Tetrahedron 66 (2010) 2390–2397

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Straightforward stereoselective synthesis of polyfunctionalised cyclohexenols using a multicomponent approach

Andrea Basso *, Luca Banfi, Giuseppe Guanti, Renata Riva

Università degli Studi di Genova, Dipartimento di Chimica e Chimica Industriale. Via Dodecaneso 31, 16146 Genova, Italy

ARTICLE INFO

Article history:
Received 5 October 2009
Received in revised form
14 December 2009
Accepted 27 January 2010
Available online 2 February 2010

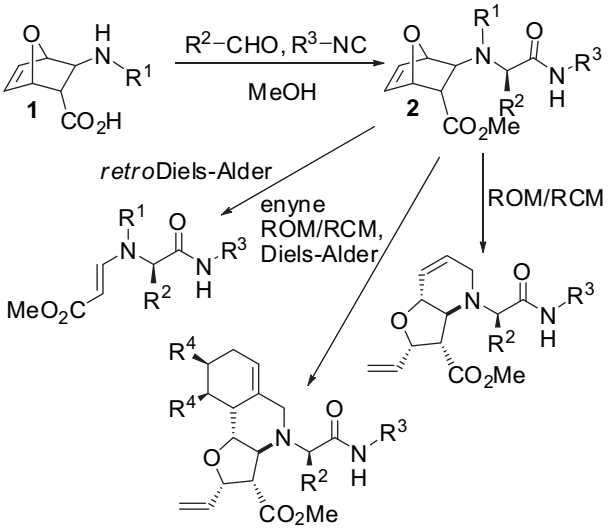
Keywords:
Cyclohexenols
Multicomponent reactions
Norbornenyl amino acids
Ring-opening reactions
Enantioselective synthesis
Diversity oriented synthesis

ABSTRACT

An intramolecular Ugi 5-centre-4-component reaction (U-5C-4CR) followed by a palladium-catalysed ring-opening has been employed to transform oxabicycloheptene-based β-amino acids into two families of regioisomeric polyfunctionalised cyclohexenols. The whole process is completely stereoselective and enantiomerically pure products are obtained in high overall yields.

1. Introduction

Isocyanide-based multicomponent reactions (I-MCRs)[1] followed by post-condensation transformations[2] are currently widely used by both academia and industry[3] to modify the classic Passerini and Ugi adducts into more valuable, pharmacologically relevant compounds. Within this strategy we have recently reported[4] the behaviour of oxabicycloheptene β-amino acids of general formula **1** that, reacted with various aldehydes and isocyanides in alcoholic medium, give a stereoselective Ugi 5-centre-4-component reaction leading to final compounds **2** (Scheme 1). Depending on the different functionalities displayed by **2**, various transformations can follow the multicomponent step, such as *retro*Diels–Alder reaction,[5] ring-opening/ring-closing metathesis or enyne metathesis followed by cycloadditions[6] leading to structurally different complex molecules in a highly convergent manner. In view of all the possible transformations that Ugi adducts **2** can undergo, these compounds can be defined *pluripotent substrates*[7] and can find applications in Diversity Oriented Synthesis.[8] In this paper we report the transformation of pluripotent substrate **2** into two classes of regioisomeric cyclohexenols exploiting a transition-metal catalysed ring-opening of the oxanorbornene system. Although this reaction has been widely explored by Lautens et al.,[9] three features make our approach interesting and original: (1) the presence of various additional functional groups that could interfere with the reaction, (2) the non-symmetrical bicyclic system that could lead to two distinct regioisomers, (3) the chiral information, that is,



Scheme 1. Oxabicycloheptene derivatives as pluripotent substrates.

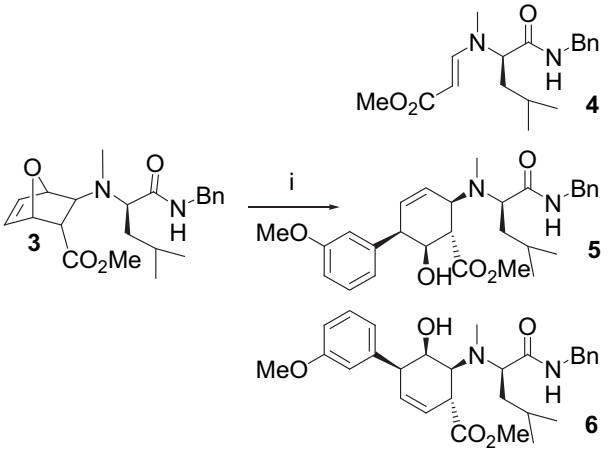
* Corresponding author. Tel.: +39 010 3536117; fax: +39 010 3536118.
E-mail address: andreab@chimica.unige.it (A. Basso).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.097

intrinsic in the substrate and therefore renders the search for enantioselective catalysts unnecessary.

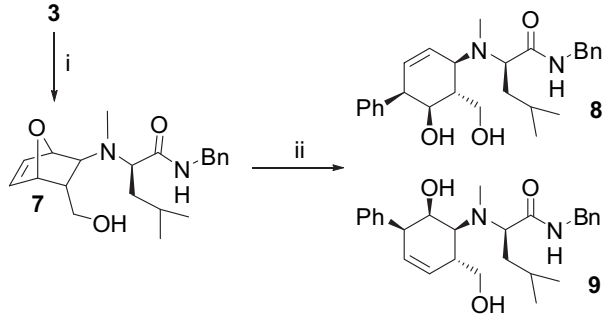
2. Discussion

In order to find the optimal procedure to perform the ring-opening reaction, we prepared racemic compound **3** (Scheme 2) according to our reported procedure[4] and submitted it to different experimental conditions. Our first attempts regarded simple acid- or base-mediated fragmentation reactions to break the bicyclic C–O bond: in a first experiment we investigated a KHMDS-mediated fragmentation reaction, reported by Steel et al.[10] on a similar substrate, however treatment of **3** with base did not afford any product, neither did the reaction with BuLi and catalytic $TiCl_4$ according to Arjona et al.,[11] or the reaction with stoichiometric $TiCl_4$ according to Harwood et al.[12] The presence of a basic nitrogen and/or an acidic NH on the substrate probably prevented these reactions occurring. We therefore investigated alternative ring-opening reactions mediated by nucleophiles in the presence of metal catalysts, proceeding this time in a nearly neutral environment; the final products, with this alternative strategy, would also incorporate the nucleophile as an additional diversity input, increasing the number of different molecules obtainable. In particular we investigated two distinct processes, one with Ni, Zn and iodoarenes,[13] and another with Pd and boronic acids.[14] At this stage we had to face another problem, due to the lability of substrate **3** to the moderately high temperatures required by these reactions: indeed, under these conditions the main product isolated was the *retro*Diels–Alder adduct **4**, with only trace amounts of the desired ring-opening adducts. Thoroughly optimised conditions for the reaction with iodoarenes furnished a 60% yield of a nearly 1:1 mixture of the regioisomeric compounds **5** and **6**; however the large excess of metal species employed and the persistent presence of adduct **4** (10%), stimulated us to look for an alternative strategy that could suppress the undesired *retro*Diels–Alder reaction.



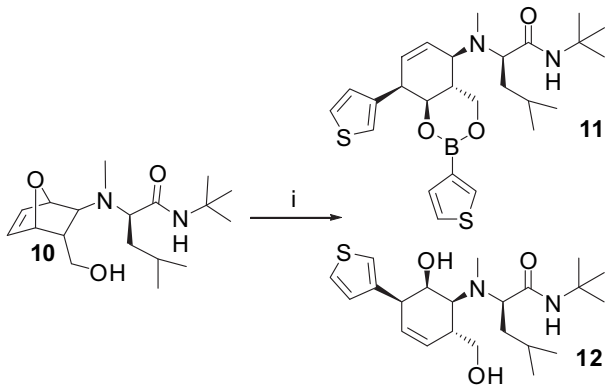
Scheme 2. Ring-opening reaction of racemic ester derivative **3**. Reagents and conditions:(i) 3-Iodoanisole, Zn dust, $Ni(PPh_3)_2Cl_2$, acetonitrile, 50 °C.

We postulated that removal of the ester moiety, endowed with strong electron withdrawing properties, would kinetically disfavour *retro* cycloaddition processes, while being of little or no influence in the ring-opening reaction. Gratifyingly, treatment of **3** with LAH[15] gave the corresponding alcohol **7** in high yields (Scheme 3), without affecting the other functionalities in the molecule; curiously compound **7** was unreactive under the conditions previously optimised, while the expected mixture of regioisomers **8** and **9** was obtained in moderate yield (64%) when the alternative reaction with phenylboronic acid and a Pd(II) catalyst was performed instead. Further optimisation, in particular the use of bis(triphenylphosphine)propane as ligand for the metal catalyst, allowed us to obtain the final products in 80% yield and as a 7:3 mixture of regioisomers in favour of the one with the two hydroxy groups far apart.



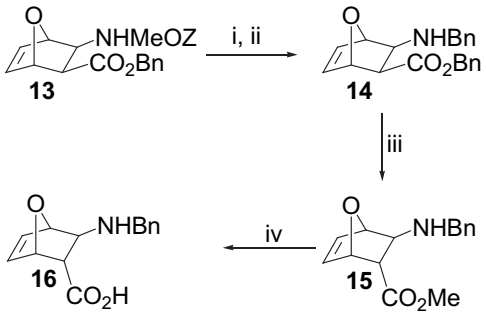
Scheme 3. Ring-opening reaction of racemic alcohol derivative **7**. Reagents and conditions: (i) LAH, Et_2O, 0 °C, 96%; (ii) Phenylboronic acid, $[Pd(C_6H_5CN)_2]Cl_2$, 1,3-bis(diphenyl-phosphino)propane, Cs_2CO_3, H_2O, MeOH, 60 °C, 80%.

The correct assignment of the two regioisomers was made thanks to 2D NMR experiments and was confirmed by the fact that when compound **10**, obtained similarly to **3**, was reacted under the same conditions with excess thiopheneboronic acid, the regioisomer with the two vicinal hydroxy groups was isolated as the corresponding cyclic boronate **11**, while regioisomer **12** would be sterically prevented to form such a species (Scheme 4). As expected for the mechanism of this reaction[16] and as demonstrated by NMR experiments, the ring-opening occurred with *syn* stereoselectivity, as a result of *exo* attack of the nucleophile to the oxabicyclic unit.



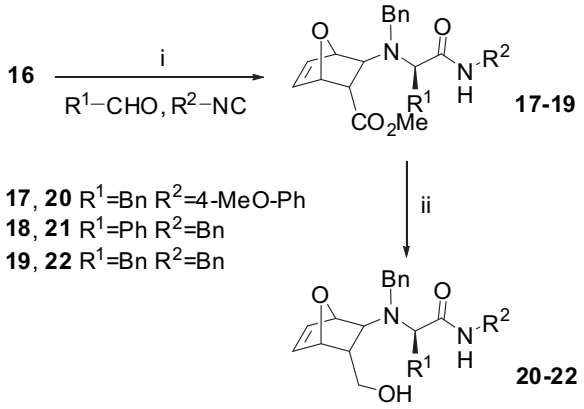
Scheme 4. Ring-opening reaction with 3-thiopheneboronic acid. Reagents and conditions: (i) 3-Thiopheneboronic acid, $[Pd(C_6H_5CN)_2]Cl_2$, 1,3-bis(diphenyl-phosphino)-propane, Cs_2CO_3, H_2O, MeOH, 60 °C, 100%.

This synthetic approach was employed to prepare a small library of optically pure cyclohexenol derivatives starting either from derivative **13** or from its enantiomer, both obtained according to a previously reported procedure.[5] Amino acid **16**, to be employed in the U-5C-4CR, was synthesised by a modification of the above mentioned methodology: cleavage of the MeOZ protecting group and reductive amination with benzaldehyde furnished **14** nearly quantitatively. This was subjected to epimerisation with NaOMe in MeOH to give the desired *trans*-configured derivative **15**, which was finally hydrolysed to **16** (Scheme 5); *ent*-**16** was obtained similarly from *ent*-**13**.



Scheme 5. Synthesis of optically pure oxabicycloheptene amino acid **16**. Reagents and conditions: (i) TFA, DCM, 95%; (ii) Benzaldehyde, AcOH, MeOH then NaBH3CN, 0 °C, 97%; (iii) NaOMe, MeOH, 77%; (iv) 1 M NaOH, dioxane then neutralisation with 1 M HCl, 100%.

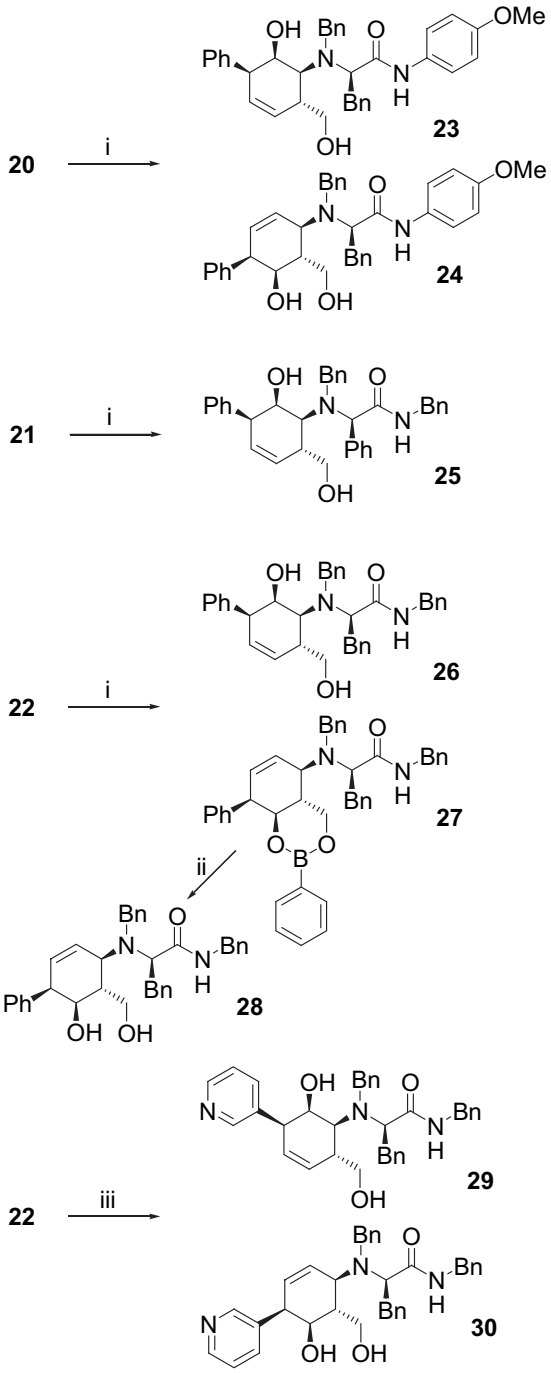
N-Benzylamino acid **16** was separately reacted with various aldehydes and isocyanides to afford compounds **17**, **18** and **19**, that were then treated with LAH to give, respectively, **20**, **21** and **22** in high yields (Scheme 6); *ent*-**20**–**22** were prepared analogously from *ent*-**16**.



Scheme 6. Synthesis of optically pure substrates for ring-opening reactions. Reagents and conditions: (i) MeOH, 57–93%; (ii) LAH, Et_2O, 0 °C, 85–86%.

Finally, Ugi adducts **20**, **21** and **22** and their enantiomers were reacted, under the conditions described for racemic **7** and **10**, with phenylboronic acid. Compound **22** was also reacted with 3-pyridineboronic acid. Interestingly, the reaction outcome was highly dependent on the nature of the substrates. In fact, while compound **20** gave the expected regioisomers **23** and **24** in a 65:35 ratio, compound **21** furnished only regioisomer **25**. Moreover, compound **22** gave, together with regioisomer **26**, cyclic boronate **27** when reacted with phenylboronic acid, but not when reacted with 3-pyridineboronic acid: in this case the two regioisomers **29** and **30** were obtained regularly in a 6:4 ratio (Scheme 7). Compound **28** was then quantitatively recovered from boronate **27** via basic hydrolysis.

These reaction outcomes revealed that the nature of the substituents of the bicyclic moiety could not direct the ring-opening process to the selective formation of one regioisomer, while conformational issues seemed more important. Indeed, in the case of compound **21** it is likely that one of the aromatic rings of the amino acidic side chain is in close proximity of the bicyclic double bond, as confirmed by the shielded signals of H-1, H-5 and H-6 in the ^{1}H NMR spectrum (respectively, 3.41, 6.12 and 6.07 ppm instead of 4.82–4.90, 6.31–6.34 and 6.41–6.44 ppm); according to the reaction mechanism[16] the attack of the Pd species would therefore be favoured on H-5, generating solely compound **25**. More difficult is to explain why cyclic boronates are formed only in some cases, and probably this is influenced not only by specific conformations assumed by the cyclohexenol derivatives but also by the different reactivity of the boronic acids employed. It is worth noting that in the case of



Scheme 7. Ring-opening reaction of optically pure substrates. Reagents and conditions: (i) Phenylboronic acid, $[Pd(C_6H_5CN)2]Cl_2$, 1,3-bis(diphenyl-phosphino)propane, Cs_2CO_3, H_2O, MeOH, 60 °C, 68–82%; (ii) 4 M NaOH, dioxane, 77%; (iii) 3-Pyridineboronic acid, $[Pd(C_6H_5CN)_2]Cl_2$, 1,3-bis(diphenyl-phosphino)propane, Cs_2CO_3, H_2O, MeOH, 60 °C, 74%.

compounds **10** and **22** the formation of cyclic boronates was faster than the ring-opening reaction: indeed when stoichiometric amount of boronic acid was employed the reaction did not reach completion, and the cyclic boronate was stable enough not to be hydrolysed under the reaction conditions. The hypothesis that specific conformational dispositions are influencing the reaction outcomes is somehow confirmed by the fact that compounds of general formula **31** (Fig. 1), prepared by us with an alternative synthetic approach,[17] having a similar but more flexible side chain, underwent the ring-opening reactions with reproducible outcomes, independent of the nature of the R group and the boronic acid.

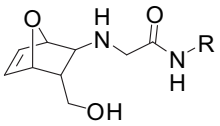


Figure 1. General structure of substrates that underwent the ring-opening reaction with reproducible outcomes.

In order to prove the complete stereoselectivity of the whole synthetic process and that no racemisation occurred throughout the various reactions, compound **28** and its enantiomer were analysed by HPLC using a chiral column (Diacel Chiralpak) and the absence of cross contaminant peaks confirmed our hypothesis.

3. Conclusions

In conclusion in this paper we have reported an additional transformation of pluripotent substrates **2** to yield two novel classes of regioisomeric cyclohexenol derivatives and have demonstrated that ring-opening reactions can be performed also on complex polyfunctionalised norbornene derivatives, although probably the conformation of the substrate has an influence on the reaction outcome. It is worth noting that this synthetic approach is completely stereoselective, both at the stage of the multicomponent condensation and of the ring-opening reaction, and that both enantiomers of the final compounds can be independently prepared.

This diversity-oriented approach has been recently exploited to discover novel inhibitors of protein–protein interactions involved in apoptotic processes[17] and will be further developed to produce an even larger collection of diversified structures, starting from common substrates, such as **2**, to be tested for their biological activity.

4. Experimental part

4.1. General

All solvents and reagents were obtained from commercial suppliers and used without further purification. NMR spectra were recorded with a VARIAN 'MERCURYplus 300' spectrometer. IR spectra were recorded on a Perkin–Elmer 881 spectrophotometer in $CHCl_3$ solution. GC–MS analyses were carried out on a Hewlett Packard 5890 Series II, using a HP-1 column, coupled with a HP-5971A spectrometer (electron impact). HRMSs were recorded with a MicroMass Autospec Instrument. Optical rotations were determined with a Jasco DP-181 polarimeter, using a Jasco cyclindrical cell 10×100 mm.

4.2. Ring-opening of racemic bicyclic ester 3

A mixture of zinc dust (420 mg, 6.5 mmol) and $Ni(PPh_3)_2Cl_2$ (42 mg, 65 μmol) in dry acetonitrile (2 mL) was vigorously stirred for 20 min under Ar at 50 °C, then substrate **3** (50 mg, 0.13 mmol) dissolved in acetonitrile (1 mL) was added and after 15 min also 3-iodoanisole (31 μL, 0.26 mmol) was added. The reaction mixture was stirred for 48 h, then filtered over a Celite pad and purified by flash chromatography (PE/AcOEt 7:3 to 1:1) yielding 4 mg of adduct **4** (10%), 19 mg of adduct **5** (30%) and 19 mg of adduct **6** (30%).

*4.2.1. (E)-Methyl 3-(N-(1-(benzylcarbamoyl)-3-methylbutyl)-N-methylamino)acrylate (**4**).* Colourless oil. R_f 0.30 (EtOAc/PE 3:7). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, *J*=6.6, 3H), 0.94 (d, *J*=6.6, 3H), 1.40–1.80 (m, 3H), 2.72 (s, 3H), 3.62 (s, 3H), 3.89 (dd, *J*=9.9, 5.4, 1H), 4.42 (d, *J*=5.7, 1H), 4.68 (d, *J*=13.2, 1H), 6.38 (t, *J*=5.4, 1H), 7.20–7.40 (m, 5H) 7.52 (d, *J*=12.9, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5 (CH_3), 23.2 (CH_3), 24.6 (CH), 33.3 (CH_3), 37.5 (CH_2), 43.6 (CH_2), 50.7 (CH_3), 65.8 (CH), 86.4 (CH), 127.6 (CH), 127.8 (CH), 128.7 (CH), 137.8 (C), 152.1 (CH), 169.7 (C), 170.2 (C). ν_{max}(liquid film) 3430, 2932, 2870, 1675, 1599, 1506, 1440, 1352, 1255, 1140 cm^{-1}. GC–MS (9.8 min) 318 (3, M) 185 (12), 184 (M−BnNHCO, 100), 110 (9), 91 (21), 84 (12), 82 (7), 69 (8), 59 (7), 43 (6), 42 (16), 41 (6). HRMS expected for $C_{18}H_{26}N_2O_3$: 318.1943, found: 318.1934, −2.8 ppm.

*4.2.2. (1SR,2RS,5RS,6SR)-Methyl 2-(N-((RS)-1-(benzylcarbamoyl)-3-methylbutyl)-N-methylamino)-6-hydroxy-5-(3-methoxyphenyl)cyclohex-3-enecarboxylate (**5**).* Colourless oil. R_f 0.17 (EtOAc/PE 3:7). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, *J*=6.6, 3H), 0.98 (d, *J*=6.3, 3H), 1.40–1.80 (m, 4H), 2.38 (s, 3H), 2.67 (t, *J*=10.8, 1H), 3.23 (dd, *J*=8.2, 6.7, 1H), 3.44 (s, 3H), 3.73 (dd, *J*=5.4, 4.2, 1H), 3.79 (s, 3H), 3.96 (dd, *J*=10.5, 1.8, 1H), 4.18 (dd, *J*=11.1, 6.1, 1H), 4.37 (dd, *J*=14.7, 5.5, 1H), 4.46 (dd, *J*=14.7, 5.8, 1H), 5.84 (ddd, *J*=10.2, 4.5, 2.1, 1H), 5.91 (d, *J*=10.2, 1H), 6.66 (t, *J*=5.4, 1H), 6.76–6.90 (m, 3H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5 (CH_3), 23.3 (CH_3), 25.2 (CH), 33.8 (CH_3), 39.9 (CH_2), 43.2 (CH_2), 46.7 (CH), 48.5 (CH), 51.6 (CH_3), 55.2 (CH_3), 60.4 (CH), 65.5 (CH), 69.8 (CH), 113.2 (CH), 116.1 (CH), 126.0 (CH), 127.5 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 129.4 (CH), 129.7 (CH), 138.1 (C), 138.3 (C), 159.8 (C), 174.0 (C), 174.2 (C). ν_{max}(liquid film) 3567, 3355, 2947, 1725, 1656, 1598, 1451, 1208, 1155, 1046 cm^{-1}. HRMS expected for $C_{29}H_{38}N_2O_5$: 494.2781, found: 494.2800, 3.8 ppm.

*4.2.3. (1RS,4SR,5RS,6SR)-Methyl 6-(N-((RS)-1-(benzylcarbamoyl)-3-methylbutyl)-N-methylamino)-5-hydroxy-4-(3-methoxyphenyl)cyclohex-2-enecarboxylate (**6**).* Colourless oil. R_f 0.30 (EtOAc/PE 3:7). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, *J*=6.6, 3H), 0.94 (d, *J*=6.6, 3H), 1.17 (br s, 1H), 1.42–1.80 (m, 3H), 2.44 (s, 3H), 3.42 (dd, *J*=8.1, 6.6, 1H), 3.51 (d, *J*=11.1, 1H), 3.54 (s, 3H), 3.65 (br s, 1H), 3.76 (ddt, *J*=10.8, 3.6, 2.1, 1H), 3.82 (s, 3H), 4.10 (br s, 1H), 4.33 (dd, *J*=14.7, 5.1, 1H), 4.46 (dd, *J*=14.7, 6.0, 1H), 5.69 (br d, *J*=10.2, 1H), 5.78 (dt, *J*=10.2, 2.1, 1H), 6.70 (m, 1H), 6.75 (d, *J*=7.5, 1H), 6.86 (dd, *J*=8.1, 2.5, 1H), 7.08 (t, *J*=5.1, 1H), 7.20–7.27 (m, 5H), 7.30 (t, *J*=7.8, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5 (CH_3), 23.3 (CH_3), 25.2 (CH), 34.5 (CH_3), 38.8 (CH_2), 42.9 (CH), 43.3 (CH_3), 49.0 (CH), 52.0 (CH_3), 55.3 (CH_3), 62.5 (CH), 63.6 (CH), 69.7 (CH), 112.7 (CH), 114.2 (CH), 120.7 (CH), 126.2 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 128.6 (CH), 130.1 (CH), 138.6 (C), 141.4 (C), 160.1 (C), 174.6 (C), 174.8 (C). ν_{max}(liquid film) 3553, 3361, 2948, 1724, 1660, 1596, 1454, 1363, 1227, 1025 cm^{-1}. HRMS expected for $C_{29}H_{38}N_2O_5$: 494.2781, found: 494.2789, 1.6 ppm.

4.3. Ring-opening of racemic bicyclic alcohol 7

Substrate **7** (69 mg, 0.19 mmol), phenylboronic acid (28 mg, 0.23 mmol), $Pd(C_6H_5CN)_2Cl_2$ (7 mg, 0.019 mmol) and 1,3-bis(diphenylphosphine)propane (8 mg, 0;021 mmol) were placed under Ar and MeOH (2.4 mL) and 5 M Cs_2CO_3 (0.19 mmol, 38 μL) were added. The reaction was heated at 60 °C overnight, then diluted with brine and extracted with EtOAc. The crude was purified by flash chromatography (PE/EtOAc 4:6 to 3:7), yielding 67 mg (80%) of a 62:38 mixture of compounds **8** and **9**.

*4.3.1. (RS)-2-(N-((1RS,4RS,5SR,6RS)-5-Hydroxy-6-(hydroxymethyl)-4-phenylcyclohex-2-enyl)-N-methylamino)-N-benzyl-4-methylpentanamide (**8**).* Colourless oil. R_f 0.38 (EtOAc/PE 6:4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, *J*=6.4, 6H), 1.55–1.70 (m, 3H), 1.85–1.95 (m, 1H), 2.44 (s, 3H), 3.27 (t, *J*=7.2, 1H), 3.53 (d, *J*=9.6, 1H), 3.66 (dd, *J*=5.8, 3.6, 1H), 3.74 (dd, *J*=10.9, 6.3, 1H), 3.85 (dd, *J*=10.9, 4.5, 1H), 3.91 (dd, *J*=10.8, 6.1, 1H), 4.41 (dd, *J*=14.6, 5.6, 1H), 4.50 (dd, *J*=14.6, 6.0, 1H), 5.85 (m, 2H), 6.40 (t, *J*=5.7, 1H), 7.20–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.6 (CH_3), 23.5 (CH_3), 25.4 (CH), 33.3 (CH_3), 39.8 (CH and CH_2), 43.7 (CH_2), 47.1 (CH), 61.7 (CH), 64.3 (CH_2), 66.5 (CH), 70.7 (CH), 127.79 (CH), 127.85 (CH), 128.1 (CH), 128.3 (CH), 128.8 (CH), 128.9 (CH), 130.2 (CH), 130.5 (CH), 137.5 (C), 138.3 (C), 173.4 (C). ν_{max}(liquid film) 3600–3200 (br), 3427, 2953, 1661, 1452,

1251, 1168, 1028 cm^{-1}. HRMS expected for $C_{27}H_{36}N_2O_3$: 436.2726, found: 436.2712, −3.2 ppm.

*4.3.2. (RS)-2-(N-((1SR,2RS,5SR,6RS)-6-Hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)-N-methylamino)-N-benzyl-4-methylpentanamide (**9**).* Colourless oil. R_f 0.44 (EtOAc/PE 6:4). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, J=5.9, 6H), 1.25 (br s, 1H), 1.50–1.80 (m, 3H), 2.57 (s, 3H), 2.92 (m, 1H) 3.21 (dd, J=10.6, 0.8, 1H), 3.35 (dd, J=8.4, 6.1, 1H), 3.62 (m, 1H), 3.66 (dd, J=10.6, 7.4, 1H), 3.79 (dd, J=10.6, 3.9, 1H), 4.11 (m, 1H), 4.32 (dd, J=14.5, 5.1, 1H), 4.54 (dd, J=14.5, 6.2, 1H), 5.64 (dm, J=10.2, 1H), 5.70 (ddd, J=10.2, 2.1, 1.8, 1H), 6.50 (t, J=5.3, 1H), 7.10–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7 (CH_3), 23.3 (CH_3), 25.5 (CH), 34.3 (CH_3), 35.6 (CH), 39.5 (CH_2), 43.8 (CH_2), 49.5 (CH), 65.2 (CH), 66.5 (CH), 66.9 (CH_2), 70.7 (CH), 127.4 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 129.1 (CH), 130.1 (CH), 138.3 (C), 140.5 (C), 173.9 (C). ν_{max}(liquid film) 3600–3200 (br), 3429, 2949, 1664, 1601, 1490, 1184, 1023 cm^{-1}. HRMS expected for $C_{27}H_{36}N_2O_3$: 436.2726, found: 436.2718, −1.8 ppm.

*4.3.3. (RS)-2-(N-((1RS,2SR,3RS,4SR)-3-(Hydroxymethyl)-7-oxa-bicyclo[2.2.1]hept-5-en-2-yl)-N-methylamino)-N-benzyl-4-methylpentanamide (**7**).* Compound **3** (256 mg, 0.66 mmol) dissolved in dry diethylether (2 mL) was added at 0 °C to a suspension of LAH (50 mg, 1.32 mmol) in dry diethylether (2 mL) under a nitrogen atmosphere. After 1 h the reaction was complete by TLC analysis and was quenched by addition of EtOAc and 0.2 M HCl; the mixture was then filtered over a Celite pad and the organic phase washed with saturated sodium bicarbonate and brine. The crude (228 mg, 96%) did not need further purification. Colourless oil. R_f 0.10 (EtOAc/PE 7:3). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J=6.9, 3H), 0.94 (d, J=6.9, 3H), 1.40–1.95 (m, 3H), 2.29 (m, 1H), 2.52 (s, 3H), 2.58 (d, J=3.6, 1H), 3.20 (dd, J=11.4, 7.8, 1H), 3.36 (dd, J=11.1, 6.3, 1H), 3.57 (dd, J=9.9, 4.5, 1H), 4.40 (d, J=6.0, 2H), 4.84 (d, J=4.2, 1H), 4.96 (s, 1H), 6.20 (dd, J=6.0, 1.8, 1H), 6.32 (dd, J=6.0, 1.5, 1H), 7.20–7.40 (m, 5H) 8.37 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (CH_3), 23.7 (CH_3), 25.6 (CH), 34.4 (CH_3), 37.4 (CH_2), 43.6 (CH_2), 44.1 (CH), 64.1 (CH_2), 65.7 (CH), 66.8 (CH), 79.3 (CH), 81.3 (CH), 127.6 (CH), 128.3 (CH), 128.8 (CH), 135.3 (CH), 136.0 (CH), 138.4 (C), 171.5 (C). ν_{max}(liquid film) 3600–3200 (br), 3430, 2986, 1655, 1448, 1224, 1134, 1045 cm^{-1}. GC–MS (9.8 min) 318 (3, M), 185 (12), 184 (M−BnNHCO, 100), 110 (9), 91 (21), 84 (12), 82 (7), 69 (8), 59 (7), 43 (6), 42 (16), 41 (6). HRMS expected for $C_{21}H_{30}N_2O_3$: 358.2256, found: 358.2271, 4.1 ppm.

*4.3.4. (RS)-2-(N-((1RS,2SR,3RS,4SR)-3-(Hydroxymethyl)-7-oxa-bicyclo[2.2.1]hept-5-en-2-yl)-N-methylamino)-N-tert-butyl-4-methylpentanamide (**10**).* It was obtained similarly to **7** from the corresponding ester (yield 91%). Colourless oil. R_f 0.85 (EtOAc/PE 7:3). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, J=6.6, 3H), 0.94 (d, J=6.6, 3H), 1.34 (s, 9H), 1.38–1.74 (m, 3H), 2.26 (tdd, J=11.1, 4.2, 3.5, 1H), 2.33 (s, 3H), 2.48 (d, J=3.6, 1H), 2.96 (br s, 1H), 3.19 (dd, J=9.0,5.5, 1H), 3.38 (dd, J=11.1, 7.4, 1H), 3.44 (dd, J=11.1, 6.7, 1H), 4.86 (s, 1H), 4.92 (d, J=4.5, 1H), 6.37 (dd, J=5.8, 1.4, 1H), 6.41 (dd, J=5.8, 1.8, 1H), 6.49 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.2 (CH_3), 23.6 (CH_3), 25.6 (CH), 28.6 (CH_3), 34.4 (CH_3), 38.7 (CH_2), 43.2 (CH), 50.9 (C), 64.7 (CH_2), 65.2 (CH), 66.7 (CH), 79.3 (CH), 82.2 (CH), 135.4 (CH), 135.7 (CH), 173.5 (C). ν_{max}(liquid film) 3600–3200 (br), 3425, 2994, 1660, 1443, 1332, 1181, 1041 cm^{-1}. HRMS expected for $C_{18}H_{32}N_2O_3$: 324.2413, found: 324.2413, 0 ppm.

*4.3.5. (RS)-2-(N-((4aRS,5RS,8RS,8aSR)-4a,5,8,8a-Tetrahydro-2,8-di(thiophen-3-yl)-4H-benzo[d][1,3,2]dioxaborinin-5-yl)-N-methylamino)-N-tert-butyl-4-methylpentanamide (**11**).* It was obtained according to the procedure described in Section 4.3, purification by flash chromatography (eluent: PE/EtOAc 8:2, yield 38%). Colourless oil. R_f 0.85 (EtOAc/PE 7:3). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, J=7.5, 3H), 0.97 (d, J=7.5, 3H), 1.35 (s, 9H), 1.50–1.73 (m, 3H), 2.17 (qd, J=10.6, 4.4, 1H), 2.32 (s, 3H), 3.00 (dd, J=8.7, 6.2, 1H), 3.40 (d, J=10.6, 1H), 3.83 (t, J=10.6, 1H), 3.96 (t, J=4.0, 1H), 4.24–4.33 (m, 2H), 5.85 (d, J=10.4, 1H), 6.01–6.09 (m, 1H), 6.07 (s, 1H), 7.04 (br s, 1H), 7.16 (dd, J=4.9, 1.1, 1H), 7.21 (dd, J=7.3, 2.8, 1H), 7.29 (dd, J=7.3, 2.8, 1H), 7.32 (dd, J=4.8, 1.1, 1H), 7.76 (dd, J=4.9, 1.1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.4 (CH_3), 23.6 (CH_3), 25.2 (CH), 28.7 (CH_3), 33.9 (CH_3), 35.1 (CH), 40.3 (CH_2), 41.2 (CH), 50.6 (C), 59.1 (CH), 64.7 (CH_2), 67.1 (CH), 72.6 (CH), 123.5 (CH), 124.6 (CH), 125.0 (CH), 127.5 (CH), 129.9 (CH), 130.3 (CH), 131.4 (CH), 134.8 (CH), 139.1 (C), 173.3 (C). ν_{max}(liquid film) 3426, 2957, 1665, 1500, 1394, 1284, 1190, 1028 cm^{-1}. GC–MS (14.8 min) 400 (31, M−*t*-BuNHCO) 200 (9), 175 (23), 153 (13), 128 (13), 100 (100), 97 (89), 79 (14), 57 (32), 42 (25). HRMS expected for $C_{26}H_{37}BN_2O_3S_2$: 500.2339, found: 500.2321, −3.5 ppm.

*4.3.6. (RS)-2-(N-((1SR,2RS,5SR,6RS)-6-Hydroxy-2-(hydroxymethyl)-5-(thiophen-3-yl)cyclohex-3-enyl)-N-methylamino)-N-tert-butyl-4-methylpentanamide (**12**).* It was obtained according to the procedure described in Section 4.3, purification by flash chromatography (eluent: PE/EtOAc 4:6, yield 62%). Colourless oil. R_f 0.48 (EtOAc/PE 7:3). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, J=6.0, 6H), 1.37 (s, 9H), 1.37–1.68 (m, 5H), 2.59 (s, 3H), 2.95 (m, 1H), 3.14–3.21 (m, 2H), 3.67 (dd, J=10.0, 8.9, 1H), 3.77 (t, J=3.1, 1H), 3.84 (dd, J=10.7, 3.6, 1H), 4.20 (br s, 1H), 5.68 (m, 2H), 5.73 (br s, 1H), 6.94 (dd, J=5.0, 1.3, 1H), 7.10 (br s, 1H), 7.36 (dd, J=5.0, 2.9, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.6 (CH_3), 23.6 (CH_3), 25.5 (CH), 28.9 (CH_3), 34.4 (CH_3), 35.4 (CH), 39.7 (CH_2), 45.4 (CH), 51.4 (C), 65.1 (CH), 67.3 (CH_2), 67.5 (CH), 69.7 (CH), 122.3 (CH), 126.8 (CH), 127.4 (CH), 127.7 (CH), 129.8 (CH), 141.3 (C), 173.1 (C). ν_{max}(liquid film) 3600–3200 (br), 3430, 2998, 2955, 1667, 1451, 1364, 1191, 1046 cm^{-1}. GC–MS (11.2 min) 308 (100, M−*t*-BuNHCO), 161 (5), 142 (6), 123 (6), 100 (60), 84 (10), 72 (5), 58 (21), 57 (15), 42 (14). HRMS expected for $C_{22}H_{36}N_2O_3S$: 408.2447, found: 408.2454, 1.7 ppm.

4.4. Synthesis of optically pure bicyclic amino acids

*4.4.1. (1S,2R,3S,4R)-Benzyl 3-(benzylamino)-7-oxa-bicyclo[2.2.1]-hept-5-ene-2-carboxylate (**14**).* Compound **13** (865 mg, 2.11 mmol) was dissolved in dry DCM (9 mL) and treated with trifluoroacetic acid (1 mL) under a N_2 atmosphere. After 1 h (TLC monitoring) the solvents were removed under reduced pressure and the crude was partitioned between Et_2O and 1 M HCl; the aqueous phase was then neutralised with solid sodium carbonate (pH 9) and extracted with DCM/MeOH 9:1. The organic phase was dried and the solvents removed under vacuum, the crude material (95%) was used without further purification in the following reaction. Deprotected bicyclic amino ester (491 mg, 2.00 mmol) was dissolved in MeOH (12.8 mL) and AcOH (3.2 mL) and benzaldehyde (304 μL, 3.00 mmol) was added under a N_2 atmosphere. After 1.5 h the reaction mixture was cooled to 0 °C and $NaBH_3CN$ (220 mg, 3.51 mmol) was added portionwise over a 10 min period. After 0.5 h the reaction mixture was poured into saturated $NaHCO_3$ (30 mL) and the aqueous phase extracted with DCM (3×25 mL). The combined organics were dried and concentrated under vacuum, yielding 651 mg (97%) of a colourless oil. R_f 0.40 (EtOAc/PE 1:1). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.79 (s, 1H), 2.77 (d, J=8.1, 1H), 3.18 (d, J=8.1, 1H), 3.71 (d, J=13.8, 1H), 3.87 (d, J=13.8, 1H), 4.83 (s, 1H), 5.08 (s, 1H), 5.16 (d, J=12.6, 1H), 5.21 (d, J=12.6, 1H), 6.30 (dd, J=6.0, 1.5, 1H), 6.35 (dd, J=6.0, 1.5, 1H), 7.20–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.8 (CH), 51.8 (CH_2), 59.8 (CH), 66.6 (CH_2), 79.5 (CH), 80.9 (CH), 126.8 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 135.5 (CH), 135.8 (C), 137.1 (CH), 139.8 (C), 172.3 (C). ν_{max}(liquid film) 3036, 2942, 1722, 1601, 1442, 1367, 1163, 1107, 1010 cm^{-1}. HRMS expected for $C_{21}H_{21}NO_3$: 335.1521, found: 335.1518, −0.8 ppm.

*4.4.2. (1S,2S,3S,4R)-Methyl 3-(benzylamino)-7-oxa-bicyclo[2.2.1]-hept-5-ene-2-carboxylate (**15**).* Derivative **14** (710 mg, 2.12 mmol)

was dissolved in dry MeOH (7.5 mL) and sodium hydride (60% in mineral oil, 127 mg, 3.18 mmol) was added portionwise. The reaction mixture was left stirring at room temperature under a nitrogen atmosphere for 4 h, then diluted with EtOAc and washed with saturated $NaHCO_3$. The organic phase was dried, concentrated in vacuo and purified by flash chromatography (eluent from PE/EtOAc 7:3 to 4:6), yielding 450 mg (1.74 mmol, 82%) of product as a colourless oil. R_f 0.32 (PE/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63 (s, 1H), 2.77 (dd, J=4.9, 2.7, 1H), 3.18 (d, J=2.7, 1H), 3.66 (s, 3H), 3.88 (s, 2H), 4.83 (s, 1H), 5.12 (d, J=2.7, 1H), 6.37 (dd, J=6.0, 1.4, 1H), 6.41 (dd, J=6.0, 1.7, 1H), 7.24–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.8 (CH), 52.1 (CH_2), 52.4 (CH_3), 62.2 (CH), 78.5 (CH), 83.5 (CH), 127.0 (CH), 128.1 (CH), 128.8 (CH), 135.4 (CH), 135.5 (CH), 139.8 (C), 171.8 (C). ν_{max}(liquid film) 2947, 1728, 1490, 1434, 1342, 1269, 1053 cm^{-1}. HRMS expected for $C_{15}H_{17}NO_3$: 259.1208, found: 259.1209, 0.4 ppm.

*4.4.3. (1S,2S,3S,4R)-3-(Benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**16**)*[5]. Compound **15** (450 mg, 1.74 mmol) was dissolved in dioxane (3 mL) and a 1 M volumetric standard NaOH solution (1.91 mmol, 2.021 g) was added. After consumption of the starting material a 1 M volumetric standard HCl solution (1.91 mmol, 1.980 g) was added and the solvents were removed in vacuo. The resulting white solid containing 1.74 mmol of product and 1.91 mmol of NaCl was used without further purification.

4.4.4. (1R,2R,3R,4S)-3-(Benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid ent-(16). The compound was prepared similarly to **16** starting from *ent*-**13**, prepared according to a previously reported procedure.[5]

4.5. Synthesis of optically pure bicyclic alcohols 20–22

Derivative **16** (1.00 mmol) or *ent*-**16** was suspended in dry MeOH (1 mL) and the aldehyde (1.10 mmol) and isocyanide (1.10 mmol) were added at room temperature. The reaction mixture was left stirring at room temperature for 24–48 h, then the solvent evaporated and the crude purified by flash chromatography (PE/EtOAc eluent). Ugi adducts **17**–**19** were reduced to the corresponding alcohols according to the procedure described in Section 4.3.3.

*4.5.1. (1S,2S,3S,4R)-Methyl 3-(N-((R)-1-(4-methoxyphenylcarbamoyl)-2-phenylethyl)-N-benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**17**).* Yield 72%. Colourless oil. R_f 0.4 (PE/EtOAc 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.04 (dd, J=13.8, 6.0, 1H), 3.05 (t, J=4.2, 1H), 3.38 (d, J=4.0, 1H), 3.43 (s, 3H), 3.48 (dd, J=13.8, 7.1, 1H), 3.80 (s, 3H), 3.85 (dd, J=7.2, 6.0, 1H), 3.96 (d, J=14.9, 1H), 4.17 (d, J=14.9, 1H), 4.92 (s, 1H), 5.32 (d, J=4.5, 1H), 6.39 (dd, J=5.8, 1.2, 1H), 6.43 (dd, J=5.8, 1.3, 1H), 6.82 (d, J=9.0, 2H), 7.18–7.39 (m, 12H), 8.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.4 (CH_2), 48.3 (CH), 52.1 (CH_3), 55.5 (CH_3), 64.5 (CH), 64.6 (CH), 78.4 (CH), 82.4 (CH), 114.1 (CH), 121.0 (CH), 126.3 (CH), 127.4 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.3 (CH), 131.2 (C), 135.6 (CH), 136.2 (CH), 139.36 (C), 139.42 (C), 156.1 (C), 170.4 (C), 172.4 (C). ν_{max}(liquid film) 3004, 1725, 1676, 1601, 1504, 1428, 1297, 1181, 1026 cm^{-1}. $[\alpha]_D^{20}$ −24.8 (c 1.0, $CHCl_3$). HRMS expected for $C_{31}H_{32}N_2O_5$: 512.2311, found: 512.2319, 1.6 ppm.

*4.5.2. (1R,2R,3R,4S)-Methyl 3-(N-((S)-1-(4-methoxyphenylcarbamoyl)-2-phenylethyl)-N-benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate ent-(**17**).* $[\alpha]_D^{20}$ +25.5 (c 1.0, $CHCl_3$).

*4.5.3. (1S,2S,3S,4R)-Methyl 3-(N-((R)-1-(benzylcarbamoyl)(phenyl)methyl)-N-benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**18**).* Yield 57%. Colourless oil. R_f 0.28 (PE/EtOAc 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (t, J=4.5, 1H), 3.44–3.45 (m, 2H), 3.59 (s, 3H), 3.61 (d, J=15.0, 1H), 4.25 (dd, J=15.0, 3.8, 1H), 4.26 (d, J=15.0, 1H), 4.57 (s, 1H), 4.88 (dd, J=15.0, 7.5, 1H), 4.95 (d, J=4.5, 1H), 6.07 (dd, J=5.8, 1.8, 1H), 6.29 (dd, J=5.8, 1.5, 1H), 7.24–7.44 (m, 15H), 8.22 (dd, J=7.5, 3.8, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.1 (CH_2), 47.3 (CH), 50.3 (CH_2), 52.2 (CH_3), 65.1 (CH), 67.2 (CH), 77.8 (CH), 80.2 (CH), 127.1 (CH), 127.47 (CH), 127.52 (CH), 128.2 (CH), 128.48 (CH), 128.58 (CH), 128.64 (CH), 128.8 (CH), 130.3 (CH), 135.4 (CH), 136.0 (C), 136.8 (CH), 138.6 (C), 138.8 (C), 171.0 (C), 172.7 (C). ν_{max}(liquid film) 3425, 3025, 1720, 1663, 1490, 1449, 1269, 1164, 1007 cm^{-1}. $[\alpha]_D^{20}$ −26.3 (c 1.0, $CHCl_3$). HRMS expected for $C_{30}H_{30}N_2O_4$: 482.2206, found: 482.2198, −1.7 ppm.

*4.5.4. (1R,2R,3R,4S)-Methyl 3-(N-((S)-1-(benzylcarbamoyl)(phenyl)methyl)-N-benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate ent-(**18**).* $[\alpha]_D^{20}$ +27.0 (c 1.0, $CHCl_3$).

*4.5.5. (1S,2S,3S,4R)-Methyl 3-(N-((R)-1-(benzylcarbamoyl)-2-phenylethyl)-N-benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (**19**).* Yield 93%. Colourless oil. R_f 0.40 (PE/EtOAc 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.90 (t, J=4.2, 1H), 2.99 (dd, J=12.0, 6.3, 1H), 3.33 (d, J=3.9, 1H), 3.38 (dd, J=12.0, 7.5, 1H), 3.55 (s, 3H), 3.78 (t, J=6.0, 1H), 3.97 (d, J=15.3, 1H), 4.06 (d, J=15.3, 1H), 4.31 (dd, J=15.0, 6.6, 1H), 4.43 (dd, J=15.0, 6.6, 1H), 4.79 (s, 1H), 4.86 (d, J=4.2, 1H), 6.32 (dd, J=6.0, 1.3, 1H), 6.35 (dd, J=6.0, 1.7, 1H), 6.88 (t, J=6.0, 1H), 7.13–7.33 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.6 (CH_2), 43.2 (CH_2), 47.3 (CH), 51.4 (CH_2), 51.9 (CH_3), 63.5 (CH), 64.1 (CH), 78.2 (CH), 82.7 (CH), 126.3 (CH), 127.0 (CH), 127.3 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 129.3 (CH), 135.7 (CH), 136.0 (CH), 138.2 (C), 139.2 (C), 139.4 (C), 172.26 (C), 172.28 (C). ν_{max}(liquid film) 3388, 3029, 1727, 1665, 1492, 1218, 1026 cm^{-1}. $[\alpha]_D^{20}$ −28.9 (c 1.0, $CHCl_3$). HRMS expected for $C_{31}H_{32}N_2O_4$: 496.2362, found: 496.2344, −3.6 ppm.

*4.5.6. (1R,2R,3R,4S)-Methyl 3-(N-((S)-1-(benzylcarbamoyl)-2-phenylethyl)-N-benzylamino)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate ent-(**19**).* $[\alpha]_D^{20}$ +24.7 (c 1.0, $CHCl_3$).

*4.5.7. (R)-2-(N-Benzyl-N-((1R,2S,3R,4S)-3-(hydroxymethyl)-7-oxa-bicyclo[2.2.1]hept-5-en-2-yl)amino)-N-(4-methoxyphenyl)-3-phenylpropanamide (**20**).* Yield 85%. Colourless oil. R_f 0.28 (EtOAc/PE 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 1H), 2.38 (m, 1H), 2.80 (d, J=4.0, 1H), 3.04 (dd, J=13.6, 5.1, 1H), 3.37 (dd, J=13.6, 8.4, 1H), 3.43–3.53 (m, 2H), 3.76 (s, 3H), 3.77 (dd, J=8.4, 5.1, 1H), 3.88 (d, J=14.7, 1H), 4.28 (d, J=14.7, 1H), 4.90 (s, 1H), 4.96 (d, J=4.4, 1H), 6.34 (dd, J=5.9, 1.4, 1H), 6.44 (dd, J=5.9, 1.8, 1H), 6.80 (d, J=9.0, 2H), 7.17–7.41 (m, 12H), 8.17 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.9 (CH_2), 45.9 (CH), 51.1 (CH_2), 55.4 (CH_3), 63.1 (CH), 64.5 (CH), 65.0 (CH_2), 79.0 (CH), 81.8 (CH), 114.1 (CH), 121.0 (CH), 126.3 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.3 (CH), 130.9 (C), 135.3 (CH), 135.9 (CH), 139.3 (C), 139.7 (C), 156.1 (C), 171.0 (C). ν_{max}(liquid film) 3600–3200 (br), 3425, 3021, 1660, 1502, 1195, 1023 cm^{-1}. $[\alpha]_D^{20}$ +11.1 (c 1.0, $CHCl_3$). HRMS expected for $C_{30}H_{32}N_2O_4$: 484.2362, found: 484.2349, −2.7 ppm.

*4.5.8. (S)-2-(N-Benzyl-N-((1S,2R,3S,4R)-3-(hydroxymethyl)-7-oxa-bicyclo[2.2.1]hept-5-en-2-yl)amino)-N-(4-methoxyphenyl)-3-phenylpropanamide ent-(**20**).* $[\alpha]_D^{20}$ −10.8 (c 1.0, $CHCl_3$).

*4.5.9. (R)-2-(N-Benzyl-N-((1R,2S,3R,4S)-3-(hydroxymethyl)-7-oxa-bicyclo[2.2.1]hept-5-en-2-yl)amino)-N-benzyl-2-phenylacetamide (**21**).* Yield 86%. Colourless oil. R_f 0.42 (EtOAc/PE 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.30 (m, 1H), 2.46 (dd, J=5.5, 3.4, 1H), 3.00 (d, J=4.3, 1H), 3.17 (td, J=9.9, 3.1, 1H), 3.41 (s, 1H), 3.56 (d, J=15.1, 1H), 3.67 (dt, J=9.9, 5.2, 1H), 4.31 (d, J=15.1, 1H), 4.38 (dd, J=14.7, 5.4, 1H), 4.49 (s, 1H), 4.50 (dd, J=14.7, 6.4, 1H), 4.68 (d, J=4.4, 1H), 6.07 (dd, J=5.8, 1.8, 1H), 6.12 (dd, 1H, J=5.8, 1.6, 1H), 7.19–7.42 (m, 15H), 7.72 (t, J=5.7, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.1 (CH_2), 44.6 (CH), 50.1 (CH_2), 65.0 (CH), 65.1 (CH_2), 67.0 (CH), 78.3 (CH), 80.1 (CH), 127.18 (CH), 127.23 (CH), 127.6 (CH), 128.1 (CH), 128.47 (CH), 128.53 (CH), 128.6 (CH),

130.1 (CH), 133.9 (CH), 136.0 (C), 136.9 (CH), 138.7 (C), 139.3 (C), 171.7 (C). ν_{max}(liquid film) 3600–3200 (br), 3349, 2997, 1655, 1493, 1205, 1015 cm^{-1}. $[\alpha]_D^{20}$ −33.2 (*c* 1.0, $CHCl_3$). HRMS expected for $C_{29}H_{30}N_2O_3$: 454.2256, found: 454.2251, −1.1 ppm.

*4.5.10. (S)-2-(N-Benzyl-N-((1S,2R,3S,4R)-3-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)amino)-N-benzyl-2-phenylacetamide ent-(**21**).* $[\alpha]_D^{20}$ +31.1 (*c* 1.0, $CHCl_3$).

*4.5.11. (R)-2-(N-Benzyl-N-((1R,2S,3R,4S)-3-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)amino)-N-benzyl-3-phenylpropanamide (**22**).* Yield 85%. Colourless oil. R_f 0.28 (PE/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (t, *J*=4.8, 1H), 2.21 (m, 1H), 2.88 (d, *J*=3.9, 1H), 3.02 (dd, *J*=18.9, 5.4, 1H), 3.27 (dd, *J*=18.9, 8.7, 1H), 3.33–3.34 (m, 2H), 3.62 (dd, *J*=8.7, 5.4, 1H), 3.92 (d, *J*=15.0, 1H), 4.17 (d, *J*=15.0, 1H), 4.25 (dd, *J*=14.7, 5.7, 1H), 4.33 (dd, *J*=14.7, 5.7, 1H), 4.79 (d, *J*=4.5, 1H), 4.82 (s, 1H), 6.31 (dd, *J*=5.9, 1.5, 1H), 6.41 (dd, *J*=5.9, 1.8, 1H), 6.45 (t, *J*=6.0, 1H), 7.09–7.32 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.7 (CH_2), 43.2 (CH_2), 45.5 (CH), 50.9 (CH_2), 62.8 (CH), 64.1 (CH), 65.1 (CH_2), 78.9 (CH), 82.3 (CH), 126.3 (CH), 127.1 (CH), 127.4 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 129.2 (CH), 135.2 (CH), 135.9 (CH), 138.1 (C), 139.0 (C), 139.9 (C), 172.8 (C). ν_{max}(liquid film) 3600–3200 (br), 3419, 3005, 1653, 1496, 1214, 1017 cm^{-1}. $[\alpha]_D^{20}$ +7.2 (*c* 1.0, $CHCl_3$). HRMS expected for $C_{30}H_{32}N_2O_3$: 468.2413, found: 468.2401, −2.6 ppm.

*4.5.12. (S)-2-(N-Benzyl-N-((1S,2R,3S,4R)-3-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-en-2-yl)amino)-N-benzyl-3-phenylpropanamide ent-(**22**).* $[\alpha]_D^{20}$ −6.9 (*c* 1.0, $CHCl_3$).

4.6. Ring-opening of optically pure bicyclic alcohols 20–22

Compounds **20**–**22** and *ent*-**20**-*ent*-**22** underwent the ring-opening process according to the procedure described in Section 4.3.

*4.6.1. (R)-2-(N-Benzyl-N-((1S,2R,5S,6R)-6-hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)amino)-N-(4-methoxyphenyl)-3-phenylpropanamide (**23**).* Yield 44%. Yellowish foam. R_f 0.48 (PE/EtOAc 6:4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (d, *J*=2.3, 1H), 2.87 (br s, 1H), 3.21–3.50 (m, 5H), 3.70 (br s, 1H), 3.74 (s, 3H) 3.77–3.80 (m, 1H) 3.94 (d, *J*=13.7, 1H), 3.92–3.98 (m, 1H), 4.42 (br s, 1H), 4.50 (d, *J*=13.7, 1H), 5.66 (d, *J*=10.2, 1H), 5.78 (dt, *J*=10.2, 1.9, 1H), 6.77 (d, *J*=9.0, 1H), 7.12–7.43 (m, 17H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.8 (CH_2), 37.4 (CH), 49.7 (CH), 52.3 (CH_2), 55.4 (CH_3), 60.0 (CH), 64.0 (CH), 65.3 (CH_2), 70.5 (CH), 114.0 (CH), 121.8 (CH), 126.4 (CH), 126.9 (CH), 127.4 (CH), 127.5 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 129.0 (CH), 129.26 (CH), 129.29 (CH), 130.5 (CH), 131.1 (C), 139.0 (C), 140.0 (C), 140.4 (C), 156.4 (C), 171.3 (C). ν_{max}(liquid film) 3600–3200 (br), 2998, 1675, 1598, 1494, 1188, 1053, 1022 cm^{-1}. $[\alpha]_D^{20}$ −92.7 (*c* 1.0, $CHCl_3$). HRMS expected for $C_{36}H_{39}N_2O_4$: 563.2910, found: 563.2892, −3.2 ppm.

*4.6.2. (S)-2-(N-Benzyl-N-((1R,2S,5R,6S)-6-hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)amino)-N-(4-methoxyphenyl)-3-phenylpropanamide ent-(**23**).* $[\alpha]_D^{20}$ +99.8 (*c* 1.2, $CHCl_3$).

*4.6.3. (R)-2-(N-Benzyl-N-((1R,4R,5S,6R)-5-hydroxy-6-(hydroxymethyl)-4-phenylcyclohex-2-enyl)amino)-N-(4-methoxyphenyl)-3-phenylpropanamide (**24**).* Yield 24%. Yellowish foam. R_f 0.25 (PE/EtOAc 6:4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 (m, 1H), 1.90 (d, *J*=5.9, 1H), 2.88 (br s, 1H), 3.13 (dd, *J*=11.9, 1.8, 1H), 3.43–3.56 (m, 2H), 3.66–3.85 (m, 3H), 3.74 (s, 3H), 3.90 (d, *J*=8.5, 1H), 3.98 (d, *J*=13.8, 1H), 4.02–4.12 (m, 1H), 4.14 (d, *J*=13.8, 1H), 5.89 (ddd, *J*=10.3, 4.9, 2.4, 1H), 6.22 (d, *J*=10.3, 1H), 6.77 (d, *J*=9.0, 1H), 7.18–7.38 (m, 19H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.4 (CH_2), 42.3 (CH), 46.6 (CH), 52.4 (CH_2), 55.4 (CH_3), 56.2 (CH), 61.1 (CH_2), 65.4 (CH), 69.7 (CH), 114.1 (CH), 121.6 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.4 (CH), 129.6 (CH), 130.1 (CH), 130.3 (CH), 130.5 (C), 137.9 (C), 138.8 (C), 140.0 (C), 156.4 (C), 171.1 (C). ν_{max}(liquid film) 3600–3200 (br), 3002, 1667, 1597, 1505, 1189, 1026 cm^{-1}. $[\alpha]_D^{20}$ +47.9 (*c* 1.2, $CHCl_3$). HRMS expected for $C_{36}H_{39}N_2O_4$: 563.2910, found: 563.2899, −1.9 ppm.

*4.6.4. (S)-2-(N-Benzyl-N-((1S,4S,5R,6S)-5-hydroxy-6-(hydroxymethyl)-4-phenylcyclohex-2-enyl)amino)-N-(4-methoxyphenyl)-3-phenylpropanamide ent-(**24**).* $[\alpha]_D^{20}$ −54.8 (*c* 0.9, $CHCl_3$).

*4.6.5. (R)-2-(N-Benzyl-N-((1S,2R,5S,6R)-6-hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)amino)-N-benzyl-2-phenylacetamide (**25**).* Yield 82%. Yellowish foam. R_f 0.38 (PE/EtOAc 6:4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (br s, 2H), 3.33 (br s, 1H), 3.70–3.90 (m, 3H), 4.29–4.48 (m, 5H), 4.83 (t, *J*=6.3, 1H), 5.63 (d, *J*=9.9, 1H), 5.81 (t, *J*=5.4, 1H), 5.94 (dt, *J*=9.9, 2.1, 1H), 6.84–7.47 (m, 20H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.3 (CH), 43.4 (CH_2), 49.0 (CH), 52.8 (CH_2), 58.5 (CH), 63.0 (CH_2), 66.0 (CH), 71.7 (CH), 126.7 (CH), 126.8 (CH), 127.1 (CH), 127.4 (CH), 127.7 (CH), 128.09 (CH), 128.14 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.7 (CH), 133.0 (CH), 137.4 (C), 137.9 (C), 140.4 (C), 140.7 (C), 172.9 (C). ν_{max}(liquid film) 3600–3200 (br), 3419, 2991, 1664, 1598, 1491, 1447, 1206, 1042 cm^{-1}. $[\alpha]_D^{20}$ −153.0 (*c* 1.1, $CHCl_3$). HRMS expected for $C_{35}H_{37}N_2O_3$: 533.2804, found: 533.2800, −0.8 ppm.

*4.6.6. (S)-2-(N-Benzyl-N-((1R,2S,5R,6S)-6-hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)amino)-N-benzyl-2-phenylacetamide ent-(**25**).* $[\alpha]_D^{20}$ +151.2 (*c* 0.9, $CHCl_3$).

*4.6.7. (R)-2-(N-Benzyl-N-((1S,2R,5S,6R)-6-hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)amino)-N-benzyl-3-phenylpropanamide (**26**).* Yield 40%. Yellowish foam. R_f 0.25 (PE/EtOAc 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56 (br s, 1H), 2.77 (br s, 1H), 3.18 and 3.24 (part AB of an ABX system, J_{ax}=3.4, J_{bx}=11.8, J_{ab}=11.8, 2H), 3.24–3.51 (m, 3H), 3.66–3.75 (m, 3H), 3.90 (d, *J*=13.5, 1H), 4.18 (dd, *J*=14.8, 5.4, 1H), 4.31 (dd, *J*=14.8, 4.3, 1H), 4.38 (s, 1H), 4.57 (d, *J*=13.5, 1H), 5.41 (t, *J*=4.8, 1H), 5.67 (d, *J*=10.5, 1H), 5.80 (dt, *J*=10.5, 1.9, 1H), 6.90–7.42 (m, 20H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.8 (CH_2), 37.4 (CH), 43.2 (CH_2), 49.7 (CH), 52.2 (CH_2), 59.1 (CH), 63.8 (CH), 64.6 (CH_2), 71.3 (CH), 126.3 (CH), 126.9 (CH), 127.28 (CH), 127.31 (CH), 127.7 (CH), 128.45 (CH), 128.47 (CH), 128.51 (CH), 128.6 (CH), 128.95 (CH), 129.03 (CH), 129.3 (CH), 131.4 (CH), 137.7 (C), 138.5 (C), 140.2 (C), 140.5 (C), 172.9 (C). ν_{max}(liquid film) 3600–3200(br), 3425, 3021, 1658, 1600, 1490, 1449, 1210, 1135, 1062 cm^{-1}. $[\alpha]_D^{20}$ −91.0 (*c* 1.5, $CHCl_3$). HRMS expected for $C_{36}H_{39}N_2O_3$: 547.2961, found: 547.3001, 7.3 ppm.

*4.6.8. (S)-2-(N-Benzyl-N-((1R,2S,5R,6S)-6-hydroxy-2-(hydroxymethyl)-5-phenylcyclohex-3-enyl)amino)-N-benzyl-3-phenylpropanamide ent-(**26**).* $[\alpha]_D^{20}$ +94.8 (*C* 0.7, $CHCl_3$).

*4.6.9. (R)-2-(N-Benzyl-N-((1R,4R,5S,6R)-5-hydroxy-6-(hydroxymethyl)-4-phenylcyclohex-2-enyl)amino)-N-benzyl-3-phenylpropanamide (**28**).* Yield 71% from **27**. Yellowish foam. R_f 0.10 (PE/EtOAc 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (tt, *J*=10.6, 3.2, 1H) 1.97 (d, *J*=7.4, 1H), 3.12 (d, *J*=3.1, 1H), 3.19–3.38 (m, 3H), 3.65–3.74 (m, 3H), 3.94 (d, *J*=14.0, 1H), 4.07–4.15 (m, 2H), 4.12 (d, *J*=14.0, 1H), 4.17 (dd, *J*=14.8, 5.6, 1H), 4.27 (dd, *J*=14.8, 6.0, 1H), 5.42 (br s, 1H), 5.88 (ddd, *J*=10.1, 5.0, 2.4, 1H), 6.18 (d, *J*=10.2, 1H), 6.88–7.27 (m, 20H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.3 (CH_2), 42.2 (CH), 43.2 (CH_2), 46.7 (CH), 52.2 (CH_2), 55.4 (CH), 60.0 (CH_2), 65.3 (CH), 69.1 (CH), 126.4 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.3 (CH), 129.6 (CH), 130.4 (CH), 130.9 (CH), 137.5 (C), 138.4 (2×C), 140.4 (C), 172.8 (C).

ν_{max}(liquid film) 3600–3200 (br), 3425, 3042, 2917, 1659, 1599, 1490, 1448, 1356, 1223, 1040 cm^{-1}. $[\alpha]_D^{20}$ +23.4 (*c* 1.1, $CHCl_3$). HPLC (Diacel Chiralpack): 5.34 min (100%). HRMS expected for $C_{36}H_{39}N_2O_3$: 547.2961, found: 547.2958, −0.5 ppm.

*4.6.10. (S)-2-(N-Benzyl-N-((1S,4R,5R,6S)-5-hydroxy-6-(hydroxymethyl)-4-phenylcyclohex-2-enyl)amino)-N-benzyl-3-phenylpropanamide ent-(**28**).* $[\alpha]_D^{20}$ −22.7 (*c* 1.1, $CHCl_3$). HPLC (Diacel Chiralpack): 12.99 min (100%).

*4.6.11. (R)-2-(N-Benzyl-N-((1S,2R,5S,6R)-6-hydroxy-2-(hydroxymethyl)-5-(pyridin-3-yl)cyclohex-3-enyl)amino)-N-benzyl-3-phenylpropanamide (**29**).* Yield 40%. Yellowish foam. R_f 0.70 (DCM/Acetone 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78 (br s, 1H), 2.77 (d, *J*=8.7, 1H), 3.15 and 3.25 (part AB of an ABX system, J_{ab}=11.9, J_{ax}=3.4, J_{bx}=11.7, 2H), 3.29–3.45 (m, 1H), 3.50 (d, *J*=10.6, 1H), 3.63 (m, 2H), 3.79 (m, 2H), 3.95 (d, *J*=13.9, 1H), 4.20 (dd, *J*=14.7, 5.4, 1H), 4.31 (dd, *J*=14.7, 6.0, 1H), 4.37 (s, 1H), 4.57 (d, *J*=13.9, 1H), 5.39 (t, *J*=5.4, 1H), 5.62 (d, *J*=10.0, 1H), 5.89 (dt, *J*=10.1, 2.3, 1H), 6.92 (m, 1H), 7.16–7.34 (m, 15H), 7.56 (d, *J*=7.9, 1H), 8.40 (d, *J*=4.7, 1H), 8.44 (d, *J*=1.8, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.0 (CH_2), 37.7 (CH), 43.3 (CH_2), 47.5 (CH), 52.4 (CH_2), 58.3 (CH), 64.1 (CH_2 and CH), 72.0 (CH), 123.6 (CH), 126.0 (CH), 126.5 (CH), 127.4 (CH), 127.8 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 132.6 (CH), 136.3 (CH), 136.5 (C), 137.6 (C), 138.2 (C), 140.2 (C), 148.4 (CH), 150.0 (CH). ν_{max}(liquid film) 3600–3200 (br), 3428, 2987, 1660, 1493, 1177, 1123, 1067 cm^{-1}. $[\alpha]_D^{20}$ −86.0 (*c* 1.26, $CHCl_3$). HRMS expected for $C_{35}H_{38}N_3O_3$: 548.2913, found: 548.2902, −2.0 ppm.

*4.6.12. (S)-2-(N-Benzyl-N-((1R,2S,5R,6S)-6-hydroxy-2-(hydroxymethyl)-5-(pyridin-3-yl)cyclohex-3-enyl)amino)-N-benzyl-3-phenylpropanamide ent-(**29**).* $[\alpha]_D^{20}$ +89.0 (*c* 0.35, $CHCl_3$).

*4.6.13. (R)-2-(N-Benzyl-N-((1R,4R,5S,6R)-5-hydroxy-6-(hydroxymethyl)-4-(pyridin-3-yl)cyclohex-2-enyl)amino)-N-benzyl-3-phenylpropanamide (**30**).* Yield 26%. Yellowish foam. R_f 0.58 (DCM/Acetone 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (t, *J*=10.5, 1H), 2.67 (br s, 1H), 3.13 and 3.28 (part AB of an ABX system, J_{ab}=15.9, J_{ax}=2.0, J_{bx}=10.1, 2H), 3.21 (d, *J*=10.1, 1H), 3.64–3.84 (m, 3H), 3.91 (d, *J*=14.1, 1H), 4.02 (d, *J*=14.1, 1H), 4.24–4.36 (m, 4H), 5.26 (br s, 1H), 5.88 (ddd, *J*=10.1, 5.1, 2.4, 1H), 6.22 (d, *J*=10.4, 1H), 6.88 (m, 1H), 7.16–7.34 (m, 15H), 7.58 (d, *J*=7.8, 1H), 8.42 (d, *J*=4.6, 1H), 8.47 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.1 (CH_2), 42.1 (CH), 43.1 (CH_2), 44.4 (CH), 52.4 (CH_2), 54.7 (CH), 59.0 (CH_2), 65.4 (CH), 68.6 (CH), 122.9 (CH), 126.4 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.3 (CH), 132.3 (CH), 134.6 (C), 137.5 (C), 137.9 (CH), 138.1 (C), 140.0 (C), 147.9 (CH), 151.3 (CH), 173.0 (C). ν_{max}(liquid film) 3600–3200 (br), 3427, 2962, 1651, 1491, 1229, 1116, 1046 cm^{-1}. $[\alpha]_D^{20}$ +4.5 (*c* 1.5, $CHCl_3$). HRMS expected for $C_{35}H_{38}N_3O_3$: 548.2913, found: 548.2928, 2.7 ppm.

*4.6.14. (S)-2-(N-Benzyl-N-((1S,4S,5R,6S)-5-hydroxy-6-(hydroxymethyl)-4-(pyridin-3-yl)cyclohex-2-enyl)amino)-N-benzyl-3-phenylpropanamide ent-(**30**).* $[\alpha]_D^{20}$ −11.0 (*c* 0.93, $CHCl_3$).

Acknowledgements

The authors thank Dott.ssa Romina Vitale for her important contribution to this work. Financial assistance by the University of Genova, the Ministry of University and Research (PRIN 2006 project "Diversity-oriented synthetic methodologies and strategies for the preparation of biologically active compounds") and Fondazione S. Paolo is gratefully acknowledged.

References and notes

1. Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.
2. Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147.
3. Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324–331.
4. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron Lett.* **2004**, *45*, 587–590.
5. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575–579.
6. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *Tetrahedron* **2006**, *62*, 8830–8837.
7. Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.
8. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
9. Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58.
10. Bunnage, M. E.; Ganesh, T.; Masesane, I. B.; Orton, D.; Steel, P. G. *Org. Lett.* **2003**, *5*, 239–242.
11. Arjona, O.; Delapradilla, R. F.; Garcia, E.; Martindomenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437–6440.
12. Harwood, L. M.; Jackson, B.; Prout, K.; Witt, F. J. *Tetrahedron Lett.* **1990**, *31*, 1885–1888.
13. Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538–3543.
14. Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695–3698.
15. Winkler, J. D.; Asselin, S. M.; Shepard, S.; Yuan, J. *Org. Lett.* **2004**, *6*, 3821–3824.
16. Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834–6839.
17. Di Micco, S.; Vitale, R.; Pellecchia, M.; Rega, M. F.; Riva, R.; Basso, A.; Bifulco, G. *J. Med. Chem.* **2009**, *52*, 7856–7867.