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Research paper

Iminolactones as tools for inversion of the absolute configuration of α-amino acids and as inhibitors of cancer cell proliferation

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ABSTRACT

A library of iminolactones was prepared by esterification of several 2-hydroxyketones with a number of N-protected D- and L-α-amino acids. Some of the hydroxyketones were of terpenoid origin while others were obtained via synthesis. After N-deprotection of the intermediate esters, the free amines spontaneously underwent condensation with the ketone to form iminolactones. Esters of (*1S,2S,5S*)-2-hydroxypinan-3-one with both D- and L-α-amino acids were partially epimerized at the α-carbon atom to give a diastereomeric ester mixture. Only iminolactones of L-amino acids were formed after cyclization of (*1S,2S,5S*)-2-hydroxypinan-3-one, and correspondingly only D-amino acid iminolactones were formed after reaction with (*1R,2R,5R*)-2-hydroxypinan-3-one. The protocol thus enables inversion of the absolute configuration of amino acids. Some members of the prepared library of iminolactones displayed significant anti-proliferative effects toward three cancer cell lines (EL4, MCF7, PC3) with insignificant effect on non-malign cell lines (McCoy, MCF10A, NIH3T3). Thus, iminolactones appear to be potential lead structures for preparation of drugs selectively affecting proliferation of malign cell lines.

1. Introduction

Natural products constitute an important source of chemotherapeutics [1–3], important examples being vincristine, vinblastine, doxorubicin and paclitaxel, for which the actual drug is the original natural product. For other therapeutics like podophyllotoxin the registered drugs are derivatives of natural product leads, *e.g.* etoposide and teniposide [1,4,5]. These natural products are all isolated from higher plants or bacteria. In contrast no registered chemotherapeutics have been isolated from basidomycetes even though fungi have been sources for important drugs like the penicillins, cephalosporins and griseofulvins [5–7]. Basidomycetes have only to a very limited extend been used in traditional Western medicine, whereas they have been used intensively in Asian traditional medicine [8–10]. Although no drugs originating from basidomycetes have been registered, several compounds with significant biological effects are known, suggesting that basidomycetes have been disregarded as sources of new drugs [6,11–13]. Encouraged by these ideas we performed a screening of the fruiting bodies of Danish basidomycetes for activity toward cancer cells, and by this an extract of *Schizophyllum commune* was found to reduce proliferation of cancer cells far more efficiently than it inhibited growth of non-malign cells [14]. A bioguided fractionation of this fungal extract afforded three iminolactones schizine A and B (i.e. **1a** and **1b**) and epischizine A (**2a**), of which the latter probably is an artifact having the configuration at C-2′ inverted during the isolation procedure. The schizines (Scheme 1) constitute a group of unprecedented natural products that appear to be formed by esterification of an amino acid with 2-hydroxy-1-keto-mniopetal followed by a condensation to give the iminolactone or *vice versa* [14].

In cell growth assays schizine A and B (**1a, b**) displayed enhanced growth inhibition of cancer cell lines in the low μM range, whereas epischizine A (**2a**) did not show any inhibitory effects up to a concentration of 200 μM [14]. In contrast to most other cytotoxic agents no significant activity was seen against non-malignant human cell lines when using the SRB assay [15].

Iminolactones of terpenoids have been intensively investigated as chiral auxiliaries in stereoselective synthesis of amino acids [16–18]. Nevertheless biological testing of this type of compounds

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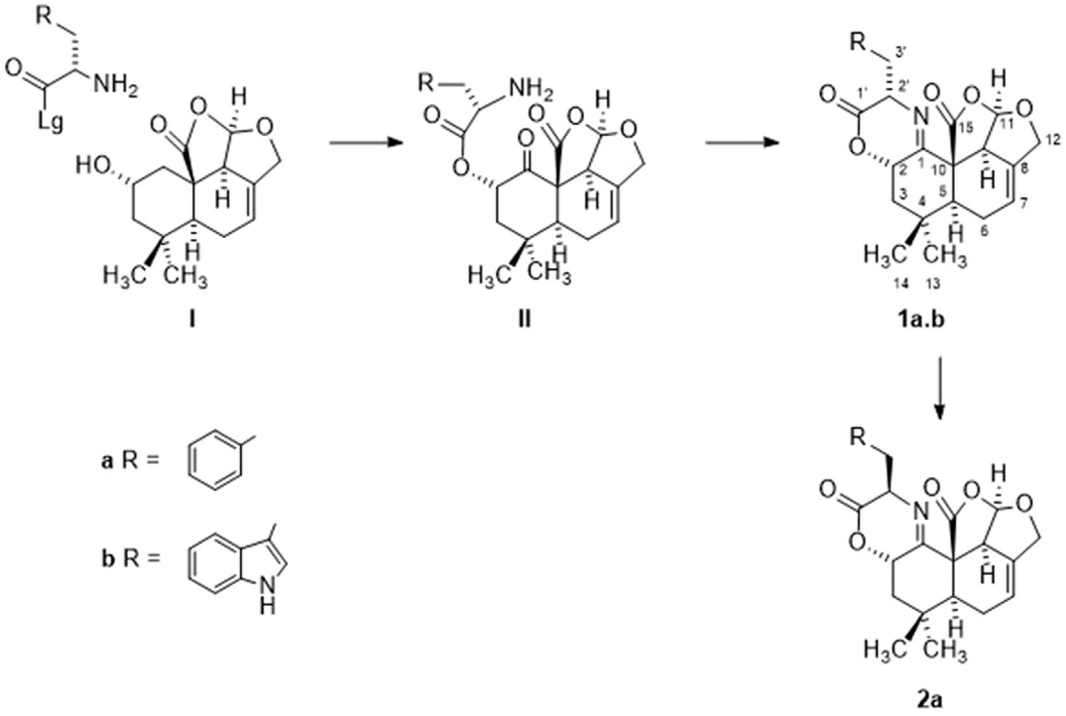


Scheme 1. Hypothetic late stages in biosynthesis of schizines (1a,b) via two suggested intermediates I and II. Lg depicts a leaving group.

has not received much attention.

2. Results and discussion

2.1. Chemistry

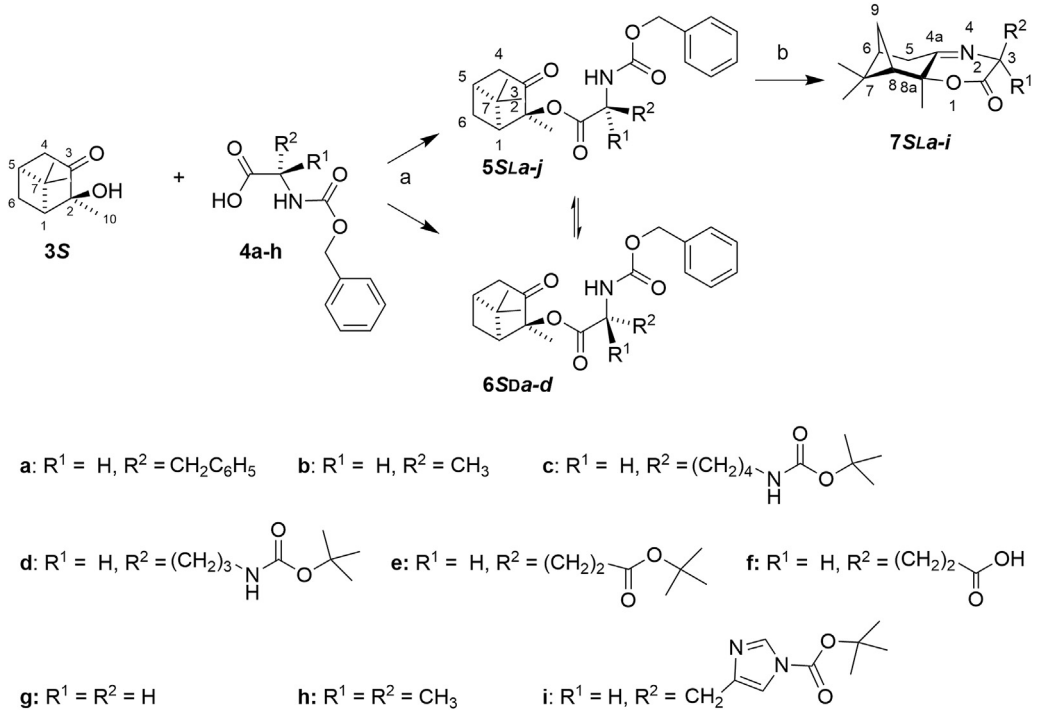
2.1.1. Iminolactones of α-amino acids and 2-exo-hydroxypinan-3-one

Initially a series of iminolactones was prepared by using N^{α}-benzyloxycarbonyl-protected amino acids and 2-*exo*-hydroxypinanones as the starting materials (Scheme 2).

As previously found, an optimal yield of Steglich esterification of (*1S,2S,5S*)-2-hydroxypinan-3-one (**3*S***) with N^{α}-benzyloxycarbonyl-protected L-phenylalanine (**4La**) was obtained when dicyclohexylcarbodiimide (DCC) was used as coupling reagent with 4-dimethylaminopyridine (DMAP) as catalyst to give **5*S*La** [19]. Somewhat unexpectedly, we observed that esterification of **3*S*** with Z-(D-Phe)-OH (**4Da**) afforded a mixture of the epimers **5*S*La** and **6*S*Da**, while subsequent hydrogenation only afforded iminolactone **7*S*La**, inferring that an isomerization at C-α in the amino acid moiety of **6*S*Da** had occurred. To ensure that only the ***S*L**-configurated product was formed, irrespectively of whether D- or L-amino amino acid derivatives or the racemic mixture were used as starting materials, an X-ray structural analysis of such a product was performed. The crystalline nature of the Boc-protected Lys derivative encouraged us to examine **7*S*Lc**. Unequivocal proof of the identity of this iminolactone as **7*S*Lc**, independently of the absolute configuration of the starting amino acid, was obtained by X-ray analysis of the products obtained from the conversions involving D- and L-forms of Z-Lys(Boc)-OH (i.e. **4Dc** or **4Lc**). In both cases the product was **7*S*Lc** (Fig. 1.). Since iminolactones can be hydrolyzed in hydrochloric acid to yield the hydroxyketone and the amino acid [16,20], this procedure presents a formal protocol for inversion of α-amino acids.

To understand the reaction path in details NMR spectra of the reaction mixtures were recorded (Fig. 2). The prevalent product after esterification of **3*R*** with Z-L-Phe-OH (**4La**) is the enantiomer of **5*S*La**, as evidenced by the triplet at 2.82 ppm originating from H-1 in **5*R*Da**, which will be at the same shift value as that of H-1 in **5Sla**. A signal corresponding to only a trace amount of **6*R*La** was present as a triplet at 2.78 ppm originating from its H-1. In the spectrum of the product mixture from reaction of **3*S*** with racemic Z-Phe (*i.e.* **4a**) a low-intensity triplet could be seen at 2.78 ppm in addition to the major signal at 2.82 ppm, revealing only a minor degree of isomerization. By analogy, even in the reaction mixture of **3*S*** with Z-D-Phe-OH (**4Da**) the major product was **5*S*La** indicating that a major part of the D-Phe moiety had isomerized to the L-form. These results constitute an elaboration of a previous observation [19]. Previously, only racemic amino acids were used as starting materials for iminolactones of (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one (**3*S***) or the enantiomer. Since the yields in previous work were below 50% the possibility that an enantiospecific iminolactone formation took place could not be excluded. We have observed that a true isomerization of the α-atom of the amino acid takes place when an N^{α}-protected D-amino acid is reacted with a (*1S,2S,5S*)-2-hydroxypinan-3-one (**3*S***) to give the iminolactone of the L-amino acid (**7*S*L**) and *vice versa*.

The investigation was expanded to include N^{α}-Z-protected alanine (**4b**) and N^{α}-Z-protected lysine (**4c**) and ornithine (**4d**) with N^{ε}-Boc-protected side chains. In all cases the reaction runs analoguous to the reaction of 2-hydroxypinan-3-one with phenylalanine. A similar in-depth analysis of the removal of the protecting group by hydrogenation and the concomitant spontaneous cyclization to the iminolactone was performed (Fig. 3). Thus, after hydrogenation of **5*S*La** for 24 h, the product mixture only contained trace amounts of **6*S*Da**, while no signals from the Z protecting group could be detected (purple graph in Fig. 3). In contrast, the spectrum of the product mixtures obtained from **3*S*** to **4Da** showed that significant amounts of **5*S*La** and **6*S*Da** were present after hydrogenation for 24 h (Fig. 3 red graph), and thus hydrogenation was extended to 48 h to reach complete conversion (green graph in Fig. 3), after which almost pure iminolactone **7*S*La** was seen.



Scheme 2. Conditions: (a) DCC, DMAP, (b) H_2, Pd/C. In the scheme only one of the enantiomers is depicted, and consequently 7RDa is the enantiomer of 7SLa.

Hence, irrespective of the absolute configuration of the α-amino acid, esterification of (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one followed by hydrogenation and cyclization affords only iminolactones **7*S*L**. By using this procedure the four possible iminolactones from **3*S*** and the four amino acids **4a-d** as well as the four possible isomers employing **3*R*** and the same four amino acids were prepared to give **7*S*La-d** and **7*R*Da-d**, respectively. In addition, iminolactones **7*S*Le-i** were prepared. Since hydrolysis of the iminolactones with hydrochloric acid to afford the amino acids is described this is a formal method for converting D-amino acids into L-amino acids and *vice versa* [16].

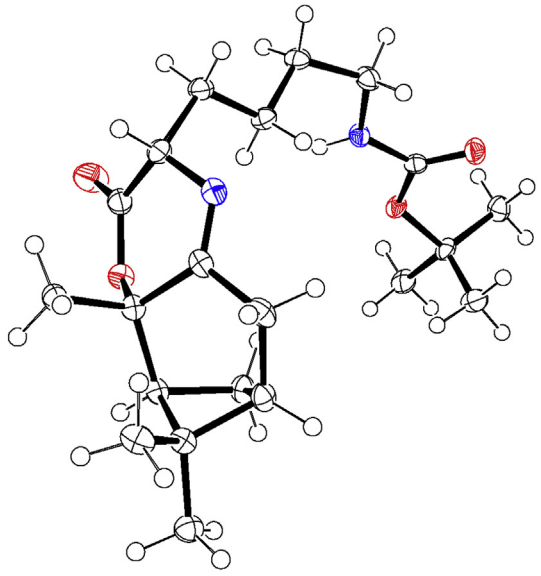


Fig. 1. Perspective drawing (ORTEP-3) [21] of compound 7SLc. Displacement ellipsoids of the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms have been shown as spheres of arbitrary size. Nitrogen atoms are shown in blue, while oxygen atoms are colored red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The protecting group from **7SLe** was removed by using trifluoroacetic acid in dichloromethane to give **7SLf**. However, removal of the protecting group from **7SLc** and **7SLd** lead to the free amine which turned out to be unstable.

2.1.2. Iminolactones of α-L-amino acids and (1R,2S,4S)-exo-hydroxycamphan-3-one

2-*exo*-Hydroxycamphan-3-one (**8**) was esterified with glycine and L-phenylalanine to give **11a** and **11b** by using a procedure very similar to that employed for preparation of the iminolactones of 2-*exo*-hydroxypinan-3-one (Scheme 3). No isomerization was observed when *(1R,2S,4S)*-2-exo-hydroxycamphan-3-one was reacted with L-phenylalanine. Compound **11b** has previously been prepared by benzylation of **11a** [16].

2.1.3. Iminolactones of α-amino acids and (2S,4aS,8aR)-2-hydroxy-8a-methyltransdecalin-1-one

(*4aS,8aR*)-8a-Methyltransdecalin-1-one (**12**) was prepared as previously described [22].

α-Bromination of ketone **12** with pyridinium bromide perbromide (PBB) afforded selectively bromide **13** in almost quantitative yield (Scheme 4). The equatorial position of the bromine substituent was established by the ^3J coupling constants between H-2 and H_{ax}-3/H_{eq}-3 of 13 Hz and 6 Hz, respectively. Treatment of **13** with a diluted solution of sodium hydroxide afforded **14**. A likely explanation for retention of the stereochemistry at C-2 is that an S_N2 reaction is followed by base-catalyzed epimerization [23,24]. Again the stereochemistry of the 2-hydroxy substituent was verified by the characteristic values of the two ^3J coupling constants of 12.0 Hz and 7.6 Hz. Esterification and subsequent hydrogenation to give iminolactones **16a-d** were performed by using the procedures described above for the series based on 2-*exo*-hydroxy-pinanones. While the pinane-derived iminolactones **7Sa-d** only could be formed as *R*,D or *S*,L isomers both epimers of the decalin-based

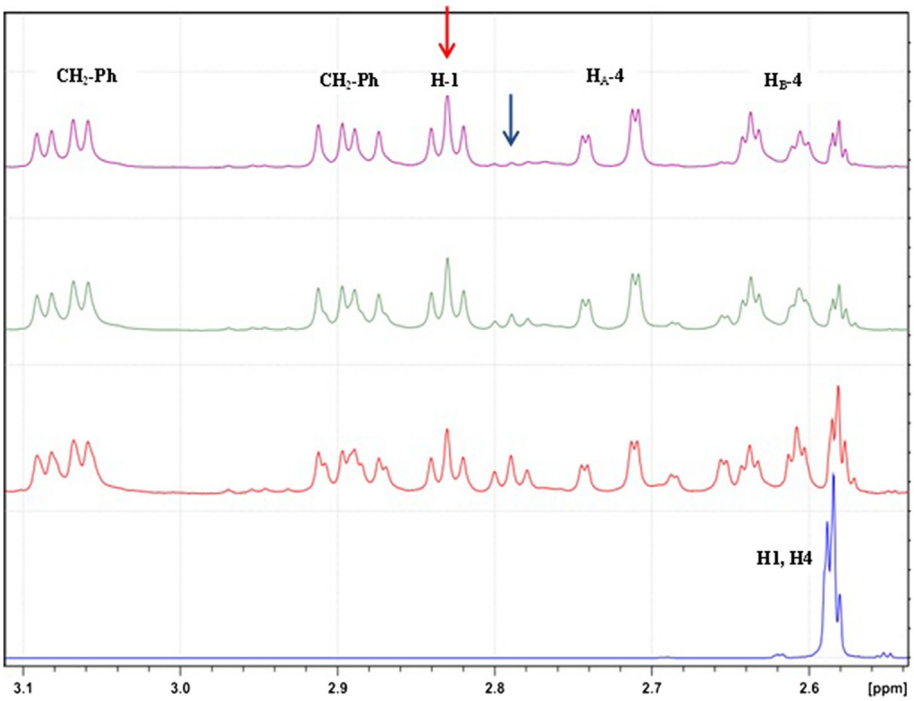


Fig. 2. ^{1}H NMR spectra illustrating the reaction sequence starting with 3S and Z-Phe-OH (**4a**); blue entry: **3*S***, red entry: product from acylation of **3*S*** with **4Da**, green entry: product mixture from acylation of **3*S*** with racemic **4a**, and purple entry: product mixture from acylation of **3*S*** with **4La**. Blue entry is numbered according to that of **3*S***. The red arrow indicates the signal from H-1 in the terpenoid moiety in ***5SLa*** while the blue arrow indicates the signal from H-1 in **6Sa**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

iminolactones, *e.g.* **1c** and **16d**, were obtained. However, the decalin iminolactones generally appeared to be less stable than the pinane-based iminolactones. This is illustrated by the isolation and identification of the two byproducts **17** and **18** (Fig. 4) from the reaction mixture obtained in the preparation of **16a**.

2.1.4. Iminolactones of 2-hydroxytetral-1-ones

The bromine in 2-bromotetralin-1-one (**19**) was substituted with the carboxylate of N^{α}-Boc-protected L-phenylalanine or L-tryptophan (Scheme 5). After removal of the Boc group the free amine spontaneously formed the iminolactone. The two pairs of epimeric iminolactones (**21a** and **22a**, **21b** and **22b**) were separated by HPLC. The relative configuration of **21a** was established by the presence of a NOE correlation between H-2 and H-4a, proving a *cis*-disposition of these protons. No correlation between H-2 and H-4a was found in **22a**.

2.2. Biological testing

In order to verify the hypothesis that the cell growth-inhibiting activity of the natural schizines could be attributed to the presence of an iminolactone functionality the prepared iminolactones were tested in the SRB assay [15]. The results are presented in Tables 1–4.

Inspection of the data in Tables 1–4 reveals that six of the 27 iminolactones (i.e. **7*R*Da**, **7*R*Dc**, **7*S*Lc**, **7*S*Ld**, **16a**, and **16d**) exhibit IC_{50} values in the low micromolar range. Remarkable selectivity toward cancer cell lines is observed for these compounds, since they did not show significant anti-proliferative effects on non-malignant cell lines up to 900 μM or even higher concentrations. Comparison of the activities for enantiomeric pairs show that for most analogues significant differences in potency are found for enantiomers except for **7*R*Dc** and **7*S*Lc**, which are equipotent. Among the tested amino acids only Gly, Phe, Lys and Orn gave rise to potent iminolactones. Among the selected skeletons highly active compounds were only found among derivatives of (1*R*,2*R*,5*R*)- and (1*S*,2*S*,5*S*)-2-hydroxypinan-3-one (**3*R*** and **3*S***, respectively) and (4a*S*,8a*R*)-8a-methyl-*trans*-decalin-1-one (**12**).

2.3. Conclusion

In conclusion preparation of iminolactones of (*1S,2S,5S*)-2-hydroxypinan-3-one with D-α-amino acids or (*1R,2R,5R*)-2-hydroxypinan-3-one with L-α-amino acids offers a possibility for inversion of the absolute configuration of the amino acids. In addition iminolactones appear to be promising starting points for development of agents exhibiting selective anti-proliferative effect against cancer cell lines leaving non-malignant cell lines unaffected. Significant differences in the activities of stereoisomers indicate a selective interaction with an at present unknown target characteristic for cancerous cell lines. Future investigations may reveal the target and thus allow for optimization of iminolactones to give drug leads.

3. Experimental

3.1. Chemistry

All reactions requiring anhydrous conditions were carried out under an atmosphere of argon or nitrogen in dry solvents according to standard procedures. Reagents were purchased at the highest commercial quality and solvents were HPLC grade. Reagents and solvents were used without further purification unless otherwise stated. Reactions were followed by TLC using silica-coated aluminum plates (Merck, 60 F_{254}) and visualized with UV light and/or spraying with a ceric ammonium molybdate solution followed by heating. Flash column chromatography was performed with silica gel (35–75 μm, Fisher Scientific). All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, COSY, HSQC, and HMBC in

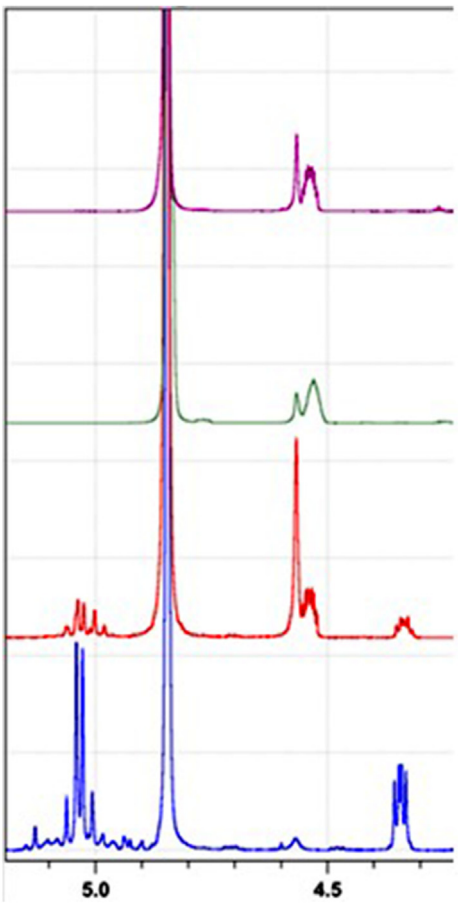
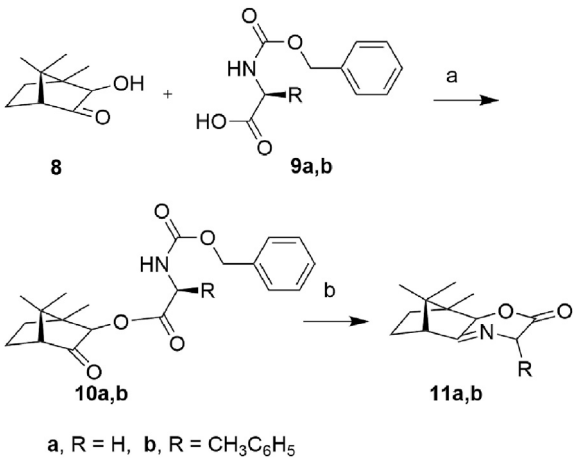
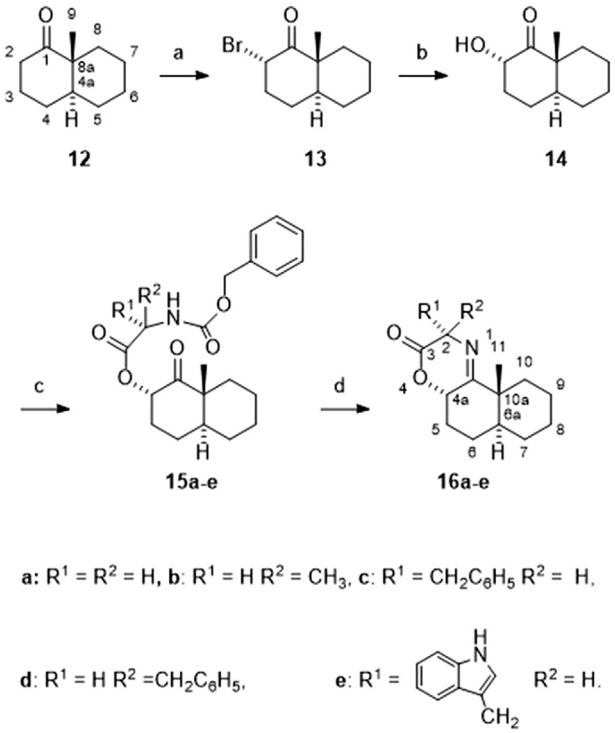


Fig. 3. ^{1}H NMR spectra of the product mixture obtained when a **3*S*** is reacted with **4La** to give a mixture of 90% of **5SLa** and 10% of **6SDa** (blue entry) b: crude product after hydrogenation for 24 h of a 60:40 mixture of **5SLa** and **6SDa** (red entry); c: crude product after continued hydrogenation for 48 h of the 60:40 mixture of **5SLa** and **6SDa** (green entry); and d: crude product after hydrogenation for 24 h of a 90:10 mixture of **5SLa** and **6SDa** (purple entry). Numbering is according to **7**. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

addition to HRMS. NMR spectra were recorded on Bruker Avance 400 MHz and 600 MHz, or Varian Mercury 300 MHz spectrometers. The chemical shifts (δ) are given in parts per million (ppm) relative to residual signals of the solvent: $CDCl_3$ (7.26 ppm and 77.16 ppm),



Scheme 3. Conditions: (a) DCC, DMAP; (b) H_2, Pd/C.



Scheme 4. Conditions: (a) pyridinium hydrobromide perbromide (PBB); (b) 6% NaOH; (c) Z-α-L-Amino acid, DCC, and DMAP; (d) H_2 and Pd/C.

CD_3CN (1.94 ppm and 118.26 ppm) or CD_3OD (3.31 ppm and 49.00 ppm). Coupling constants (*J*) are given in Hertz (Hz). HRMS were recorded on a Bruker micrOTOF-Q instrument using electrospray ionization (ESI). Low-resolution mass spectra were recorded on a Bruker microflex MALDI-TOF mass spectrometer. Optical rotations were measured on a Bellingham + Stanley ADP410 polarimeter. Melting points were measured on a Mettler Toledo MP70 Melting Point System. Analytical HPLC was performed on a Shimadzu HPLC system consisting of an SCL-10A VP controller, an SIL-10AD VP auto injector, an LC-10AT VP Pump, a diode array detector SPDM10A VP DAD, and a CTO-10AC VP column oven, using a Phenomenex Luna C18(2) column (150 × 4.6 mm; 3 μm) eluted at a rate of 0.8 mL/min. Injection volumes were 5–10 μL of a 1 mg/mL solution and separations were performed at 40 °C. The system was controlled by Class VP 6 software. Eluents A (H_2O/MeCN/TFA) 95:5:0.1) and B (MeCN/H_2O/TFA 95:5:0.1) were employed for linear gradient elution. Preparative HPLC was performed on an Agilent 1100 Series system with a multiple-wavelength UV detector using a Phenomex Luna C18(2) column (250 × 21.2 mm; 5 μm) with gradients of eluent A and B as above and a flow rate of 20 mL/min.

*3.1.1. (5R,8S,8aR)-8,9,9-trimethyl-3,5,6,7,8,8a-hexahydro-2H-5,8-methanobenzo[b][1,4]oxazin-2-one (**11a**) was prepared according to Xu et al. [16].*

*3.1.1.1. (1S,2R,4R)-1,7,7-Trimethyl-3-oxobicyclo[2.2.1]heptan-2-yl (S)-2-((benzyloxycarbonyl)amino)-3-oxo-3-phenylpropanoate (**11b**).* Z-Phenylalanine (213.5 mg, 1.2 equiv.) was stirred with DMAP (72.6 mg, 1 equiv.) and DCC (159.4 mg, 1.3 equiv.) in dry THF (2 mL) at 0 °C for 15 min. A solution of **9** (100 mg, 594 μmol) in THF (0.5 mL) was added dropwise to the reaction mixture and the mixture was stirred at 0 °C for 2 h and then at room temperature for 20 h. After filtration though a celite filter the filtrate was concentrated in vacuo to give **11b** as a crude product (190.6 mg, 339.2 μmol, 77%), which was used without further purification.

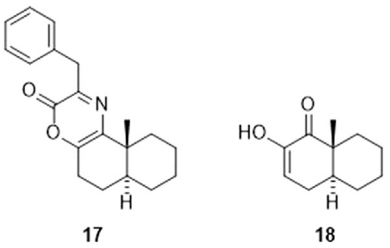
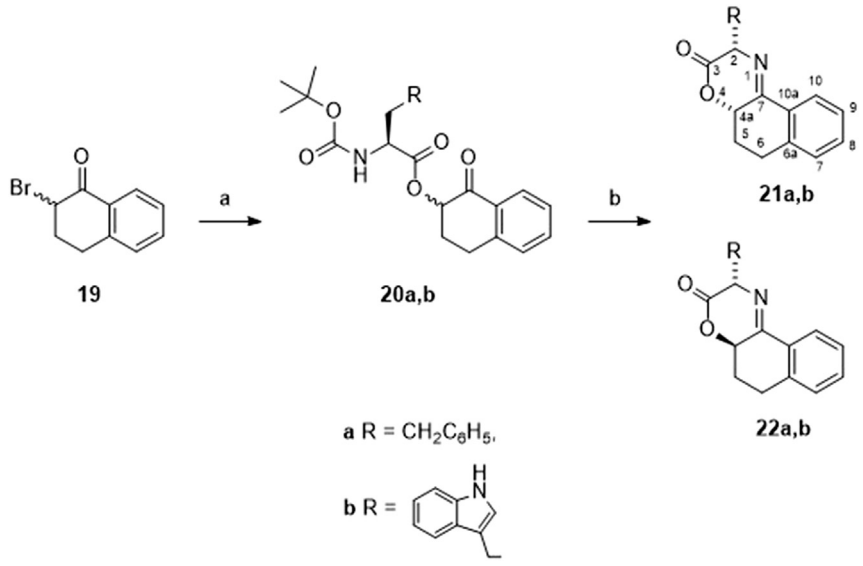


Fig. 4. Structures of the side products isolated after hydrogenation of 16a.

Schlenk tube was charged with Pd/C (5–10 mg, 10%), and the tube was purged with argon and then hydrogen. A solution of crude **10b** (150 mg, 267 μmol) in EtOH (99.9%, 2 mL) was added to the Schlenk tube, and the flask was purged with hydrogen. A hydrogen-filled balloon was attached and the mixture was stirred overnight. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated and purified by flash chromatography using heptane-EtOAc (4:1) to give **11b** (38.1 mg, 128 μmol, 48%). Spectral data were in agreement with those published [16].

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.11–7.40 (m, 5H, Ph), 4.27 (d,



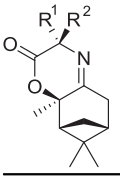
Scheme 5. Conditions: (a) Boc-Amino acid and DIPEA, (b) TFA, and then Na_2CO_3. The reaction sequence is shown for the L-form of the amino acids.

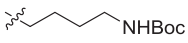
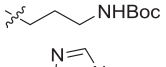
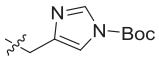
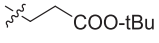
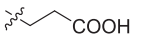
Spectral data are in agreement with those published [16].

*3.1.1.2. (3S,5R,8S,8aR)-3-Benzyl-8,9,9-trimethyl-3,5,6,7,8,8a-hexahydro-2H-5,8-methanobenzo[b][1,4]oxazin-2-one (**11b**).* A flame-dried

J = 1.2 Hz, 1H, H-8a), 3.96 (ddd, J = 8.6, 4.6, 1.5 Hz, 1H, H-3$_{endo}$), 3.56 (dd, J = 14.7, 4.4 Hz, 1H, CH_2-Ph), 3.23 (dd, J = 14.4, 8.5 Hz, 1H, CH_2-Ph), 2.44 (d, J = 4.4 Hz, 1H, H-5), 1.77–2.04 (m, 2H, H-6, H-7), 1.29–1.58 (m, 2H, H-6, H-7), 1.08 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.80 (s, 3H, CH_3).

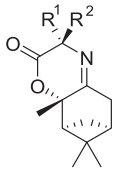
Table 1
In vitro anti-proliferative effect (as IC_{50} values in μM) of iminolactones of 3R with D-amino acids on three cancer cell lines: EL4, MCF7, and PC3 and on three non-malignant cell lines: McCoy, MCF10A, and NIH 3T3.

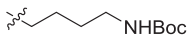
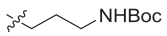
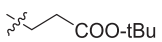
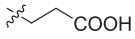


	R^1	R^2	EL4	MCF7	PC3	McCoy	MCF10A	NIH 3T3
7Rg	H	H	>300	>300	>300	>2000	>2000	>2000
7RDa	H	CH_2-Ph	7.7 ± 1.7	8.4 ± 4.4	9.4 ± 4.7	>1500	>1500	>1500
7RDb	H	CH_3	27 ± 11	38 ± 16	42 ± 17	>1800	>1800	>1800
7RDc	H		14.5 ± 9.3	15.3 ± 9.3	15.9 ± 8.7	>1300	>1300	>1300
7RDd	H		48 ± 10	56 ± 10	60 ± 12	>1500	>1500	>1500
7RDi	H		139 ± 13	142 ± 17	147 ± 17	>1300	>1300	>1300
7RDe	H		51 ± 12	54 ± 10	55 ± 14	>1200	>1200	>1200
7RDf	H		30 ± 9.8	34 ± 10	38 ± 13	>1200	>1200	>1200
7RDh	CH_3	CH_3	149 ± 19	162 ± 20	166 ± 19	>2000	>2000	>2000

Data are given as mean ± SD from three experiments. EL4: Leukemic cell line, MCF7: Human breast cancer cell line, and PC3: Human prostate cancer cell line, McCoy: synovial cell line (murine), MCF10A: Epithelial cells from mammary gland (human), NIH 3T3: Embryonic fibroblasts (murine).

Table 2
In vitro anti-proliferative effect (as IC_{50} values in μM) of iminolactones of 3S with L-amino acids on three cancer cell lines: EL4, MCF7, and PC3 and on three non-malignant cell lines: McCoy, MCF10A, and NIH 3T3.



	R^1	R^2	EL4	MCF7	PC3	McCoy	MCF10A	NIH 3T3
7Sg	H	H	19 ± 0.8	22 ± 0.2	43 ± 0.01	>900	>900	>900
7SLa	CH_2-Ph	H	>300	>300	>300	>1000	>1000	>1000
7SLb	CH_3	H	145 ± 25	154 ± 31	149 ± 24	>2000	>2000	>2000
7SLc		H	15 ± 4	17 ± 7	18 ± 8	>800	>800	>800
7SLd		H	4.1 ± 6.6	6.3 ± 6.6	6.6 ± 4.9	>1200	>1200	>1200
7SLe		H	36 ± 8.4	40 ± 10	42 ± 7.5	>1000	>1000	>1000
7SLg		H	36 ± 9.3	38 ± 9	42 ± 12	>1200	>1200	>1200

Data are given as mean ± SD from three experiments. EL4: Leukemic cell line, MCF7: Human breast cancer cell line, and PC3: Human prostate cancer cell line, McCoy: synovial cell line (murine), MCF10A: Epithelial cells from mammary gland (human), NIH 3T3: Embryonic fibroblasts (murine).

*3.1.2. General procedure for esterification of 2-exo-hydroxypinanone (**3**) with Z-protected amino acids (**4**)*

A solution of N^{α}-benzyloxycarbonyl-protected amino acid (1.5 mmol), 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** (200 mg, 1.19 mmol), and DMAP (0.2 mmol) in dry THF (5 mL) was stirred at 0 °C for 15 min. After addition of a solution of DCC (1.5 equiv) in dry THF (1 mL), the mixture was stirred at 0 °C for 2 h, and then at room temperature for 17 h. The reaction mixture was concentrated. The residue was suspended in cold EtOAc (5 °C) and 1,3-dicyclohexylurea (DCU) was removed by filtration through a pad of celite. The filtrate (about 15 mL) was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), H_2O (2 × 5 mL), and brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel 15–40 μm).

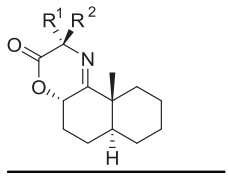
*3.1.2.1. (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl (benzyloxycarbonyl)-D-phenylalaninate (**5RDa**) and (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl (benzyloxycarbonyl)-L-phenylalaninate (**6RLa**).*

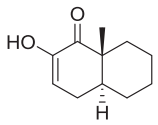
The mixture of **5RDa** and **6RLa** was prepared from 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** and D-α-phenylalanine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc in the eluent yielding a colorless oil (76.0%). Compounds ***5RDa*** and ***6RLa*** were formed in a 90:10 ratio. Compound ***5RDa***: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12–7.39 (m, 10H), 5.02–5.17 (m, 2H), 4.50–4.60 (m, 1H), 3.12 (dd, $J = 14$, 5.8 Hz, 1H), 3.02 (dd, $J = 14$, 5.8 Hz, 1H), 2.90 (t, $J = 6.1$ Hz, 1H), 2.60–2.78 (m, 2H), 2.39 (d, $J = 2.9$ Hz, 1H), 2.06–2.15 (m, 1H), 1.57 (s, 3H), 1.51 (d, $J = 11.0$ Hz, 1H), 1.35 (s, 3H), 0.86 (s, 3H).

The ratios between the formed diastereomers are based on the relative integrals of the respective H-1 signals. The general NMR assignment of the acylation products is shown for ***6R*Db**.

3.1.2.2. (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl (benzyloxycarbonyl)-L-alaninate (6RLb) and (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl (benzyloxycarbonyl)-D-

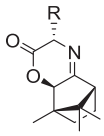
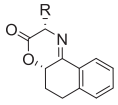
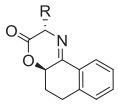
Table 3
In vitro anti-proliferative effect (as IC_{50} values in μM) of iminolactones of (4aS,8aR)-8a-methyltransdecalin-1-one (13) with amino acids on three cancer cell lines: EL4, MCF7, and PC3 and on three non-malignant cell lines: McCoy, MCF10A, and NIH 3T3.



	R^1	R^2	EL4	MCF7	PC3	McCoy	MCF10A	NIH 3T3
16a	H	H	7.7 ± 15	11 ± 10	13 ± 11	>2000	>2000	>2000
16b	H	CH_3	53 ± 24	57 ± 23	57 ± 15	>2000	>2000	>2000
16c	CH_2-Ph	H	50 ± 21	53 ± 14	51 ± 11	>1700	>1700	>1700
16d	H	CH_2-Ph	12 ± 3.5	12 ± 4.2	12 ± 3.9	>1200	>1200	>1200
16e	CH_2–In	H	71 ± 10	77 ± 10	83 ± 10	>1500	>1500	>1500
18			114 ± 37	119 ± 25	119 ± 21	>2000	>2000	>2000

Data are given as mean ± SD IC_{50} (μM) from three experiments. EL4: Leukemic cell line, MCF7: Human breast cancer cell line, and PC3: Human prostate cancer cell line, McCoy: synovival cell line (murine), MCF10A: Epithelial cells from mammary gland (human), NIH 3T3: Embryonic fibroblast (murine).

Table 4
In vitro anti-proliferative effect (as IC_{50} values in μM) of iminolactones of (1R,2S,4S)-exo-hydroxycamphan-3-one with α-L-amino acids and 2-hydroxytetralin-3-ones with α-L-amino acids on three cancer cell lines: EL4, MCF7, and PC3 and on three non-malignant cell lines: McCoy, MCF10A, and NIH 3T3.

Compound			Mean IC_{50} (μM)					
			EL4	MCF7	PC3	McCoy	MCF10A	NIH 3T3
11a		R = H	82.0 ± 17	135 ± 17	145 ± 21	>900	>900	>900
11b		R = CH_2Ph	ND	ND	160	ND	ND	ND
21a		R = CH_2Ph	39 ± 17	41 ± 14	45 ± 14	>1000	>1000	>1000
21b		R = CH_2In	36 ± 11	39 ± 13	39 ± 12	>1000	>1000	>1000
22a		R = CH_2Ph	24 ± 15	27 ± 11	30 ± 12	>1000	>1000	>1000
22b		R = CH_2In	22 ± 8	25 ± 12	26 ± 11	>1000	>1000	>1000

Data are given as mean ± SD from three experiments. EL4: Leukemic cell line, MCF7: Human breast cancer cell line, and PC3: Human prostate cancer cell line, McCoy: synovial cell line (murine), MCF10A: Epithelial cells from mammary gland (human), NIH 3T3: Embryonic fibroblasts (murine).

*alaninate (**5RDb**).* The mixture of ***6R*LLb** and ***5R*DDb** was prepared according to the general procedure for acylation using 2-*exo*-hydroxy-(*R*)-pinanone ***(3R)*** and Z-L-alanine as starting materials. The product was purified by using toluene-DCM-EtOAc (13:1:1) as the eluent to yield ***6R*LLb** and ***5R*DDb** (66:34) as an oil (43.0%). Compound ***6R*LLb**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.30–7.40 (m, 5H), 5.18 (d, *J* = 8.5 Hz, 1H), 5.06–5.13 (m, 2H), 4.21–4.37 (m, 1H), 2.90 (t, *J* = 6.2 Hz, 1H), 2.65–2.74 (m, 2H), 2.37–2.50 (m, 1H), 2.08–2.18 (m, 1H), 1.46–1.68 (m, 1H), 1.60 (s, 3H), 1.34–1.42 (s, 3H), 1.36 (s, 3H), 0.87 (s, 3H). Compound ***5R*DDb:** ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27–7.38 (m, 5H, Z-Ph), 5.24 (d, *J* = 6.5 Hz, 1H, NH), 5.09 (dd, *J* = 17.3, 12.0 Hz, 2H, Z-CH_2), 4.19–4.33 (m, 1H, H-α), 2.95 (t, *J* = 6.0 Hz, 1H, H_{eq}-1), 2.59–2.80 (m, 2H, H-4), 2.37–2.49 (m, 1H, H-7_{ax}), 2.07–2.17 (m, 1H, H_{eq}-5), 1.52–1.61 (m, 1H, H_{eq}-7), 1.59 (s, 3H, H-10), 1.32–1.39 (m, 3H, Ala-CH_3), 1.36 (m, 3H, H-9), 0.86 (s, 3H, H-8), ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 205.8 (C-3), 171.8 (O–C=O), 155.6 (N-(C=O)–O) 136.4 (Z-Ph), 128.6 (Z-Ph), 128.3 (Z-Ph), 128.2 (Z-Ph), 87.6 (C-2), 70.0 (Z-CH_2), 50.1 (C-α), 48.9 (C-1), 43.4 (C-4), 39.3 (C-6), 38.3 (C-5), 27.9 (C-7), 27.5 (C-9), 22.6 (C-8), 21.0 (C-10), 18.6 (Ala-CH_3).

If the reaction was run using 2-*exo*-hydroxy-(*R*)-pinanone and D-Z- alanine as starting materials the yield was 66% and the ratio ***6R*LLb** and ***5R*DDb** was 13:87.

*3.1.2.3. (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^{\alpha}$-(benzyloxycarbonyl)-N$^{\varepsilon}$-(tert-butoxycarbonyl)-L-lysinate (6**RLc**) and (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^{\alpha}$-(benzyloxycarbonyl)-N$^{\varepsilon}$-(tert-butoxycarbonyl)-D-lysinate (5**RDc**).* The mixture of **6*RLc*** and **5*RDc*** was prepared from 2-exo-hydroxy-(*R*)-pinanone (**3R**) and N$^{\alpha}$-Z-N$^{\varepsilon}$-L-Boc-lysine. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc aseluents yielding a colorless oil (75.3%) consisting of **5*RDc*** and **6*RLc*** in a 58:42 ratio. Compound **6*RLc***: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29–7.37 (m, 5H), 4.99–5.38 (m, 3H), 4.51–4.68 (m, 1H), 4.16–4.32 (m, 1H), 3.01–3.15 (m, 2H), 2.86 (t, J = 6.1 Hz, 1H), 2.60–2.79 (m, 1H), 2.37–2.48 (m, 1H), 2.09–2.17 (m, 1H), 1.69–1.89 (m, 3H), 1.61 - 1.52 (m, 4H), 1.53 - 1.11 (m, 2H), 1.42 (s, 9H), 1.36 (m, 3H), 0.86 (s, 3H). Compound **5*RDc***:. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.29–7.38 (m, 5H), 4.99–5.38 (m, 3H), 4.60–4.68 (m, 1H), 4.20–4.26 (m, 1H), 3.03–3.15 (m, 2H), 2.95 (t, J = 6.1 Hz, 1H), 2.61–2.78 (m, 2H), 2.40–2.47 (m, 1H), 2.10–2.16 (m, 1H), 1.22–1.83 (m, 6H), 1.60 (s, 3H), 1.42 (s, 9H), 1.36 (s, 3H), 0.87 (s, 3H).

When the reaction was run using 2-*exo*-hydroxy-(*R*)-pinanone and N$^{\alpha}$-Z-N$^{\varepsilon}$-Boc-D-lysine as starting materials the yield was 66% and the ratio between **6*RLc*** and **5*RDc*** was 3:97.

*3.1.2.4. (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^{\alpha}$-(benzyloxycarbonyl)-N$^{\delta}$-(tert-butoxycarbonyl)-L-ornithinate (6**RLd**) and (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl-N$^{\alpha}$-(benzyloxycarbonyl)-N$^{\delta}$-(tert-butoxycarbonyl)-D-ornithinate (5**RDd**).* The mixture of **6*RLd*** and **5*RDd*** was prepared from 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** and N$^{\alpha}$-Z-N$^{\delta}$-Boc-L-ornithine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc as the eluents to give a colorless oil (35.0%) consisting of **6*RLd*** and **5*RDd*** in a 57:43 ratio. Compound **6*RLd***: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.30–7.38 (m, 5H), 5.74 (br. s, 1H), 5.06–5.26 (m, 3H), 4.51–4.61 (br.s, 1H), 4.22–4.34 (m, 1H), 3.96–4.03 (m, 1H), 3.50–3.56 (m, 1H), 3.09–3.13 (m, 2H), 2.85 (t, *J* = 6.1 Hz, 1H), 2.71–2.78 (m, 1H), 2.61–2.69 (m, 1H), 2.39–2.47 (m, 1H), 2.09–2.16 (m, 1H), 1.71–1.99 (m, 1H), 1.55–1.61 (m, 4H), 1.40–1.46 (m, 9H), 1.36 (s, 3H), 1.23–1.32 (m, 2H), 0.87 (s, 3H). Compound **5*RDd***: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28–7.39 (m, 5H), 5.07–5.27 (m, 3H), 4.52–4.63 (br.s, 1H), 4.19–4.29 (m, 1H), 3.95–4.03 (m, 1H), 3.48–3.57 (m, 1H), 3.07–3.16 (m, 1H), 2.93 (t, *J* = 6.1 Hz, 1H), 2.61–2.80 (m, 2H), 2.09–2.17 (m, 1H), 1.70–1.87 (m, 1H), 1.56–1.67 (m, 4H), 1.43 (s, 9H), 1.36 (s, 3H), 1.23–1.30 (m, 2H), 0.87 (s, 3H).

If the reaction was run using 2-*exo*-hydroxy-(*R*)-pinanone and N$^{\alpha}$-Z-N$^{\delta}$-Boc-D-ornithine as starting materials the yield was 66% and the ratio between **6*RLd*** and **5*RDd*** was 1:99. The spectrum of **5*RDd*** was identical to that of **5*SLd*.**

*3.1.2.5. (1R,2R,5R)-2,6,6-trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl 2-((benzyloxycarbonyl)amino)-2-methylpropanoate (5**Rh**).* Compound **5*Rh*** was prepared from 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** and α-methyl-N$^{\alpha}$-Z-L-alanine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc as the eluents to give **5*Rh*** (37.1%) as a colorless oil.

*3.1.2.6. (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl (benzyloxycarbonyl)glycinate (5**Rg**).* Compound **5*Rg*** was made according to the general procedure for acylation using 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** and N$^{\alpha}$-Z-glycine as starting material. The

product was purified by using heptane-EtOAc with increasing amounts of EtOAc as the eluents to yield **5*R*g** as a colorless oil (23.6%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.29–7.38 (m, 5H), 5.12 (dd, J = 16.1, 12.1 Hz, 3H), 3.91 (dd, J = 5.5, 3.3 Hz, 2H), 2.94 (t, J = 6.1 Hz, 1H), 2.74 (s, 1H), 2.66 (dt, J = 19.1, 2.9 Hz, 1H), 2.42–2.48 (m, 1H), 2.12–2.16 (m, 1H), 1.62 (s, 3H), 1.51–1.56 (m, 1H), 1.37 (s, 3H), 0.87 (s, 3H).

*3.1.2.7. 5-(tert-Butyl) 1-((1R,2R,5R)-2,6,6-trimethyl-3-oxobicyclo [3.1.1]heptan-2-yl) (benzyloxycarbonyl)-L-glutamate (6**RLd**) and 5-(tert-Butyl) 1-((1R,2R,5R)-2,6,6-trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl) (benzyloxycarbonyl)-D-glutamate (5**RDd**).* The mixture of **6*R*Ld** and the epimer **5*R*Dd** was prepared from 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** and N$^\alpha$-Z-δ-(*tert*-butyl)-glutaminate using the general procedure for acylation. The product was purified by using toluene-EtOAc with increasing amounts of EtOAc as the eluents to give a colorless oil consisting of **6RLd** and **5RDd** (45.5%) in a 71:29 ratio. Compound **6*R*Ld**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.29–7.40 (m, 5H), 5.24–5.35 (m, 1H), 5.09 (s, 2H), 4.21–4.36 (m, 1H), 2.87 (t, J = 6.2 Hz, 1H), 2.58–2.80 (m, 2H), 2.37–2.48 (m, 1H), 2.23–2.35 (m, 2H), 2.05–2.17 (m, 2H), 1.80–1.97 (m, 1H), 1.60 (s, 3H), 1.51–1.59 (m, 1H), 1.40–1.44 (m, 9H), 1.36 (m, 3H), 0.86 (s, 3H). The NMR spectrum of the epimer was identical to that of **5*R*Dd**.

*3.1.2.8. (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\delta$-Boc-N$^\alpha$-Z-L-histidinate (6**RLi**) and (1R,2R,5R)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\delta$-Boc-N$^\alpha$-Z-D-histidinate (5**RDi**).* The mixture of **6*R*Li** and the epimer was prepared from 2-*exo*-hydroxy-(*R*)-pinanone **(3*R*)** and N$^\delta$-Boc-N$^\alpha$-Z-L-histidine using the general procedure for acylation The product was purified by using toluene-EtOAc with increasing amounts of EtOAc as the eluents to give a colorless oil consisting of **6*R*Li** and its D-epimer **5*R*Di** (55.0%) in a 37:63 ratio. Compound ***6R*Li**:^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.95 (s, 1H), 7.27–7.37 (m, 5H), 7.12–7.19 (m, 1H), 6.04 (d, J = 8.5 Hz, 1H), 5.03–5.15 (m, 2H), 4.46–4.58 (m, 1H), 2.96–3.09 (m, 2H), 2.85 (t, J = 6.2 Hz, 1H), 2.74 (dd, J = 19.3, 2.1 Hz, 1H), 2.59–2.68 (m, 1H), 2.28–2.44 (m, 1H), 2.09 (dtt, J = 12.2, 6.1, 6.1, 2.9, 2.9 Hz, 1H), 1.68 (dt, J = 13.5, 3.8 Hz, 1H), 1.59–1.63 (m, 9H), 1.53 (s, 3H), 1.33 (s, 3H), 0.83 (s, 3H). The spectrum of **5*R*Di** was identical to that of **6SLi**.

*3.1.2.9. (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-L-phenylalaninate (5**SLa**) and (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-D-phenylalaninate (6**SDa**).* The mixture of compound **5SLa** and **6SDa** was prepared from 2-*exo*-hydroxy-(*S*)-pinanone (**3*S***) and N$^\alpha$-Z-L–phenylalanine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc as an eluent to give a colorless oil (66.4%) consisting of **5SLa** and the epimer **6SDa** in a ratio of 38:62. The ^{1}H NMR data were identical to those of **5*R*Da** and **6*R*La**, respectively.

*3.1.2.10. (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)- L-alaninate (5**SLb**) and (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-D-alaninate (6**SDb**)..* The mixture of compound **5SLb** and **6SDb** was prepared from 2-*exo*-hydroxy-(*S*)-pinanone (**3*S***) and N$^\alpha$-Z-L-alanine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc as the eluents to give a colorless oil (70.4%) consisting of **5SLb** and **6SDb** in a 78:22 ratio. NMR data were identical to those of **5*R*Db** and **6*R*Lb**, respectively.

When N$^\alpha$-Z-D-alanine was used as starting material the obtained ratio of **5SLb** to **6SDb** was 39:61.

*3.1.2.11. (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-N$^\varepsilon$-(tert-butoxycarbonyl)-L-lysinate (5**SLc**) and (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-N$^\varepsilon$-(tert-butoxycarbonyl)-D-lysinate (6**SDc**).* Compound **5SLc** was prepared from 2-*exo*-hydroxy-(S)-pinanone (**3S**) and N$^\alpha$-Z-N$^\varepsilon$-Boc-L-lysine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc as eluents to give **5SLc** as a colorless oil (69.1%). ^{1}H NMR data were identical to those of 5RDc.

When N$^\alpha$-Z-N$^\varepsilon$-Boc-D–lysine was used as a starting material a mixture of **5SLc** and **6SDc** (50:50) was obtained.

*3.1.2.12. (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-N$^\delta$-(tert-butoxycarbonyl)-L-ornithinate (5**SLd**) and (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)-N$^\delta$-(tert-butoxycarbonyl)-D-ornithinate (6**SDd**).* Compound **5SLd** was prepared from 2-*exo*-hydroxy-(*S*)-pinanone (**3*S***) and N$^\alpha$-Z-N$^\delta$-Boc-L-ornithine using the general procedure for acylation. The product was purified by using toluene-DCM -EtOAc (13:1:1) as the eluent to give **5SLd** as a colorless oil (46.9%). ^{1}H NMR data identical to those of **5*R*Dd**.

When N$^\alpha$-Z-N$^\delta$-Boc-D-ornithine was used as a starting material a mixture of **6SDd** and **5SLd** (55%) was obtained in a ratio of 46:54.

*3.1.2.13. 5-(tert-Butyl) 1-((1S,2S,5S)-2,6,6-trimethyl-3-oxobicyclo [3.1.1]heptan-2-yl) N$^\alpha$-(benzyloxycarbonyl)-L-glutamate (5**SLe**) and 5-(tert-butyl) 1-((1S,2S,5S)-2,6,6-trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl) N$^\alpha$-(benzyloxycarbonyl)-D-glutamate (6**SDe**).* The mixture of compound **5SLe** and its epimer was prepared from 2-*exo*-hydroxy-(*S*)-pinanone (**3*S***) and N$^\alpha$-Z-5-*t*butyl L-glutaminate using the general procedure for acylation. The crude product was purified by using toluene with increasing amounts of EtOAc as the eluents to give a colorless oil (71.9%) consisting of **5SLe** and **6SDe** in a ratio of 81:18. Compound **6SDe** ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.27–7.39 (m, 5H), 5.48 (d, J = 8.2 Hz, 1H), 5.09 (dd, J = 15.2, 12.3 Hz, 2H), 4.25 (td, J = 8.4, 4.8 Hz, 1H), 2.94 (t, J = 6.2 Hz, 1H), 2.59–2.80 (m, 2H), 2.38–2.49 (m, 1H), 2.25–2.36 (m, 2H), 2.03–2.17 (m, 2H), 1.80–1.97 (m, 1H), 1.54–1.62 (m, 1H), 1.60 (s, 3H), 1.41–1.45 (m, 9H), 1.36 (s, 3H), 0.86 (s, 3H). The NMR spectrum of the epimer **6*S*De** was identical to that of compound **6*R*Le**.

*3.1.2.14. (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl N$^\alpha$-(benzyloxycarbonyl)glycinate (5**Sg**).* Compound **5*S*g** was prepared from 2-*exo*-hydroxy-(*S*)-pinanone (**3*S***) and N$^\alpha$-Z-glycine using the general procedure for acylation. The product was purified by using heptane-EtOAc with increasing amounts of EtOAc as the eluents to give **5Sg** (75%) as a colorless oil. ^{1}H NMR data were identical to those of **5*R*g**.

*3.1.2.15. tert-Butyl 4-((S)-2-(((benzyloxy)carbonyl)amino)-3-oxo-3-(((1S,2S,5S)-2,6,6-trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl)oxy)propyl)-1H-imidazole-1-carboxylate (5**SLi**).* Compound **5SLi** was prepared from 2-*exo*-hydroxy-(S)-pinanone (**3S**) and N$^\alpha$-Z-N$^\delta$-Boc-L-histidine using the general procedure for acylation. The crude product was purified by using toluene with increasing amounts of EtOAC as the eluents to give **5SLi** as a colorless oil (26.8%). 1H NMR (300 MHz, $CDCl_3$) δ ppm 7.96 (d, J = 1.2 Hz, 1H), 7.27–7.37 (m, 5H), 7.18 (br. s, 1H), 6.15 (d, J = 8.2 Hz, 1H), 5.07–5.12 (m, 2H), 4.52 (dt, J = 8.2, 5.1 Hz, 1H), 3.01 (dd, J = 6.7, 5.6 Hz, 2H), 2.92 (t, J = 6.2 Hz, 1H), 2.73 (dd, J = 19.0, 2.3 Hz, 1H), 2.63 (dt, J = 18.8, 2.8 Hz, 1H), 2.36–2.44 (m, 1H), 2.10 (tt, J = 6.0, 2.8 Hz, 1H), 1.88–1.97 (m, 1H), 1.60 (s, 9H), 1.53 (s, 3H), 1.34 (s, 3H), 0.84 (s, 3H).

*3.1.3. General procedure for cyclization of N^{α}-Z-protected esters-(5) of amino acids with 2-exo-hydroxypinanone to give oxazinols (**7**)*

In a 50 mL flame-dried Schlenk flask was added 10% Pd/C (20 mg) and then the flask was purged with argon. A solution of the ester (350 mg) in EtOAc (5 mL) was added, and then the flask was purged with hydrogen. A balloon filled with hydrogen was attached to the flask, and the mixture was stirred overnight. The reaction mixture was filtered through a pad of Celite, washing the Celite with EtOAc, and the resulting filtrate was concentrated. Chromatography was performed over silica gel (15–40 μm, column dimensions 2 × 5 cm).

*3.1.3.1. (3R,6R,8R,8aR)-3-Benzyl-7,7,8a-trimethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**RDa**).* Compound **7*R*Da** was obtained from **5*R*Da** and **6*R*La** (87:13) using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as the eluents to give **7*R*Da** as a colorless oil (80.4%). $[a]_D^{25} = 237^{\circ}$ (*c* 0.24). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.39 (d, *J* = 7.7 Hz, 2H, H_o-Ph), 7.31 (t, *J* = 7.5 Hz, 2H, H_m-Ph), 7.23 (t, *J* = 7.3 Hz 1H, H_p-Ph), 4.25 (dtd, *J* = 8.3, 4.3, 4.3, 2.2 Hz, 1H, H-3$_{endo}$), 3.59 (dd, *J* = 13.9, 4.4 Hz, 1H, CH_2-Ph), 3.19 (dd, *J* = 14.3, 8.4 Hz, 1H, CH_2-Ph), 2.84 (ddt, *J* = 17.6, 3.7, 2.2, 2.2 Hz, 1H, H_{end} −5), 2.73 (ddd, *J* = 17.6, 4.4, 2.2 Hz, 1H, H_{exo}-5), 2.34 (dtd, *J* = 11.2, 5.6, 5.6, 2.2 Hz, 1H, H_{exo}-9), 2.19 (t, *J* = 5.7 Hz, 1H, H-8), 2.08–2.12 (m, 1H, H-6), 1.60 (s, 3H, H-12), 1.38 (s, 3H, H-11), 1.12 (d, *J* = 11.1 Hz, 1H, H_{endo}-9), 1.02 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 172.65 (C-4a), 171.80 (C-2), 139.01 (C_{Ph}-1), 129.99 (C_{Ph}-2 and 6), 128.37 (C_{Ph}-3 and 5), 126.57 (C_{Ph}-4), 85.42 (C-8a), 60.82 (C-3), 50.57 (C-8), 39.72 (C-7), 39.49 (C-6), 38.37 (CH_2-Ph), 37.22 (C-5), 27.70 (C-9), 27.55 (C-11), 23.09 (C-10), 22.31 (C-12). HRMS *m/z* 298.1808 $[M+H]^+$ (298.1802, calc. for $C_{19}H_{24}NO_2^+$).

*3.1.3.2. (3R,6R,8R,8aR)-3,7,7,8a-Tetramethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**RDb**).* Compound 7***RDb*** was obtained from the mixture 5***RDb*** and **6*RSb*** (87:13) using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as the eluents to give 7***RDb*** as a colorless amorphous powder (83.6%). mp = 82 °C. $[a]_D^{25} = 254^{\circ}$ (*c* 0.31). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.13 (qdd, *J* = 6.9, 6.9, 6.9, 4.2, 2.5 Hz, 1H, H_{endo}-3), 2.85 (ddt, *J* = 17.6, 3.5, 2.1, 2.1, Hz, 1H, H_{exo}-5), 2.70 (dddd, *J* = 17.6, 3.8, 2.6, 1.2 Hz, 1H, H_{endo}-5), 2.35 (dtdd, *J* = 11.1, 5.6, 5.6, 2.1, 1.2H z, 1H, H_{exo}-9), 2.18 (t, *J* = 3.6, 1H, H-8), 2.06–2.13 (m, 1H, H-6), 1.65 (dd, *J* = 7.0, 1.5 Hz, 3H, H-13), 1.63–1.61 (m, 3H, H-12), 1.37 (s, 3H, H-11), 1.15 (d, *J* = 11.4 Hz, 1H, H_{endo}-9), 1.03 (s, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.86 (C-4a), 172.60 (C-2), 85.49 (C-8a), 55.01 (C-3), 50.52 (C-8), 39.70 (C-7), 39.43 (C-6), 37.07 (C-5), 27.71 (C-9), 27.55 (C-11), 23.16 (C-10), 22.23 (C-12), 18.46 (C-13). HRMS *m/z* 222.1509 $[M+H]^+$ (222.1489, calc. for $C_{13}H_{20}NO_2^+$).

*3.1.3.3. tert-Butyl (4-((3R,6R,8R,8aR)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) butyl)carbamate (7**RDc**)..* Compound **7*R*Dc** was obtained from **5*R*Dc** and **6*R*Lc** (87:13) using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as the eluents to give **7*R*Dc**. The product was crystallized from EtOAc and heptane (68%). mp = 80–81 °C. $[a]_D^{25} = 162^{\circ}$ (*c* 0.28). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.61 (br. s, 1H, NH), 3.99 (dtd, *J* = 7.2, 4.4, 4.4, 2.2 Hz, 1H, H-3$_{endo}$), 3.12–3.20 (m, 2H, H_{Lys}-ε), 2.87 (ddt, *J* = 17.6, 4.0, 1.8, 1.8 Hz, 1H, H_{exo}-5), 2.75 (ddd, *J* = 17.6, 4.4, 2.2 Hz, 1H, H_{endo}-5), 2.37 (dtd, *J* = 11.3, 5.5, 5.5, 2.2 Hz, 1H, H_{exo}-9), 2.20 (t, *J* = 5.7 Hz, 1H, H-8), 2.10–2.18 (m, 2H, H_{Lys}-β, H-6), 1.92–1.99 (m, 1H, H_{Lys}-β), 1.62 (s, 3H, H-12), 1.50–1.61 (m, 4H, $H_{\mathbf{Lys}}$-γ, H_{Lys}-δ), 1.44 (s, 9H, $C(CH_3)_3$) 1.39 (s, 3H, H-11), 1.16 (d, *J* = 11.4 Hz, 1H, H_{endo}-9), 1.06 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 173.05 (C-4a), 171.99 (C-2), 156.11 (NH-(C═O)–O), 85.29 (C-8a), 79.13 (O–C-$CH_3)_3$), 59.03 (C-3), 50.55 (C-8), 40.55 (C_{Lys}-ε), 39.73 (C-7), 39.48 (C-6), 37.13 (C-5), 31.78 (C_{Lys}−β), 30.09 (C_{Lys}−γ_), 28.60 ($C(CH_3)_3$), 27.75 (C-9), 27.57 (C-11), 23.21 (C_{Lys}-δ), 23.14 (C-10), 22.27 (C-12). HRMS *m/z* 379.2587 $[M+H]^+$ (379.2591, calc. for $C_{21}H_{35}N_2O_4^+$).

*3.1.3.4. tert-Butyl (3-((3R,6R,8R,8aR)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) propyl)carbamate (7**RDd**).* Compound 7***RDd*** was obtained from mixture **5*R*Dd** and **6*R*Ld** (87:13) using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as the eluents to give 7***RDc*** as colourless crystals (49.3%). mp 96–98 °C. $[a]_D^{25} = 163^{\circ}$ (*c* 0.33). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.85 (br.s., 1H, NH), 4.00–4.06 (m, 1H, H_{endo}-3), 3.16–3.27 (m, 2H, H_{Orn}-δ), 2.87 (ddt, *J* = 17.6, 3.7, 1.8, 1.8 Hz, 1H, H_{exo}-5), 2.75 (ddd, *J* = 17.6, 4.2, 2.4 Hz, 1H, H_{endo}-5), 2.37 (dtd, *J* = 11.2, 5.7, 5.7, 2.4 Hz, 1H, H_{exo}-9), 2.20 (t, *J* = 5.7 Hz, 1H, H-8), 2.16–2.24 (m, 1H, H_{Orn}-β), 2.10–2.14 (m, 1H, H-6), 1.97 (td, *J* = 14.4, 7.5 Hz, 1H, H_{Orn}-β), 1.72–1.80 (m, 2H, H_{Orn}-γ), 1.63 (s, 3H, H-12), 1.44 (m, 9H, $C(CH_3)_3$), 1.40 (s, 3H, H-11), 1.15 (d, *J* = 11.5 Hz, 1H, H_{endo}-9), 1.06 (s, 3H, H-10), ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 173.37 (C-4a), 171.85 (C-2), 156.18 (NH-(C═O)–O), 85.38 (C-8a), 79.12 (O–$C(CH_3)_3$), 58.74 (C-3), 50.55 (C-8), 40.46 (C_{Orn}-δ), 39.76 (C-7), 39.47 (C-6), 37.10 (C-5), 29.32 (C_{Orn}-β), 28.61 ($C(\mathbf{C}H_3)_3$), 27.78 (C-9), 27.56 (C-11), 26.21 (C_{Orn}-γ), 23.15 (C-10), 22.25 (C-12). HRMS *m/z* 365.2431 $[M+H]^+$ (365.2435, calc. for $C_{20}H_{33}N_2O_4^+$).

*3.1.3.5. tert-Butyl 3-((3R,6R,8R,8aR)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) propanoate (7**RDd**).* Compound 7***RDd*** was obtained from the mixture **5*R*Dd** and the epimer **6*R*Li** (87:13) using the general procedure for hydrogenation followed by flash chromatography using toluene with increasing amounts of EtOAc as the eluents to give 7***RDd*** (58.0%) as a colourless amorphous powder. $[a]_D^{25} = 188^{\circ}$ (*c* 0.32). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.06–4.19 (m, 1H, H_{endo}-3), 2.84 (d, *J* = 17.6 Hz, 1H, H_{exo}-5), 2.69 (ddd, *J* = 17.3, 3.8, 1.8 Hz, 1H, H_{endo}-5), 2.44–2.52 (m, 2H, H_{Glu}-γ), 2.28–2.43 (m, 2H, H_{exo}-9, H_{Glu}-β), 2.17 (t, *J* = 5.9 Hz, 1H, H-8), 2.05–2.23 (m, 2H, H-6, H_{Glu}-β), 1.59 (s, 3H, H-12), 1.41 (s, 9H, O–$C(CH_3)_3$), 1.36 (s, 3H, H-11), 1.11 (d, *J* = 11.4 Hz, 1H, H-9$_{endo}$), 1.02 (s, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.91 (C-4a), 172.56 (O–C = O_{Glu}), 171.50 (C-2), 85.35 (C-8a), 80.25 (O–$C(CH_3)_3$), 57.89 (C-3), 50.42 (C-8), 39.69 (C-7), 39.38 (C-6), 37.06 (C-5), 31.47 (C_{Glu}-γ), 28.27 (O–$C(CH_3)_3$), 27.70 (C-9), 27.53 (C-11), 27.40 (C_{Glu}-β), 23.14 (C-10), 22.18 (C-12). HRMS *m/z* 358.1970 $[M+H]^+$ (358.1989, calc. for $C_{19}H_{30}NO_4^+$).

*3.1.3.6. 3-((3R,6R,8R,8aR)-7,7,8a-Trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl)propanoic acid (7**RDf**).* TFA (0.5 mL) was added dropwise to a cooled solution of 7***RDd*** (50 mg, 149 μmol) in DCM (1 mL), and then the reaction mixture was stirred at rt for 2 h. Concentration of the reaction mixture followed by flash chromatography starting elution toluene-Et_2O-acetic acid (80:20:0.5) continuing with increasing amounts of Et_2O in the elutent to yield 7***RDf*** as a colourless amorphous powder (32.8 mg, 78.8%). $[a]_D^{25} = 191^{\circ}$ (*c* 0.26). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.14–4.22 (m, 1H, H_{endo}-3), 2.88 (ddt, *J* = 17.6, 3.8, 1.8, 1.8 Hz, 1H, H_{exo}-5), 2.74 (ddd, *J* = 17.9, 4.1, 2.3 Hz, 1H, H_{endo}-5), 2.67 (t, *J* = 6.7, 2H, H_{Glu}-γ), 2.43–2.56 (m, 1H, H_{Glu}-β, 2.38 (dtd, *J* = 11.1, 5.8, 5.8, 2.1 Hz, 1H, H_{exo}-9), 2.26 (dt, *J* = 14.4, 7.0 Hz, 1H, H_{Glu}-β), 2.21 (t, *J* = 5.7 Hz, 1H, H-8), 2.08–2.16 (m, 1H, H-6), 1.64 (s, 3H, H-12), 1.39 (s, 3H, H-11), 1.14 (d, *J* = 11.1 Hz, 1H, H-9$_{endo}$), 1.05 (s, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 177.97 (HO–C═O), 174.41 (C-4a), 171.03 (C-2), 85.61 (C-8a), 57.98 (C-3), 50.44 (C-8), 39.80 (C-7), 39.33 (C-6), 36.97 (C-5), 30.72 ($C_{γ-Glu}$), 27.79 (C-9),

27.53 (C-11), 26.68 ($C_{\beta-Glu}$), 23.16 (C-10), 22.21 (C-12). HRMS *m/z* 280.1532 $[M+H]^+$ (280.1544, calc. for $C_{15}H_{22}NO_4^+$).

*3.1.3.7. (6R,8R,8aR)-7,7,8a-Trimethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**Rg**).* Compound 7**Rg** was obtained from of 5**Rg** using the general procedure for hydrogenation to give 7**Rg** as a colorless amorphous powder (94.8%). $[a]_D^{25}$ = 253° (*c* 0.29). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.63 (d, *J* = 19.8 Hz, 1H, H_{exo}-3), 4.17 (ddd, *J* = 19.6, 4.2, 2.4 Hz, 1H, H_{endo}-3), 2.89 (m, 1H, H_{exo}-5), 2.75 (ddd, *J* = 17.6, 4.2, 2.4 Hz, 1H, H_{endo}-5), 2.40 (dtd, *J* = 11.3, 5.7, 5.7, 2.1 Hz, 1H, H_{exo}-9), 2.21 (t, *J* = 5.7 Hz, 1H, H-8), 2.13 (q, *J* = 5.7 Hz, 1H, H-6), 1.62 (s, 3H, H-12), 1.40 (s, 3H, H-11), 1.21 (d, *J* = 11.2 Hz, 1H, H_{endo}-9), 1.06 (s, 3H, H-10). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 173.72 (C-4a), 170.20 (C-2), 85.03 (C-8a), 51.74 (C-3), 50.42 (C-8), 39.84 (C-7), 39.42 (C-6), 37.11 (C-5), 27.79 (C-9), 27.60 (C-11), 23.16 (C-10), 22.39 (C-12). HRMS *m/z* 208.1354 $[M+H]^+$ (208.1332, calc. for $C_{12}H_{18}NO_2^+$).

*3.1.3.8. (6R,8R,8aR)-3,3,7,7,8a-Pentamethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**Rh**).* Compound **7Rh** was obtained from **5Rh** using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as the eluents to give **7Rh** as a colourless amorphous powder (29.6%). $[a]_D^{25}$ = 128° (*c* 0.13). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 2.90 (d, *J* = 16.5 Hz, 1H, H_{exo}-5), 2.69 (dd, *J* = 16.5 Hz, 1H, H_{endo}-5), 2.39 (dtd, *J* = 11.0, 5.4, 5.4, 2.0 Hz, 1H, H_{exo}-9), 2.11–2.18 (m, 1H, H-6, H-8), 1.66 (s, 3H, H-12), 1.62 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.39 (s, 3H, H-11), 1.22 (d, *J* = 11.4 Hz, 1H, H_{endo}-9), 1.09 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 176.12 (C-4a), 168.76 (C-2), 85.62 (C-8a), 59.07 (C-3), 51.73 (C-8), 40.36 (C-7), 40.03 (C-6), 37.37 (C-5), 31.29 (CH_3), 28.03 (C-9), 27.80 (C-11), 27.51 (CH_3), 27.34 (C-12), 23.15 (C-10). HRMS *m/z* 236.1663 $[M+H]^+$ (236.1645, calc. for $C_{14}H_{22}NO_2^+$).

*3.1.3.9. tert-Butyl 4-(((3R,6R,8R,8aR)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) methyl)-1H-imidazole-1-carboxylate (7**RDi**).* Compound 7**RDi** was obtained from the mixture **5RDi** and the epimer **6RLi** (87:13) using the general procedure for hydrogenation followed by flash chromatography using toluene with increasing amounts of EtOAc as eluents to give 7**RDi** as a colourless amorphous powder (47.9%). $[a]_D^{25}$ = 122° (*c* 0.14). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.01 (d, *J* = 1.47 Hz, 1H, N=CH–N), 7.17 (s, 1H, C=CH–N), 4.54 (dtd, *J* = 8.30, 4.38, 4.38, 2.38 Hz, 1H, H_{endo}-3), 3.51 (ddd, *J* = 15.22, 4.59, 1.10 Hz, 1H, CH_2-Im), 3.10 (dd, *J* = 15.04, 8.44 Hz, 1H, CH_2-Im), 2.85 (ddt, *J* = 17.61, 3.85, 2.11, 2.11 Hz, 1H, H_{exo}-5), 2.72 (ddd, *J* = 17.6, 4.4, 2.2 Hz, 1H, H_{endo}-5), 2.36 (dtd, *J* = 11.2, 5.6, 5.6, 2.4 Hz, 1H, H_{exo}-9), 2.20 (t, *J* = 5.7 Hz, 1H, H-8), 2.10 (tdd, *J* = 5.5, 4.4, 1.5 Hz, 1H, H-6), 1.65 (s, 3H, H-12), 1.59 (s, 9H, $C(CH_3)_3$), 1.38 (s, 3H, H-11), 1.17 (d, *J* = 11.3 Hz, 1H, H_{endo}-9), 1.03 (s, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 173.01 (C-4a), 171.51 (C-2), 147.04 (O=**C**–O–$C(CH_3)_3$), 140.36 (CH=C=N), 136.55 (N=CH–N), 114.66 (C=CH=N), 85.47 (C-8a), 85.26 (O=C–O–**C**$(CH_3)_3$), 58.74 (C-3), 50.53 (C-8), 39.67 (C-7), 39.43 (C-6), 37.21 (C-5), 31.25 (CH_2-Im), 28.03 (O=C–O–C(**C**$H_3)_3$), 27.73 (C-9), 27.52 (C-11), 23.10 (C-10), 22.29 (C-12). HRMS *m/z* 388.2243 $[M+H]^+$ (388.2231, calc. for $C_{21}H_{30}N_3O_4^+$).

*3.1.3.10. (3S,6S,8S,8aS)-3-Benzyl-7,7,8a-trimethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**SLa**).* Compound **7SLa** was obtained from a mixture of **5SLa** and **6SLa** (90:10) using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as eluents to yield **7SLa** as colourless oil (94.2%). $[a]_D^{25}$ = −233° (*c* 0.29). ^{1}H NMR (600 MHz, CD_3OD) δ ppm 7.34 (d, *J* = 7.0 Hz, 2H, H_{Phe}-2 and 6), 7.26 (t, *J* = 7.7 Hz, 2H, H_{Ph}-3 and 5), 7.18 (m, *J* = 7.3 Hz, 1H, H_{Ph}-4), 4.54 (dtd, *J* = 7.7, 4.4, 4.4, 2.2 Hz, 1H, H_{endo}-3), 3.50 (dd, *J* = 14.3, 4.8 Hz, 1H, CH_2-Ph), 3.14 (dd, *J* = 14.3, 7.7 Hz, 1H, CH_2-Ph), 2.89 (ddt, *J* = 17.5, 3.9, 2.0, 2.0 Hz, 1H, H_{exo}-5), 2.69 (ddd, *J* = 17.6, 4.4, 2.2 Hz, 1H, H_{endo}-5), 2.38 (dtd, *J* = 11.2, 5.6, 5.6, 2.2 Hz, 1H, H_{exo}-9), 2.16 (t, *J* = 5.7 Hz, 1H, H-8), 2.07–2.11 (m, 1H, H-6), 1.66 (s, 3H, H-12), 1.39 (s, 3H, H-11), 1.06 (s, 3H, H_{endo}-9), 0.99 (d, *J* = 11.0 Hz, 1H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 172.51 (C-4a), 171.64 (C-2), 138.82 (C_{Ph}-1), 129.84 (C_{Ph}-2 and 6), 128.25 (C_{Ph}-3 and 5), 126.47 (C_{Ph}-4), 85.41 (C-8a), 60.80 (C-3), 50.53 (C-8), 39.77 (C-7), 39.48 (C-6), 38.37 (CH_2-Phe), 37.26 (C-5), 27.76 (C-9), 27.61 (C-11), 23.18 (C-10), 22.36 (C-12). HRMS *m/z* 298.1808 $[M+H]^+$ (298.1802, calc. for $C_{19}H_{24}NO_2^+$).

3.1.3.11. (1S,2S,5S)-2,6,6-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl phenylalaninate. A small amount of the non-cyclized free amine could be isolated from the reaction mixture for preparing 7**SLa** affording **5SLa** not protected at the nitrogen atom. ^{1}H NMR (600 MHz, CD_3OD) δ ppm 7.16–7.35 (m, 5H, H_{Phe}), 3.63 (t, *J* = 7.0 Hz, 1H, H-α), 2.97 (dd, *J* = 13.8, 7.2 Hz, 1H, CH_2-Ph), 2.85 (dd, *J* = 13.6, 7.0 Hz, 1H, CH_2-Ph), 2.78 (t, *J* = 6.2 Hz, 1H, H-1), 2.74 (dd, *J* = 19.1, 2.2 Hz, 1H, H_{exo}-4), 2.61 (dt, *J* = 18.7, 3.1 Hz, 1H, H_{endo}-4), 2.34 (dtd, *J* = 11.3, 6.1, 6.1, 2.9 Hz, 1H, H_{exo}-7), 2.08 (tt, *J* = 6.1, 2.9 Hz, 1H, H-5), 1.50 (s, 3H, H-10), 1.42 (d, *J* = 11.0 Hz, 1H, H-7_{endo}), 1.36 (s, 3H, H-9), 0.86 (s, 3H, H-8).

*3.1.3.12. (3S,6S,8S,8aS)-3,7,7,8a-Tetramethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**SLb**).* Compound **7SLb** was obtained from the mixture of **5SLb** and **6SDb** (78:22) using the general procedure for hydrogenation followed by flash chromatography using toluene with increasing amounts of EtOAc as eluents to yield **7SLb** as a colourless crystals (52.5%), mp = 80–81 °C. $[a]_D^{25}$ = −244° (*c*. 0.26). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.15 (qdd, *J* = 7.0, 7.0, 7.0, 4.4, 2.2 Hz, 1H, H_{endo}-3), 2.87 (ddt, *J* = 17.6, 4.0, 2.2, 2.2 Hz, 1H, H_{exo}-5), 2.74 (ddd, *J* = 17.6, 4.0, 2.2 Hz, 1H, H_{endo}-5), 2.38 (dtd, *J* = 11.3, 5.6, 5.6, 2.4 Hz, 1H, H_{exo}-9), 2.21 (t, *J* = 5.6 Hz, 1H, H-8), 2.12 (tdd, *J* = 5.9, 5.9, 4.4, 1.5 Hz, 1H, H-6), 1.68 (d, *J* = 7.0 Hz, 3H, H-13), 1.64 (s, 3H, H-12), 1.40 (s, 3H, H-11), 1.19 (d, *J* = 11.4 Hz, 1H, H_{endo}-9), 1.06 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 173.08 (C-4a), 172.79 (C-2), 85.56 (C-8a), 55.09 (C-3), 50.60 (C-8), 39.73 (C-7), 39.50 (C-6), 37.09 (C-5), 27.72 (C-9), 27.55 (C-11), 23.16 (C-10), 22.24 (C-12), 18.45 (C-13). HRMS *m/z* 222.1492 $[M+H]^+$ (222.1489, calc. for $C_{13}H_{20}NO_2^+$).

*3.1.3.13. tert-Butyl (4-((3S,6S,8S,8aS)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) butyl)carbamate (7**SLc**).* Compound **7SLc** was obtained from **5SLc** using the general procedure for hydrogenation followed by flash chromatography using heptane to which increasing amounts of EtOAc were added as an eluent yielded **7SLc** as an oil which was crystallized from ethyl acetate-heptane (86.5%). Mp 81–82 °C. $[a]_D^{25}$ = −157° (*c*. 0.28). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.62 (br. s., 1H, NH), 3.99 (dtd, *J* = 7.3, 4.4, 4.4, 2.2 Hz, 1H, H_{endo}-3), 3.11–3.20 (m, 2H, H_{Lys}-ε), 2.87 (ddt, *J* = 17.6, 3.8, 1.8, 1.8 Hz, 1H, H_{exo}-5), 2.75 (ddd, *J* = 17.6, 4.4, 2.2 Hz, 1H, H_{endo}-5), 2.37 (dtd, *J* = 11.2, 5.7, 5.7, 2.4 Hz, 1H, H_{exo}-9), 2.20 (t, *J* = 5.7 Hz, 1H, H-8), 2.10–2.18 (m, 2H, H-β_{Lys}, H-6), 1.92–1.99 (m, 1H, H_{Lys}-β), 1.62 (s, 3H, H-12), 1.49–1.65 (m, 4H, H_{Lys}-γ, H_{Lys}-δ), 1.44 (s, 9H, $C(CH_3)_3$), 1.39 (s, 3H, H-11), 1.16 (d, *J* = 11.4 Hz, 1H, H_{endo}-9), 1.05 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 173.15 (C-4a), 171.96 (C-2), 156.11 (NH-(C=O)–O), 85.30 (C-8a), 79.12 (O–$C(CH_3)_3$), 59.02 (C-3), 50.55 (C-8), 40.53 (C_{Lys}-ε), 39.73 (C-7), 39.47 (C-6), 37.11 (C-5), 31.75 (C-β_{Lys}), 30.07 (C-γ_{Lys}), 28.59 ($C(CH_3)_3$), 27.75 (C-9), 27.56 (C-11), 23.19 (C-δ_{Lys}), 23.13 (C-10), 22.25 (C-12). HRMS *m/z* 379.2587 $[M+H]^+$ (379.2591, calc. for $C_{21}H_{35}N_2O_4^+$).

*3.1.3.14. tert-Butyl (3-((3S,6S,8S,8aS)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) propyl)carbamate (7**SLd**).* Compound 7**SLd** was obtained from **5SLd** using the general procedure for hydrogenation followed by flash chromatography using heptane with increasing amounts of EtOAc as eluents to yield 7**SLd** as an oil, which was crystallized from *i*-PrOH (50.3%). Mp 114–116 °C. $[a]_D^{25} = -168°$ (*c* 0.30). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.99–4.06 (m, 1H, H_{endo}-3), 3.21 (m, 2H, H_{Orn}-δ), 2.87 (ddt, *J* = 17.6, 3.9, 1.7, 1.7 Hz, 1H, H_{exo}-5), 2.75 (ddd, *J* = 17.6, 4.2, 2.2 Hz, 1H, H_{endo}-5), 2.37 (dtd, *J* = 11.2, 5.6, 5.6, 2.2 Hz, 1H, H_{exo}-9), 2.20 (t, *J* = 5.7 Hz, 1H, H-8), 2.16–2.26 (m, 1H, H_{Orn}-β), 2.09–2.15 (m, 1H, H-6), 1.97 (td, *J* = 14.4, 7.5 Hz, 1H, H_{Orn}-β), 1.70–1.80 (m, 2H, H_{Orn}-γ), 1.63 (s, 3H, H-12), 1.44 (m, 9H, $C(CH_3)_3$), 1.39 (s, 3H, H-11), 1.15 (d, *J* = 11.5 Hz, 1H, H-9_{endo}), 1.06 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 173.19 (C-4a), 171.92 (C-2), 156.17 (NH-(C=O)–O), 85.37 (C-8a), 79.11 (O–$C(CH_3)_3$), 58.75 (C-3), 50.55 (C-8), 40.46 (C_{Orn}-δ), 39.75 (C-7), 39.47 (C-6), 37.12 (C-5), 29.36 (C_{Orn}-β), 28.60 ($C(CH_3)_3$), 27.76 (C-9), 27.56 (C-11), 26.20 (C_{Orn}-γ), 23.14 (C-10), 22.24 (C-12). HRMS *m/z* 365.2441 $[M+H]^+$ (365.2435, calc. for $C_{20}H_{33}N_2O_4^+$).

*3.1.3.15. tert-Butyl 3-((3S,6S,8S,8aS)-7,7,8a-trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl) propanoate (7**SLe**).* Compound **7SLe** was obtained from the mixture of **5SLe** and its D-epimer **6SDe** (82:18) using the general procedure for hydrogenation followed by flash chromatography using toluene-Et_2O with increasing amounts of Et_2O as eluents to give **7SLe** as a colourless amorphous solid (78.1%). $[a]_D^{25} = -190°$ (*c* 0.28). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.11–4.19 (m, 1H, H_{endo}-3), 2.87 (ddt, *J* = 17.6, 3.8, 1.8, 1.8 Hz, 1H, H_{exo}-5), 2.72 (ddd, *J* = 17.6, 3.8, 1.8 Hz, 1H, H_{endo}-5), 2.47–2.56 (m, 2H, H_{Glu}-γ), 2.39–2.47 (m, 1H, H_{Glu}-β), 2.36 (ddd, *J* = 11.2, 5.9, 2.1 Hz, 1H, H_{exo}-9), 2.07–2.26 (m,3H, H-6, H-8, H_{Glu}-β), 1.62 (s, 3H, H-12), 1.44 (s, 11H, O–$C(CH_3)_3$), 1.39 (s, 3H, H-11), 1.14 (d, *J* = 11.2 Hz, 1H, H_{endo}-9), 1.05 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 173.12 (C-4a), 172.81 (O–C = O_{Glu}), 171.72 (C-2), 85.43 (C-8a), 80.35 (O–$C(CH_3)_3$), 58.01 (C-3), 50.55 (C-8), 39.74 (C-7), 39.48 (C-6), 37.12 (C-5), 31.56 (C_{Glu}-γ), 28.31 (O–$C(CH_3)_3$), 27.75 (C-9), 27.56 (C-11), 27.49 (C_{Glu}-β), 23.14 (C-10), 22.22 (C-12). HRMS *m/z* 358.1975 $[M+H]^+$ (358.1989, calc. for $C_{19}H_{30}NO_4^+$).

*3.1.3.16. 3-((3S,6S,8S,8aS)-7,7,8a-Trimethyl-2-oxo-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-3-yl)propanoic acid (7**SLf**).* TFA (0.5 mL) was added dropwise to a cooled solution of **7SLf** (103 mg, 307 μmol) in DCM (1 mL) and the mixture was stirred at rt for 2 h. Concentration of the reaction mixture followed by flash chromatography using toluene-Et_2O (4:1) with increasing amounts of Et_2O as eluents yielded **7SLf** as colourless amorphous solid (72.7 mg, 84.8%). $[a]_D^{25} = -187°$ (*c* 0.31). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.15–4.23 (m, 1H, H $_{endo}$-3), 2.92 (ddt, *J* = 17.9, 3.8, 2.1, 2.1 Hz, 1H, H_{exo}-5), 2.78 (ddd, *J* = 17.6, 4.1, 2.6 Hz, 1H, H_{endo}-5), 2.70 (t, *J* = 6.4, 2H, H_{Glu}-γ), 2.47–2.59 (m, 1H, H_{Glu}-β), 2.42 (dtd, *J* = 11.4, 5.6, 5.6, 2.3 Hz, 1H, H_{exo}-9), 2.27–2.37 (m, 1H, H_{Glu}-β), 2.24 (t, *J* = 5.7 Hz, 1H, H-8), 2.12–2.19 (m, 1H, H-6), 1.67 (s, 3H, H-12), 1.41 (s, 3H, H-11), 1.16 (d, *J* = 11.1 Hz, 1H, H-9_{endo}), 1.07 (s, 3H, H-10). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 175.75 (HO–C=O), 175.25 (C-4a), 170.58 (C-2), 85.72 (C-8a), 58.45 (C-3), 50.50 (C-8), 39.83 (C-7), 39.29 (C-6), 36.95 (C-5), 31.47 (C_{Glu}-γ), 27.83 (C-9), 27.46 (C-11), 26.33 (C_{Glu}-β), 23.11 (C-10), 22.18 (C-12). HRMS *m/z* 280.1528 $[M+H]^+$ (280.1544, calc. for $C_{15}H_{22}NO_4^+$).

*3.1.3.17. (6S,8S,8aS)-7,7,8a-Trimethyl-3,5,6,7,8,8a-hexahydro-2H-6,8-methanobenzo[b][1,4]oxazin-2-one (7**Sg**).* Compound **7Sg** was obtained from **5Sg** by using the general procedure for hydrogenation followed by flash chromatography using toluene with increasing amounts of EtOAc as eluents to give **7Sg** as a colourless amorphous powder (74.4%). $[a]_D^{25} = -225°$ (*c* 0.32). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.60 (d, *J* = 19.6 Hz, 1H, H_{exo}-3), 4.16 (ddd, *J* = 19.9, 4.4, 2.6 Hz, 1H, H_{endo}-3), 2.86 (dquin, *J* = 17.6, 2.3, 2.3, 2.3, 2.3 Hz, 1H, H_{exo}-5), 2.72 (ddd, *J* = 17.6, 4.1, 2.3 Hz, 1H, H_{endo}-5), 2.37 (dtd, *J* = 11.1, 5.6, 5.6, 2.3 Hz, 1H, H_{exo}-9), 2.18 (t, *J* = 5.9 Hz, 1H, H-8), 2.11 (m, *J* = 3.9, 3.9, 2.2 Hz, 1H, H-6), 1.59 (s, 3H, H-12), 1.38 (s, 3H, H-11), 1.17 (d, *J* = 11.4 Hz, 1H, H_{endo}-9), 1.04 (s, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 173.41 (C-4a), 170.03 (C-2), 85.12 (C-8a), 51.68 (C-3), 50.28 (C-8), 39.80 (C-7), 39.32 (C-6), 37.08 (C-5), 27.77 (C-9), 27.58 (C-11), 23.17 (C-10), 22.37 (C-12). HRMS *m/z* 208.1371 $[M+H]^+$ (208.1332, calc. for $C_{12}H_{18}NO_2^+$).

*3.1.4. (2S,4aS,8aR)-2-Bromo-8a-methyloctahydronaphthalen-1(2H)-one (**13**)*

Pyridinium bromide perbromide (PBB, 14.99 g 42 mmol, 90%) was added to a solution of ketone **12** (6.98 g, 42 mmol) in acetic acid (350 ml), and then the mixture was stirred for 3 h at rt. The mixture was poured onto ice (200 mL) and extracted with Et_2O (400 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ until effervescence ceased. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give **13** as a white solid (10.29 g, 42.0 mmol, 97% purity, quant.) which was used without further purification. The product was contaminated with a trace amount of the starting material. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 5.03 (dd, J_{aa} = 13.2 Hz, J_{ae} = 6.5 Hz, H_{ax}-2), 2.62 (dddd, *J* = 13.2, 6.5, 3.9, 2.8 Hz, H_{eq}-3), 2.08 (qd, *J* = 13.2, 4.8 Hz, H_{ax}-3), 1.66–1.78 (m, 3H, H-4, H-5, H-8), 1.59–1.65 (m, 1H, H-7), 1.49–1.59 (m, 3H, H-4, H-4a, H-8), 1.44–1.49 (m, 1H, H-6), 1.41 (tt, *J* = 13.6, 4.0 Hz, 1H, H-7), 1.32–1.40 (m, 1H, H-6), 1.18 (qt, *J* = 13.2, 4.3 Hz, 1H, H-5), 1.13 (s, 3H, H-9). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 205.67 (C-1), 54.62 (C-2), 49.25 (C-8a), 46.09 (C-4a), 39.11 (C-3), 33.09 (C-8), 29.19 (C-4), 27.35 (C-6), 25.76 (C-5), 20.76 (C-7), 15.62 (C-9). HRMS *m/z* 245.0361 $[M+H]^+$ (245.0536, calc. for $C_{11}H_{19}BrO^+$).

*3.1.4.1. (2S,4aS,8aR)-2-Hydroxy-8a-methyloctahydronaphthalen-1(2H)-one (**14**).* To a solution of the bromide **13** (10.55 g, 42 mmol) in DMF (150 ml) aqueous NaOH (36.27 ml, 6%) was slowly added at rt, and then the mixture was stirred for 2 h before neutralization at 0 °C by addition of 1% HCl. The mixture was extracted with Et_2O, and the organic phase washed with brine, dried ($MgSO_4$), and concentrated to yield a crude product (16.2 g), which was purified by flash chromatography using heptane-acetic acid (100:1) with increasing amounts of EtOAc to give **14** as a colourless oil (6.61 g, 36.3 mmol, 87%). $[\alpha]_D^{22}$ +63° (*c* 0.29). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 4.46 (dddd, *J* = 12.0, 7.6, 3.8, 1.7 Hz, 1H, H-2), 3.65 (d, *J* = 3.8 Hz, 1H, OH), 2.37–2.46 (m, 1H, H_{eq}-3), 1.65–1.73 (m, 3H, H-4, H-5, H-8), 1.59–1.65 (m, 1H, H-7), 1.52–1.59 (m, 1H, H-8), 1.38–1.52 (m, 6H, H_{ax}-3, H-4, H-4a, H-6, H-7), 1.14–1.24 (m, 1H, H-5), 1.11–1.14 (m, 3H, H-9). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 215.94 (C-1), 71.34 (C-2), 47.51 (C-8a), 47.02 (C-4a), 36.49 (C-3), 32.30 (C-8), 27.43 (C-6), 26.22 (C-4), 25.89 (C-5), 20.47 (C-7), 15.52 (C-9). HRMS *m/z* 165.1278 $[M + H - H_2O]^+$ (165.1274, calc. for $C_{11}H_{18}O^+$).

*3.1.5. General procedure for acylation of **14***

(2S,4aS,8aR)-2-Hydroxy-8a-methyloctahydronaphthalen-1(2H)-one (**14**) (200 mg) was acylated according to the general procedure for acylating hydroxy-pinan-2-ones. The crude product was purified by flash chromatography over silica gel (15–40 μm).

*3.1.5.1. (2S,4aS,8aR)-8a-Methyl-1-oxodecahydronaphthalen-2-yl 2-((benzyloxycarbonyl)-glycinate (**15a**).* Compound **15a** was prepared from (2*S*,4a*S*,8a*R*)-2-hydroxy-8a-methyloctahydronaphthalen-1(2*H*)-one (**14**) and N^{α}-Z-glycine using the general acylation procedure followed by flash chromatography using heptane with

increasing amounts of EtOAc as eluents to yield **15a** as a colorless oil (77.7%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.29–7.37 (m, 5H, Ph), 5.58 (dd, J = 12.3, 7.2 Hz, 1H, H-2), 5.24 (br s., 1H, NH), 5.09–5.16 (m, 2H, CH_2-Ph), 4.16 (dd, J = 18.3, 6.2 Hz, 1H, H-α), 4.07 (dd, J = 18.1, 4.8 Hz, 1H, H-α), 2.28 (br s., 1H, H_{eq}-3), 1.67–1.78 (m, 3H, H-5, H-4, H_{ax}-3), 1.57–1.66 (m, 3H, H-8, H-7, H-4), 1.34–1.54 (m, 5H, H-8, H-7, H-4a, H-2 H-6), 1.13–1.22 (m, 1H, H-5), 1.17 (s, 3H CH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 208.19 (C-1), 169.41 (C=O), 156.40 (C_{Ph}-1), 136.42 (C_{Ph}-4), 128.65 and 128.28 (C_{Ph}-2 and C_{Ph}-6), 128.22 (C_{Phe}-3 and C_{Phe}-5), 74.65 (C-2), 67.20 (C-α), 48.50 (C-8a), 46.41 (C-4a), 42.78 (C-13), 32.30 (C-3), 32.21 (C-8), 27.52 (C-6), 26.52 (C-4), 26.01 (C-5), 20.56 (C-7), 15.09 (CH_3).

*3.1.5.2. (2S,4aS,8aR)-8a-Methyl-1-oxodecahydronaphthalen-2-yl 2-((benzyloxycarbonyl)- D-alaninate (**15b**).* Compound **15b** was prepared from (2*S*,4a*S*,8a*R*)-hydroxy-8a-methyloctahydronaphthalen-1(*2H*)-one (**14**) and N$^{\alpha}$-Z-D-alanine using the general acylation procedure followed by flash chromatography using heptane with increasing amounts of EtOAc to yield **15b** as a colorless oil (78.0%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.29–7.38 (s, 5H), 5.53 (dd, J = 11.6, 7.5 Hz, 1H), 5.35 (d, J = 6.6 Hz, 1H, NH), 5.18–5.16 (m, 2H), 4.51 (quint, J = 7.1 Hz, 1H), 2.21–2.27 (m, 1H), 1.67–1.78 (m, 3H), 1.56–1.67 (m, 3H), 1.34–1.53 (m, 5H), 1.48 (d, J = 7.3 Hz, 3H, Ala-Me), 1.18 (qt, J = 13.2, 4.0 Hz, 1H), 1.17 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 208.00, 172.02, 155.66, 136.55, 128.65, 128.26, 74.49, 66.98, 50.00, 48.52, 46.39, 32.32, 32.14, 27.55, 26.53, 26.04, 20.59, 19.01 (Ala), 15.10. For assignment see **15a**.

*3.1.5.3. (S)-(2S,4aS,8aR)-8a-Methyl-1-oxodecahydronaphthalen-2-yl 2-((benzyloxycarbonyl)-L-phenylalaninate (**15c**).* Compound **15c** was prepared from (2*S*,4a*S*,8a*R*)-hydroxy-8a-methyloctahydronaphthalen-1(*2H*)-one (**14**) and N$^{\alpha}$-Z-L-phenylalanine using the general acylation procedure followed by flash chromatography using heptane with increasing amounts of EtOAc as eluents to yield **15c** as a colorless oil (73.9%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.21–7.35 (m, 10H), 5.59 (dd, J = 12.3, 7.2 Hz, 1H), 5.10 (d, J = 8.4 Hz, 1H), 5.00–5.08 (m, 2H), 4.70 (td, J = 8.1, 5.5 Hz, 1H, Phe), 3.41 (dd, J = 14.3, 5.1 Hz, 1H, Phe), 3.09 (dd, J = 14.3, 8.1 Hz, 1H, Phe), 2.23–2.32 (m, 1H), 1.56–1.80 (m, 6H), 1.35–1.54 (m, 5H), 1.14–1.24 (m, 1H), 1.19 (s, 3H), ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 208.42, 171.27, 155.95, 136.40, 136.22, 129.59, 128.67, 128.63, 128.25, 128.18, 127.08, 74.42, 67.06, 54.77, 48.59, 46.45, 38.32 (Phe), 32.37, 27.56, 26.59, 26.05, 22.85, 20.62, 15.16. For assignment see **15a**.

*3.1.5.4. (2S,4aS,8aR)-8a-Methyl-1-oxodecahydronaphthalen-2-yl 2-((benzyloxycarbonyl)-D-phenylalaninate (**15d**).* Compound **15d** was prepared from (2*S*,4a*S*,8a*R*)-hydroxy-8a-methyloctahydronaphthalen-1(*2H*)-one (**14**) and N$^{\alpha}$-Z-D-phenylalanine using the general acylation procedure followed by flash chromatography using heptane with increasing amounts of EtOAc as eluents to yield **15d** as a colorless oil (71.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.11–7.39 (m, 10H), 5.51 (dd, J = 11.7, 6.6 Hz, 1H), 5.27 (d, J = 8.1 Hz, 1H), 5.05–5.13 (m, 2H), 4.77 (q, J = 6.8 Hz, 1H), 3.23 (dd, J = 14.1, 5.6 Hz, 1H), 3.13 (dd, J = 14.1, 6.6 Hz, 1H), 2.13–2.22 (m, 1H), 1.32–1.78 (m, 11H), 1.11–1.24 (m, 1H), 1.15 (s, 3H). For assignment see **15a**.

*3.1.5.5. (2S,4aS,8aR)-8a-Methyl-1-oxodecahydronaphthalen-2-yl 2-((benzyloxycarbonyl)-L-tryptophanate (**15e**).* Compound **15e** was prepared from (2*S*,4a*S*,8a*R*)-hydroxy-8a-methyloctahydronaphthalen-1(*2H*)-one (**14**) and N$^{\alpha}$-Z-L-tryptophan using the general acylation procedure followed by flash chromatography using heptane with increasing amounts of EtOAc as eluents to yield **15e** as a white powder (24.5%). ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.04 (br. s., 1H, NH), 7.59 (d, J = 8.1 Hz, 1H, H_{In}-4), 7.27–7.37 (m, 6H, H_{In}-7), 7.18 (t, J = 7.3 Hz, 1H, H_{In}-2), 7.08 (t, J = 7.7 Hz, 1H, H_{In}-6), 5.58 (dd, J = 11.9, 7.2 Hz, 1H), 5.18 (d, J = 8.4 Hz, 1H), 5.07 (d, J = 12.1 Hz, 1H), 5.03 (t, J = 12.1 Hz, 1H), 4.78 (dt, J = 7.7, 5.9 Hz, 1H), 3.54 (dd, J = 15.0, 5.1 Hz, 1H), 3.35 (dd, J = 15.0, 6.2 Hz, 1H), 2.21–2.27 (m, 1H), 1.55–1.80 (m, 6H), 1.35–1.53 (m, 4H), 1.15–1.33 (m, 2H), 1.19 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 208.70, 171.45, 156.09, 136.49, 136.22, 128.59, 128.20, 123.81, 122.19, 119.77, 118.81, 111.26, 110.01, 74.37, 66.97, 54.63, 48.62, 46.47, 32.42, 27.82, 27.56, 26.61, 26.06, 22.84, 20.63, 15.20. For assignment see **15a**.

*3.1.6. General procedure for oxazinonization of **15***

The general procedure for oxazinonization of **15** (200 mg) to give compounds **16** is the same as used for preparation of the 2-hydroxy-pinan-3-one derived iminolactones **7**.

*3.1.6.1. (4aS,6aS,10aR)-10a-Methyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**16a**).* Compound **16a** was prepared from **15a** by using the general hydrogenation procedure followed by flash chromatography using heptane with increasing amounts of EtOAc as eluents to yield an oil which precipitated from EtOAc-heptane to give **16a** as a colorless amorphous powder (49.0 mg, 25%). $[a]_D^{25}$ = 15.2° (*c* 0.18). ^{1}H NMR (600 MHz, CD_3CN) δ ppm 5.21 (dddd, J = 12.2, 6.3, 3.9, 2.2 Hz, 1H, H-4a), 4.29 (dd, J = 21.7, 2.1 Hz, 1H, H-2), 4.10 (dd, J = 21.7, 4.0 Hz, 1H, H-2′), 2.29 (m, J = 3.7 Hz, 1H, H-5), 1.40–1.75 (m, 9H, H-5′, H-6, H-7, 2H-8, 2H-9, 2H-10), 1.32–1.39 (m, 2H H-7, H-6a), 1.17–1.26 (m, 1H, H-6′), 1.04 (s, 3H, CH_3). ^{13}C NMR (151 MHz, CD_3CN) δ ppm 173.75 (C-10b), 166.92 (C-3), 77.65 (C-4a), 49.81 (C-2), 46.05 (C-6a), 44.46 (C-10a), 35.47 (C-10), 34.94 (C-5), 28.49 (C-7), 27.07 (C-6), 26.93 (C-8), 21.75 (C-9), 16.86 (CH_3). HRMS *m/z* 240.1622 $[M + H_3O]^+$ (240.1594, calc. for $C_{13}H_{20}NO_2^+$).

*3.1.6.2. (2S,4aS,6aS,10aR)-2,10a-Dimethyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**16b**).* Compound **16b** was prepared from 15b by using the general hydrogenation procedure to give **16b** (97.3%) as a colorless oil. $[a]_D^{25}$ +41.8° (c 0.50). ^{1}H NMR (600 MHz, CD_3CN) δ ppm 5.23 (ddd, J = 11.8, 6.7, 1.7 Hz, 1H, H-4a), 4.29 (qd, J = 7.4, 1.8 Hz, 1H, H-2), 2.26–2.31 (m, 1H, H_{eq}-5), 1.74–1.78 (m, 1H, H-10), 1.67–1.72 (m, 1H, H-8), 1.31–1.67 (m, 9H, H-5_{ax}, H-6, H-6a, 2H-7, H-8, 2H-9, H-10), 1.34 (d, J = 7.4 Hz, 3H, Ala-Me), 1.14–1.26 (m, 1H, H-6), 1.02 (s, 3H, CH_3). ^{13}C NMR (151 MHz, CD_3CN) δ ppm 172.68 (C-10b), 170.26 (C-3), 77.17 (C-4a), 54.43 (C-2), 45.91 (C-6a), 44.23 (C-10a), 35.49 (C-10), 34.96 (C-5), 28.55 (C-7), 27.00 (C-6), 26.94 (C-8), 21.77 (C-9), 19.96 (C_{Ala}-β), 17.03 (CH_3). HRMS *m/z* 236.1651 $[M+H]^+$ (236.1645, calc. for $C_{14}H_{22}NO_2^+$).

*3.1.6.3. (2S,4aS,6aS,10aR)-2-Benzyl-10a-methyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**16c**).* Compound **16c** was prepared from 15c using the general hydrogenation procedure to give **16c** in quantitative yield as a colorless oil. $[a]_D^{25}$ = 39.2° (c 0.26). ^{1}H NMR (600 MHz, CD_3CN) δ ppm 7.25–7.32 (m, 2H, H_{Phe}-2 and 6), 7.20–7.23 (m, 1H, H_{Ph}-4), 7.11–7.15 (m, 2H, H_{Ph}-3 and 5), 4.99 (ddd, J = 12.6, 6.3, 3.5 Hz, 1H, H-4a), 4.47 (td, J = 4.9, 3.5 Hz, 1H, H-2), 3.31 (dd, J = 13.2, 5.1 Hz, 1H, CH_2-Ph), 3.22 (dd, J = 13.2, 4.8 Hz, 1H, CH_2-Ph), 1.83 (dddd, J = 12.1, 6.4, 3.8, 2.8 Hz, 1H H-5_{eq}), 1.59–1.71 (m, 4H, H-8, 2H-10, H-9), 1.43–1.53 (m, 1H, H-9′), 1.38 (tdd, J = 13.9, 13.9, 12.5, 3.5 Hz, 1H, H-6), 1.16–1.34 (m, 4H, H_2-7, H-8, H-6′), 1.05–1.11 (m, 1H, H-6a), 0.98 (s, 3H, CH_3), 0.23 (dtd, J = 13.6, 12.1, 12.1, 4.8 Hz, 1H, H_{ax}-5). ^{13}C NMR (151 MHz, CD_3CN) δ ppm 172.85 (C-10b), 168.60 (C-3), 137.78 (C_{Ph}-1), 131.50 (C_{Ph}-2 and 6), 128.94 (C_{Ph}-3 and 5), 127.74 (C_{Ph}-4), 77.99 (C-4a), 59.45 (C-2), 45.96 (C-6a), 44.39 (C-10a), 40.52 (CH_2-Ph), 35.44 (C-10), 34.91 (C-5), 28.46 (C-7), 27.10 (C-6), 27.02 (C-8), 21.81 (C-9), 16.52 (CH_3). HRMS *m/z* 312.1974 $[M+H]^+$ (312.1958, calc. for $C_{20}H_{26}NO_2^+$).

*3.1.6.4. (6aS,10aR)-2-Benzyl-10a-methyl-5,6,6a,7,8,9,10,10a-octahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**17**).* When compound **16c** was adsorbed on celite and eluted as described for **15c** degradation was observed to give compound **17** and **18**. Compound **17**: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.36 (d, J = 7.7 Hz, 2H, H_{Phe}-2 and 6), 7.29 (t, J = 7.5 Hz, 2H, H_{Phe}-3 and 5), 7.22 (t, J = 7.7 Hz, 1H, H_{Phe}-4), 4.02 (dd, J = 18.3, 13.9 Hz, 2H, CH_2-Phe), 2.59 (ddd, J = 18.7, 11.0, 7.7 Hz, 1H, H-5), 2.45 (dd, J = 18.7, 6.6 Hz, 1H, H-5), 2.28 (d, J = 13.2 Hz, 1H, H_{eq}-10), 1.78 (d, J = 12.5 Hz, 1H, H-8), 1.51–1.68 (m, 4H, H-6 and H-9), 1.41–1.47 (m, 2H, H-6a, H-7), 1.37 (qd, J = 12.8, 3.3 Hz, 1H, H-7), 1.29 (qt, J = 12.8, 4.4 Hz, 2H, H-8), 1.14 (td, J = 13.3, 4.2 Hz, 1H, H_{ax}-10), 1.06 (s, 3H, H-11). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm 154.89 (C-3), 152.75 (C-2) 147.83 (C-4a), 136.62 (C_{Phe}-1 and C-10b), 129.59 (C_{Phe}-2 and 6) 128.55 (C_{Phe}-3 and 5) 126.82 (C_{Phe}-4), 43.07 (C-6a), 40.00 (CH_2-Phe), 37.07 (C-10a), 35.25 (C-10), 28.00 (C-7), 26.80 (C-8), 26.60 (C-5), 24.34 (C-6), 21.46 (C-9), 18.71 (C-11). HRMS *m/z* 310.1821 $[M+H]^+$ (310.1802, calc. for $C_{20}H_{24}NO_2^+$).

*3.1.6.5. (4aS,8aR)-2-Hydroxy-8a-methyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one (**18**).* When compound **16c** was adsorbed on celite and eluted as describedfor **15c** degradation was observed to give **17** and **18**. Compound **18**: ^{1}H NMR (600 MHz, CD_3CN) δ ppm 6.15 (s, 1H, OH), 5.94–5.96 (m, 1H, H-3), 2.10–2.15 (m, 2H, H-4, H-5), 1.83–1.91 (m, 2H, H-8, H-4a), 1.66–1.71 (m, 1H, H-6), 1.58–1.63 (m, 1H, H-7), 1.41–1.51 (m, 2H, H-4, H-5, H-7), 1.29 (td, *J* = 13.7, 3.9 Hz, 1H, H-8), 1.17–1.26 (m, 1H, H-6), 1.03 (s, 3H, H-9). ^{13}C NMR (151 MHz, CD_3CN) δ ppm 202.52 (C-1), 146.16 (C-2), 116.59 (C-3), 44.74 (C-8a), 42.81 (C-4a), 33.07 (C-8), 28.55 (C-4), 28.37 (C-5), 26.43 (C-6), 21.88 (C-7), 14.88 (CH_3). HRMS *m/z* 163.1117 $[M + H - H_2O]^+$ (163.1069, calc. for $C_{11}H_{17}O_2^+$).

*3.1.6.6. (2R,4aS,6aS,10aR)-2-Benzyl-10a-methyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**16d**).* Compound **16d** was prepared from **15d** by using the general hydrogenation procedure to give **16d** (quant.) as a colorless oil. $[a]_D^{25}$ = 53.7° (c 0.34). ^{1}H NMR (400 MHz, CD_3CN) δ ppm 7.16–7.35 (m, 3H, H_{Ph}-2, 6 and 4), 7.08–7.13 (m, 2H, H_{Ph}-3 and 5), 4.61 (td, *J* = 5.3, 2.0 Hz, 1H, H-2), 4.41 (ddd, *J* = 11.7, 6.7, 1.8 Hz, 1H, H_{ax}-4a), 3.22 (dd, *J* = 13.4, 5.6 Hz, 1H, CH_2-Ph), 3.11 (dd, *J* = 13.4, 4.9 Hz, 1H, CH_2-Ph), 2.09–2.16 (m, 1H, H_{eq}-5), 1.75–1.81 (m, 1H, H-10_{ax}), 1.63–1.70 (m, 1H, H-8), 1.56–1.62 (m, 1H, H-9), 1.33–1.55 (m, 6H, H-5, H-6, H-7, H-8, H-9, H_{eq}-10), 1.25–1.33 (m, 2H, H_{ax}-6a, H-7), 1.12–1.20 (m, 1H, H-6) 0.83 (s, 3H, H-11). ^{13}C NMR (101 MHz, CD_3CN) δ ppm 173.42 (C-10b), 168.84 (C-3), 137.53 (C_{Ph}-1), 131.02 (C_{Ph}-2 and 6), 129.15 (C_{Ph}-3 and 5), 127.80 (C_{Ph}-4), 77.25 (C-4a), 59.77 (C-2), 45.91 (C-6a), 44.32 (C-10a), 40.45 (CH_2-Ph), 35.73 (C-10), 35.19 (C-5), 28.43 (C-7), 26.93 (C-6), 26.90 (C-8), 21.76 (C-9), 16.92 (C-11). HRMS *m/z* 312.1973 $[M+H]^+$ (312.1958, calc. for $C_{20}H_{26}NO_2^+$).

*3.1.6.7. (2S,4aS,6aS,10aR)-2-((1H-Indol-3-yl)methyl)-10a-methyl-2,4a,5,6,6a,7,8,9,10,10a-decahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**16e**).* Compound **16e** was prepared from 15e by using the general hydrogenation procedure to give 16e in quantitative yield as a colorless powder. $[a]_D^{25}$ = −25.5° (c 0.24). ^{1}H NMR (400 MHz, CD_3CN) δ ppm 9.14 (br s., 1H, NH), 7.56 (d, J = 7.8 Hz, 1H, H_{In}-4), 7.34 (dt, J = 7.8, 1.0 Hz, 1H, H_{In}-7), 7.09 (ddd, J = 7.8, 7.1, 1.5 Hz, 1H, H_{Im}-6), 7.03 (ddd, J = 7.8, 7.1, 1.2 Hz, 1H, H_{In}-5), 6.97 (d, J = 2.4 Hz, 1H, H_{In}-2), 4.92 (ddd, J = 12.5, 6.3, 3.4 Hz, 1H, H_{ax}-4a), 4.48 (td, J = 4.4, 3.4 Hz, 1H, H-2), 3.48 (ddd, J = 14.2, 4.5, 0.6 Hz, 1H, CH_2–In), 3.38 (ddd, J = 14.2, 4.4, 0.5 Hz, 1H, CH_2–In), 1.65–1.79 (m, 2H, H_{eq}-5, H-10), 1.52–1.64 (m, 3H, H-8, H-9, H-10), 1.41–1.49 (m, 1H, H-9), 1.26 (qd, J = 13.4, 3.9 Hz, 1H, H-6) 1.09–1.21 (m, 3H, 2 H-7, H-8) 0.94–0.99 (m, 1H, H-6), 0.93 (d, J = 0.7 Hz, 3H, H-11), 0.50 (dddd, J = 15.4, 6.8, 5.7, 3.3 Hz, 1H, H_{ax}-6a), −0.03 (dtd, J = 13.2, 12.2, 12.2, 4.9 Hz, 1H, H_{ax}-5). ^{13}C NMR (151 MHz, CD_3CN) δ ppm 172.41 (C-10b), 169.39 (C-3), 136.89 (C_{In}-7a), 129.10 (C_{In}-3a), 125.08 (C_{In}-2), 122.32 (C_{In}-6), 120.75 (C_{In}-4), 119.77 (C_{In}-5), 111.97 (C_{In}-7), 110.92 (C_{In}-3), 77.88 (C-4a), 60.03 (C-2), 45.14 (C-6a), 44.20 (C-10a), 34.94 (C-5), 34.82 (C-10), 30.22 (CH_2–In), 28.43 (C-7), 27.15 (C-6), 26.72 (C-8), 21.82 (C-9), 16.38 (C-11). HRMS *m/z* 351.2079 $[M+H]^+$ (351.2067, calc. for $C_{22}H_{27}N_2O_2^+$).

*3.1.7. 2-Bromo-3,4-dihydronaphthalen-1(2H)-one (**19**)*

Freshly recrystallized N-bromosuccinimide (0.91 g, 5.1 mmol) was added to a solution of *p*-toluenesulfonic acid (1.53 g, 8.1 mmol) and 1-tetralone (0.742 g, 5.1 mmol) in acetonitrile (60 mL), and then the solution was refluxed for 22 h. After concentration, the residue was dissolved in DCM and washed with water. The organic phase was concentrated and **19** was isolated from the residue by flash chromatography using heptane-toluene (1:1 with increasing amounts of toluene) as eluent to give **19** (0.941 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.10 (dd, *J* = 7.8, 1.5 Hz, 1H, H-8), 7.53 (td, *J* = 7.6, 1.5 Hz, 1H, H-6), 7.36 (ddd, *J* = 7.8, 7.6, 1.0 Hz, 1H, H-7), 7.29 (dd, *J* = 7.6, 1.0 Hz, 1H, H-5), 4.74 (t, *J* = 4.1 Hz, 1H, H-2), 3.33 (ddd, *J* = 17.0, 10.0, 5.0 Hz, 1H, H-3), 2.93 (dt, *J* = 17.0, 4.4 Hz, H-3′), 2.41–2.60 (m, 2H, H-4).

*3.1.7.1. 1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl (tert-butoxycarbonyl)-L-phenylalaninate (**20a**).* A solution of **19** (0.566 g, 2.5 mmol), Boc-protected L-Phe (798 mg, 3.0 mmol) and diisopropylethylamine (456 mg, 3.5 mmol) in MeCN (13 mL) was refluxed for 23 h. After concentration the residue was dissolved in DCM and washed with water. The organic phase was concentrated and the residue was purified by flash chromatography using heptane-EtOAc (1:7 with increasing amounts of EtOAc) to give the epimer mixture **20a** (0.55 g, 54%) with the two epimers in the ratio 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.05 (dd, *J* = 7.4, 1.2 Hz, 1H, H-8), 8.02 (dd, *J* = 7.4, 1.4 Hz, 1H H-8′), 7.53 (td, *J* = 7.4, 1.4 Hz, 1H, H-6), 7.52 (td, *J* = 7.4, 1.4 Hz, 2H H-7 and H-6′), 7.21 − 7-39 (m, 14H), 5.62 (dd, *J* = 13.2, 5.3 Hz, 1H, H-2), 5.53 (dd, *J* = 12.0, 6.2, 1H, H-2′), 5.08 (d, *J* = 8.2 Hz, 1H, NH), 4.95 (d, *J* = 8.8 Hz, 1H, NH), 4.65–4.80 (m, 2H, H-α and H-α′), 3.39 (dd, *J* = 14.1, 5.2 Hz, 1H, H-β), 3.02–3.31 (m, 7H), 2.19–2.48 (m, 4H), 1.42 (s, 9H, $(CH_3)_3$), 1.40 (s, 9H, $(CH_3)_3$).

*3.1.7.2. 1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl (tert-butoxycarbonyl)-L-tryptophanate (**20b**).* A solution of **19** (366 mg, 1.6 mmol), Boc-protected L-Trp (612 mg, 2.0 mmol) and diisopropylethylamine (305 mg, 1.4 mmol) in MeCN (8 mL) was refluxed for 23 h. After concentration the residue was dissolved in DCM and washed with water. The organic phase was concentrated and the residue was purified by flash chromatography using heptane-EtOAc (1:7 with increasing amounts of EtOAc) as elunt to give the epimer mixture **20b** (0.48 g, 66%) with the two epimers in the ratio 1:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.12 (br.s., 2H, NH) 8.05 (dd, *J* = 7.9, 1.0 Hz, 1H, H-8), 8.01 (dd, *J* = 7.9, 1.0 Hz, 1H, H-8′), 7.65 (d, *J* = 7.6 Hz, 1H, H-6). 7.63 (d, *J* = 7.6 Hz, H-6′), 7 53 (td, *J* = 7.4, 1.0 Hz, 1H, H-7), 7.51 (td, *J* = 7.4, 1.4 Hz, 2H H-6 and H-6′), 7.09 − 7-45 (m, 12H), 5.62 (dd, *J* = 12.8, 5.8 Hz, 1H, H-2), 5.48 (dd, *J* = 12.0, 6.4, 1H, H-2′), 5.17 (d, *J* = 8.0 Hz, 1H, NH), 5.05 (d, *J* = 8.0 Hz, 1H, NH), 4.73–4.84 (m, 2H, H-α and H-α′), 3.55 (dd, *J* = 15.0, 5.2 Hz, 1H, H-β), 3.31–3.49 (m, 3H), 2.97–3.26 (m, 4H), 2.13–2.42 (m, 4H), 1.49 (s, 9H, $(CH_3)_3$), 1.41 (s, 9H, $(CH_3)_3$).

*3.1.7.3. (2S,4aR)-2-benzyl-2,4a,5,6-tetrahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**22a**) and (2S,4aS)-2-benzyl-2,4a,5,6-tetrahydro-3H-naphtho[2,1-b][1,4]oxazin-3-one (**21a**).* TFA (3 mL) was added to a solution of **20a** (520 mg, 1.3 mmol) in DCM (3 mL), and then the mixture was stirred for 30 min. After concentration the residue was dissolved in DCM and the solution washed with saturated aq.

Na_2CO_3. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue (391 mg) was purified by HPLC (20 ml/min, gradient: 40% MeCN 60% water to 80% MeCN over 30 min) afforded **21a** (154 mg, 20%) as a colorless powder and **22a** (150 mg, 20%) as a colorless powder. **22a** $[a]_D^{25} = -10.5°$ (c 0.17). ^{1}H NMR (300 MHz, CD_3CN) δ ppm 8.11 (dd, J = 7.9, 1.3 Hz, 1H, H-10), 7.41–7.46 (m, 2H, H_{Ph}-2 and 6), 7.19–7.40 (m, 5H, H-7-H-10, H_{Ph}- 3 and 5, H_{Ph}-4), 5.10 (ddd, J = 12.2, 5.9, 3.0 Hz, 1H, H-4a), 4.32 (ddd, J = 8.2, 4.5, 3.2, 1H, H-2), 3.53 (dd, J = 14.1, 4.5 Hz, 1H, CH_2-Ph), 3.24 (dd, J = 14.1, 8.2 Hz, 1H, CH'_2-Ph), 2.93 (ddd, J = 16.5, 5.0, 3.5 Hz, 1H, H-6), 2.88 (ddd, J = 16.5, 12.6, 3.8 Hz, 1H, H-6′), 2.47 (dddd, J = 12.3, 5.9, 3.8, 3.5 Hz, 1H, H-5), 1.90 (dddd, J = 12.6, 12.3, 12.2, 5.2, Hz, 1H, H-5′). ^{13}C NMR (75 MHz, CD_3CN) δ ppm 171.3 (C-3), 165.2 (C-1), 141.4 (C-6a), 140.0 (C_{Ph}-1), 132.3 (C-8), 131.6 (C-10a), 131.0 (C_{Ph}-2 and 6), 129.5 (C-7), 129.0 (C_{Ph}-3 and 5), 127.8 (C_{Ph}-4), 127.2 (C-9), 126.0 (C-10), 76.0 (C-4a), 62.2 (C-2), 38.3 (C-Ph), 29.3 (C-5), 27.2 (C-6). HRMS *m/z* 292.1325 $[M+H]^+$ (292.1332, calc. for $C_{19}H_{19}NO_2^+$).

22a $[a]_D^{25} = -16.0°$ (c 0.09). ^{1}H NMR (300 MHz, CD_3CN) δ ppm 8.18 (dd, J = 8.0, 1.2 Hz, 1H, H-10), 7.42 (td, J = 7.4, 1.3, 1H, H-8), 7.32 (ddd, J = 8.0, 7.4, 1.1, 1H, H-9), 7.25–7.19 (m, 6H, H-7, Ph), 4.96 (ddd, J = 12.2, 5.9, 3.0 Hz, 1H, H-2), 4.07 (ddd, J = 13.0, 5.2, 1.4, 1H, H-4a), 3.28 (dd, J = 13.5, 6.2 Hz, 1H, CH_2-Ph), 3.16 (dd, J = 13.5, 5.5 Hz, 1H, CH_2-Ph), 2.93 (ddd, J = 17.0, 5.0, 2.6 Hz, 1H, H-6), 2.79 (ddd, J = 17.0, 13.0, 4.4 Hz, 1H, H-6′), 2.25 (dddd, J = 12.2, 5.2, 4.4, 2.6 Hz, 1H, H-5), 1.90 (tdd, J = 13.0, 12.2, 5.0, Hz, 1H, H-5′). ^{13}C NMR (75 MHz, CD_3CN) δ ppm 170.0 (C-3), 163.0 (C-10b), 137.5 (C_{Ph}-1), 132.3 (C-8), 131.6 (C-10a), 130.8 (C_{Ph}-2 and 6), 129.6 (C-7), 129.3. (C_{Ph}-3 and 5), 128.0 (C_{Ph}-4), 127.7 (C-9), 126.4 (C-10), 76.8 (C-4a), 62.5 (C-2), 39.5 (CH_2-Ph), 30.4 (C-5), 27.8 (C-6). HRMS *m/z* 292.1328 $[M+H]^+$ (292.1332, calc. for $C_{19}H_{19}NO_2^+$).

*3.1.7.4. (2S,4aR)-2-[(1H-indol-3-yl)methyl]-5,6-dihydro-2H-naphto [2,1-b][1,4]oxazin-3(4aH)-one (**22b**) and (2S,4aS)-2-[(1H-indol-3-yl) methyl]-5,6-dihydro-2H-naphto[2,1-b][1,4]oxazin-3(4aH)-one (**21b**)..* TFA (2.3 mL) was added to a solution of **20b** (482 mg, 1.1 mmol) in DCM (2.3 mL) and stirred for 30 min. After concentration the residue was dissolved in DCM and the solution washed with a saturated aqueous solution of Na_2CO_3. The organic phase was dried ($MgSO_4$) and concentrated in vacuum. Preparative HPLC of the residue (355 mg) (20 ml/min, gradient: 40% MeCN 60% water to 80% MeCN over 30 min) afforded **21b** (54 mg, 15%) as a colorless powder and **22b** (72 mg, 20%)) as a colorless powder.

22b $[a]_D^{25} = +8°$ (c 0.09). ^{1}H NMR (400 MHz, CD_3CN) δ ppm 9.16 (br.s., 1H, NH), 8.22 (dd, J = 7.9, 1.2 Hz, 1H, H-10), 7.49 (dd, J = 8.1, 0.5 Hz, 1H, H_{In}-4) 7.39 (ddd, J = 7.6, 7.3, 1.2 Hz, 1H, H-8), 7.34 (dd, J = 8.2, 0.8 Hz, 1H, H_{In}-7), 7.32 (ddd, J = 7.9, 7.3, 0.6, 1H, H-9), 7.17 (dd, J = 7.6, 0.5 Hz, 1H, H-7), 7.05 (ddd, J = 8.0, 7.2, 0.6, 1H, H_{In}-6), 6.97 (d, J = 2.3, 1H, H_{In}-2), 4.99 (ddd, J = 5.5, 5.1, 1.4 Hz, 1H, H-2), 3.93 (ddd, J = 13.1, 5.1, 1.2, 1H, H-4a), 3.50 (dd, J = 14.5, 5.5 Hz, 1H, CH_2–In), 3.32 (dd, J = 14.5, 5.1 Hz, 1H, CH_2–In), 2.85 (ddd, J = 17.1, 4.5, 2.5 Hz, 1H, H-6), 2.64 (ddd, J = 17.1, 13.2, 4.4 Hz, 1H, H-6′), 2.14 (dddd, J = 12.4, 5.1, 4.4, 2.5 Hz, 1H, H-5), 1.84 (dddd, J = 13.2, 13.1, 12.4, 4.6, Hz, 1H, H-5′). ^{13}C NMR (100 MHz, CD_3CN) δ ppm 170.7 (C-3), 162.6 (C-10b), 140.7 (C-6a), 137.1 (C_{In}–7a), 132.1 (C-8), 131.6 (C-10a), 129.5 (C-7), 127.5 (C-9), 126.7 (C-10), 128.2 (C_{In}-3a), 125.2 (C_{In}-2), 122.5 (C_{In}-6), 119.9 (C_{In}-4), 119.8 (C_{In}-5), 112.2 (C_{In}-7), 110.5 (C_{In}-3), 76.8 (C-4a), 62.4 (C-2), 30.4 (C-5), 29.4 (C–In), 27.7 (C-6). HRMS *m/z* 331.1431 $[M+H]^+$ (331.1441, calc. for $C_{21}H_{19}N_2O_2^+$).

21b $[a]_D^{25} = -99°$ (c 0.09). ^{1}H NMR (400 MHz, CD_3CN) δ ppm 9.10 (br.s, 1H, NH), 8.12 (dd, J = 7.8, 1.2 Hz, 1H, H-10), 7.75 (dddd, J = 7.9, 1.2, 0.8, 0.6 Hz, 1H, H_{In}-4) 7.42–7.40 (overlaid, 1H, H-8), 7.34–7.31 (overlaid, 1H, H_{In}-7), 7.23 (dd, J = 7.8, 0.5 Hz, 1H, H-7), 7.22 (d, J = 2.4, 1H, H_{In}-2), 7.11 (ddd, J = 8.0, 7.0, 1.2, 1H, H_{In}-6), 5.08 (ddd, J = 12.2, 5.8, 3.1 Hz, 1H, H-4a), 4.33 (ddd, J = 7.5, 4.4, 3.1 Hz, 1H, H-2), 3.64 (ddd, J = 14.7, 4.4, 0.9 Hz, 1H, CH_2In), 3.40 (ddd, J = 14.7, 7.5, 0.7 Hz, 1H, CH_2In), 2.96–2.85 (overlaid, 2H, H-6), 2.44 (ddt, J = 12.3, 5.9, 3.8, 1H, H-5), 1.84 (dddd, J = 12.4, 12.2, 12.3, 5.5, Hz, 1H, H-5′). ^{13}C NMR (100 MHz, CD_3CN) δ ppm 171.5 (C-3), 165.0 (C-10b), 141.3 (C-6a), 137.1 (C_{In}-7a), 132.1 (C-8), 131.7 (C-10a), 129.5 (C-7), 127.7 (C-9), 126.1 (C-10), 129.1 (C_{In}-3a), 124.8 (C_{In}-2), 122.2 (C_{In}-6), 120.2 (C_{In}-4), 119.6 (C_{In}-5), 112.9 (C_{In}-3), 112.1 (C_{In}-7), 76.0 (C-4a), 62.1 (C-2), 29.4 (C-5), 28.1. (CH_2–In), 27.3 (C-6). HRMS *m/z* 331.1441 $[M+H]^+$ (331.1441, calc. for $C_{21}H_{19}N_2O_2^+$).

3.2. X-ray crystallography

Single crystals of **7SLc** suitable for X-ray diffraction studies were grown from a solution in ethyl acetate and heptane. Data were collected (T = 123(1)K), using graphite-monochromated MoKα radiation (λ = 0.71073 Å) on a Bruker D8 Venture diffractometer. Data collection and cell refinement were performed using the Bruker Apex2 Suite software [25]. Data reduction using SAINT [26] and multi-scan correction for absorption using SADABS-2012/1 [27] were performed within the Apex2 Suite. The crystal data, data collection and the refinement data are given in Table S1 (Supplementary data).

3.3. Structure solution and refinement

Positions of all non-hydrogen atoms were found by direct methods (SHELXS97) [28]. Full-matrix least-squares refinements (SHELXL97) [28] were performed on F^2, minimizing $\Sigma w(F_o^2 - kF_c^2)^2$. The position of hydrogen atoms were included in calculated position with fixed isotropic displacement parameters ($U_{iso} = 1.2U_{eq}$ for CH, and CH_2 and $U_{iso} = 1.5U_{eq}$ for CH_3), except for the hydrogen atoms bonded to chiral CH or NH. They were refined with fixed isotropic displacement parameters ($U_{iso} = 1.2U_{eq}$). Refinement (263 parameters, 4585 unique reflections) converged at $R_F = 0.0372$, $wR_F^2 = 0.0766$ [4015 reflections with Fo > $4\sigma(F_o)$; $w^{-1} = (\sigma^2(F_o^2) + (0.0300P)^2 + 0.1854P)$, where $P = (F_o^2 + 2F_c^2)/3$; $S = 1.044$]. The residual electron density varied between −0.18 and 0.22 e Å^{-3}. Non-centrosymmetric space group is assigned, but the absolute configuration cannot be determined (Flack = 0.0(9) [29]). However the chirality for three chiral centers is known, and the fourth center is assigned relative to those. Complex scattering factors for neutral atoms were taken from International Tables for Crystallography as incorporated in SHELXL97 [28,30]. Crystallographic data for compound **7SLc** have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 1404090). Copies of the data can be obtained, free of charge, on application to the director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.4. Anti-proliferative assay

Three different cancer cell lines, murine leukemic cell line (EL4), human breast cancer cell line (MCF7), and human prostate cancer cell line (PC3) purchased from National Cancer Institute, were tested by a standard high-flux anticancer-drug screening method [15]. Briefly, cancer cells were incubated with the test compound in different concentrations at 37 °C for 48 h. Cultures were fixed with trichloroacetic acid, then stained with sulforhodamine B and read at 490 nm by ELISA reader.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.02.037.

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