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Asymmetric synthesis of *tert*-butyl ((1*R*,4a*R*,8*R*,8a*R*)-1-hydroxyoctahydro-1*H*-isochromen-8-yl)carbamate

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Dedicated to the memory of Dr. Howard Flack

ABSTRACT

The asymmetric synthesis of methyl (*E*)-4-((1*R*,2*S*,3*R*)-3-amino-2-((*E*)-2-methoxycarbonyl-eten-1-yl)cyclohexyl)but-2-enoate **14** has been achieved from dimethyl (2*E*,7*E*)-nona-2,7-dienedioate **2**. A key step is the asymmetric synthesis of 1-hydroxyoctahydro-1*H*-isochromene derivative **5** whose X-ray analysis corroborated the stereochemistry of the new stereocenters. The asymmetric synthesis of the isochromenyl acetate derivative **11** shows the potential of this methodology for fused cyclohexanic system heterocyclic synthesis.

1. Introduction

The strategies for building stereoselectively substituted cyclohexanic ring are very powerful synthetic tools as they are incorporated in naturally occurring products. Representative examples are: morphine[1] with a cyclohexanic ring *trans,trans*-trisubstituted, luciduline[2] *cis,cis*-trisubstituted and with a *cis*-decahydroquinoline skeleton pumiliotoxin C.[3] Because of its structure, featuring several stereogenic centers (Fig. 1), an impressive effort has been devoted to its asymmetric synthesis and nowadays we have developed a methodology towards the synthesis of morphine analogues in view to search for structure activity relationship (SAR).[4]

Davies et al. have illustrated the scope, limitations and synthetic applications of the conjugate addition of enantiomerically pure lithium amides as homochiral ammonia equivalents.[5] We have demonstrated the use of chiral lithium (α-methylbenzyl)benzylamide (*R*)- or (*S*)-**1** to initiate the asymmetric conjugate addition cyclisation of nona-2,7-diendioate (Scheme 1) to generate chiral cyclohexane derivatives **3**,[6] and applied it to the synthesis of (1*R*,5*R*,9*R*)-2-azabicyclo[3.3.1]nonane-9-carboxylic acid (morphanic acid), with a morphan scaffold, which was used in the synthesis of a new class of opioid receptor ligands.[4]

Elimination of the chiral auxiliary gave (*R*)-methyl cyclohex-1-enecarboxylate, which has been used in the synthesis of pumiliotoxin C.[6a,7] Since cyclohexane can incorporate the amine of the chiral auxiliary, which is used in this methodology or can be removed as detailed above, it gives greater versatility to the above procedure.

Herein, we have focused on the potential of domino reactions initiated by the Michael addition of chiral lithium amide (*R*)- or (*S*)-*N*-benzyl-*N*-α-methylbenzylamide (*R*)- or (*S*)-**1** to (2*E*,7*E*)-nonadiendioate **2** to provide stereoselectively the corresponding cyclohexane derivative **3**, that is a powerfull tool in the synthesis of heterocyclic derivatives by transformation of the side chains and it is used in the synthesis of a diester incorporating a cyclohexanic ring in its structure.

2. Results and discussion

With the amino-cyclohexane derivative **3** in hand[6] (Scheme 1) and given the large steric volume represented by the benzyl groups in the N atom and taking into account the nucleophilicity of the amine, we decided to synthesize carbamate **4** by hydrogenolysis of **3** in the presence of Boc anhydride.[8] This provided **4** in 90% yield in a single step, the reduction of which with DIBALH was performed as shown in Scheme 2 and with the results shown in Table 1.

When using a DIBALH ratio of 1.2 (entry 1), reduction products, lactols **5** and **6** and a large amount of starting material (50%) were separated from the reaction mixture. Using a ratio of 4 mmol per mmol (entry 3) the lactols were obtained in 58% in a 3:1 ratio, but 38% of the diol **7** is obtained, which nevertheless is readily available by reduction with LAH (77%). Using an amount of 3.2 mmol per mmol in addition to the diol (25%), 57% of lactols are obtained in a 1:1 ratio. This implies a non-chemoselective

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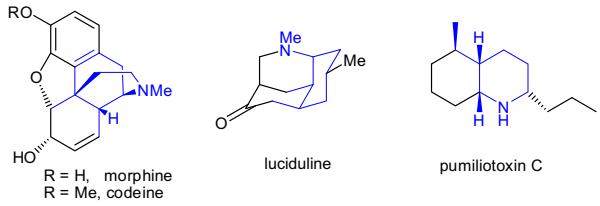


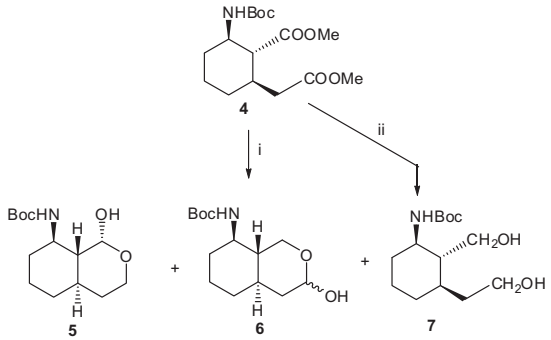
Figure 1. Representative aminocyclohexanic structures.

reduction of each of the esters to the corresponding alcohol. When the remaining ester was reduced to the aldehyde, it was stabilized as a lactol, either 1-hydroxyperhydroisochromene **5** or 3-hydroxyperhydroisochromene **6**, which have two fused six membered rings and possess the functionality required for homologation.

Compound **5**, with an α-hydroxyl group at C-1, was obtained by chromatography; its ^{1}H NMR showed relevant signals at δ (ppm): 3.43 (1H, cd, J = 8.3 and 2.5 Hz (1H, broad s, OH), 4.64 (1H, dd, J = 11.2 and 3.9 Hz, H-3eq), 4.39 (1H, td, J = 11.2 and 2.5 Hz, H-3a), 5.12 (1H, brs, H-1). The coupling constants allow the assignment of the axial and equatorial arrangement of some of the hydrogens. The ^{1}H/^{1}H (COSY) and heteronuclear ^{1}H/^{13}C HMQC and HMBC two-dimensional correlation experiments, allows the determination of the structure as well as the assignment of all of the spectroscopic data. The connectivity of C-1 with H-8a fixes the hydroxyl position. The relative stereochemistry was established by ROESY and NOE differential experiments whose results are shown in Figure 2.

H-1 saturation shows an NOE with the hydrogen attached to the nitrogen, which fixes the stereochemistry of hydrogen on C-1 as β (equatorial) and that on hydroxyl as α (axial). Finally, the absolute stereochemistry of **5** was confirmed by X-ray diffraction (Fig. 3), with an (*R*)-configuration for the four stereogenic centers of the molecule. It therefore corroborates the absolute stereochemistry assigned to diester **3**, the direct cyclization product of dimethyl nona-2,7-dienedioate, which was assigned based on the known sense of the stereoselective addition of the chiral lithium amide and exhaustive ^{1}H NMR analysis.

Colourless prism-like crystals of **5** were obtained by slow evaporation of EtAcO/hexane solution at room temperature. The solid-state structure (Fig. 3) was determined by single crystal X-ray diffraction techniques. Molecules of **5** were crystallized in the orthorhombic $P2_12_12_1$ space group. The crystal contains one molecule in the asymmetric unit. The molecule of **5** is a carbamate compound with a *tert*-butyl group and a 1-hydroxyoctahydro-1*H*-isochromen-8-yl group as substituents. The planar conformation of the carbamate group is established from the torsion angle N1–C9–O3–O4 = 179.4(3)°. The hydroxyl group at the C1 atom is twisted with the isochroman derivative being the O2–C1–C8′–C4′ torsion angle of 67.3(4)°. The N1–C8 bond length of 1.457(4) Å is



Scheme 2. Reagents and conditions: (i) DIBALH, results in Table 1; (ii) LAH, 77%.

Table 1
Reduction results within different ratio of DIBALH.

Entry	**4**/ mmol	DIBALH ratio	T/°C	Time (min)	**5**/ %	**6**/ %	**7**/ %	**4**/ %	η_{global}/ %
1	0.128	1.2	−78	20	15	18	4	50	87
2	0.269	4.0	−78	30	15	43	38	–	96
3	0.515	3.2	−78	35	27	30	25	–	82

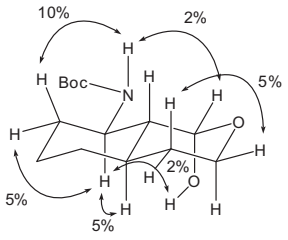
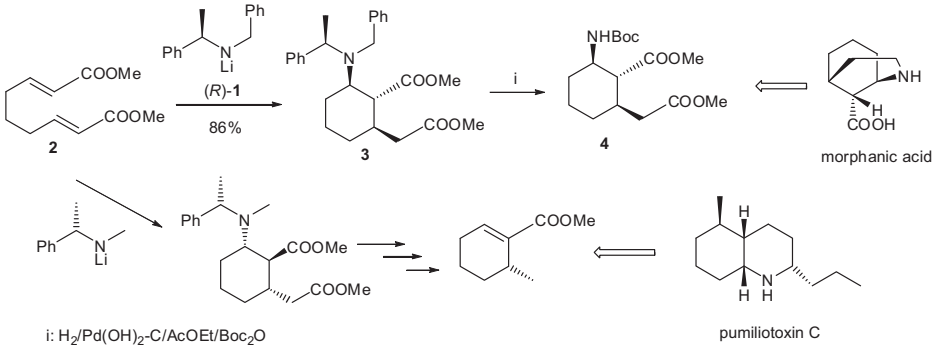


Figure 2. ^{1}H NMR stereo chemical analysis of **5**.

very close to the value for the $C_{cyclohexane}$-Nsp^2 distance of 1.455 (3) Å reported for methyl N-cyclohexylcarbamate.[9] On the other hand, the C9–N1 and C9–O3 bond lengths are approximately the same as those found in most amides and in carboxylic acids.[10] Such distances, along with the angles about C9 suggest a structure for the carbamate group with a delocalized double bond involving O3–C9–N1, with the O4 atom experiencing a slight reduction in electron density, thus weakening the C9–O4 bond. The cyclohexane ring [C4′–C5–C6–C7–C8–C8′] and ^{t}butyl group [C10–C11–C12–C13] are inclined to the mean plane of the carbamate [N1–C9–O3–O4] unit by 82.4(2) and 88.4(1)°, respectively. In the extended structure of **5**, the hydrogen bonds are one of the primary



Scheme 1. Domino reaction to obtain cyclohexane rings and their application to the synthesis of morphanic acid and pumiliotoxine C.

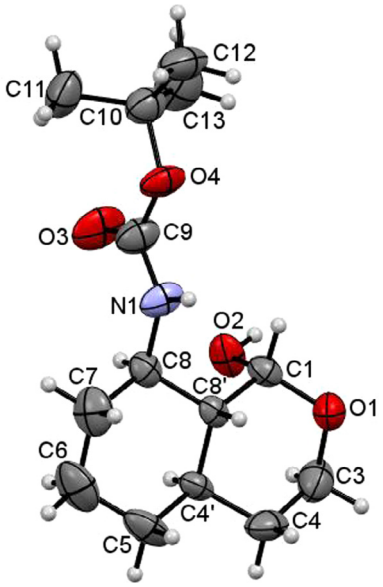


Figure 3. Molecular structure of $C_{14}H_{25}NO_4$ **5**. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radius.

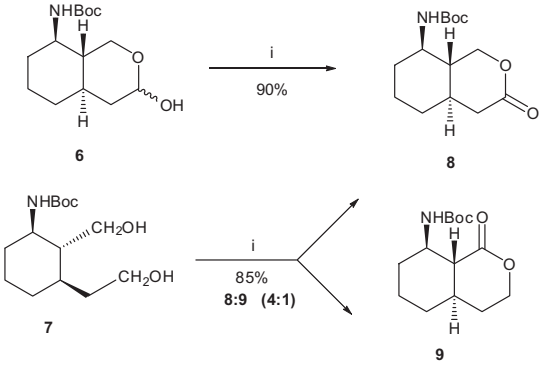
factors in the building of the crystal network (Table 2). In the crystal, O2–H2···O1 *(dotted light-blue lines)* hydrogen bonds between the hydroxyl group and the oxygen atom of the *isochromene derivative* link adjacent molecules, which are oriented in opposite directions (Fig. 4a). The NH groups act as hydrogen-bond donors and the C=O groups as acceptors to form intermolecular N1–HN1···O3 (dotted purple lines) hydrogen bonding, thus generating extended ribbons along the *a axis* (Fig. 4b). The two six-membered rings in the isochromene derivative adopt a chair conformation. The amide H atom is antiperiplanar to the carbonyl group, as has been observed for monosubstituted amides.[11]

The oxidation of diol **7** with TPAP gave isomeric lactones **8** and **9** in 85% yield and a 4:1 ratio. This shows that the less hindered alcohol is oxidized more easily (the mixture could not be resolved chromatographically), the same happens with other oxidants such as Collins reagent (CrO_3/Pyr).[12] When the epimer mixture **6** was oxidized with TPAP, isochromen-3-one **8** (Scheme 3) was obtained as the only reaction product.

Once the lactols were synthesized, we decided to test the Wittig reaction to obtain an unsaturated ester group that could be used as a new Michael acceptor. When lactol **6** was treated with methoxycarbonylmethylenetriphenylphosphorane in refluxing toluene (Scheme 4), the expected alcohol **10** was obtained in low yield (25%).

When the Horner–Wadsworth–Emmons reaction was carried out using dimethyl methoxycarbonylmethylphosphonate in the presence of NaH and K_2CO_3, in addition to alcohol **10** (20%), tetrahydropyran derivative **11** was obtained in 45%. As shown in Figure 5, the cyclic product was formed by Michael addition of the alcoholate formed by deprotonation of the hydroxyl group with NaH.

The stereochemistry of the new stereogenic center of the perhydroisochromene derivative **11** was determined by the ROESY



Scheme 3. Reagents and conditions: (i) TPAP/NMO.

Table 2
Hydrogen-bond geometry (Å, °).

D–H···A	D–H	H···A	D···A	D–H···A
O2–H2···O1	0.82	1.980	2.747(4)	155.4
N1–HN1···O3	0.86	2.202	3.019(4)	158.6

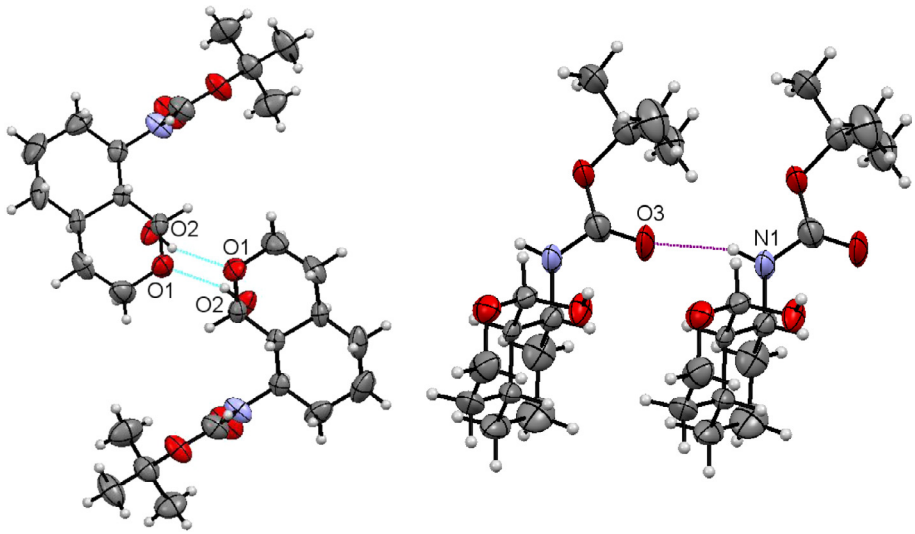
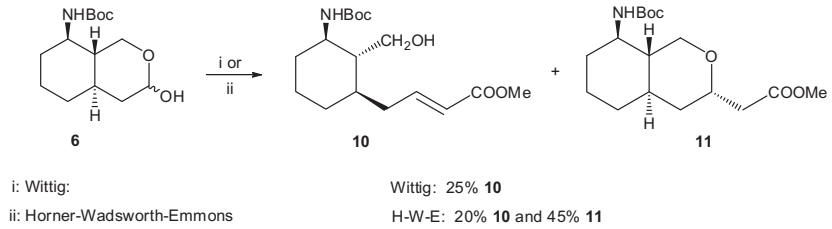


Figure 4. (a) A view of the O2–H2···O1 (dotted light-blue lines), (b) N1–HN1···O3 (dotted purple lines) hydrogen bonds in the structure of $C_{14}H_{25}NO_4$ **5**.



Scheme 4. Reagents and conditions: (i) $MeOCOCHPPh_3/NaH$; (ii) $(EtO)_2POCH_2COOMe/NaH/K_2CO_3$.

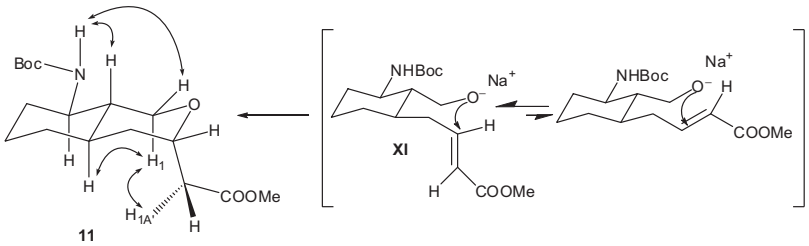


Figure 5. ROESY experiment for compound **11** and proposed mechanism for its formation.

experiment, with the most important correlations shown in Figure 5; the coupling between H-1ax and H-1′ established the configuration of C-3 to be (*S*).

An efficient method for synthesizing derivatives with an isochromene skeleton in a single reaction step from lactol **6** type compounds (Fig. 5) is described. The α,β-unsaturated alcohol **10** is an interesting intermediate for the preparation of condensed cyclohexane rings with different substitution patterns, as it already has a Michael acceptor by oxidation of the alcohol and a further Wittig or Horner–Wadsworth–Emmons reaction to guarantee the required bisunsaturated system.

We decided to synthesise the bisunsaturated compound from diol **7**, by Swern oxidation reaction (Scheme 5) to obtain dialdehyde **12**, but it proved very labile and decomposed on attempted purification.

Thus, the crude from the Swern reaction[13] was subjected directly to the Horner–Wadsworth–Emmons reaction and after chromatography, diene **13** (45%) was obtained. The ^{1}H NMR spectrum clearly showed the existence of two conjugated ester groups, δ: 5.78 (1H, d, J = 15.6 Hz, H-2′), 6.70 (1H, dd, J = 15.6 and 10.3 Hz, H-1′) for one of them and 5.81 (1H, d, J = 15.2 Hz, H-2), 6.80 (1H, ddd, J = 15.2, 8.0 and 6.0 Hz, H-3) for the other. In the ^{13}C NMR spectrum, the carbonyls of the esters at 166.4 and 166.9 ppm and that of four olefinic methines are observed at 123.1, 123.9, 146.9 and 149.6 ppm. When the amine was deprotected with TFA, the expected product **14** was obtained (85%). Compounds **13** and **14** are an upper homologue diene of the nona-2,7-diendioate **6** starting product, with an additional cyclohexane ring and three stereogenic centers.

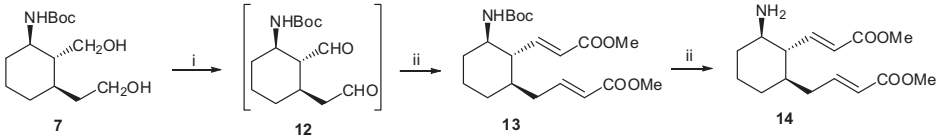
3. Conclusions

X-ray diffraction data of 8-boc-amino-perhydroisochromen-1-ol **5** have been obtained, which allowed the determination of its relative stereochemistry and corroborate that of the direct cyclization product **3**, and that of the related compounds. The asymmetric synthesis of cyclohexane dienes **13** and **14** has also been carried out. The synthesis involved the homologation of the initial diene **3** with an extra cyclohexanic ring and an additional amine function; we anticipate that this could be used to obtain important polycyclic systems. The synthesis of the cyclohexane alcohol **11**, which has an α,β-unsaturated ester, could allow homologation in a sequential manner.

4. Experimental

4.1. General

All chemical reagents were purchased from Sigma–Aldrich or Acros. High-purity reaction solvents were purified accordingly to literature. All reactions were carried out in borosilicate Pyrex® type glassware and under inert conditions, using Ar as inert gas. Reaction monitoring was followed by TLC, type Merck 60 F254, which visualization was achieved with UV light and ninhydrin as appropriate stain. Flash chromatography was carried out on Kieselgel 40 (Merck, 0.040–0.063) silica. Yields and characterization data belong to chromatography purified compounds. Deuterated solvents were purchased from Carlo Erba. Optical rotations were measured on a Perkin Elmer 241 polarimeter in 1 dm cells ($[\alpha]_D^{20}$). Infrared spectra were recorded on a Shimadzu IRAffinity-1 (IR). NMR experiments were recorded on a Varian 200 VX (^{1}H MR/200 MHz, ^{13}C NMR/50 MHz) and on a Bruker DRX 400 (^{1}H NMR/400 MHz). 2D HMBC and HMQC or representative compounds were also recorded to assign protons and carbons on new structures. Chemical shifts are reported in ppm (parts per million) relative to referenced values. High-resolution mass spectrometry (HRMS) analyses were performed on an Applied Biosystems QSTAR XL (ESI, electrospray ionization) and in a VG-TS 250 (EI, electronic impact), at 70 eV (m/z).



Scheme 5. Reagents and conditions: (i) (a) $(COCl)_2$; (b) DMSO; (c) NEt_3; (ii) $NaH/(EtO)_2POCH_2COOMe$; (iii) TFA.

4.2. Methyl (1*R*,2*R*,6*R*)-2-*N*-benzyl-*N*-α-methylbenzylamino-6-(methoxycarbonylmethyl)-cyclohexanecarboxylate 3

At first, *n*-BuLi 12.4 ml (19.9 mmol) of 1.6 M was added dropwise to a stirred solution of 5.1 g (22.0 mmol) of *N*-benzyl-*N*-α-methylbenzylamine (*R*)-**1** in 15 ml of THF at −78 °C under an N_2 atmosphere and the resulting solution stirred for 30 min. Subsequently a solution of the α,β-unsaturated diester **2** (2.3 g, 11.0 mmol), dissolved in 8 ml of THF was added dropwise to the lithium amide solution *via* cannula and stirred at −78 °C for 4 h before the addition of saturated aqueous NH_4Cl (18 mL) and warming to room temperature. The crude reaction mixture was partitioned between DCM and brine and the organic layers concentrated *in vacuo*. The residue was partitioned between DCM and 10% citric acid solution, organic layer washed in succession with aqueous $NaHCO_3$ solution and brine, dried and concentrated *in vacuo*. Purification via column chromatography on silica (1:4, EtAcO: Hexane) gave **3** (4.5 g, 86%) as a clear oil; $[\alpha]_D^{26}$ = +3.9 (*c* 1.9, $CHCl_3$); IR (neat): ν_{max} = 3459, 2947, 1738, 1435, 1028; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85(1H, m, H-4A), 1.20–1.30(1H, m, H-3A), 1.30(1H, m, H-5A), 1.36(3H, d, *J* = 6.8 Hz, C(α)Me), 1.65(1H, m, H-3B), 1.73(1H, m, H-4B), 1.95 (1H, m, H-5B), 1.95(1H, m, H-6), 2.01(1H, dd, *J* = 11.8, 10.3 Hz, H-8A), 2.15(1H, dd, *J* = 11.8, 2.8 Hz, H-8B), 2.29(1H, dd, *J* = 11.4, 11.0 Hz, H-1), 3.12(1H, ddd, *J* = 11.0, 11.0, 3.6 Hz, H-2), 3.41(3H, s, OCH_3), 3.63(3H, s, OCH_3), 3.64(1H, AB, *J* = 13.6 Hz, NCH_AHPh), 3.83(1H, AB, *J* = 13.6 Hz, $NCHH_BPh$), 3.96(1H, c, *J* = 6.8 Hz, C(α)H), 7.15–7.35(10H, m, Ar-H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 16.1(CH_3, C(α)Me), 24.5(CH_2, C-3), 28.5(CH_2, C-5), 30.2(CH_2, C-4), 37.3(CH, C-6), 39.4(CH_2, C-8), 49.9(CH_2, NCH_2Ph), 51.2(CH_3, OCH_3), 51.4(CH_3, OCH_3), 54.5(CH, C-1), 56.8(CH, C(α)), 58.6(CH, C-2), 126.4–129.1(10H, C-Ar), 140.6(C, C_{ipso}), 144.1(C, C_{ipso}), 172.4 (C, COOMe), 174.1(C, COOMe) ppm; HRMS (ESI): *m*/*z* (M+H) calcd for $C_{26}H_{34}NO_4$, 424.2488; found, 424.2486.

4.3. Methyl (1*R*,2*R*,6*R*)-2-((*tert*-butoxycarbonyl)amino)-6-(2-methoxycarbonylmethyl)cyclohexanecarboxylate 4

To a solution of 1.8 g (4.69 mmol) of **3** in 8 ml of AcOEt were added 710 mg of 20% $Pd(OH)_2$ on carbon and 1.1 g (5.16 mmol) of Boc_2O. This mixture was stirred under a hydrogen atmosphere (4 atm) for 72 h. The solution was filtered over Celite while washing with CH_2Cl_2. The solvent was evaporated to give 1.57 g of reaction crude. The excess Boc_2O was removed by distilling under reduced pressure of 10-1 mmHg and in the temperature range of 60 to 70 °C. 1.4 g (90%) of **4** were obtained as a clear oil; $[\alpha]_D^{26}$ = +10.6 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} = 3367, 2956, 1734, 1517, 1170; ^{1}H NMR (400 MHz, $CDCl_3$): *d* = 0.95(1H, m, H-4A), 1.10(1H, m, H-3A), 1.42(9H, s, $C(CH_3)_3$), 1.30–1.50(1H, m, H-5A), 1.75–1.95 (2H, m, H-3B, H-4B), 2.05–2.20(4H, m, H-6, H-5, H-8), 2.30(1H, m, H-1), 3.60–3–70(1H, m, H-2), 3.62(3H, s, OCH_3), 3.71(3H,s, OCH_3), 4.52(1H, d, *J* = 5.6 Hz, NH); ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1(CH_2, C-4), 28.5($3CH_3$, $C(CH_3)_3$, 30.6(CH_2, C-5), 33.0(CH_2, C-3), 36.3(CH, C-6), 39.3(CH_2, C-8), 51.1(CH_3, OCH_3), 51.8(CH_3, OCH_3), 56.1(2CH, C-1, C-2), 79.0(C, $C(CH_3)_3$), 155.0(C, NCOOtBu), 172.4(C, $COOCH_3$), 173.7(C, $COOCH_3$) ppm; HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{16}H_{27}NO_6$, 325.1736; found 352.1672.

4.4. *tert*-Butyl ((1*R*,4a*R*,8*R*,8a*R*)-1-hydroxyoctahydro-1*H*-isochromen-8-yl)carbamate 5 and *tert*-butyl ((4a*R*,8*R*,8a*R*)-3-hydroxyoctahydro-1*H*-isochromen-8-yl)carbamate 6

To a solution of 184 mg (0.56 mmol) of **4** dissolved in 6 ml of CH_2Cl_2, 0.187 ml (1.28 mmol) of 1.5 M DIBALH were slowly added at −78 °C and allowed to stir at this temperature for 35 min. Next, 4 ml of water were added and the reaction mixture allowed to return to room temperature. It was then poured into an ether solution containing 17.4 g of $NaHCO_3$ and 6 spatulas of anhydrous Na_2SO_4 and then stirred at room temperature, filtered over Celite and the solvent evaporated to give 161 mg of reaction crude, which was chromatographed on flash silica and eluted with hexane/EtAcO 1:1, 25 mg (27%) of **5** being isolated and 27 mg (30%) of **6** and 24 mg (25%) of **7** as a clear oil.

Compound **5** was crystallized from Hexane/EtAcO 9:1, m.p. = 174 °C; $[\alpha]_D^{26}$ = −38.0 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} = 3352, 2917, 1680, 1527, 1057; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–1.02(1H, cd, *J* = 9.5, 3.7 Hz, H-5A), 1.05–1.52(1H, t, *J* = 11.4 Hz, H-8a), 1.15–1.35(1H, m, H-7A), 1.30–1.38(1H, m, H-4A), 1.35–1.50(1H, m, H-6A), 1.42(9H, s, $C(CH_3)_3$), 1.45–1.55(1H, broad d, *J* = 13.0), 1.55–1.70(1H, m, H-5), 1.70–1.80(1H, m, H-6A), 1.75–1.85(1H, m, H-4a), 1.90–2.00(1H, broad d, *J* = 13.0 Hz, H-7A), 3.43(1H, cd, *J* = 8.3, 2.5 Hz, H-8), 3.64(1H, dd, *J* = 11.2, 3.9 Hz, H-3ec), 4.39(1H, broad d, *J* = 8.2 Hz, NH), 4.45(1H, broad s, OH), 4.64(1H, td, *J* = 11.2, 2.5 Hz, H-3ax), 5.12(1H, broad s, H-1) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.4(CH_2, C-6), 28.3($3CH_3$, $C(CH_3)_3$), 31.9(CH, C-4a), 32.4(CH_2, C-4), 32.5(CH_2, C-5), 33.5(CH_2, C-6), 49.9(CH, C-8), 52.6 (CH, C-8a), 59.9(CH_2, C-3), 80.1(C, $C(CH_3)_3$), 90.7(CH, C-1), 156.8 (C, COO), HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{14}H_{25}NO_4$, 294.1676; found 294.1672.

Crystal structure determination. A suitable single crystal of **5** compound was mounted on glass fibre for data collection on a four circle Seifert XRD 3003 SC diffractometer. Data were collected at 298(2) K using Cu K_α radiation (λ = 1.54178 Å), graphite monochromator and the ω-2θ scan technique. The unit cell parameters were determined by least squares refinement on the 2θ values of 25 strong well centered reflections in the range 16 < 2θ < 40°. The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. The refinement was based on F^2 for all reflections, and weighted R factors (wR) and all goodness-of-fit (GoF) values are based on F^2, while conventional R factors (R) are based on F. The $Fo^2 > 2\sigma(Fo^2)$ criterion was used only for calculating the R factors and it is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. Scattering factors were taken from the International Tables for Crystallography.[14] The hydrogen atoms were positioned geometrically. All calculations were performed using CRYSOM[15] software for data collection, XRAY80[16] for data reduction, SHELXTL[17] to resolve and refine the structure and MERCURY to prepare molecular and crystal structures drawings.[18] Crystallographic data for the structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC 1565401.

Compound **6**: $[\alpha]^{26}{}_D$ = +5.0 (*c* 1, $CHCl_3$); IR (neat): ν_{max} = 3332, 2936, 1670, 1522, 1175; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–2.01 (6H, m, H-5, H-6, H-7), 2.02(1H, m, H-4a), 1.43(9H, s, $C(CH_3)_3$), 2.43(1H, m, H-8a), 3.30(1H, m, H-4A), 3.80(1H, t, *J* = 11.2 Hz, H-4B), 3.70(1H, m, H-8), 4.03(1H, dd, *J* = 11.8 and 3 Hz, H-1A), 4.28 (1H, t, *J* = 11.8 Hz, H-1B), 4.72(1H, m, H-3), 5.07(1H, d, *J* = 6.6 Hz, NH), 5.30(1H, s, OH) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.7, 24.8(CH_2, C-6), 28.2×2(CH_2, C-5), 28.3, 28.6($3CH_3$, $C(CH_3)_3$), 32.3, 32.3(CH_2, C-7), 33.1, 38.8(CH, C-4a), 37.1, 39.8(CH_2, C-4), 47.6, 48.1(CH, C-8a), 50.4×2(CH, C-8), 62.0, 68.6(CH_2, C-1), 79.5, 79.6 (C, $C(CH_3)_3$), 91.8, 96.6(CH, C-3), 155.7×2(C, COO); HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{14}H_{25}NO_4$, 294.1676; found, 294.1672.

4.5. *tert*-Butyl ((1*R*,2*R*,3*R*)-3-(2-hydroxyethyl)-2-(hydroxymethyl) cyclohexyl)carbamate 7

To a solution of 57 mg (1.7 mmol) of **4** in 1.5 ml of THF were added 132 mg (3.5 mmol) of $LiAlH_4$ at 0 °C. The mixture was allowed to return to room temperature and left stirring for 4 h.

After this time an ether-water mixture was added and extracted with ether. The organic phase was dried over anhydrous Na_2SO_4, filtered over Celite and evaporated to yield 40 mg (77%) of **7** as a clear oil; $[\alpha]_D^{26}$ = +45.9 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max} = 3342, 2912, 1670, 1517, 1146; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85(1H, m, H-4A), 0.95(1H, m, H-3A), 1.20–1.40(2H, m, H-5A, H-4B), 1.44(9H, s, $C(CH_3)_3$), 1.60–1.80(4H, m, H-3B, H-5B, H-8A, H-8B), 1.90–2.05 (2H, m, H-1, H-6), 3.50 (1H, m, H-2), 3.60–3.80(4H, m, $2CH_2OH$), 4.53(1H, d, *J* = 5.6 Hz, NH) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 25.1(CH_2, C-4), 28.5($3CH_3$, $C(CH_3)_3$), 29.9(CH_2, C-5), 32.0(CH_2, C-3), 33.5(CH, C-6), 36.3(CH_2, C-8), 50.0(CH, C-1), 52.0(CH, C-2), 58.4(CH_2, CH_2OH), 61.1(CH_2, CH_2OH), 80.2(C, $C(CH_3)_3$), 157.2(C, NCOOtBu); HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{14}H_{27}NO_4$, 296.1838; found, 296.1799.

4.6. *tert*-Butyl ((4a*R*,8*R*,8a*R*)-3-oxooctahydro-1*H*-isochromen-8-yl)carbamate 8

To 7 mg (0.03 mmol) of **6** were added 7.5 mg (0.06 mmol) of NMO and then both compounds were dissolved in 0.5 ml of CH_2Cl_2. Half spatula of sieves was added and stirred at room temperature. Finally 2 mg (0.03 mmol) of TPAP were added and the mixture left to stir for 25 min, after which it was filtered with Celite and normal silica washing with CH_2Cl_2. The solvent was evaporated to yield 5 mg (90%) of **8** as a clear oil; IR (neat): ν_{max} = 3357, 2922, 1739, 1705, 1175; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.80(6H, m, H-5, H-6, H-7), 1.44(9H, s, $C(CH_3)_3$), 1.85(1H, m, H-4a), 2.01(1H, m, H-8a), 2.10(1H, dd, *J* = 18.4, 12.0 Hz, H-4A), 2.91(1H, dd, *J* = 18.4, 5.5 Hz, H-4B), 3.35(1H, m, H-8a), 4.11(1H, t, *J* = 11.6 Hz, H-1ax), 4.35(1H, d, *J* = 8.7 Hz, NH), 4.50(1H, dd, *J* = 11.6, 4.3 Hz, H-1ec) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.3(CH_2, C-6), 28.5($3CH_3$, C $(CH_3)_3$), 32.0(CH_2, C-5), 33.4(CH_2, C-7), 36.0(CH, C-4a), 36.9(CH_2, C-4), 44.7(CH, C-8a), 50.5(CH, C-8), 73.0(CH_2, C-1), 80.1(C, C $(CH_3)_3$), 155,6(C, COOtBu), 170.4(C, COO); HRMS (ESI): *m*/*z* (M +Na) calcd for $C_{14}H_{23}NO_4$, 292.1519; found 292.1518.

4.7. ((4a*R*,8*R*,8a*R*)-1-Oxooctahydro-1*H*-isochromen-8-yl)carbamate 9

To 18 mg (0.06 mmol) of **7** were added 30 mg (0.22 mmol) of NMO and molecular sieves. Both compounds were dissolved in 1 ml of CH_2Cl_2 and stirred at room temperature. Next, 4 mg (0.14 mmol) of TPAP were added and allowed to stir for 1.5 h, and then filtered with normal silica and Celite washing with CH_2Cl_2. The solvent was evaporated to give 15 mg (90%) of a mixture of lactones **8** and **9** in a 4:1 ratio, which were not separable by chromatography. Compound **9**: ^{13}C NMR (200 MHz, $CDCl_3$): δ = (Deduced from the spectrum of the mixture) 24.5(CH_2, C-6), 28.6($3CH_3$, $C(CH_3)_3$), 29.5(CH_2, C-5), 32.4(CH_2, C-7), 33.4(CH_2, C-4), 35.7(CH, C-4a), 47.0(CH, C-8a), 51.0(CH, C-8), 73.0 (CH_2, C-1), 80.0(C, $C(CH_3)_3$), 155,6(C, COOtBu), 173.0(C, COO); HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{14}H_{23}NO_4$, 292.1519; found, 292.1518.

4.8. Methyl (*E*)-4-((1*R*,2*R*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-(hydroxymethyl)cyclohexyl)but-2-enoate 10

Approximately 20 mg (0.077 mmol) of **6**, 45.6 mg (0.16 mmol) of methoxycarbonylmethylenephosphorane and 5 ml of toluene were added and refluxed (110 °C) for 38 h. After this time some of the solvent was evaporated and the residue was flash chromatographed on flash silica, isolating 4 mg of unreacted starting material and 6 mg (25%) of **10** as a clear oil; IR (neat): ν_{max} = 3362, 2917, 1720, 1640, 1512, 1166; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–2.01(6H, m, H-4, H-5, H-6), 1.46(9H, s, $C(CH_3)_3$), 2.05(1H, m, H-3), 2.16(1H, dd, *J* = 6.0, 1.5 Hz, H-2), 2.27(1H, t, *J* = 5.2 Hz, H-1A″), 2.52(1H, m, H-1B″), 3.47(1H, m, H-1), 3.60–3.80(2H, m, CH_2-OH), 3.72(3H, s, $COOCH_3$), 4.42(1H, d, *J* = 8.6 Hz, NH), 5.84(1H, d, *J* = 15.4 Hz, H-3″), 6.95(1H, m, H-2″); HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{17}H_{29}NO_5$, 350.1934; found, 350.1929.

4.9. Methyl 2-((3*S*,4a*R*,8*R*,8a*R*)-8-((*tert*-butoxycarbonyl)amino) octahydro-1*H*-isochromen-3-yl)acetate 11

At first, 5 mg (0.12 mmol) of NaH are dissolved in 0.5 ml of THF and cooled to 0 °C. Next, 0.02 ml of diethyl methoxycarbonylmethylphosphonate wereadded and the mixture was allowed to stir for 30 min. Then 26 mg (0.10 mmol) of **6** dissolved in 0.5 ml of THF were added via cannula to room temperature. This mixture allowed to react for 22 h after which 7 mg (0.05 mmol) of K_2CO_3 were added and then stirred for 60 h. The organic phase was extracted with ether, washed with saturated NaCl, dried over anhydrous Na_2SO_4, filtered and evaporated to obtain 46 mg of reaction crude, which was chromatographed on flash silica eluting with hexane/EtOAc 8:2, isolating 5 mg (20%) of **10** and 15 mg (45%) of **11**, 10 mg of starting product and 16 mg of unreacted phosphonate. Compound **11**: IR (neat): ν_{max} = 3352, 2922, 1739, 1705, 1527, 1170; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.00(2H, m, H-5A, H-6A), 1.10–1.70(3H, m, H-5B, H-6B, H-7A), 1.16(1H, m, H-8a), 1.42(9H, s, $C(CH_3)_3$), 1.50–1.65(2H, m, H-4), 1.77(1H, m, H-4a), 1.96(1H, m, H-7B), 2.50(1H, dd, *J* = 8.2, 6.6 Hz, H-1A′), 2.86 (1H, dd, *J* = 8.2 and 6.6 Hz, H-1B′), 3.25(1H, m, H-8), 3.39(1H, t, *J* = 11.6 Hz, H-1ax), 3.60–3.80(1H, m, H-1ec), 3.69(3H, s, $COOCH_3$), 4.25(1H, d, *J* = 9.0 Hz, NH), 4.44(1H, m, H-3) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.7 (CH_2, C-6), 28.6($3CH_3$, $C(CH_3)_3$), 32.5(CH_2, C-5), 32.5(CH_2, C-1′), 34.1(CH_2, C-7), 34.4(CH, C-4a), 35.4(CH_2, C-4), 48.5(CH, C-8a), 50.5(CH, C-8), 52.0(CH_3, OCH_3), 63.5(CH_2, C-1), 70.0(CH, C-3), 79.6(C, $C(CH_3)_3$), 155.7(C, COOtBu), 172.2(C, COOMe); HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{17}H_{29}NO_5$, 350.1938; found, 350.1939.

4.10. Methyl (*E*)-4-((1*R*,2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-((*E*)-2-methoxycarbonyl-eten-1-yl)cyclohexyl)but-2-enoate 13

To 6 mL of CH_2Cl_2 were added 0.084 mL (0.96 mmol) of $(COCl)_2$ to room temperature. Next, 0.14 ml of DMSO were added. The mixture was cooled to −60 °C and 120 mg (0.44 mmol) of **7** dissolved in 2 ml of CH_2Cl_2 was then added via cannula and the stirring is maintained at this temperature for 1 h. After this time 0.351 ml (2.2 mmol) of NEt_3 is added and the mixture is stirred for an additional 15 min, after which the reaction mixture is brought to room temperature and stirred for 15 min. Add 10 ml of water and extract with CH_2Cl_2. The organic phase is dried over anhydrous Na_2SO_4, filtered and evaporated, yielding 133 mg (90%) of **12**.

To 24 mg (1.04 mmol) of a suspension of NaH (60% in paraffin, previously washed with THF) in 5 ml of THF were slowly added 0.25 ml (1.38 mmol) of diethyl methoxycarbonylmethylphosphonate. It is stirred for 10 min and after which, 122 mg (0.45 mmol) of **12** dissolved in 1.5 ml of THF is added via cannula. The mixture was left stirring for 62 h after which 10 ml of water were added and extracted with ether. The ether phase was washed with H_2O and saturated NaCl, dried over anhydrous Na_2SO_4, filtered and evaporated to afford 51 mg (36%) of **13** as a clear oil; IR (neat): ν_{max} = 3357, 2941,1729, 1363, 1166; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90(1H, m, H-4A), 1.10(1H, m, H-3A), 1.30–1.50(1H, m, H-5A), 1.42(9H, s, $C(CH_3)_3$), 1.55–1.85(3H, m, H-3B, H-4B, H-5B), 2.05(1H, m, H-4″A), 2.15(1H, m, H-6), 2.25(1H, m, H-4″B), 2.30 (1H, m, H-1), 3.40 (1H, m, H-2), 4.55(1H, d, *J* = 5.6 Hz, NH), 3.64 (3H, s, OCH_3), 3.72(3H, s, OCH_3), 5.78(1H, d, *J* = 15.6 Hz, H-2′), 5.81(1H, d, *J* = 15.2 Hz, H-3″), 6.70(1H, dd, *J* = 15.6, 10.3 Hz, H-1′), 6.80(1H, ddd, *J* = 15.2, 7.0, 6.0 Hz, H-3″) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.5(CH_2, C-4), 28.5($3CH_3$, $C(CH_3)_3$, 30.6(CH_2, C-5),

33.3(CH_2, C-3), 37.3(CH_2, C-1″), 40.1(CH, C-6), 51.7(2CH_3, s, OCH_3), 52.8(CH, C-1), 54.4(CH, C-2) 80.0(C, C(CH_3)$_3$), 123.1(CH, C-3″), 123.9(CH, C-2′), 146.9(CH, C-2″), 149.6(CH, C-1′), 155.2(C, NCOOtBu), 166.4(C, COOMe), 166.9(C, COOMe); HRMS (ESI): *m*/*z* (M+Na) calcd for $C_{20}H_{31}NO_6$, 404.2014; found, 404.2043.

4.11. Methyl (*E*)-4-((1*R*,2*S*,3*R*)-3-amino-2-((*E*)-2-methoxycarbonyl-eten-1-yl)cyclohexyl)but-2-enoate 14

To 15 mg (0.039 mmol) of **13** were added 0.5 mL of TFA and 2 mL of CH_2Cl_2. Stirring was continued for 3.5 h, after which 0.5 ml of water were added and extracted with CH_2Cl_2. The organic phase was washed with 10% $NaHCO_3$ and saturated NaCl and dried over anhydrous Na_2SO_4. It was then filtered and evaporated to give 14.5 mg of reaction crude, which was chromatographed on flash silica eluting with 98:2 $CHCl_3$/MeOH, isolating 13 mg (85%) of **14** as a clear oil; ν_{max} = 3367, 2917, 1725, 1650, 1433, 1161; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.70(3H, m, H-4A, H-5A, H-6A), 1.70–2.01(4H, m, H-1, H-4B, H-5B, H-6B), 2.30(2H, m, H-4″), 2.64 (1H, m, H-2), 3.65–3.80(1H, m, H-3), 3.73(3H, s, OCH_3), 3.75(3H, s, OCH_3), 5.75(1H, d, *J* = 15.6 Hz, H-2″), 5.98(1H, d, *J* = 15.6 Hz, H-2′), 6.67(1H, dd, *J* = 15.6, 10.2 Hz, H-1′), 6.86(1H, ddd, *J* = 15.6, 8.4, 6.8 Hz, H-3″) ppm; ^{13}C NMR (200 MHz, $CDCl_3$): δ = 24.1(CH_2, C-5), 29.0(CH_2, C-4), 30.6(CH_2, C-6), 37.3(CH_2, C-4″), 39.7(CH, C-3), 51.7, 51.9(2CH_3, OCH_3), 53.3(CH, C-2), 54.5(CH, C-1), 123.1(CH, C-2′), 125.5(CH, C-2″), 147.1(CH, C-3′), 149.0(CH, C-3″), 166.5, 167.0 (2C, $COOCH_3$); HRMS (ESI): *m*/*z* (M+H) calcd for $C_{15}H_{24}NO_4$, 282.1700; found, 282.1692.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.005.

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