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Synthesis of conformationally restricted 1,2,3-triazole-substituted ethyl β- and γ-aminocyclopentanecarboxylate stereoisomers. Multifunctionalized alicyclic amino esters

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ABSTRACT

Stereoisomers of 1,2,3-triazole-functionalized, conformationally restricted β- or γ-amino esters with a cyclopentane skeleton were efficiently synthetized from the bicyclic β-lactam 6-azabicyclo[3.2.0]hept-3-en-7-one (**1**) and Vince γ-lactam (**15**) in five or six steps involving the azide–alkyne 1,3-dipolar cycloaddition of azido-substituted amino ester stereoisomers with nonsymmetric acetylenes. The azide–alkyne click reactions were investigated under thermal and Cu(I)-catalyzed conditions. Surprisingly, the thermally induced cycloaddition furnished the corresponding 1,4-triazoles regioselectively, which also took place selectively in response to Cu(I) catalysis.

1. Introduction

Alicyclic β-amino acids have received significant interest in recent years by virtue of their pharmacological potential.[1] The naturally occurring β-amino acid cispentacin (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid, an antifungal antibiotic, is a member of this highly important class of compounds. (1*R*,2*S*)-2-Amino-4-methylenecyclopentanecarboxylic acid (Icofungipen) is a strong antifungal agent.[1e] The conformationally restricted β-amino acids have been used as building blocks for the synthesis of new peptides.[2]

Among the large family of γ-amino acids, 4-aminocyclopent-2-enecarboxylic acid and its derivatives, conformationally constrained, potentially valuable scaffolds for pharmaceutical assays, are known as anticancer and antiviral agents and as important building blocks in the synthesis of peptides.[3] They may also be regarded as conformationally restricted GABA mimetics.[4] Several mono- and dihydroxylated γ-aminocyclopentanecarboxylic acid diastereomers have been incorporated into peptide sequences.[5]

1,2,3-Triazoles possess important antiviral, antibacterial or antiallergic activities.[6] Triazole-modified analogues of several bioactive compounds, e.g., those of zanamivir,[7] modified nucleosides or carbanucleosides with antiviral, anti-HIV or cytostatic activities[8–10] have been described. The 1,2,4-triazole ring is the key element of the antiviral agent ribavirin and its carbocyclic equivalent.[11] In recent years, many carbocyclic 1,2,3-triazole-modified carbanucleoside analogues have been described as bioactive derivatives.[8d,12]

2. Results and discussion

Azide–alkyne cycloaddition is a useful and convenient method for the preparation of 1,2,3-triazoles.[13] The aim of this work was the synthesis of multifunctionalized, 1,2,3-triazole-substituted aminocyclopentanecarboxylate stereoisomers, starting from the bicyclic β- or γ-lactams (**1** and **15**), via stereoselective epoxidation, regioselective oxirane opening and a click chemistry strategy involving 1,3-dipolar cycloaddition of the corresponding azido-substituted aminocyclopentanecarboxylate intermediates[15,17] with an acetylenic compound.

The approach for the synthesis of 1,2,3-triazole-substituted β-amino esters with a cyclopentane framework consisted in transformation of the γ-azido-β-amino ester diastereoisomers **2**, **3**, **8** and **9** through their azide function in 1,3-dipolar cycloadditions with acetylenes. The above azido esters (**2**, **3**, **8** and **9**) have been prepared starting from the bicyclic β-lactam **1**, via diastereoselective epoxidation of the olefinic bond with opposite selectivities, followed by

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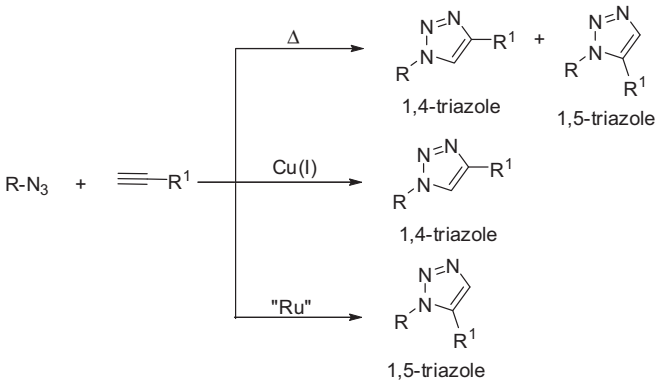
regioselective oxirane opening with NaN_3.[15] These azido esters were recently reported to undergo facile 1,3-dipolar cycloaddition with symmetrical diethyl acetylenedicarboxylate to yield the corresponding 1,2,3-triazole-substituted cyclopentanes.[16]

When submitted to Huisgen 1,3-dipolar cycloaddition with different nonsymmetric dipolarophiles (acetylenes), forming triazoles or triazolines, organic azides afford two possible regioisomers: the *anti* (1,4-disubstituted 1,2,3-triazoles) and *syn* (1,5-disubstituted 1,2,3-triazoles) regioisomers.[13] The thermally induced 1,3-dipolar azide–alkyne cycloaddition in general results in an approximately 1:1 mixture of 1,4- and 1,5-triazole isomers (Scheme 1). In contrast, the Cu(I)-catalyzed click reaction has been reported to give exclusively the 1,4-triazole derivative.[8a,13a–d] Selective 1,5-triazole-forming 1,3-azide–alkyne dipolar cycloadditions under ruthenium catalysis conditions have been reported (Scheme 1).[12b,14]



Scheme 1. 1,3-Dipolar azide–akyne cycloadditions.[13a–d,14]

Azido β-amino esters **2**, **3**, **8** and **9** were first reacted with the nonsymmetric acetylene ethyl propiolate (with an electron-withdrawing function attached to a triple bond carbon) in an azide–alkyne dipolar cycloaddition. The transformations could be performed without a Cu(I) catalyst, in EtOH at 70 °C for 6 h.

Surprisingly, under these thermal conditions, azido ester **2** selectively only the *anti* (1,4-triazole) regioisomer **4**, in 71% yield (Scheme 2, Fig. 1) gave. No traces of the *syn* regioisomer (**5**) were observed in this reaction. However, when subjected to the azide–alkyne cycloaddition under similar conditions, azido ester **3**, in which the ester and the Boc-protected amino functions are in a trans steric arrangement, furnished both *anti* (**6**, Scheme 2, Fig. 2) and *syn* (**7**) regioisomers, in a ratio of 4:1 (Scheme 2). Both of the above transformations were also performed in the presence of CuI, which had no significant effect on either the yield or the ratio of the products (**6**/**7**=3:1, in comparison with 4:1 without CuI). In the presence of $Cu/CuSO_4$ or $CuSO_4$/ascorbate, the above reaction resulted in the formation of triazole derivatives in an approximately similar ratio, but with a lower conversion.

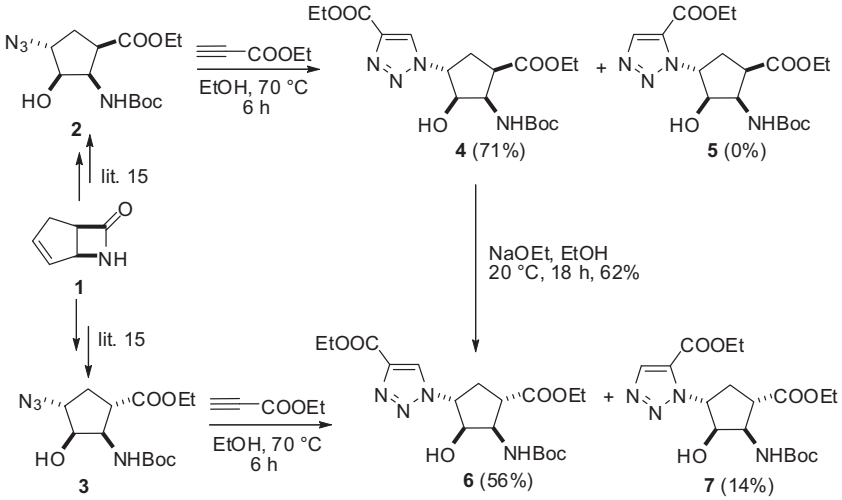
Azido β-amino ester diastereoisomers **8** and **9** reacted regioselectively with ethyl propiolate in EtOH at 70 °C for 6 h to give exclusively the corresponding *anti* triazole-functionalized β-aminocyclopentanecarboxylate diastereomers **10** and **11**, in yields of 63% and 59% (after crystallization), respectively (Scheme 3).

Our efforts to prepare various triazole-functionalized derivatives by performing azide–alkyne cycloadditions with different electron-rich alkynes under the above thermal conditions (without a Cu catalyst) failed. An electron-withdrawing group (e.g., –COOEt) on the acetylenic moiety proved essential for rapid and efficient triazole formation under thermal conditions in reactions with azides. Despite the difference in reactivity of the acetylenes, electron-rich derivatives such as 1-pentyne or phenylacetylene were successfully transformed by changing the reaction conditions. When reacted with phenylacetylene or 1-pentyne in the presence of CuI in MeCN at 70 °C, azido ester **2** regioselectively furnished the corresponding *anti* triazole-substituted amino ester derivatives **12** and **13** in moderate yields (69% and 39%, Scheme 4).

Interestingly, while both the thermally and Cu(I)-catalyzed reactions of *trans* amino ester **3** with ethyl propiolate gave two triazole-substituted products (**6** and **7**, Scheme 2), the reaction with phenylacetylene in the presence of Cu(I) resulted in only one 1,2,3-triazole-substituted derivative **14** (Scheme 4). The selectivity is probably due to higher reactivity of ethyl propiolate than that of phenylacetylene.

The commercially available Vince lactam (**15**) as starting material offered a possibility for the synthesis of other new 1,2,3-triazole-substituted cyclopentanecarboxylate stereoisomers. Lactam **15** was earlier transformed selectively to two azido-substituted γ-amino esters, **16** and **17**.[17]

To obtain the 1,2,3-triazole ring, both azido esters (**16** and **17**) were first reacted with ethyl propiolate without a Cu(I) catalyst (Scheme 5). The thermally induced reaction again resulted in 100% regioselectively: only the corresponding 1,4-triazole (*anti*) derivatives **18** (Fig. 3) and **19** were formed in good yields (80 and 71%); no traces of the 1,5-isomers were detected in the reaction mixture. The reactions in the presence of CuI selectively gave the corresponding 1,2,3-triazole derivatives, with slightly higher yields (83% and 78%).



Scheme 2. Synthesis of 1,2,3-triazolo-β-amino esters **4**, **6** and **7**.

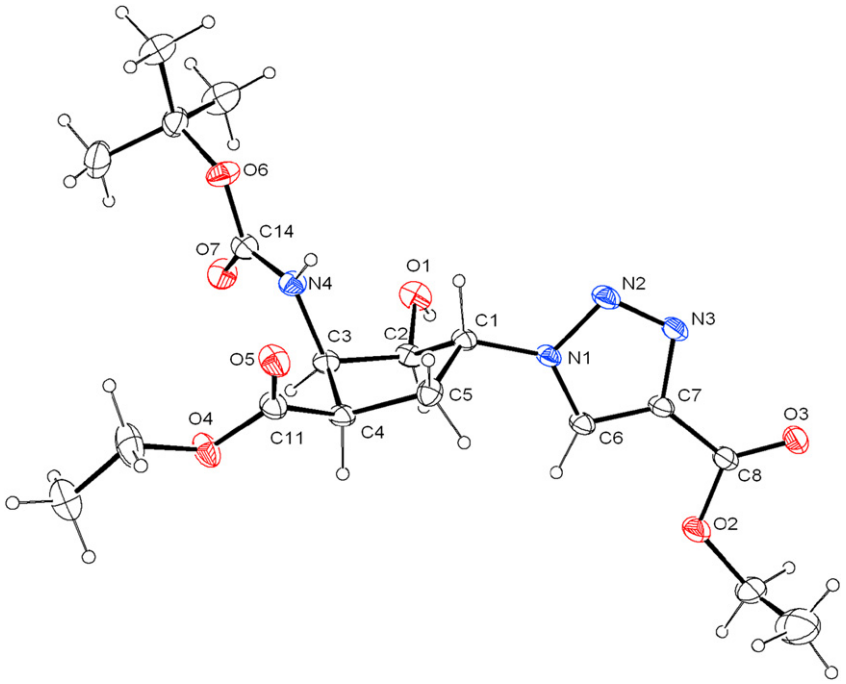


Figure 1. ORTEP diagram of compound **4**.

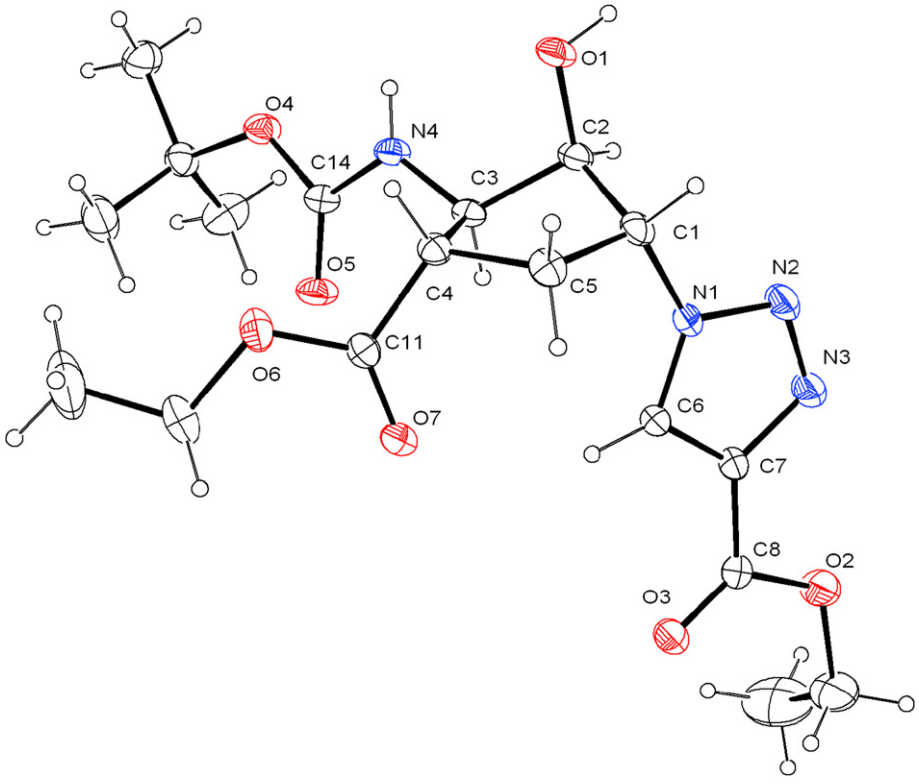
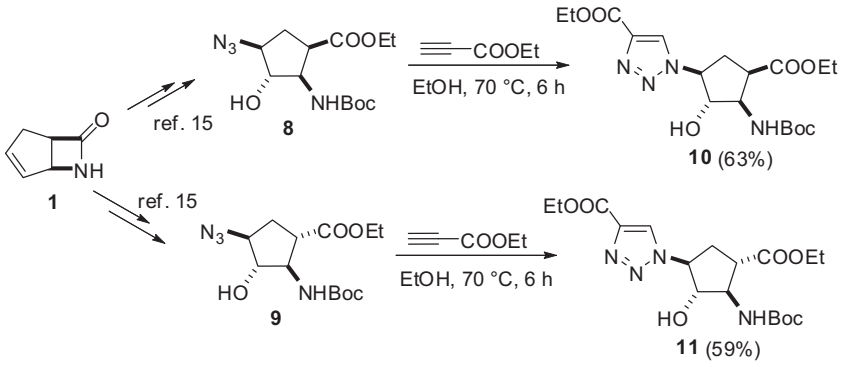


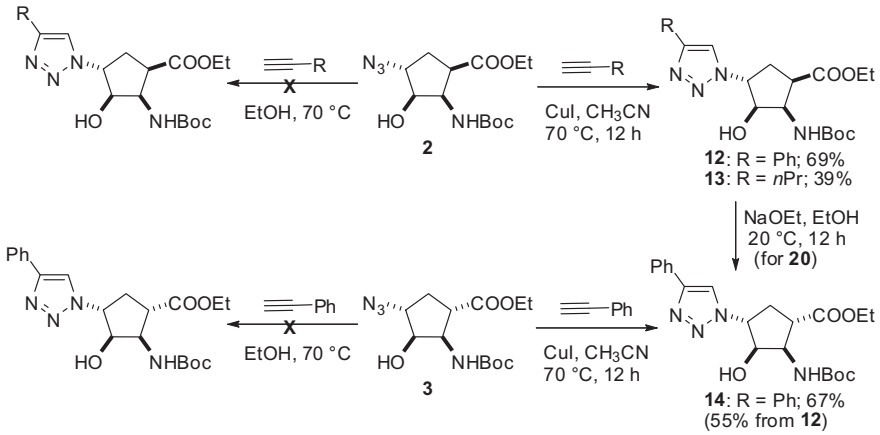
Figure 2. ORTEP diagram of compound **6**.

For these γ-amino azido esters (**16** and **17**), preparation of the 1,2,3-triazole skeleton was again attempted with other substituted acetylenes. The thermal reactions with phenylacetylene or 1-pentyne under environmentally friendly conditions without a Cu(I) catalyst failed. In the presence of CuI in refluxing CH_3CN, the desired 1,2,3-triazole-functionalized cyclopentanecarboxylates (**20**–**23**) were formed in good yields (67–74%, Scheme 6).

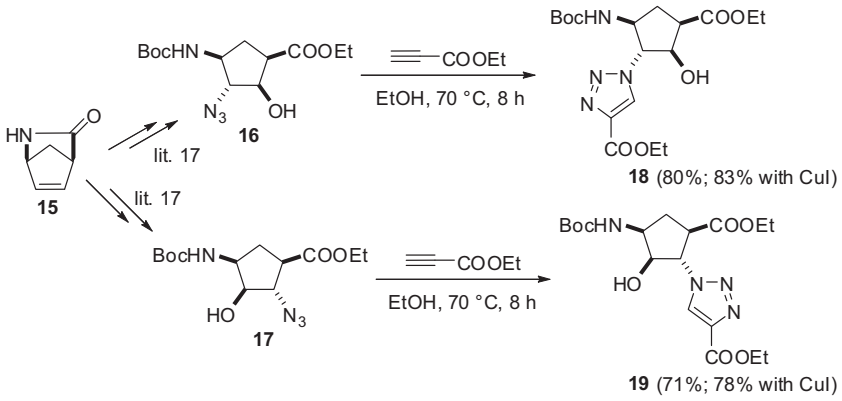
The method for the synthesis of 1,2,3-triazole-functionalized γ-amino ester derivatives was extended to the enantiomeric substances, as shown in Scheme 7. The target compounds, the enantiomerically pure triazolo amino esters **18** and **19**, were prepared from the enantiopure lactam (+)-**15** (ee >99%), synthetized according to a slightly modified literature procedure.[18] The enantioselective (E >200) ring cleavage of commercially available



Scheme 3. Synthesis of 1,2,3-triazolo-β-amino esters **10** and **11**.



Scheme 4. Synthesis of 1,2,3-triazolo-β-amino esters **12**–**14**.



Scheme 5. Synthesis of 1,2,3-triazolo-γ-amino esters **18** and **19**.

2-azabicyclo[2.2.1]hept-5-en-3-one (Vince lactam, **15**) in the presence of CAL-B (lipase B from *Candida antarctica*, produced by the submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism and adsorbed on a macroporous resin) was performed with H_2O in *t*-BuOMe.

γ-Lactam (+)-**15** was transformed to Boc-protected amino ester (+)-**25** through amino ester hydrochloride (+)-**24**. On treatment with *m*-CPBA in CH_2Cl_2 at 0 °C, the γ-amino ester (+)-**25** then diastereoselectively furnished epoxide (+)-**26**. The oxirane ring opening of (+)-**26** with NaN_3 in EtOH/H_2O as solvent in the presence of a catalytic amount of NH_4Cl afforded two regioisomers, (−)-**16** and (−)-**17**, in a ratio of 1:2, which could be separated in good yields by crystallization from a mixture of *n*-hexane/EtOAc (Scheme 7). On treatment with ethyl propiolate in EtOH under thermal conditions, both azido amino esters (−)-**16** and (−)-**17** gave the corresponding enantiomerically pure 1,2,3-triazolo-γ-amino-cyclopentane carboxylates (−)-**18** and (−)-**19** (Scheme 7).

3. Conclusions

Several 1,2,3-triazole-substituted conformationally rigid amino ester stereoisomers with a cyclopentane skeleton were prepared selectively via 1,3-alkyne–azide cycloaddition of azido-functionalized amino esters with different terminal acetylenes

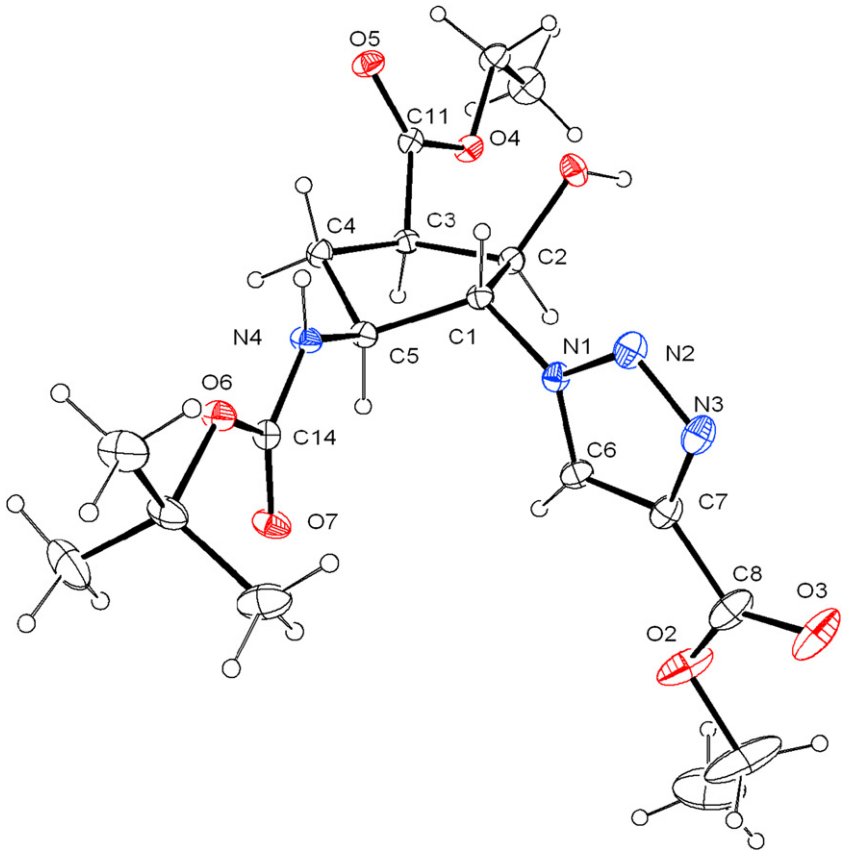
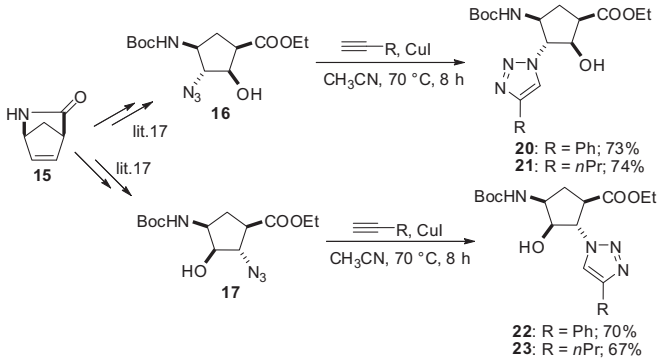


Figure 3. ORTEP diagram of compound **18**.



Scheme 6. Synthesis of 1,2,3-triazolo-γ-amino esters **20**–**23**.

with or without a Cu(I) catalyst. The reactions were performed for the enantiomeric substances involving enzymatic resolution of the racemic Vince lactam.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich or Fluka. Melting points were determined with a Kofler apparatus. NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are given in parts per million relative to TMS as internal standard, with $CDCl_3$ or DMSO as solvent. The solvents were used as received from the supplier. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. The IR spectra were recorded on a Perkin–Elmer Spektrum 100 FT-IR spectrometer. The mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer.

The ee for (−)-**18** was determined by HPLC on a Chiralcel OD-RH column [eluent TEAA buffer (pH 4.1)/MeCN 80/20, flow rate: 0.4 mL min^{-1}, room temperature, detection at 210 nm, retention times (min): 64.5 (antipode: 87.5)], while the ee for (+)-**19** was determined by GC on a Chromopack Chiralsil-Dex CB column (25 m) [120 °C for 10 min → 190 °C (temperature rise 10 °C min^{-1}; 140 kPa); retention times (min): 27.73 (antipode: 27.50)]

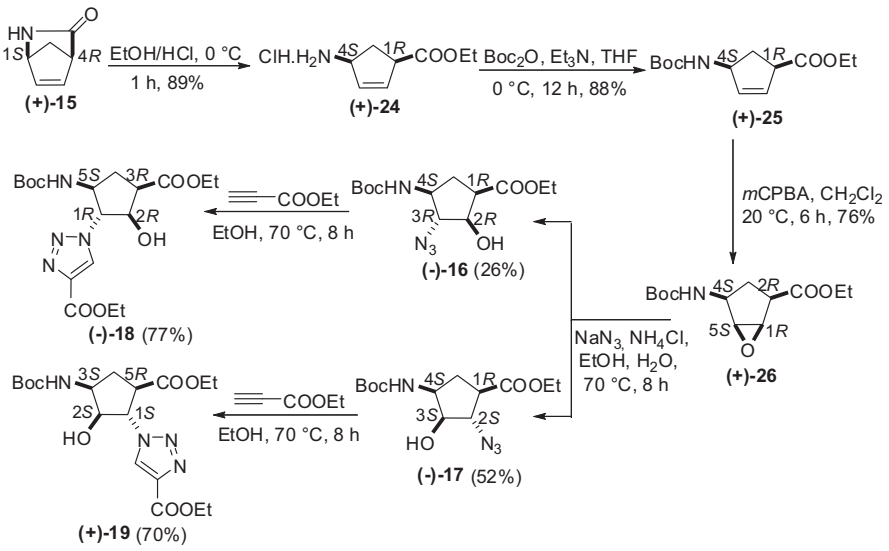
4.2. General procedure for the cycloaddition of azido aminocyclopentanecarboxylates with acetylenes

Method A. To a solution of azido β-amino ester **2**, **3**, **8** or **9** or azido γ-amino ester **16** or **17** (1 g, 3.2 mmol) in EtOH (15 mL), ethyl propiolate (340 mg, 3.5 mmol, 1.1 equiv) was added and the solution was stirred at 70 °C for 6 h. The mixture was then concentrated under reduced pressure and crystallized from a mixture of *n*-hexane/EtOAc or purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc) to give the triazolo amino esters.

Method B. To a solution of azido β-amino ester **2** (500 mg, 1.6 mmol) in MeCN (15 mL), phenylacetylene or 1-pentyne (1.76 mmol, 1.1 equiv) and CuI (336 mg, 1.76 mmol, 1.1 equiv) were added and the solution was stirred at 70 °C for 12 h. The solid was then filtered off, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc) to give the triazolo amino esters.

4.3. General procedure for the epimerization reaction

A solution of triazolo-aminocarboxylate **4** or **12** (2.4 mmol) and NaOEt (165 mg, 1 equiv) in EtOH (20 mL) was stirred at 20 °C for



Scheme 7. Preparation of enantiomerically pure 1,2,3-triazole-substituted amino esters (−)-**18** and (+)-**19**.

14 h. The mixture was then concentrated to one-third of its volume and taken up in EtOAc (70 mL). The organic layer was washed with H_2O (3×20 mL), dried (Na_2SO_4) and concentrated. The crude product was crystallized from a mixture of *n*-hexane/EtOAc.

4.3.1. Ethyl 1-[(1R,2R*,3R*,4R*)-3-(tert-butoxycarbonylamino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-4-carboxylate (**4**).* A white solid; yield: 936 mg, 71%; mp 142–144 °C. R_f=0.55 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.15 (t, 3H, CH_3, J=7.1 Hz), 1.23 (t, 3H, CH_3, J=7.2 Hz), 1.36 (9H, *t*-Bu), 1.90–1.98 (m, 1H, CH_2), 2.67–2.76 (m, 1H, CH_2), 3.39–3.46 (m, 1H, H-4), 3.95–4.09 (m, 2H, OCH_2), 4.24–4.33 (4H, OCH_2, H-2 and H-3), 5.05–5.11 (m, 1H, H-1), 5.46 (br s, 1H, O–H), 6.69 (br s, 1H, N–H), 8.72 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.9, 15.1, 29.2, 29.8, 44.1, 56.1, 60.9, 61.3, 65.3, 77.7, 78.6, 128.4, 140.0, 156.3, 161.2, 172.1. IR (KBr): ν_{max} 3369, 2982, 1719, 1696, 1543, 1368, 1207. MS: (ES, pos) m/z=413 (M+1). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.08; H, 6.50; N, 13.20.

4.3.2. Ethyl 1-[(1R,2R*,3R*,4S*)-3-(tert-butoxycarbonylamino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-4-carboxylate (**6**).* A white solid; yield: 738 mg, 56% (255 mg, 62% from the epimerization reaction); mp 158–161 °C. R_f=0.50 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.17 (t, 3H, CH_3, J=7.1 Hz), 1.28 (t, 3H, CH_3, J=7.2 Hz), 1.39 (s, 9H, *t*-Bu), 2.10–2.19 (m, 1H, CH_2), 2.50–2.54 (m, 1H, CH_2), 2.84–2.90 (m, 1H, H-4), 4.03–4.08 (m, 2H, OCH_2), 4.11–4.18 (m, 2H, H-2 and H-3), 4.25–4.20 (m, 2H, OCH_2), 4.81–4.86 (m, 1H, H-1), 5.57 (br s, 1H, O–H), 6.62 (br s, 1H, N–H), 8.81 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.9, 15.0, 29.0 31.5, 46.7, 55.4, 61.3, 61.4, 66.3, 75.8, 79.6, 129.0, 140.1, 152.8, 160.3, 173.9. IR (KBr): ν_{max} 3345, 2984, 1710, 1680, 1546, 1369, 1232. MS: (ES, pos) m/z=413 (M+1). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 51.92; H, 6.43; N, 13.13.

4.3.3. Ethyl 1-[(1R,2R*,3R*,4S*)-3-(tert-butoxycarbonylamino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-5-carboxylate (**7**).* A white solid, yield: 186 mg, 14%; mp 153–156 °C. R_f=0.50 (*n*-hexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.29 (t, 3H, CH_3, J=7.1 Hz), 1.40 (t, 3H, CH_3, J=7.2 Hz), 1.45 (s, 9H, *t*-Bu), 2.70–2.82 (m, 2H, CH_2), 3.05–3.17 (m, 1H, H-4), 3.89–3.95 (m, 1H, H-3), 4.18–4.23 (m, 2H, OCH_2), 4.39–4.45 (m, 3H, OCH_2 and H-2), 4.72–4.80 (m, 1H, H-1), 5.12 (br s, 1H, O–H), 5.25 (br s, 1H, N–H), 8.22 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.8, 15.0, 29.0, 29.8, 44.9, 59.9, 61.2, 61.4, 64.6, 78.8, 79.4, 127.2, 129.7, 153.6, 161.1, 174.3. IR (KBr): ν_{max} 3398, 2981, 1728, 1688, 1524, 1373, 1233. MS: (ES, pos) m/z=413 (M+1). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.01; H, 6.40; N, 13.21.

4.3.4. Ethyl 1-[(1S,2S*,3R*,4R*)-3-(tert-butoxycarbonylamino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-4-carboxylate (**10**).* A white solid, mp 150–152 °C; yield: 831 mg, 63%. R_f=0.45 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.17 (t, 3H, CH_3, J=7.1 Hz), 1.28 (t, 3H, CH_3, J=7.2 Hz), 1.42 (s, 9H, *t*-Bu), 2.39–2.46 (m, 2H, CH_2), 3.23–3.31 (m, 1H, H-4), 3.98–4.10 (m, 3H, OCH_2 and H-3), 4.17–4.21 (m, 1H, H-2), 4.26–4.31 (m, 2H, OCH_2), 4.70–4.75 (m, 1H, H-1), 5.58 (br s, 1H, O–H), 7.02 (br s, 1H, N–H), 8.72 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.9, 15.0, 29.3, 31.0, 43.9, 57.7, 61.1, 61.4, 65.6, 78.8, 79.8, 128.6, 140.6, 155.9, 161.1, 172.8. IR (KBr): ν_{max} 3365, 2977, 1743, 1698, 1541, 1380, 1207. MS: (ES, pos) m/z=413 (M+1). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.16; H, 6.60; N, 13.12.

4.3.5. Ethyl 1-[(1S,2S*,3R*,4S*)-3-(tert-butoxycarbonylamino)-4-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-4-carboxylate (**11**).* A white solid, mp 185–187 °C, yield: 778 mg, 59%. R_f=0.45 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.18 (t, 3H, CH_3, J=7.1 Hz), 1.28 (t, 3H, CH_3, J=7.2 Hz), 1.40 (s, 9H, *t*-Bu), 2.26–2.30 (m, 1H, CH_2), 2.39–2.48 (m, 1H, CH_2), 2.84–2.90 (m, 1H, H-4′), 3.77–3.83 (m, 1H, H-3′), 3.98–4.12 (m, 2H, OCH_2), 4.18–4.23 (m, 1H, H-2′), 4.26–4.30 (m, 2H, OCH_2), 4.71–4.78 (m, 1H, H-1′), 5.59 (br s, 1H, O–H), 6.74 (br s, 1H, N–H), 8.74 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.8, 15.0, 29.1, 29.8, 44.9, 59.9, 61.2, 61.4, 64.6, 78.8, 79.4, 129.7, 139.6, 156.1, 161.1, 174.3. IR (KBr): ν_{max} 3396, 2980, 1727, 1687, 1524, 1373, 1220. MS: (ES, pos) m/z=413 (M+1). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.09; H, 6.99; N, 13.23.

4.3.6. Ethyl (1R,2R*,3R*,4R*)-2-(tert-butoxycarbonylamino)-3-hydroxy-4-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**12**).* A white solid, mp 154–156 °C, yield: 459 mg, 69%. R_f=0.60 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.17 (t, 3H, CH_3, J=7.10 Hz), 1.40 (s, 9H, *t*-Bu), 1.97–2.08 (m, 1H, CH_2), 2.75–2.87 (m, 1H, CH_2), 3.43–3.51 (m, 1H, H-1), 3.99–4.12 (m, 2H, OCH_2), 4.39–4.46 (m, 2H, H-2 and O–H), 5.05–5.10 (m, 1H, H-3), 5.49–5.56 (m,

1H, H-4), 6.72 (br s, 1H, N–H), 7.35–7.40 (m, 1H, Ar–H), 7.46–7.63 (m, 2H, Ar–H), 7.83–7.88 (m, 2H, Ar–H), 8.64 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.9, 29.1, 30.0, 44.3, 56.2, 60.9, 65.1, 77.8, 78.6, 121.1, 126.0, 128.7, 129.7, 131.7, 147.4, 156.3, 172.2. MS: (ES, pos) m/z=417 (M+1). Anal. Calcd for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.21; H, 6.42; N, 13.21.

4.3.7. Ethyl (1R,2R*,3R*,4R*)-2-(tert-butoxycarbonylamino)-3-hydroxy-4-(4-propyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**13**).* A white solid, mp 89–91 °C, yield: 238 mg, 39%. R_f=0.55 (*n*-hexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=0.99 (t, 3H, CH_3, J=7.10 Hz), 1.32 (t, 3H, CH_3, J=7.15 Hz), 1.47 (s, 9H, *t*-Bu), 1.66–1.74 (m, 2H, CH_2), 2.56–2.77 (m, 4H, CH_2), 3.56–3.63 (m, 1H, H-1), 4.06 (br s, 1H, O–H), 4.17–4.22 (m, 2H, OCH_2), 4.23–4.29 (m, 1H, H-2), 4.46–4.53 (m, 1H, H-3), 4.88–4.94 (m, 1H, H-4), 5.30 (br s, 1H, N–H), 7.36 (s, 1H, Ar–H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ=14.2, 14.5, 23.0, 28.0, 28.8, 32.1, 45.6, 54.9, 62.1, 66.6, 78.5, 80.5, 121.0, 148.8, 150.2, 152.0. MS: (ES, pos) m/z=383 (M+1). Anal. Calcd for $C_{18}H_{30}N_4O_5$: C, 56.53; H, 7.91; N, 14.65. Found: C, 56.15; H, 7.62; N, 14.36.

4.3.8. Ethyl (1S,2R*,3R*,4R*)-2-(tert-butoxycarbonylamino)-3-hydroxy-4-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**14**).* A white solid, mp 120–122 °C, yield: 446 mg, 67%. R_f=0.55 (*n*-hexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.31 (t, 3H, CH_3, J=7.15 Hz), 1.47 (s, 9H, *t*-Bu), 2.48–2.54 (m, 1H, CH_2), 2.79–2.88 (m, 1H, CH_2), 3.14–3.20 (m, 1H, H-1), 4.18–4.25 (m, 2H, OCH_2), 4.30–4.43 (m, 1H, H-2), 4.51–4.55 (m, 1H, H-3), 5.00–5.06 (m, 1H, H-4), 5.40 (br s, 1H, N–H), 7.46–7.51 (m, 3H, Ar–H), 7.81–7.88 (m, 2H, Ar–H), 8.13 (s, 1H, Ar–H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ=14.6, 28.7, 31.5, 47.2, 56.8, 61.8, 66.4, 77.6, 78.8, 119.4, 126.2, 128.7, 129.3, 130.6, 136.4, 156.2, 172.0. Anal. Calcd for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.16; H, 6.39; N, 13.13.

4.3.9. Ethyl 1-[(1R,2R*,3R*,5S*)-5-(tert-butoxycarbonylamino)-3-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-4-carboxylate (**18**).* A white solid, mp 159–162 °C, yield: 1054 mg, 80%. R_f=0.50 (*n*-hexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.28 (t, 3H, CH_3, J=7.1 Hz), 1.38 (t, 3H, CH_3, J=7.2 Hz), 1.40 (s, 9H, *t*-Bu), 2.12–2.20 (m, 1H, CH_2), 2.59–2.68 (m, 1H, CH_2), 3.38–3.44 (m, 1H, H-3), 4.20–4.26 (m, 2H, OCH_2), 4.39–4.45 (m, 3H, OCH_2 and H-5), 4.73–4.77 (m, 2H, H-1 and H-2), 5.13 (br s, 1H, N–H), 8.28 (s, 1H, Ar–H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ=14.6, 14.7, 28.6, 32.5, 46.4, 55.1, 61.7, 61.8, 73.0, 76.4, 80.1, 125.6, 130.0, 150.2, 160.6, 175.0. MS: (ES, pos) m/z=847.5 (2 M+Na). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.02; H, 6.49; N, 13.84.

4.3.10. Ethyl 1-[(1S,2S*,3S*,5R*)-3-(tert-butoxycarbonylamino)-5-(ethoxycarbonyl)-2-hydroxycyclopentyl]-1H-1,2,3-triazole-4-carboxylate (**19**).* A white solid, mp 123–125 °C, yield: 936 mg, 71%. R_f=0.45 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.28 (t, 3H, CH_3, J=7.20 Hz), 1.46 (t, 3H, CH_3, J=7.20), 1.53 (s, 9H, *t*-Bu), 2.12–2.18 (m, 1H, CH_2), 2.55–2.61 (m, 1H, CH_2), 3.31–3.36 (m, 1H, H-5), 4.14–4.20 (m, 3H, H-3 and OCH_2), 4.43 (m, 1H, H-2), 4.48–4.57 (m, 2H, OCH_2), 5.21–5.28 (m, 1H, H-1), 5.75–5.78 (br s, 1H, O–H), 6.78 (br s, 1H, N–H), 9.09 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.7, 15.0, 29.2, 32.3, 40.8, 51.4, 60.8, 61.4, 69.0, 75.9, 78.7, 129.2, 139.8, 156.0, 161.1, 172.3. MS: (ES, pos) m/z=847.5 (2 M+Na). Anal. Calcd for $C_{18}H_{28}N_4O_7$: C, 52.42; H, 6.84; N, 13.58. Found: C, 52.08; H, 6.50; N, 13.22.

4.3.11. Ethyl (1R,2R*,3R*,4S*)-4-(tert-butoxycarbonylamino)-2-hydroxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**20**).* A white solid, mp 180–182 °C, yield: 486 mg, 73%. R_f=0.55 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.22 (t, 3H, CH_3, J=7.15 Hz), 1.28 (s, 9H, *t*-Bu), 2.10–2.21 (m, 2H, CH_2), 3.23–3.30 (m, 1H, H-1), 4.06–3.14 (m, 2H, OCH_2), 4.20–4.24 (m, 1H, H-4), 4.56–4.62 (m, 1H, H-2), 4.66–4.71 (m, 1H, H-3), 5.81 (br s, 1H, O–H), 7.24 (br s, 1H, N–H), 7.30–7.36 (m, 2H, Ar–H), 7.43–7.49 (m, 2H, Ar–H), 7.82–7.89 (m, 1H, Ar–H), 8.61 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=15.0, 28.9, 31.69, 45.9, 54.0, 60.8, 72.3, 74.9, 78.9, 121.7, 125.9, 128.6, 129.8, 131.8, 147.0, 155.9, 172.5. Anal. Calcd for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.25; H, 6.40; N, 13.20.

4.3.12. Ethyl (1R,2S*,3S*,4S*)-4-(tert-butoxycarbonylamino)-3-hydroxy-2-(4-phenyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**22**).* A white solid, mp 198–200 °C, yield: 466 mg, 70%. R_f=0.55 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=1.11 (t, 3H, CH_3, J=7.10 Hz), 1.40 (s, 9H, *t*-Bu), 1.93–2.04 (m, 1H, CH_2), 2.40–2.53 (m, 1H, CH_2), 3.38–3.43 (m, 1H, H-1), 4.02–4.12 (m, 3H, H-4 and OCH_2), 4.28–4.33 (m, 1H, H-3), 4.98–5.05 (m, 1H, H-2), 5.55–5.60 (br s, 1H, O–H), 6.58 (br s, 1H, N–H), 7.30–7.50 (m, 3H, Ar–H), 7.84–7.89 (m, 2H, Ar–H), 8.68 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.8, 29.1, 32.5, 45.5, 51.8, 61.4, 69.0, 76.0, 78.8, 121.9, 126.0, 128.7, 129.8, 131.6, 147.2, 156.0, 172.9. Anal. Calcd for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.17; H, 6.39; N, 13.14.

4.3.13. Ethyl (1R,2R*,3R*,4S*)-4-(tert-butoxycarbonylamino)-2-hydroxy-3-(4-propyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**21**).* A white solid, mp 223–226 °C, yield: 452 mg, 74%. R_f=0.45 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=0.91 (t, 3H, CH_3, J=7.15 Hz), 1.20 (t, 3H, CH_3, J=7.10 Hz), 1.29 (s, 9H, CH_3), 1.56–1.64 (m, 2H, CH_2), 2.07–2.15 (m, 2H, CH_2), 2.55–2.64 (m, 2H, CH_2), 3.17–3.23 (m, 1H, H-1), 4.04–4.13 (m, 3H, OCH_2 and H-4), 4.48–4.52 (m, 1H, H-2), 4.53–4.59 (m, 1H, H-3), 5.71 (br s, 1H, O–H), 7.15 (br s, 1H, N–H), 7.85 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.4, 15.0, 23.1, 27.9, 28.9, 31.7, 45.9, 53.9, 60.8, 71.9, 74.7, 78.8, 122.1, 147.3, 155.8, 172.5. Anal. Calcd for $C_{18}H_{30}N_4O_5$: C, 56.53; H, 7.91; N, 14.65. Found: C, 56.18; H, 7.60; N, 14.38.

4.3.14. Ethyl (1R,2S*,3S*,4S*)-4-(tert-butoxycarbonylamino)-3-hydroxy-2-(4-propyl-1H-1,2,3-triazol-1-yl)cyclopentanecarboxylate (**23**).* A white solid, mp 104–105 °C, yield: 410 mg, 67%. R_f=0.40 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz): δ=0.92 (t, 3H, CH_3, J=7.15 Hz), 1.10 (t, 3H, CH_3, J=7.15 Hz), 1.39 (s, 9H, CH_3), 1.57–1.66 (m, 2H, CH_2), 1.90–1.97 (m, 1H, CH_2), 2.32–2.53 (m, 1H, CH_2), 2.56–2.63 (m, 2H, CH_2), 3.25–3.32 (m, 1H, H-1), 3.99–4.07 (m, 3H, OCH_2 and H-4), 4.11–4.18 (m, 1H, H-3), 4.87–4.94 (m, 1H, H-2), 5.49 (br s, 1H, O–H), 6.51 (br s, 1H, N–H), 7.92 (s, 1H, Ar–H). ^{13}C NMR (DMSO, 400 MHz): δ=14.5, 14.8, 23.1, 27.9, 29.1, 32.5, 45.6, 51.9, 61.3, 68.8, 75.9, 78.7, 122.4, 147.6, 156.0, 173.1. Anal. Calcd for $C_{18}H_{30}N_4O_5$: C, 56.53; H, 7.91; N, 14.65. Found: C, 56.19; H, 7.66; N, 14.33.

4.4. Preparation of (1*S*,4*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one [(+)-15]

Racemic **15** (6.00 g, 54.96 mmol) was dissolved in *t*-BuOMe (90 mL). Lipolase (3 g, 30 mg mL^{-1}) and H_2O (492 μL, 27 mmol) were added and the mixture was shaken in an incubator shaker at 60 °C for 102 h. The reaction was stopped by filtering off the enzyme at 50% conversion. The reaction was monitored by means of GC.[18] The solvent was evaporated off and the residue, (1*S*,4*R*)-**15**, crystallized out [2.91 g, 48%; recrystallized from *t*-BuOMe {$[\alpha]_D^{25}$ +541 (*c* 0.29, $CHCl_3$),[18] $[\alpha]_D^{25}$ +549 (*c* 0.26, $CHCl_3$); mp 87–89 °C; ee >99% [GC on a Chromopack Chiralsil-Dex CB column (25 m) 120 °C for 25 min → 160 °C (temperature rise 10 °C min^{-1}; 140 kPa); retention times (min), (1*S*,4*R*)-**15**: 26.66 (antipode: 26.05)]}.

4.5. Characterization of the enantiomeric substances

The ^{1}H NMR spectra of the enantiomeric substances were the same as for the racemic compounds.

*4.5.1. Ethyl (1R,4S)-4-aminocyclopent-2-enecarboxylate hydrochloride [(+)-**24**].* A white solid; yield: 89%; mp 124–125 °C; $[\alpha]_D^{20}$ +85 (*c* 0.25, EtOH).

*4.5.2. Ethyl (1R,4S)-4-(tert-butoxycarbonylamino)cyclopent-2-enecarboxylate [(+)-**25**].* A colourless oil; yield: 88%; $[\alpha]_D^{20}$ +51 (*c* 0.17, EtOH).

*4.5.3. Ethyl (1R,2R,4S,5S)-4-(tert-butoxycarbonylamino)-6-oxa-bicyclo[3.1.0]hexane-2-carboxylate [(+)-**26**].* A white solid; yield: 76%; mp 83–86 °C; $[\alpha]_D^{20}$ +6.8 (*c* 0.6, EtOH).

*4.5.4. Ethyl (1R,2R,3R,4S)-3-azido-4-(tert-butoxycarbonylamino)-2-hydroxycyclopentanecarboxylate [(−)-**16**].* White crystals; yield: 26%; mp 113–115 °C; $[\alpha]_D^{20}$ −43.5 (*c* 1, EtOH).

*4.5.5. Ethyl (1R,2S,3S,4S)-2-azido-4-(tert-butoxycarbonylamino)-3-hydroxycyclopentanecarboxylate [(−)-**17**].* A colourless oil; yield: 52%; $[\alpha]_D^{20}$ −18 (*c* 0.55, EtOH).

*4.5.6. Ethyl 1-((1R,2R,3R,5S)-5-(tert-butoxycarbonylamino)-3-(ethoxycarbonyl)-2-hydroxycyclopentyl)-1H-1,2,3-triazole-4-carboxylate [(−)-**18**].* A white solid; yield: 77%; mp 183–184 °C; ee >98%; $[\alpha]_D^{20}$ −32.7 (*c* 0.65, EtOH).

*4.5.7. Ethyl 1-((1S,2S,3S,5R)-3-(tert-butoxycarbonylamino)-5-(ethoxycarbonyl)-2-hydroxycyclopentyl)-1H-1,2,3-triazole-4-carboxylate [(−)-**19**].* A white solid; yield: 70%; mp 138–140 °C; ee >98%; $[\alpha]_D^{20}$ +5.6 (*c* 0.7, EtOH).

4.6. X-ray crystallographic study of 4, 6 and 18

Crystallographic data were collected at 173 K for **4** and **18** and at 293 K for **6** with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) as reported earlier.[19] *Crystal data for **4***: $C_{18}H_{28}N_4O_7$, M_r=412.44, monoclinic, space group $P2_1/a$ (no. 14), a=10.6273(4), b=19.3231(7), c=32.2755(11) Å, β=94.344(1), V=6608.8(4) Å^3, T=173 K, Z=12, μ(Mo Kα)=0.097 mm^{-1}, 10,757 unique reflections (R_{int}=0.043), which were used in calculations. The final $R1$ and $wR2(F^2)$ were 0.106 (for the data with $F^2>2\delta(F^2)$) and 0.251 (all data), respectively.

*Crystal data for **6***: $C_{18}H_{28}N_4O_7$, M_r=412.44, monoclinic, space group $P2_1/a$ (no. 14), a=13.2552(4), b=12.5687(6), c=13.5144(5) Å, β=104.279(2), V=2181.95(15) Å^3, T=293 K, Z=4, μ(Mo Kα)=0.096 mm^{-1}, 4752 unique reflections (R_{int}=0.045), which were used in calculations. The final $R1$ and $wR2(F^2)$ were 0.066 (for the data with $F^2>2\delta(F^2)$) and 0.164 (all data), respectively.

*Crystal data for **18***: $C_{18}H_{28}N_4O_7$, M_r=412.44, tetragonal, space group $I4_1/a$ (no. 88), a=28.5929(6), b 28.5929(6), c=10.8552(2) Å, β=90, V=8874.7(3) Å^3, T=173 K, Z=4, μ(Mo Kα)=0.096 mm^{-1}, 4305 unique reflections (R_{int}=0.055), which were used in calculations. The final $R1$ and $wR2(F^2)$ were 0.058 (for the data with $F^2>2\delta(F^2)$) and 0.141 (all data), respectively.

The structures were solved by direct methods by use of the SHELXS-97 program,[20] and full-matrix, least-squares refinements on F^2 were performed by use of the SHELXL-97 program[20] The CH hydrogen atoms were included at fixed distances from their host atoms with the fixed displacement parameters. The NH hydrogen atoms were refined isotropically with the fixed displacement parameters. The OH hydrogen atoms were refined isotropically with the fixed displacement parameters or were modelled with the fixed positions and displacement parameters. The deposition numbers CCDC 766325–766327 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk].

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