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Synthesis of non-natural L-alanine derivatives using the aza-Cope–Mannich reaction

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ABSTRACT

Non-natural L-alanine derived *trans*-octahydrocyclohepta[*b*]pyrroles were synthesized with high enantiomeric purity using the aza-Cope–Mannich reaction. The study showed that the conditions of the aza-Cope–Mannich reaction and metal catalysed cyclization are mild enough to be applied to the synthesis of molecules with stereocenters, which are prone to racemization. We believe that these compounds will be of interest to medicinal chemists.

1. Introduction

Non-natural α-amino acids have attracted significant interest from synthetic chemists; they are widely used as components of medicinally active molecules[1–3] and in chiral catalysis.[4,5] Various methods to access chiral, non-racemic, non-natural α-amino acids have been developed including chemoenzymatic methods,[6] the synthesis of racemates followed by resolution, asymmetric synthesis[7] and chiral pool synthesis.[8] Previously we have reported that several privileged[9] heterocyclic systems, such as indoles,[10–12] isatins,[13–15] pyrroles[16,17] and imidazoles[18,19] can be easily equipped with an enantiopure alanine residue.

We have recently disclosed a highly stereoselective and scalable (up to 1 mole) method to obtain natural-like compounds containing an octahydrocyclohepta[*b*]pyrrole core based on the aza-Cope–Mannich rearrangement.[20,21] Herein we report an extension of this method for the preparation of non-natural amino acid derivatives. The octahydrocyclohepta[*b*]pyrrole core and closely related scaffolds (e.g. octahydroindole) are represented in several biologically active compounds and alkaloids (e.g. perindopril, an ACE inhibitor and compound **1**, an agent for reversing amnesia,[22] Fig. 1). Herein we have chosen compound **2** as the model system (Scheme 1), because it contains an amino acid residue, which can be useful for medicinal chemistry applications. Furthermore, the alanine (the simplest chiral amino acid) moiety was used to gain a better understanding of the configurational stability of a new class of unnatural amino acids.

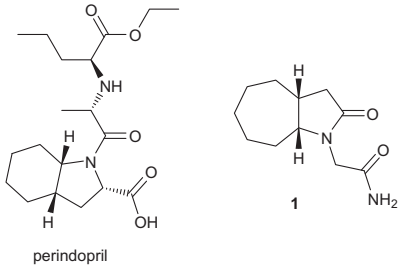

Figure 1. Examples of related biologically active compounds.

2. Results and discussion

Two distinct routes were envisioned to obtain target compound **2**. Both include the ring opening of enantiopure epoxide **5** with an *N*-nucleophile, the partial reduction of a triple bond and the aza-Cope–Mannich rearrangement (Scheme 1). In retrosynthesis A, the C—N bond could be formed by the alkylation of **3** with activated L-lactate derivatives. However, in our previous work, we had found that the direct alkylation results in significant epimerization of the resulting α-amino acids.[12,13] The alternative route (retrosynthesis B) was more attractive since the aza-Cope–Mannich rearrangement of the compound **4** proceeds under mild conditions (ambient temperature, effectively neutral pH), thus minimizing any possible epimerization of the substrate.[23] In addition, there is no need to refunctionalize the intermediates (i.e. debenzylation/alkylation).

Based on our experience[21] as well as Nicolaou et al.,[24–26] we assumed that the reaction between racemic epoxide **5** and an L-amino acid ester would lead to a separable diastereomeric

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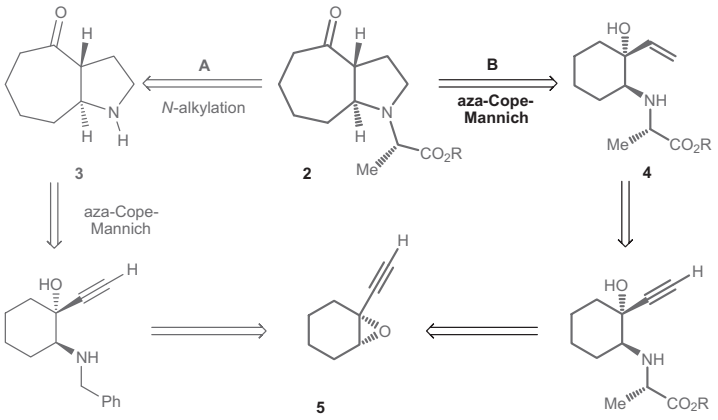
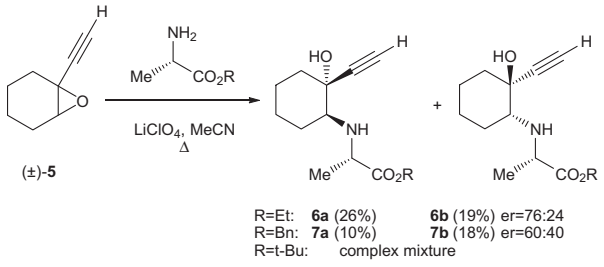


Scheme 1. Retrosynthetic analysis for a single enantiomer of **2**.



Scheme 2. Ring-opening of the racemic epoxide **5**.

mixture of aminoalcohols (both enantiopure). It was thought that such a transformation could provide convenient access to both *trans*-fused (1*S*)-diastereomers of **2** simultaneously.

Our synthesis commenced with ring-opening of the commercially available racemic epoxide **5** with L-alanine ethyl ester (Scheme 2). The reaction afforded amino alcohols **6a** and **6b** as a chromatographically separable (on 2 g scale) 1:1 mixture in a combined 45% yield. To verify the enantiomeric purity of **6a** and **6b**, we used chiral HPLC. Since the reference compounds are not easily available in a pure form, we decided to use a diastereomeric mixture, which was obtained from the reaction of racemic **5** and DL-alanine ethyl ester. The analysis showed the significant erosion of the enantiomeric purity (*er* = 76:24). These results are in an agreement with the fact that, in general, *N*-alkyl α-amino acids, such as **6**, are more prone to epimerization in basic reaction media than N-unsubstituted analogues.[27,28]

In order to improve the efficiency of the transformation we investigated other L-alanine esters. Epoxide opening with L-alanine benzyl ester[29] furnished amino alcohols **7a** and **7b** with low enantiopurity (*er* = 60:40, Scheme 2). Due to concomitant partial cleavage of the benzyl group compound **7a** was isolated as an inseparable mixture with benzyl alcohol. The reaction of **5** with L-alanine *tert*-butyl ester[30] produced an inseparable and complex mixture. This is probably due to $LiClO_4$-assisted *t*-Bu partial cleavage. In addition to its accessibility, the L-alanine ethyl ester was found to be the only nucleophile, that gave satisfactory yields of the amino alcohol products.

Having demonstrated that the preparation and separation of amino propargylic alcohols **6a** and **6b** was possible, we modified our strategy. We used enantiopure compound (+)-**5** instead of the racemic epoxide **5**. Compound (+)-**5** was prepared according to the literature from commercially available alcohol **8** by applying Shi's epoxidation protocol (Scheme 3).[31–33] The $LiClO_4$-meditated epoxide ring-opening of (+)-**5** with two equivalents of L-alanine ethyl ester[17] gave amino ethanol **6a** and a stereoisomeric product *ent*-**6b**. After chromatographic purification, compounds **6a** and

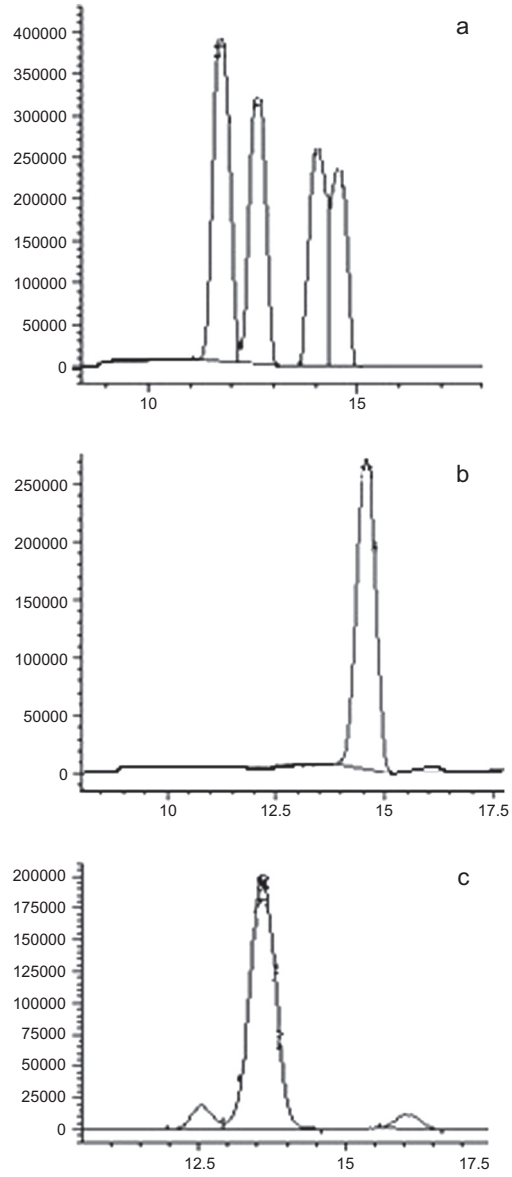
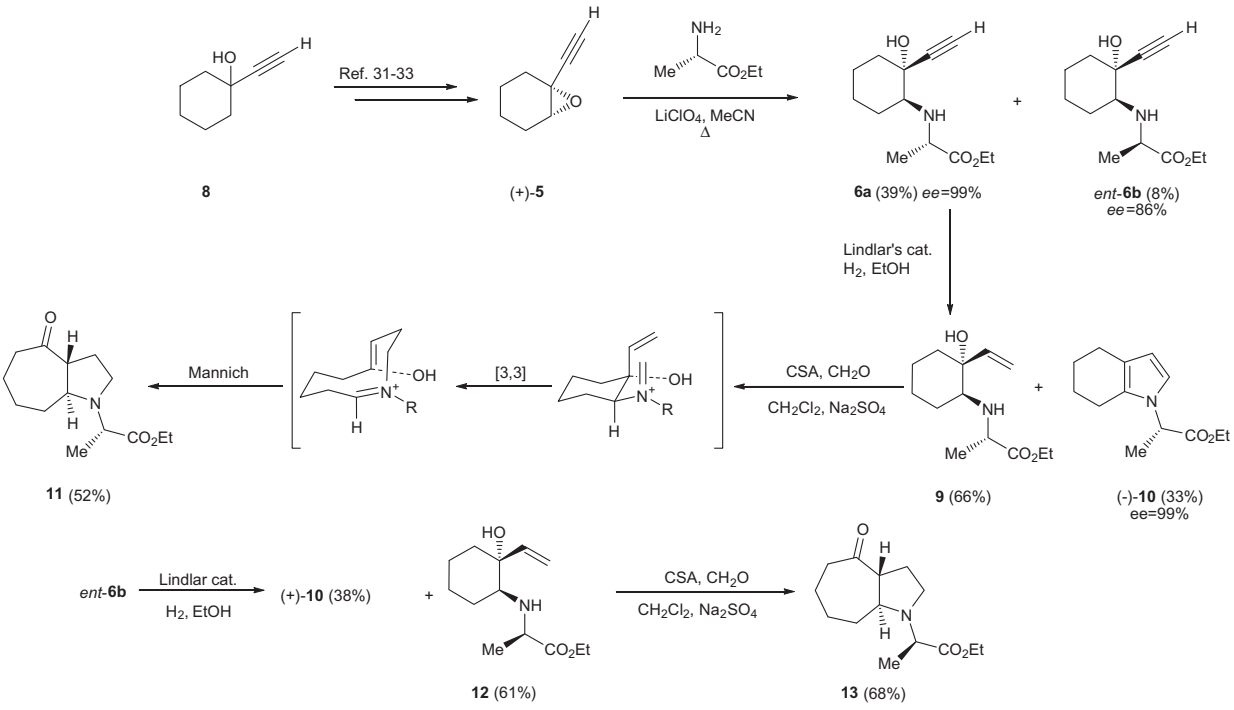


Figure 2. Chiral HPLC of the reference mixture (a), **6a** (b) and *ent*-**6b** (c).



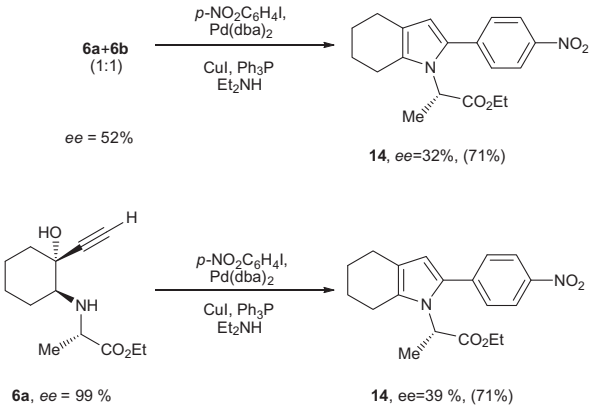
Scheme 3. Synthesis of compounds **11** and **13**.

ent-**6b** were obtained in yields of 39% and 8%, respectively. Chiral HPLC showed the presence of only one enantiomer for **6a** (Fig. 2). The hydrogenation of **6a** on Lindlar's catalyst gave a 3:2 mixture of alkene **9** and pyrrole (−)-**10** (ee = 99%, chiral HPLC) in quantitative yield. The formation of **10** is probably due to Pd-catalysed 5-*endo-dig* cyclization on the surface of the Lindlar's catalyst.[34–36]

It is well known that enantiomerically pure 1-alkenyl-2-aminocycloalkanols rearrange to enantiomerically pure pyrrolidines due to the conformational constraints of the medium-sized ring.[23,37–39] Thus, carrying out the aza-Cope–Mannich reaction under the previously optimized conditions[21] gave target product **11** as a single isomer in 52% yield (Scheme 3).

Amino alcohol *ent*-**6b** (ee = 85%) was transformed into the diastereomeric ketone **13** by the same sequence in 41% yield over two steps. The moderate yields of the rearrangement can be attributed to the fact that amino alcohols **9** and **12** contain varying amounts of inseparable impurities (5–10%).

The high enantiomeric excess of pyrrole **10** deserves additional comments. In our previous work,[17,35] we have shown that a two-step sequence involving the reaction of L-amino acid esters with racemic alkynyl epoxides and subsequent Sonogashira coupling/5-*endo-dig* cyclization of the resulting 1:1 diastereomeric mixture **6a** and **6b** led to 2-aryl-4,5,6,7-tetrahydroindoles with moderate ee values (32–70%, Schemes 2 and 4). It was not clear whether racemization occurred during the epoxide ring-opening or the Sonogashira coupling/Pd-mediated 5-*endo-dig* cyclization. We chose 1-iodo-4-nitrobenzene from a series of aryl halides as a substrate for test reactions, since pyrrole **14** showed the lowest ee value when a mixture **6a** and **6b** was used as the starting material.[35] Performing the experiment with pure **6a** led to pyrrole **10** with almost the same ee value (39%, Scheme 4). According to the data obtained, we concluded that the α-alanine residue of amino propargylic alcohols **6a**, **6b** and analogues epimerize easily when exposed to weak bases (e.g. Et_2NH). It should be emphasized that pyrroles with the α-amino acid residue are much more stable towards racemization.[35,40–42]



Scheme 4. The Pd-mediated cyclization of the diastereomeric mixture of **6a** and **6b** and enantiopure **6a**.

3. Conclusion

We have synthesized two diastereomeric non-natural L-alanine analogues in 5 steps from commercially available materials. Despite the difficulties associated with the preparation of the amino alcohols **9** and **12**, we have shown that the conditions of the aza-Cope–Mannich reaction are mild enough to be applied in complex settings, that is in the synthesis of molecules with stereocenters which are prone to racemization. The formation of pyrrole **10** in enantiopure form was observed as a side reaction during the Lindlar reduction step.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on 400 MHz Bruker Avance spectrometers. Spectra were referenced to residual chloro-

form (δ 7.26 ppm, ^{1}H; δ 77.16 ppm, ^{13}C). IR spectra were recorded on Thermo Nicolet IR-200 in KBr or film. High resolution mass spectra (HRMS) were measured on a Bruker maXis instrument using electrospray ionization (ESI). The specific rotation was measured on Perkin–Elmer 241 and Jasco DIP-360 polarimeters at 589 nm in cells with path length 5 and 10 cm. Enantiomeric purities were measured using HPLC with a chiral stationary phase: Chiralpak OD-RH 4.6*150 mm, 5 mkm, 1 mL/min, eluent: 80% 10 mMol Ammonium acetate buffer, 20% MeCN. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. 1-Ethynyl-7-oxabicyclo[4.1.0]heptane **5** was kindly provided by EDASA Scientific. Concentration under reduced pressure was performed by rotary evaporation at 30 °C (unless otherwise specified) at the appropriate pressure.

4.2. The ring-opening of epoxide 5

L-Alanine ethyl ester was prepared from its HCl salt by treating it with 1 equiv of 10% aqueous K_2CO_3, extraction with DCM and evaporation under reduced pressure at 30 °C.

To a vigorously stirred solution of epoxide (+)-**5** (2.50 g, 20.4 mmol, 1 equiv) and freshly prepared L-alanine ethyl ester (7.18 g, 61.4 mmol, 3 equiv) in MeCN (10 mL) $LiClO_4$ (3.24 g, 30.6 mmol, 1.5 equiv) was added in one portion. The mixture was stirred for 12 h at reflux. The reaction mixture was then allowed to cool to ambient temperature, poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (20:1 hexanes/EtOAc) to give **6a** and *ent*-**6b**.

4.2.1. (*S*)-Ethyl 2-((1*S*,2*R*)-2-ethynyl-2-hydroxycyclohexylamino)-propanoate 6a

Yield 39%, m = 1.91 g. Physical state: yellow oil. R_f = 0.48 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = +37$ (c 1, $CHCl_3$). t_r = 14.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.24 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 1.32–1.39 (m, 1H), 1.46 (dd, J = 12.5, 4.2 Hz, 1H), 1.58 (dt, J = 12.7, 3.9 Hz, 1H), 1.63–1.75 (m, 2H), 1.77–1.86 (m, 2H), 2.11 (dq, J = 12.2, 2.7 Hz, 1H), 2.31 (ddd, J = 6.7, 5.0, 3.8 Hz, 1H), 2.48 (s, 1H), 3.35 (q, J = 6.9 Hz, 1H), 4.18 (qd, J = 7.1, 1.6 Hz, 2H), 4.25 (br s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.3, 20.2, 23.1, 25.3, 29.8, 37.8, 55.0, 61.1, 65.3, 71.8, 74.3, 84.9, 176.4. IR: ν_{max} (KBr) = 3473 (br), 3305 (br), 2980, 2937, 2862, 1734, 1448, 1373, 1300, 1261, 1198, 1176, 1147, 1066 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{22}NO_3$ $[M+H]^+$ 240.1594; found 240.1592.

4.2.2. (*R*)-Ethyl 2-((1*S*,2*R*)-2-ethynyl-2-hydroxycyclohexylamino)-propanoate *ent*-6b

Yield 8%, m = 0.40 g. Physical state: yellow oil. R_f = 0.15 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = +41$ (c 1, $CHCl_3$). t_{major} = 13.6 min, t_{minor} = 12.5 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.25 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.38 (d, J = 6.9 Hz, 3H), 1.47 (dd, J = 12.5, 4.2 Hz, 1H), 1.59 (dt, J = 12.7, 3.4 Hz, 1H), 1.64–1.78 (m, 2H), 1.91–2.00 (m, 1H), 2.15 (dq, J = 12.2, 3.0 Hz, 1H), 2.21–2.26 (m, 1H), 2.27–2.31 (m, 1H), 2.32–2.36 (m, 1H), 2.48 (s, 1H), 3.58 (q, J = 6.9 Hz, 1H), 4.13–4.27 (m, 2H), 4.79 (br s., 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.3, 19.8, 23.2, 25.3, 30.1, 38.4, 54.3, 61.2, 64.5, 71.9, 74.0, 85.3, 175.8. IR: ν_{max} (KBr) = 3450 (br), 3305 (br), 2979, 2937, 2862, 1734, 1448, 1375, 1298, 1255, 1201, 1151, 1080, 1034 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{22}NO_3$ $[M+H]^+$ 240.1594; found 240.1594.

4.2.3. Synthesis of compounds 7a and 7b

Compounds **7a** and **7b** were prepared in the same manner as **6a** and **6b** using L-alanine benzyl ester instead of L-alanine ethyl ester. Compounds **7a** and **7b** were separated by column chromatography, but their absolute stereochemistry was not assigned unambiguously.

4.2.3.1. Diastereomer 1. Yield 10%, m = 0.51 g. Physical state: yellow oil. R_f = 0.43 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = +6.9$ (c 1, $CHCl_3$). t_{major} = 12.4 min, t_{minor} = 13.5 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.28 (m, 2H), 1.35 (d, J = 6.9 Hz, 3H), 1.47 (td, J = 12.6, 3.9 Hz, 1H), 1.53–1.81 (m, 3H), 2.10–2.17 (m, 1H), 2.19–2.39 (m, 2H), 2.49 (s, 1H), 3.45 (q, J = 6.8 Hz, 1H), 4.24 (br s, 1H), 5.19 (s, 2H), 7.29–7.43 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 20.1, 23.0, 25.2, 29.8, 37.8, 55.0, 65.1, 66.8, 71.8, 74.3, 84.8, 128.4 (2C), 128.5, 128.7 (2C), 135.6, 176.2. IR: ν_{max} (film/KBr) = 3447 (br), 3299, 2935, 2862, 1735, 1452, 1370, 1194, 1166, 1147, 1066, 1039, 872, 851, 806 cm^{-1}. HRMS (m/z): calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1751; found 302.1745.

4.2.3.2. Diastereomer 2. Yield 18%, m = 0.99 g. Physical state: yellow oil. R_f = 0.33 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = -15.4$ (c 1, $CHCl_3$). t_{major} = 11.1 min, t_{minor} = 9.9 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.50 (d+m, J = 7.1 Hz, 7H), 1.51–1.77 (m, 3H), 1.88–1.97 (m, 1H), 2.09–2.16 (m, 1H), 2.25 (dd, J = 11.5, 3.7 Hz, 1H), 2.47 (s, 1H), 3.63 (q, J = 7.0 Hz, 1H), 4.64 (br s, 1H), 5.15–5.19 (m, 2H), 7.29–7.42 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 19.6, 23.1, 25.1, 30.0, 38.3, 54.2, 64.3, 66.8, 71.9, 73.9, 85.3, 128.4 (3C), 128.7 (2C), 135.8, 175.5. IR: ν_{max} (film/KBr) = 3447 (br), 3289 (br), 3299, 2937, 2861, 1736, 1450, 1379, 1173, 1149, 1079, 1023, 871, 850, 752 cm^{-1}. HRMS (m/z): calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1751; found 302.1747.

4.3. Alkyne reduction

To an ethanolic solution of **6a** (0.97 g, 4.1 mmol), Lindlar's catalyst was added (0.50 g) and the resulting mixture was degassed and stirred under 1 atm of hydrogen until complete consumption of the starting material occurred (the reaction was monitored by TLC, hexanes/EtOAc 1:1, typically overnight). The catalyst was then removed by filtration, and the filtrate was concentrated under reduced pressure to give a mixture of **9** and (−)-**10** (3:2). The residue was purified by flash column chromatography (30:1 hexanes/EtOAc) to give **9** and (−)-**10**. Due to decomposition of (−)-**10** on silica, it was isolated only partially.

4.3.1. (*S*)-Ethyl 2-((1*S*,2*R*)-2-hydroxy-2-vinylcyclohexylamino)-propanoate 9

Yield 66%, m = 0.64 g. Physical state: yellow oil. R_f = 0.38 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = +39.7$ (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.30 (d+t, 3+3H), 1.33–1.88 (m, 9H), 2.41 (dd, J = 11.8, 3.6 Hz, 1H), 3.32 (q, J = 6.9 Hz, 1H), 3.56 (br s, 1H), 4.15 (qd, J = 21.3, 7.1 Hz, 2H), 5.24 (dd, J = 10.9, 1.7 Hz, 1H), 5.45 (dd, J = 17.1, 1.9 Hz, 1H), 6.20 (dd, J = 17.1, 10.9 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.2, 20.0, 22.7, 25.4, 29.3, 38.2, 54.9, 60.9, 64.8, 73.9, 115.6, 138.7, 175.6. IR: ν_{max} (film) = 3487 (br), 3332 (br), 2978, 2931, 2862, 1734, 1450, 1373, 1302, 1196, 1176, 1149, 1020, 928, 868, 762, 490 cm^{-1}. HRMS (m/z): calcd for $C_{13}H_{24}NO_3$ $[M+H]^+$ 242.1751; found 242.1755.

4.3.2. (*S*)-Ethyl 2-(4,5,6,7-tetrahydro-1*H*-indol-1-yl)propanoate 10

Yield 9%, m = 0.08 g. Physical state: brown oil. R_f = 0.62 (silica gel, 3:1 hexanes/AcOEt). t_r = 12.0 min. $[\alpha]_D^{23} = -26.8$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3H), 1.72 (d, J = 7.2 Hz, 3H), 1.74–1.81 (m, 2H), 1.82–1.92 (m, 2H), 2.48–2.60 (m, 4H), 4.17–4.28 (m, 2H), 4.71 (q, J = 7.2 Hz, 1H), 6.02 (d, J = 2.9 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.2, 18.0, 21.9, 23.2, 23.4, 23.7, 53.3, 61.4, 107.2, 116.2, 117.6,

127.9, 171.6. IR: ν_{max} (film) = 2995, 2948 (br), 2867, 1745, 1487, 1450, 1378, 1305, 1208, 1180, 1079, 1100, 1038, 706 cm^{-1}. HRMS (*m*/*z*): calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1489; found 222.1475.

4.3.3. (*R*)-Ethyl 2-((1*S*,2*R*)-2-hydroxy-2-vinylcyclohexylamino)-propanoate 12

Alkene **12** was prepared in the same manner as **9**. Pyrrole **10** was also isolated as a side product (yield 13%, *m* = 0.0424 g). Yield 61%, *m* = 0.2095 g. Physical state: yellow oil. R_f = 0.35 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = +27.6$ (*c* 2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.33 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 7.0, 3H), 1.40–1.55 (m, 3H), 1.60–1.68 (m, 1H), 1.73–1.81 (m, 1H), 1.85–1.94 (m, 2H), 2.34 (dd, *J* = 11.3, 4.1 Hz, 1H), 3.49 (q, *J* = 6.9 Hz, 1H), 3.68 (br s, 1H), 4.19 (t, *J* = 7.0 Hz, 2H), 5.26 (dd, *J* = 10.9, 1.9 Hz, 1H), 5.52 (dd, *J* = 17.0, 2.0 Hz, 1H), 6.20 (dd, *J* = 17.1, 10.9 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.3, 19.7, 23.0, 25.2, 29.6, 38.8, 54.3, 61.0, 64.2, 74.1, 115.6, 138.6, 176.3. IR: ν_{max} (film) = 3473 (br), 2979, 2933, 2862, 1734, 1450, 1373, 1331, 1300, 1252, 1184, 1155, 1047, 1009, 926, 862, 692, 609 cm^{-1}. HRMS (*m*/*z*): calcd for $C_{13}H_{23}NO_3Na$ $[M+Na]^+$ 264.1570; found 264.1565.

4.4. The aza-Cope–Mannich rearrangement

To a vigorously stirred mixture of **9** (0.20 g, 0.82 mmol, 1 equiv), anhydrous Na_2SO_4 (0.82 g, 5.8 mmol, 7 equiv), camphorsulfonic acid (63 mg, 0.27 mmol, 0.3 equiv) and CH_2Cl_2 (8 mL), 0.14 mL of formalin (37% in water, 1.80 mmol, 2.2 equiv) were added in one portion at room temperature. The reaction mixture was stirred vigorously overnight. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ solution (50 mL). The organic phase was separated and dried over Na_2SO_4. The product was purified via silica gel flash column chromatography using 10:1 hexanes/EtOAc followed by 20:1 DCM/MeOH.

4.4.1. (*S*)-Ethyl 2-((3a*R*,8a*S*)-4-oxooctahydrocyclohepta[*b*]pyrrol-1(2*H*)-yl)propanoate 11

Yield 52%, *m* = 0.11 g. Physical state: yellow oil. R_f = 0.20 (silica gel, 3:1 hexanes/AcOEt). $[\alpha]_D^{23} = +2.8$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.9 Hz, 3H), 1.19 (t+m, *J* = 7.1 Hz, 3+1H), 1.35–1.47 (m, 1H), 1.61–1.76 (m, 2H), 1.77–1.88 (m, 1H), 1.92–2.02 (m, 1H), 2.03–2.12 (m, 1H), 2.14–2.33 (m, 3H), 2.41–2.56 (m, 2H), 2.97 (td, *J* = 8.7, 3.5 Hz, 1H), 3.13 (ddd, *J* = 6.9, 9.5, 9.8 Hz, 1H), 3.49 (q, *J* = 6.9 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 10.8, 14.1, 22.4, 23.0, 26.7, 34.5, 43.6, 47.0, 55.8, 56.9, 60.6, 64.7, 173.6, 211.3. IR: ν_{max} (film) = 2978, 2931, 2858, 1734, 1703, 1450, 1375, 1201, 1161, 1113, 1093, 1055, 1024, 862 cm^{-1}. HRMS (*m*/*z*): calcd for $C_{14}H_{24}NO_3$ $[M+H]^+$ 254.1751; found 254.1734.

4.4.2. (*R*)-Ethyl 2-((3a*R*,8a*S*)-4-oxooctahydrocyclohepta[*b*]pyrrol-1(2*H*)-yl)propanoate 13

Ketone **13** was prepared in the same manner as **11**. Yield 68%, *m* = 0.1143 g. Physical state: colourless oil. R_f = 0.15 (silica gel, 3:1 hexanes/AcOEt), R_f = 0.68 (silica gel, 7:1 $CHCl_3$/MeOH). $[\alpha]_D^{23} = +18.2$ (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3H), 1.23–1.30 (m, 2H), 1.32 (d, *J* = 7.3 Hz, 3H), 1.64–1.78 (m, 2H), 1.84–1.94 (m, 1H), 2.00–2.08 (m, 1H), 2.24–2.37 (m, 3H), 2.37–2.45 (m, 1H), 2.52–2.61 (m, 1H), 2.69 (td, *J* = 9.1, 7.5 Hz, 1H), 3.00–3.11 (m, 2H), 3.64 (q, *J* = 7.0 Hz, 1H), 4.03–4.21 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 16.7, 22.4, 23.4, 26.8, 34.4, 43.9, 45.6, 55.0, 56.4, 60.1, 63.8, 172.4, 211.5. IR: ν_{max} (film/KBr) = 2980, 2934, 2858, 1730, 1705, 1452, 1378, 1339, 1172, 1094, 1057, 1020, 860, 823 cm^{-1}. HRMS (*m*/*z*): calcd for $C_{14}H_{24}NO_3$ $[M+H]^+$ 254.1751; found 254.1754.

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References

1. Tsantrizos, Y. S. *Acc. Chem. Res.* **2008**, *41*, 1252–1263.
2. Young, T. S.; Schultz, P. G. *J. Biol. Chem.* **2010**, *285*, 11039–11044.
3. Kast, P. *ChemBioChem* **2011**, *12*, 2395–2398.
4. Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
5. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.
6. Bommarius, A. S.; Schwarm, M.; Drauz, K. *Chimia* **2001**, *55*, 50–59.
7. Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968–970.
8. Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188–5191.
9. Kombarov, R.; Altieri, A.; Genis, D.; Kirpichenok, M.; Kochubey, V.; Rakitina, N.; Titarenko, Z. *Mol. Diversity* **2010**, *14*, 193–200.
10. Kurkin, A. V.; Golantsov, N. E.; Karchava, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2003**, *39*, 74–82.
11. Kurkin, A. V.; Nesterov, V. V.; Karchava, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2003**, *39*, 1466–1477.
12. Kurkin, A. V.; Belov, D. S.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2008**, *44*, 1123–1128.
13. Kurkin, A. V.; Bernovskaya, A. A.; Yurovskaya, M. A. *Tetrahedron: Asymmetry* **2009**, *20*, 1500–1505.
14. Kurkin, A. V.; Bernovskaya, A. A.; Yurovskaya, M. A. *Tetrahedron: Asymmetry* **2010**, *21*, 2100–2107.
15. Kurkin, A. V.; Bernovskaya, A. A.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2011**, *46*, 1208–1214.
16. Ryzhkov, I. O.; Andreev, I. A.; Belov, G. M.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2011**, *47*, 182–193.
17. Andreev, I. A.; Ryzhkov, I. O.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 715–719.
18. Kurkin, A. V.; Bukhryakov, K. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 188–193.
19. Bukhryakov, K. V.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 773–784.
20. Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. *Tetrahedron* **2011**, *67*, 9214–9218.
21. Belov, D. S.; Lukyanenko, E. R.; Kurkin, A. V.; Yurovskaya, M. A. *J. Org. Chem.* **2012**, *77*, 10125–10134.
22. Warner-Lambert Company, U.S. Patent 4,758,585 A1, 1988.
23. Overman, L. E.; Humphreys, P. G.; Welmaker, G. S. *Org. React.* **2011**, *75*, 747–820.
24. Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zécri, F. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1937–1940.
25. Nicolaou, K. C.; Zak, M.; Safina, B. S.; Lee, S. H.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5092–5097.
26. Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zécri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159–11175.
27. McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 2555–2561.
28. Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29*, 899–934.
29. Nadimpally, K. C.; Thalluri, K.; Palakurthy, N. B.; Saha, A.; Mandal, B. *Tetrahedron Lett.* **2011**, *52*, 2579–2582.
30. Wright, S. W.; Hageman, D. L.; Wright, A. S.; McClure, L. D. *Tetrahedron Lett.* **1997**, *38*, 7345–7348.
31. Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677–1696.
32. Taber, D. F.; He, Y.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900–13901.
33. Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646–7650.
34. Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277–4278.
35. Andreev, I. A.; Belov, D. S.; Kurkin, A. V.; Yurovskaya, M. A. *Eur. J. Org. Chem.* **2013**, *4*, 649–652.
36. Belov, G. M.; Belov, D. S.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 73–81.
37. Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329–4336.
38. Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005–5007.
39. Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662–4672.
40. Jefford, C. W.; de Villedon de Naide, F.; Sienkiewicz, K. *Tetrahedron: Asymmetry* **1996**, *7*, 1069–1076.
41. Grigg, R.; Yoganathan, G. *Tetrahedron: Asymmetry* **1996**, *7*, 273–276.
42. Movassaghi, M.; Siegel, D. S.; Han, S. *Chem. Sci.* **2010**, *1*, 561–566.