and dissolved in CH_2Cl_2 (200 mL). Saturated aqueous $NaHCO_3$ (140 mL) was added and the mixture was stirred at room temperature for 2 h. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield the corresponding crude imines. These products were used in the next step without further purification.

*4.2.1.1. (E)-Phenyl-N-tosylmethanimine (**10a**)*[11]. Following the general procedure and using non-distilled benzaldehyde, **10a** was obtained as a white solid in 48% yield (3.75 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=9.03 (s, 1H), 7.94 (d, J=7.2 Hz, 2H), 7.89 (d, J=8.3 Hz, 2H), 7.61 (t, J=7.4 Hz, 1H), 7.44–7.52 (m, 2H), 7.35 (d, J=8.3 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm)= 170.1, 144.6, 135.1, 134.9, 132.3, 131.3, 129.8, 129.1, 128.1, 21.6. IR (neat): ν (cm^{-1})=2921, 1596s, 1574s, 1450, 1321s, 1222, 1155s, 1088s, 864, 810, 783, 757.

*4.2.1.2. (E)-N-Tosylbutan-1-imine (**10b**)*[11]. Following the general procedure **10b** was obtained as a white solid in 78% yield (5.24 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.60 (t, J=4.6 Hz, 1H), 7.81 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 2.49 (dt, J=7.4, 4.6 Hz, 2H), 2.43 (s, 3H), 1.75–1.56 (m, 2H), 0.95 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=178.3, 144.6, 134.6, 129.8, 128.1, 37.7, 21.6, 18.1, 13.6. IR (neat): ν (cm^{-1})=2964, 2933, 1626s, 1458, 1321s, 1159s, 1092, 813, 748.

*4.2.1.3. (E)-2-Methyl-N-tosylpropan-1-imine (**10c**)*[11]. Following the general procedure **10c** was obtained as a white solid in 81% yield (5.48 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=8.51 (t, J=4.3 Hz, 1H), 7.81 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 2.69 (heptd, J=6.9, 4.3 Hz, 1H), 2.45 (s, 3H), 1.16 (d, J=6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm)=181.8, 144.6, 134.7, 129.8, 128.1, 34.6, 21.6, 18.0. IR (neat): ν (cm^{-1})=2970, 2931, 1625s, 1463, 1321s, 1159s, 1089, 813, 802, 781, 761.

*4.2.1.4. (E)-2-Methyl-N-tosylbutan-1-imine (**10d**)*[12]. Following the general procedure **10d** was obtained as a white solid in 25% yield (1.79 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.49 (d, J=5.1 Hz, 1H), 7.81 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 2.44–2.58 (m, 1H), 2.44 (s, 3H), 1.75–1.40 (m, 2H), 1.13 (d, J=6.8 Hz, 3H), 0.90 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 181.8, 144.6, 134.8, 129.8, 128.0, 41.2, 26.0, 21.6, 15.4, 11.3. IR (neat): ν (cm^{-1})=2966, 2931, 1628s, 1458, 1323s, 1159s, 1092, 813, 773.

*4.2.1.5. (E)-Cyclohexyl-N-tosylmethanimine (**10e**)*[10a]. Following the general procedure **10e** was obtained as a white solid in 78% yield (6.18 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=8.48 (d, J=4.4 Hz, 1H), 7.80 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H), 2.44 (m, 4H), 2.00–1.50 (m, 5H), 1.10–1.50 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=181.0, 144.5, 134.8, 129.7, 128.0, 43.6, 28.3, 25.6, 25.0, 21.6. IR (neat): ν (cm^{-1})=2928s, 2854, 1732, 1626s, 1450, 1325s, 1161s, 1089, 813, 779.

4.2.2. General procedure for the oxidation of imines. The previously obtained imines **10a**–**e** (5 mmol) were dissolved in toluene (50 mL) and an aqueous solution of K_2CO_3 (30 mL, 1.4 M) was added. This mixture was stirred vigorously while an aqueous solution of Oxone (30 mL, 0.4 M) was added slowly over 30 min. After an additional 30 min reaction time, if necessary, a further amount of Oxone was added to achieve complete conversion. Then, the layers were separated and the aqueous layer was extracted with toluene (30 mL). The combined organic phases were washed with 10% aqueous Na_2SO_3 solution (20 mL), dried over $MgSO_4$, filtered and concentrated to yield the corresponding oxaziridine. These products were used without further purification.

*4.2.2.1. (±)-trans-3-Phenyl-2-tosyl-1,2-oxaziridine (**9a**)*[13]. Following the general procedure **9a** was obtained as a white solid in 76% yield (1.08 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.93 (d, J=8.3 Hz, 2H), 7.52–7.32 (m, 7H), 5.45 (s, 1H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=146.4, 131.5, 131.4, 130.5, 130.0, 129.4, 128.7, 128.2, 76.3, 21.8. IR (neat): ν (cm^{-1})=3068, 2923, 1595, 1458, 1388, 1348s, 1240, 1167s, 1090, 837, 813, 779, 717.

*4.2.2.2. (±)-trans-3-Propyl-2-tosyl-1,2-oxaziridine (**9b**).* Following the general procedure **9b** was obtained as a white solid in 86% yield (1.03 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.86 (d, J=8.3 Hz, 2H), 7.39 (d, J=8.3 Hz, 2H), 4.65 (t, J=4.9 Hz, 1H), 2.47 (s, 3H), 1.83–1.72 (m, 2H), 1.62–1.43 (m, 2H), 0.98 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=146.1, 131.6, 129.9, 129.2, 78.1, 32.6, 21.7, 17.0, 13.6. IR (neat): ν (cm^{-1})=2964, 2877, 1595, 1464, 1406, 1348s, 1242, 1218, 1167s, 1090, 840, 813, 707. MS (APCI): m/z=242 ($[M+H]^+$, 92%), 226 (100%), 200 (74%), 155 (64%), 108 (44%). HRMS (ES^-): for $C_{11}H_{14}NO_3S$, calculated: 240.0694, found: 240.0706.

*4.2.2.3. (±)-trans-3-iso-Propyl-2-tosyl-1,2-oxaziridine (**9c**).* Following the general procedure **9c** was obtained as a white solid in 94% yield (1.14 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 7.86 (d, J=8.3 Hz, 2H), 7.39 (d, J=8.3 Hz, 2H), 4.48 (d, J=5.6 Hz, 1H), 2.47 (s, 3H), 1.82–1.95 (m, 1H), 1.02 (dd, J=6.9, 3.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=146.1, 131.7, 129.9, 129.2, 81.9, 29.5, 21.8, 16.5, 16.4. IR (neat): ν (cm^{-1})=2972, 2935, 1597, 1469, 1406, 1348s, 1245, 1169s, 1089, 867, 813, 759, 723s. MS (APCI): m/z=242 ($[M+H]^+$, 87%), 226 (37%), 200 (100%), 155 (48%), 108 (22%). HRMS (ES^-): for $C_{11}H_{14}NO_3S$, calculated: 240.0694, found: 240.0686.

*4.2.2.4. (±)-trans-3-sec-Butyl-2-tosyl-1,2-oxaziridine (**9d**).* Following the general procedure an approximately 2:1 mixture of diastereoisomers of **9d** was obtained as colourless oil in 79% yield (1.16 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.86 (d, J=8.3 Hz, 2H), 7.39 (d, J=8.3 Hz, 2H), 4.48 (d, J=6.0 Hz, 1H, dia1), 4.47 (d, J=5.8 Hz, 1H, dia2), 2.47 (s, 3H), 1.72–1.27 (m, 3H), 1.05–0.90 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=146.1, 131.7, 129.9, 129.2, 81.7 (dia1), 81.6 (dia2), 36.2, 25.0 (dia1), 24.8 (dia2), 21.7, 14.0 (dia2), 13.8 (dia1), 11.1. IR (neat): ν (cm^{-1})=2968, 2940, 1597, 1462, 1348s, 1169s, 1090, 867, 815, 757, 723. MS (APCI): m/z=256 ($[M+H]^+$, 85%), 240 (100%), 200 (72%), 155 (34%). HRMS (ES^-): for $C_{12}H_{16}NO_3S$, calculated: 254.0851, found: 254.0843.

*4.2.2.5. (±)-trans-3-Cyclohexyl-2-tosyl-1,2-oxaziridine (**9e**).* Following the general procedure **9e** was obtained as a white solid in 89% yield (1.25 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.85 (d, J=8.3 Hz, 2H), 7.39 (d, J=8.3 Hz, 2H), 4.47 (d, J=5.7 Hz, 1H), 2.47 (s, 3H), 1.90–1.50 (m, 5H), 1.00–1.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=146.1, 131.7, 129.9, 129.2, 81.2, 38.6, 27.0, 26.8, 25.9, 25.0, 21.8. IR (neat): ν (cm^{-1})=2929, 2854, 1597, 1450, 1348s, 1169s, 1090, 860, 813, 721. MS (APCI): m/z=282 ($[M+H]^+$, 62%), 266 (100%), 200 (18%), 184 (16%), 155 (15%). HRMS (ES^-): for $C_{14}H_{18}NO_3S$, calculated: 280.1007, found: 280.1010.

4.3. Preparation of (3*S*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzyl)amino-hexanoate 6

In a two-necked dry flask maintained under an argon atmosphere, (*S*)-*N*-benzyl-1-phenylethanamine (335 μL, 1.6 mmol, 1.6 equiv) was dissolved in dry, freshly distilled THF (9 mL). The solution was cooled to −78 °C and *n*-butyl-lithium (940 μL, 1.6 M in

hexane, 1.5 mmol, 1.5 equiv) was added dropwise. The obtained pink solution was stirred for 45 min at −78 °C then, (*E*)-*tert*-butyl hex-2-enoate (170 mg, 1.0 mmol, 1.0 equiv), dissolved in THF (1.3 ml), was added dropwise. The resulting mixture was stirred for 2 h at −78 °C, and then quenched by the addition of a saturated aqueous NH_4Cl solution (2 mL). The temperature was raised to room temperature and the THF was evaporated. Water (10 mL) was added to the residue and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate=20:1 as eluent) to furnish **6** in 87% yield (333 mg, colourless oil) as a single diastereoisomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.42 (d, *J*=7.3 Hz, 2H), 7.38–7.16 (m, 8H), 3.86–3.74 (m, 2H), 3.48 (d, *J*=15.0 Hz, 1H), 3.37–3.25 (m, 1H), 1.80–1.99 (m, 2H), 1.70–1.15 (m, 4H), 1.39 (s, 9H), 1.32 (d, *J*=7.0 Hz, 3H), 0.85 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=172.3, 143.1, 142.1, 128.2, 128.1, 128.1, 127.9, 126.9, 126.5, 79.9, 58.3, 53.6, 50.1, 37.8, 35.8, 28.0, 20.5, 20.1, 14.1. IR (neat): ν (cm^{-1})=2962, 2929, 1724s, 1492, 1454, 1367, 1298, 1255, 1145, 744, 700. MS (APCI): *m*/*z*=382 ([M+H]$^+$, 65%), 326 (44%), 222 (100%). HRMS (ES$^+$): for $C_{25}H_{36}NO_2$, calculated: 382.2746, found: 382.2753.

4.4. Preparation of (2*S*,3*S*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzyl)amino-2-hydroxyhexanoate 7

In a two-necked dry flask maintained under an argon atmosphere, (*S*)-*N*-benzyl-1-phenylethanamine (170 μL, 0.8 mmol, 1.6 equiv) was dissolved in dry, freshly distilled THF (4.5 mL). The solution was cooled to −78 °C and *n*-butyl-lithium (470 μL, 1.6 M in hexane, 0.75 mmol, 1.5 equiv) was added dropwise. The resulting pink solution was stirred for 45 min at −78 °C and then, (*E*)-*tert*-butyl hex-2-enoate (85 mg, 0.5 mmol, 1.0 equiv), dissolved in THF (0.6 mL), was added dropwise. After 2 h stirring at −78 °C, (±)-*trans*-3-*iso*-propyl-2-tosyl-1,2-oxaziridine **9c** (241 mg, 1 mmol, 2.0 equiv) was added in one portion. The reaction mixture was stirred for 1 h at −78 °C, and then the temperature was raised slowly to 0 °C where it was kept for 20 min. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (2 mL). The THF was evaporated and water (10 mL) was added to the residue. The aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product thus obtained was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate=20:1 as eluent) to provide **7** as colourless oil in 76% yield (151 mg). Scaling up this reaction mixture to 5 mmol increased the yield to 81% (1.61 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.47 (d, *J*=7.3 Hz, 2H), 7.40–7.15 (m, 8H), 4.26 (d, *J*=15.5 Hz, 1H), 4.00–3.86 (m, 2H), 3.68 (d, *J*=15.5 Hz, 1H), 3.22 (ddd, *J*=8.4, 4.7, 1.6 Hz, 1H), 2.92 (s, 1H), 1.72–1.00 (m, 4H), 1.42 (s, 9H), 1.29 (d, *J*=7.0 Hz, 3H), 0.82 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=174.4, 143.5, 142.7, 128.2, 128.1, 128.1, 126.9, 126.3, 82.3, 71.1, 58.5, 58.4, 51.0, 29.6, 28.0, 19.7, 19.4, 14.1. IR (neat): ν (cm^{-1})=3496, 2960, 2933, 1720s, 1492, 1454, 1369, 1271, 1257, 1159, 1120, 1078, 848, 750, 700. MS (APCI): *m*/*z*=398 ([M+H]$^+$, 100%), 342 (64%), 238 (76%). HRMS (ES$^+$): for $C_{25}H_{35}NO_3Na$, calculated: 420.2515, found: 420.2532.

Spectroscopic data for the minor *syn* diastereoisomer (2*R*,3*S*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzyl)amino-2-hydroxyhexanoate **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=7.45–7.15 (m, 10H), 4.07 (q, *J*=7.0 Hz, 1H), 3.95–3.72 (m, 3H), 3.44 (s, 1H), 3.05 (dd, *J*=12.4, 6.3 Hz, 1H), 1.38–1.24 (m, 4H), 1.43 (s, 9H), 1.38 (d, *J*=7.0 Hz, 3H), 0.88 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)=173.1, 143.3, 141.1, 128.6, 128.3, 128.2, 127.9, 127.1, 126.8, 81.7, 73.4, 60.4, 59.6, 50.3, 30.9, 27.9, 20.8, 17.4, 14.4. MS (APCI): *m*/*z*=398 ([M+H]$^+$, 100%), 380 (30%), 342 (23%), 266 (23%).

4.5. Preparation of (2*S*,3*S*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzyl) amino-*N*-cyclopropyl-2-hydroxyhexanamide 11

(2*S*,3*S*,α*S*)-*tert*-Butyl 3-(*N*-benzyl-*N*-α-methylbenzyl)amino-2-hydroxyhexanoate **7** (223 mg, 0.56 mmol) was dissolved in trifluoroacetic acid (5 mL) and the solution was stirred overnight at room temperature. The solvent was evaporated in vacuo and the crude product was treated with a 3 N aqueous HCl solution (2 mL). After concentration of this mixture, the residue was dissolved in CH_2Cl_2 (10 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude product thus obtained was used without further purification in the next step. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)=7.55 (d, *J*=5.8 Hz, 2H), 7.40–7.29 (m, 3H), 7.27–7.18 (m, 3H), 7.13 (d, *J*=6.8 Hz, 2H), 4.83 (s, 1H), 4.68 (d, *J*=14.0 Hz, 1H), 4.50 (s, 1H), 4.10 (d, *J*=10.1 Hz, 1H), 4.05 (d, *J*=14.0 Hz, 1H), 2.24–2.10 (m, 1H), 1.86 (d, *J*=6.8 Hz, 3H), 1.76–1.51 (m, 2H), 1.38–1.20 (m, 1H), 0.99 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm)=174.0, 135.0, 130.6, 130.1, 129.4, 129.3, 129.1, 129.0, 128.9, 69.3, 66.3, 64.7, 53.9, 26.0, 19.8, 18.0, 14.2.

The crude product of the ester hydrolysis was dissolved in CH_2Cl_2 (10 mL) and PyBOP (421 mg, 0.8 mmol, 1.4 equiv), Et_3N (230 μL, 1.6 mmol, 2.8 equiv) and cyclopropylamine (60 μL, 0.8 mmol, 1.4 equiv) were added sequentially. The mixture was then stirred at room temperature for 48 h. Then, a saturated aqueous NH_4Cl solution was added (2 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product thus obtained was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate=4:1 as eluent) to provide **11** as a white solid in 62% yield over the two steps (132 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)= 7.40–7.23 (m, 10H), 6.64 (s, 1H), 3.95 (q, *J*=6.9 Hz, 1H), 3.89 (d, *J*=14.4 Hz, 1H), 3.74–3.84 (m, 2H), 3.27 (s, 1H), 2.98–3.06 (m, 1H), 2.50–2.56 (m, 1H), 2.10–1.97 (m, 1H), 1.70–1.52 (m, 3H), 1.47–1.35 (m, 4H), 0.96 (t, *J*=7.2 Hz, 3H), 0.70–0.57 (m, 2H), 0.38–0.27 (m, 1H), 0.27–0.17 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm)=174.7, 143.7, 140.6, 128.7, 128.6, 128.4, 127.9, 127.4, 127.1, 69.8, 59.4, 57.1, 51.5, 29.9, 22.0, 20.6, 14.7, 14.4, 6.2, 5.8. IR (neat): ν (cm^{-1})=3384br s, 2956, 2929, 1647s, 1508, 1492, 1452, 1375, 1070, 700. MS (APCI): *m*/*z*=381 ([M+H]$^+$, 100%), 277 (47%), 162 (28%). HRMS (ES$^+$): for $C_{24}H_{32}N_2O_2Na$, calculated: 403.2361, found: 403.2380.

4.6. Preparation of (2*S*,3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide 3

(2*S*,3*S*,α*S*)-3-(*N*-Benzyl-*N*-α-methylbenzyl)amino-*N*-cyclopropyl-2-hydroxyhexanamide **11** (94 mg, 0.25 mmol) was dissolved in acetic acid (1.4 mL). After addition of the palladium catalyst (Pd 10% on carbon, 72 mg) the vessel was placed under an atmospheric pressure of hydrogen. After 15 h, the catalyst was filtered and the solvent was removed in vacuo. A saturated aqueous $NaHCO_3$ solution (3 mL) was then added to the residue and the mixture was extracted with CH_2Cl_2 (10 mL). The pooled organic layers were dried over $MgSO_4$, filtered and concentrated to afford **3** as a white solid in 85% yield (39 mg). ^{1}H NMR (300 MHz, D_2O, pH=5): δ (ppm)=4.39 (d, *J*=3.4 Hz, 1H), 3.70–3.58 (m, 1H), 2.58–2.72 (m, 1H), 1.68–1.20 (m, 4H), 0.90 (t, *J*=7.1 Hz, 3H), 0.84–0.75 (m, 2H), 0.63–0.52 (m, 2H). ^{13}C NMR (75 MHz, D_2O, pH=5, 1,4-dioxane as internal standard): δ (ppm)=175.0, 71.0, 53.6, 29.3, 22.4, 18.8, 13.5, 6.0, 5.9. $[\alpha]_D$ −39 (*c* 10, HCl).

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