JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01463 • Publication Date (Web): 24 Jul 2019

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Stereocontrolled Preparation of Diversely Tri-Functionalized Cyclobutanes

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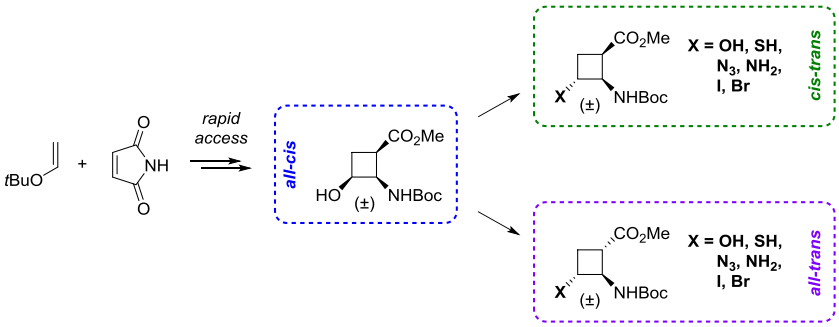
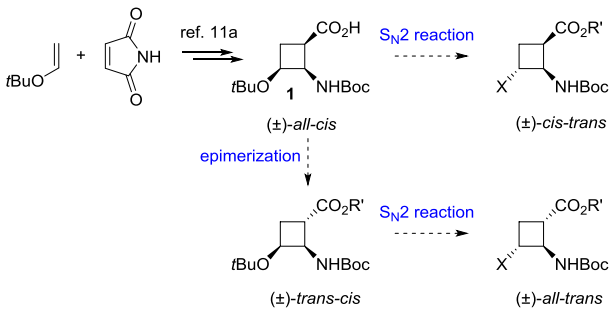
Toc graphic & Abstract

The expedient and stereoselective syntheses of small libraries of tri-functionalized cyclobutane scaffolds bearing an acid, an amine and a third functional group are described. Starting from a single precursor, the readily available protected derivative of *all-cis*-2-amino-3-hydroxycyclobutane-1-carboxylic acid, *cis-trans* stereoisomers are obtained following an S_N2 type reaction, while *all-trans* stereoisomers are obtained using the same strategy preceded by a C1 epimerization reaction.



Cyclobutanes are of wide-ranging interest in organic chemistry.[1] These four-membered rings are present in the structures of many natural products and in a large panel of synthetic compounds used in medicinal chemistry,[2] and they are high-value intermediates in organic synthesis, due to their inherent ring strain and their resulting reactivity.[3] While some noteworthy late-stage functionalization strategies have been described,[4] most of the currently used synthetic methodologies for the preparation of multiply-functionalized cyclobutanes employ precursors which provide the required functional group suite before or during the construction of the cyclobutane ring.[5] In this respect, photochemical [2+2]-cycloaddition strategies are among the most powerful synthetic tools available.[6]

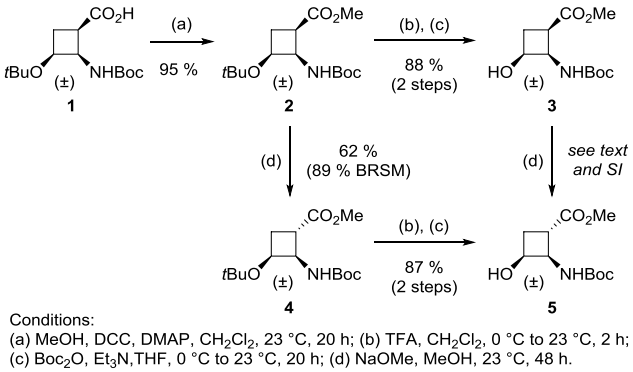
Functionalized cyclic β-amino acids[7] are valuable building blocks for the constructions of more complex molecular architectures such as biologically active molecules,[8] peptidomimetics and foldamers.[9,10] We have previously reported several syntheses of cyclobutane β-amino acid derivatives using photochemical approaches.[11,12,13] Those studies provided access to 2-aminocyclobutane-1-carboxylic acid (ACBC) derivatives with a variety of substituents at the C1 or C2 positions,[11d] but so far the only C3 or C4-substituted ACBCs which have been accessed feature a hydroxymethyl[11b,c] or a hydroxy[11a] functional group. In order to expand the inventory of ring-substituted ACBCs, we considered that the protected derivative of *all-cis*-2-amino-3-hydroxycyclobutane-1-carboxylic acid **1** was a promising intermediate. This compound can be prepared in diastereomerically pure form on multigram scale from maleimide and *t*-butyl vinyl ether in only two steps.[11a] In the present paper, we describe the selective transformations of **1** into small libraries of both *cis-trans* and *all-trans*-ACBC scaffolds featuring thiol, amine, azide or halogen substituents at the 3-position. An overview of the strategy is outlined in Scheme 1: after protecting group adjustment and activation, *cis-trans* compounds would be obtained by S_N2 type displacement of a leaving group at C3, while C1 epimerization followed by S_N2 displacement at C3 would lead to *all-trans* compounds.



Scheme 1. Synthetic strategy for the target molecules.

We first required the preparation of *all-cis* and *trans-cis* alcohols **3** and **5**. Multigram scale esterification of starting material **1** provided compound **2** in 95 % yield. Compound **3** was obtained efficiently from **2** on a large scale by performing double *N*,*O*-deprotection using TFA followed by selective reprotection of the amine using di-*tert*-butyl dicarbonate (88 % yield for two steps on 6.2 g scale). In order to access compounds with a *trans-cis* geometry, C1 epimerization of **2** was carried out. After considerable

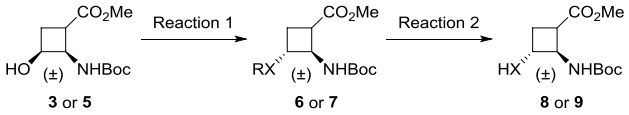
experimentation (see Table S1 in the Supporting Information), compound **4** was obtained in 62 % yield (4.0 g scale) by treating **2** with 30 equiv. of sodium methoxide (0.01 M in methanol) for two days, followed by quenching using an anhydrous methanol solution of acetic acid. Following this process, 30 % of unreacted **2** was recovered and recycled. The two-step *N*,*O*-deprotection/*N*-reprotection sequence was then applied to compound **4** to afford the *trans-cis* alcohol **5** in 87 % yield (2.1 g scale) for two steps (Scheme 2). We examined an alternative pathway and applied the epimerization conditions to derivative **3**. After two days, no trace of the starting material **3** was observed. Unfortunately, the target epimerized product **5** was accompanied by unidentified degradation products (see Scheme S1 in the Supporting Information). Based on these investigations, the preferred two-step access to compound **5** from substrate **2** proceeds via intermediate **4**.



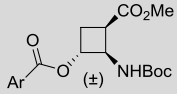
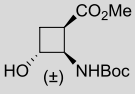
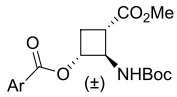
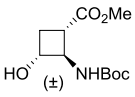
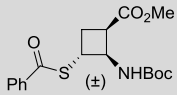
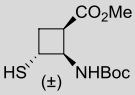
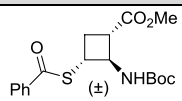
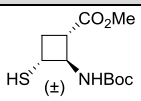
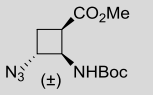
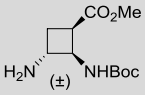
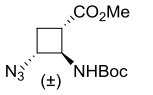
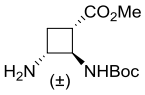
Scheme 2. Preparation of the starting materials **3** and **5**.

We then focused our attention on the central objective of introducing a new functional group at C3 in a stereoselective manner, for which a Mitsunobu reaction appeared to be the method of choice.[14] Employing triphenylphosphine and diisopropyl azodicarboxylate (DIAD) as standard reagents, some experimentation was required to determine the optimal conditions for each nucleophile, but we were able to establish efficient procedures for the installation of oxygen, sulfur and nitrogen functions using *para*-nitrobenzoic acid (entries 1-2, left), thiobenzoic acid (entries 3-4, left) and diphenylphosphorylazide (DPPA) (entries 5-6, left), respectively. In this way, the transformations of alcohols **3** and **5** provided *cis-trans* derivatives **6a-c** and *all-trans* derivatives **7a-c** in high yields (78-93 %), as unique diastereoisomers in every case. Treatment of each ester **6a-b** and **7a-b** with potassium carbonate solution in methanol furnished the corresponding alcohols **8a, 9a** and thiols **8b, 9b** in very high yields (90-95 %) (entries 1-4, right). In order to generate derivatives bearing an amine substituent, azides **6c** and **7c** were hydrogenolysed for 2 h under a hydrogen atmosphere in the presence of palladium on charcoal to provide **8c** and **9c** in high yields (96-98 %) (entries 5-6, right) (Table 1).

Table 1. Two steps sequence for the synthesis of compounds **8a-c** and **9a-c**



3 or **5** **6** or **7** **8** or **9**

Entry	Subst.	Reaction 1	6 or 7	Yield 1[a]	Reaction 2	8 or 9	Yield 2[a]
1[b]	**3**	p-$NO_2C_6H_4CO_2H$, Ph_3P, DIAD, THF, 23 °C, 8 h		**6a** 80 %	K_2CO_3, MeOH, 23 °C, 20 min		**8a** 94 %
2[b]	**5**	p-$NO_2C_6H_4CO_2H$, Ph_3P, DIAD, THF, 23 °C, 8 h		**7a** 83 %	K_2CO_3, MeOH, 23 °C, 20 min		**9a** 90 %
3	**3**	PhCOSH, Ph_3P, DIAD, THF, 23 °C, 6 h		**6b** 78 %	K_2CO_3, MeOH, 23 °C, 20 min		**8b** 95 %
4	**5**	PhCOSH, Ph_3P, DIAD, THF, 23 °C, 6 h		**7b** 82 %	K_2CO_3, MeOH, 23 °C, 20 min		**9b** 91 %
5	**3**	DPPA, Ph_3P, DIAD, THF, 50 °C, 3 h		**6c** 90 %	H_2, Pd/C, MeOH, 23 °C, 2 h		**8c** 96 %
6	**5**	DPPA, Ph_3P, DIAD, THF, 50 °C, 3 h		**7c** 93 %	H_2, Pd/C, MeOH, 23 °C, 2 h		**9c** 98 %

[a] Isolated yields. [b] Ar : p-$NO_2C_6H_4$.

Confirmation of the anticipated inversion of configuration during the Mitsunobu reaction was provided by single crystal X-ray diffraction analysis of compounds **6a** and **7a**. The *cis-trans* geometry of the former and the *all-trans* geometry of the latter are illustrated in Figure 1.

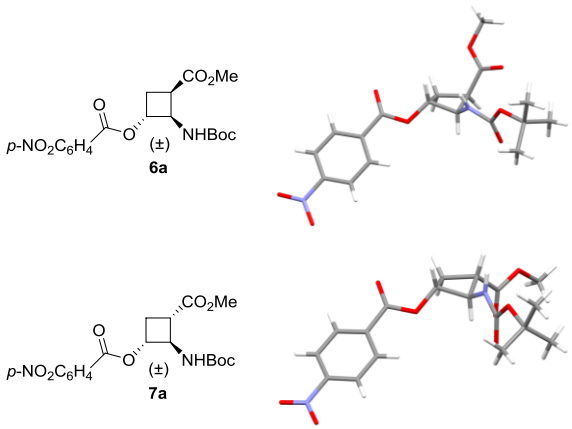
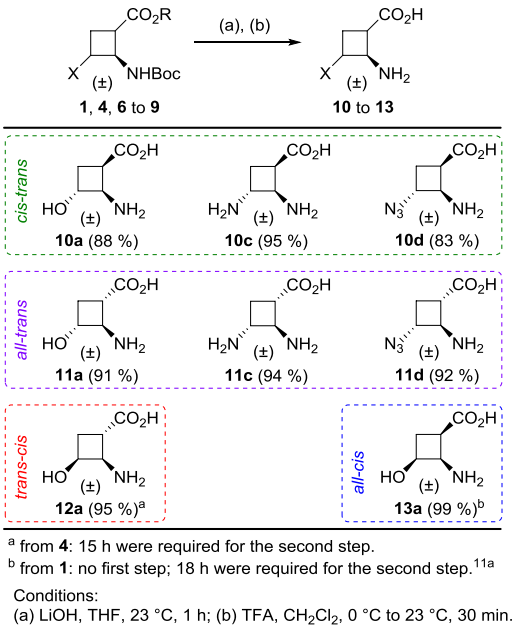


Figure 1. X-ray crystal structures of compounds **6a** and **7a**

With these collections of protected 3-substituted ACBCs in hand, we investigated the deprotection of the β-amino acid suite. For each of the compounds **6c**, **7c**, **8a,c**, and **9a,c** hydrolysis of the ester function was performed using lithium hydroxide in tetrahydrofuran then the *tert*-butoxycarbonyl group was removed using TFA in dichloromethane; the resulting amino acids were isolated after passage through a column of Dowex® cation exchange resin. This two-step protocol, which can be performed in less than 2 hours,

successfully provided the unprotected *cis-trans* ACBCs **10a,c,d** with 3-hydroxy, 3-amino and 3-azido substituents, respectively, as well as the corresponding *all-trans* amino acids **11a,c,d**. The procedure was likewise applied to the *trans-cis* intermediate **4** to provide **12a** (a longer reaction time was required for the second step). For all of these examples, isolated yields of amino acids were uniformly high (83-96 %). Surprisingly, hydrolysis in acidic or basic conditions of thiol derivatives **6b** to **9b** resulted in extensive degradation. Consequently, the corresponding thio amino acids could not be obtained successfully (Scheme 3).



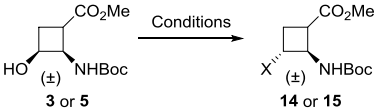
Scheme 3. Synthesis of free amino acids **10** to **13**

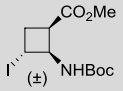
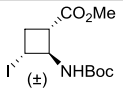
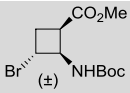
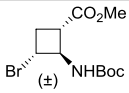
Compound **13a** was also prepared from starting material **1** by acid-mediated *N*,*O*-deprotection,[11a] meaning that this strategy provides satisfying access to all diastereoisomers of 2-amino-3-hydroxycyclobutane-1-carboxylic acid (**10a** to **13a**). Furthermore, the panel of products prepared using the above-described protocols demonstrates that any stereoisomer of protected 2-aminocyclobutane-1-carboxylic acid bearing an additional alcohol, thiol, amine, or azide at the C3 position can be achieved starting from the appropriate stereoisomer of a common intermediate (**3** or **5**).

Halogen derivatives are ideally-adapted synthetic intermediates for the installation of other functional groups via substitution reactions, organometallic reagents or transition metal coupling reactions. To increase the scope of our strategy for the preparation of tri-substituted cyclobutanes, we sought to replace the alcohol group of starting materials **3** and **5** with a bromine or an iodine atom. To provide access to halogen derivatives **14** and **15**, we considered the Appel reaction,[15] and gratifyingly the desired *cis-trans* and *all-trans* iodo-derivatives **14e** and **15e** were obtained in 34 % and 80 % yields respectively, employing PPh_3, imidazole and I_2 (entries 1-2). The corresponding bromo-derivatives **14f** and **15f** were also synthesized

in 65 % and 30 % yields, respectively, using PPh_3, tetra-*n*-butylammonium bromide (TBAB) and CBr_4 (entries 3-4, Table 2).

Table 2. Synthesis of compounds **14e-f** and **15e-f**.



Entry	Subst.	Conditions	14 or 15	Yield[a]
1	**3**	Ph_3P, imidazole, I_2, toluene, reflux, 2 h		**14e** 34 %
2	**5**	Ph_3P, imidazole, I_2, toluene, reflux, 2 h		**15e** 80 %
3	**3**	Ph_3P, TBAB, CBr_4, THF, 23 °C, 16 h		**14f** 65 %
4	**5**	Ph_3P, TBAB, CBr_4, THF, 23 °C, 16 h		**15f** 30 %

[a] Isolated yields.

To conclude, the divergent strategy established in this study employed a single, readily-available starting material, *all-cis*-2-amino-3-hydroxycyclobutane-1-carboxylic acid in a protected form, to access diversely substituted tri-functionalized cyclobutane scaffolds in a stereoselective manner. Using either a Mitsunobu reaction or an Appel reaction, hydroxy, thio, amine, azide and halogen functions were installed stereoselectively and efficiently at the C3 position of a cyclobutane ring bearing protected C1 acid and C2 amine groups. The *cis-trans* stereoisomers were obtained by a stereospecific S_N2 type reaction conducted on the *all-cis* starting material, while the *all-trans* stereoisomers were prepared from the *trans-cis* intermediate, itself obtained by C1 epimerization of the *all-cis* starting material. The above procedures provide a useful expansion of the inventory of cyclic β-amino acids.

EXPERIMENTAL SECTION

General Experimental. All reagents and solvents were of commercial grade and were used without further purification, with the exception of dichloromethane which was dried over activated alumina, THF which was distilled from sodium/benzophenone, acetonitrile which was distilled from P_2O_5, triethylamine which was distilled on potassium hydroxide. Methanol extra dry Acrosseal® was purchased from Acros. Flash chromatography was performed on 35–70 µm columns of silica gel (Merk-Chimie SAS). Analytical thin-layer chromatography was carried out on commercial 0.25 mm silica gel plates (EMD, Silica Gel $60F_{254}$) which were visualized by UV fluorescence at 254 nm then revealed using a phosphomolybdic acid solution (10 % in EtOH) or a ninhydrin solution (0.3 % in *n*-BuOH). Retention factors (R_f) are given for such TLC analyses. Melting points were determined with a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

Fourier-transform Infrared (IR) spectra were recorded for neat samples on a FT-IR PerkinElmer Spectrum Two spectrophotometer using an ATR diamond accessory; maximum absorbances (ν) are given (in cm^{-1}). Nuclear magnetic resonance (NMR) data were acquired on spectrometers operating at 360/300/250 MHz for ^{1}H and at 90/75/63 MHz for $^{13}C\{^{1}H\}$. Chemical shifts (δ) are reported in ppm with respect to tetramethylsilane (δ = 0 ppm). Splitting patterns for ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR signals are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), br. s (broad singlet), app. (apparent) or m (multiplet). Coupling constants (*J*) are reported in Hz. High-resolution mass spectrometry (HRMS) data were recorded on a Bruker Daltonics MicroTOF-Q spectrometer equipped with an electrospray ionization source either in positive or negative mode as appropriate, with a tandem Q-TOF analyzer. Details on X-ray diffraction analysis data are given in the Supporting Information.

General procedure A for deprotection of *tert*-butyl and Boc group followed by Boc reprotection. Compound **2** or **4** (1.0 equiv.) was dissolved in neat TFA (2 mL/mmol) at 0 °C. The mixture was stirred for 2 h, during this period the temperature was raised to room temperature slowly. After a completely evaporation of TFA, the residue was diluted with THF (10 mL/mmol), then Et_3N (2.15 equiv.) and Boc_2O (1.1 equiv.) in THF (2 mL/mmol) were added successively at 0 °C. The mixture was stirred at room temperature overnight. The mixture was diluted with H_2O and extracted with Et_2O. The combined organic phrases were washed with HCl (1 M), saturated $NaHCO_3$ solution, brine successively and dried over $MgSO_4$. The solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography to afford the desired product **3** or **5**.

General procedure B for Mitsunobu reaction. To a solution of ester **3** or **5** in anhydrous THF (20 mL/mmol), PPh_3 (2.0 or 3.0 equiv.), DIAD (2.0 or 3.0 equiv.) and the nucleophile (2.0 or 3.0 equiv.) were added successively at 0 °C and the temperature was raised to room temperature slowly. The reaction was followed by TLC analyses and stirred at the appropriate temperature (using an oil bath) and time as indicated in Table 1. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography to afford the desired product **6a,b,c** or **7a,b,c**.

General procedure C for methanolysis reaction. To a methanol solution (10 mL/mmol) of compound **6a**,**b** or **7a,b** (1.0 equiv.), K_2CO_3 (1.5 equiv.) was added in one portion at 0 °C, then the mixture was stirred at room temperature for 20 minutes. The reaction was quenched with HCl (1 M) and after a careful evaporation of methanol, the residue was diluted with ethyl acetate, and then washed with H_2O, brine successively and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the desired product **8a**,**b** or **9a,b**.

General procedure D for hydrogenolysis reaction. To a methanol solution of compound **6c** or **7c**, Pd/C (10 %) was added. The mixture was stirred under hydrogen atmosphere at room temperature for 2 h, after a filtration on a pad of Celite®, the filtrate was concentrated by evaporation to afford the product **8c** or **9c**.

General procedure E for saponification and Boc deprotection process. To a THF/H_2O (1:1) solution (30 mL/mmol) of compound **1**, **4**, **6c**, **7c**, **8a,c** or **9a,c** (1.0 equiv.), LiOH monohydrate (1.0 equiv.) was added in

one portion at room temperature and stirred for 1 h. After a careful removal of THF, the reaction mixture was acidified with HCl (1 M) (pH ~ 4) and extracted with ethyl acetate. The combined organic extracts were washed with H_2O, brine successively and dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in dichloromethane (5 mL/mmol), TFA (30 equiv.) was added at 0 °C and the reaction mixture was stirred for 30 minutes at room temperature (or for the appropriate time). Then solvents were evaporated under reduced pressure and the residue was applied to a column of Dowex® 50W-X8 cation exchange resin (200-400 mesh) activated with HCl (3 M) and eluted using 1 M NH_4OH to afford the free amino acid **10a,c,d, 11a,c,d, 12a** or **13a**.

General procedure F for iodination reaction. To a solution of methyl ester **3** or **5** (1.0 eq) in toluene, I_2 (1.5 equiv.), imidazole (3.0 equiv.) and PPh_3 (2.0 equiv.) were added successively. The mixture was stirred for 2 h under reflux in an oil bath. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the methyl ester **14e** or **15e**.

General procedure G for bromination reaction. To a solution of methyl ester **3** or **5** (1.0 equiv.) in anhydrous THF (16 mL/mmol), CBr_4 (2.0 equiv.), PPh_3 (2.0 equiv.), and TBAB (10 %) were added successively. The mixture was stirred for 16 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the methyl ester **14f** or **15f**.

(±)-*cis*-*cis*-Methyl 3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 2. To a solution of protected *cis*-ACBC **1**[11a] (1.44 g, 5.0 mmol) and MeOH (0.61 mL, 15 mmol) in dichloromethane, DMAP (61 mg, 0.50 mmol) and DCC (1.24 g, 6.0 mmol) were added at 0 °C and the mixture was stirred for 1 h at this temperature. After warming up to room temperature, the reaction mixture was stirred for 20 h. After filtration, the solvent was removed under reduced pressure, EtOAc was added and washed with 1 M HCl solution, brine, 5 % $NaHCO_3$ solution, brine successively. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (Et_2O/petroleum ether, 40/60) to afford the desired ester **2** (1.43 g, 95 %) as a white solid. R_f (Et_2O/petroleum ether, 50/50): 0.53; Mp: 80-81 °C; IR *v* 3446, 2973, 1717, 1485, 1362, 1154; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 5.36 (d, *J* = 6.5 Hz, 1H), 4.43-4.31 (m, 1H), 4.20 (app. dd, *J* = 15.2, 7.3 Hz, 1H), 3.57 (s, 3H), 2.89 (dt, *J* = 10.4, 7.3 Hz, 1H), 2.38 (td, *J* = 11.2, 8.8 Hz, 1H), 2.25 (dtd, *J* = 11.5, 7.5, 3.6 Hz, 1H), 1.36 (s, 9H), 1.10 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 171.7, 155.6, 79.3, 74.6, 63.0, 55.6, 51.7, 37.1, 32.4, 28.3 (3C), 28.0 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{27}NNaO_5^+$: 324.1781; Found: 324.1786.

(±)-*cis*-*cis*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-hydroxycyclobutane-1-carboxylate 3. Followed the general procedure **A**, using methyl ester **2** (6.16 g, 20.5 mmol), TFA (35 mL), Et_3N (6.2 mL, 44.1 mmol) and Boc_2O (4.91g, 22.5 mmol). Flash chromatography (EtOAc/petroleum ether, 60/40) afforded the desired product **3** (4.42 g, 88 %) as a white solid. R_f (EtOAc/petroleum ether, 50/50): 0.43; Mp: 81-82 °C; IR *v* 3468, 3353, 2956, 1735, 1161, 1530, 1337, 1276, 1248, 1150; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 5.70-5.34 (m, 1H), 4.40-4.18 (m, 2H), 4.07-4.86 (m, 1H), 3.58 (s, 3H), 3.11 (app. dd, *J* = 14.6, 7.4 Hz, 1H), 2.36-2.25 (m, 1H), 2.19-2.05

(m, 1H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (90 MHz, $CDCl_3$) δ 174.2, 155.6, 79.6, 66.9, 52.0 (2C), 39.8, 30.9, 28.1 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_5^+$: 268.1155; Found: 268.1156.

(±)-*trans*-*cis*-Methyl 3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 4. To a freshly prepared NaOMe solution in methanol (0.4 M, 1 L), a solution of methyl ester **2** (4.0 g, 13.3 mmol) in methanol (100 mL) was added at 0 °C. The mixture was stirred at room temperature for 48 h. The reaction mixture was then poured into cold (0 °C) mixture of acetic acid (114 mL) and dry methanol (114 mL). After evaporation of the solvents under reduced pressure, the residue was diluted with H_2O and extracted with Et_2O. The combined organic phases was washed with H_2O, brine and was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (EtOAc/petroleum ether, 30/70) to afford the methyl ester **4** (2.46 g, 62 %) as a white solid and recovered substrate **2** (1.20 g, 30 %). R_f (Et_2O/petroleum ether, 50/50): 0.66; Mp: 46-47 °C; IR *v* 3435, 2974, 1711, 1487, 1364, 1245; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.36-5.18 (m, 1H), 4.36-4.22 (m, 1H), 4.22-3.96 (m, 1H) 3.56 (s, 3H), 2.84 (dt, *J* = 10.3, 5.2 Hz, 1H), 2.32-2.13 (m, 1H), 1.99 (ddd, *J* = 12.3, 10.3, 5.2 Hz, 1H), 1.31 (s, 9H), 1.04 (s, 9H); $^{13}C\{^{1}H\}$ NMR (63 MHz, $CDCl_3$) δ 174.3, 155.0, 79.2, 74.6, 65.7, 53.5, 51.7, 42.9, 31.8, 28.2 (3C), 28.0 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{27}NNaO_5^+$: 324.1781; Found: 324.1779.

(±)-*trans*-*cis*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-hydroxycyclobutane-1-carboxylate 5. Followed the general procedure **A**, using methyl ester **4** (1.95 g, 6.48 mmol), TFA (13.0 mL), Et_3N (1.93 mL, 13.9 mmol) and Boc_2O (1.58 g, 6.48 mmol). Flash chromatography ($MeOH/CH_2Cl_2$, 10/90) afforded the methyl ester **5** (2.89 g, 87 %) as a white solid. R_f (EtOAc/petroleum ether, 50/50): 0.45; Mp: 81-82 °C; IR *v* 3314, 3248, 2955, 1731, 1670, 1539, 1285, 1158; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.57 (br. d, *J* = 6.9 Hz, 1H), 4.39 (br. t, *J* = 5.2 Hz, 1H), 4.30-4.05 (m, 1H), 4.02-3.76 (m, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 1H), 2.27-2.15 (m, 1H), 1.99-1.90 (m, 1H), 1.35 (s, 9H); $^{13}C\{^{1}H\}$ NMR (90 MHz, $CDCl_3$) δ 174.2, 155.5, 79.9, 68.1, 51.9 (2C), 44.1, 29.8, 28.3 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_5^+$: 268.1155; Found: 268.1148.

(±)-*cis*-*trans*-2-((*tert*-Butoxycarbonyl)amino)-3-(methoxycarbonyl)cyclobutyl 4-nitrobenzoate 6a. Followed the general procedure **B**, using methyl ester **3** (0.98 g, 4.0 mmol), PPh_3 (3.14 g, 12 mmol), DIAD (2.41 mL, 12 mmol) and *p*-nitrobenzoic acid (2.0 g, 12 mmol). The reaction was stirred for 8 h. Flash chromatography (EtOAc/petroleum ether, 30/70) afforded the desired product **6a** (1.26 g, 80 %) as a white solid. R_f (Et_2O/petroleum ether, 40/60): 0.25; Mp: 122-124 °C; IR *v* 3348, 2984, 1713, 1680, 1515, 1331, 1264, 1250, 1161, 1118, 1104, 1066, 1014, 721; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.23-8.17 (m, 2H), 8.16-8.10 (m, 2H), 5.65 (br. d, *J* = 8.8 Hz, 1H), 5.45 (app. q, *J* = 8.2 Hz, 1H), 4.56 (dd, *J* = 16.8, 8.2 Hz, 1H), 3.68 (s, 3H), 3.36 (app. br. t, *J* = 8.8 Hz, 1H), 2.51 (app. br. t, *J* = 9.6 Hz, 1H), 2.10 (dt, *J* = 12.0, 9.6 Hz, 1H), 1.35 (s, 9H); $^{13}C\{^{1}H\}$ NMR (90 MHz, $CDCl_3$) δ 173.9, 163.8, 154.7, 150.6, 134.9, 130.9 (2C), 123.5 (2C), 79.9, 73.7, 52.8, 52.2, 38.5, 28.2 (3C), 27.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{22}N_2NaO_8^+$: 417.1268; Found: 417.1254.

(±)-*trans*-*trans*-2-((*tert*-Butoxycarbonyl)amino)-3-(methoxycarbonyl)cyclobutyl 4-nitrobenzoate 7a. Followed the general procedure **B**, using methyl ester **5** (245 mg, 1.0 mmol), PPh_3 (786 mg, 3.0 mmol), DIAD

(0.59 mL, 3.0 mmol) and *p*-nitrobenzoic acid (501 mg, 3.0 mmol). The reaction was stirred for 8 h. Flash chromatography (EtOAc/petroleum ether, 30/70) afforded the desired product **7a** (329 mg, 83 %) as a white solid. R_f (EtOAc/petroleum ether, 30/70): 0.40; Mp: 116-118 °C; IR *v* 3346, 2982, 1722, 1683, 1522, 1262, 1154, 1098; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 8.25-8.19 (m, 2H), 8.18-8.12 (m, 2H), 5.75-5.40 (m, 1H), 5.33-5.06 (m, 1H), 4.27 (app. q, *J* = 7.7 Hz, 1H), 3.68 (s, 3H), 3.00-2.65 (m, 1H), 2.57 (dt, *J* = 11.2, 8.2 Hz, 1H), 2.09 (td, *J* = 10.2, 8.2 Hz, 1H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 172.9, 164.1, 154.8, 150.6, 134.9, 130.9 (2C), 123.6 (2C), 79.9, 70.9, 56.1, 52.2, 37.7, 28.3 (3C), 26.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{22}N_2NaO_8^+$: 417.1268; Found: 417.1248.

(±)-*cis*-*trans*-Methyl 3-(benzoylthio)-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 6b. Followed the general procedure **B**, using methyl ester **3** (0.98 g, 4.0 mmol), PPh_3 (2.1 g, 8.0 mmol), DIAD (1.61 mL, 8.0 mmol) and thiobenzoic acid (0.94 mL, 8.0 mmol). The reaction was stirred for 6 h. Flash chromatography (EtOAc/petroleum ether, 20/80) afforded the desired product **6b** (1.15 g, 78 %) as a white solid. R_f (Et_2O/petroleum ether, 50/50): 0.50; Mp: 133-134 °C; IR *v* 3368, 2952, 1741, 1697, 1656, 1517, 1207, 1166, 1158, 909; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 7.88-7.80 (m, 2H), 7.53-7.46 (m, 1H), 7.42-7.33 (m, 2H), 5.76-5.50 (m, 0.9H), 5.45-5.22 (m, 0.1H), 4.60-4.25(m, 2H), 3.70 (s, 3H), 3.55-3.36 (m, 1H), 2.56-2.47 (m, 1H), 2.15-1.95 (m, 1H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 191.1, 173.6, 154.7, 136.5, 133.6, 128.6 (2C), 127.3 (2C), 79.7, 52.7, 52.0, 43.4, 42.1, 28.2 (3C), 26.5; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{23}NNaO_5S^+$: 388.1189; Found: 388.1177.

(±)-*trans*-*trans*-Methyl 3-(benzoylthio)-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 7b. Followed the general procedure **B**, using methyl ester **5** (245 mg, 1.0 mmol), PPh_3 (524 mg, 2.0 mmol), DIAD (0.40 mL, 2.0 mmol) and thiobenzoic acid (0.24 mL, 2.0 mmol). The reaction was stirred for 6 h. Flash chromatography (EtOAc/petroleum ether, 20/80) afforded the desired compound **7b** (298 mg, 82 %) as a white solid. R_f (EtOAc/petroleum ether, 30/70): 0.65; Mp: 117-119 °C; IR *v* 3346, 2986, 1722, 1687, 1669, 1522, 1284, 1206, 1145; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 7.92-7.82 (m, 2H), 7.56-7.47 (m, 1H), 7.42-7.33 (m, 2H), 5.53 (d, *J* = 7.2 Hz, 1H), 4.40-4.05 (m, 2H), 3.67 (s, 3H), 3.22-2.95 (m, 1H), 2.51 (dt, *J* = 10.5, 8.4 Hz, 1H), 2.03 (app. q, *J* = 10.5 Hz, 1H), 1.38 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 191.7, 172.6, 154.7, 136.4, 133.6, 128.6 (2C), 127.3 (2C), 79.7, 55.9, 52.0, 44.2, 39.4, 28.3 (3C), 26.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{23}NNaO_5S^+$: 388.1189; Found: 388.1169.

(±)-*cis*-*trans*-Methyl 3-azido-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 6c. Followed the general procedure **B**, using methyl ester **3** (0.49 g, 2.0 mmol), PPh_3 (1.57 g, 6.0 mmol), DIAD (1.2 mL, 6.0 mmol) and DPPA (1.3 mL, 6.0 mmol). The reaction was stirred at 50 °C for 3 h (using an oil bath). Flash chromatography (EtOAc/petroleum ether, 20/80) afforded the desired product **6c** (0.49 g, 90 %) as a white solid. R_f (Et_2O/petroleum ether, 30/70): 0.40; Mp: 133-134 °C; IR *v* 3310, 2984, 2091, 1728, 1685, 1529, 1335, 1161; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 5.60-5.21 (m, 1H), 4.42-4.16 (m, 1H), 4.06 (app. q, *J* = 8.8 Hz, 1H), 3.68 (s, 3H), 3.26 (app. br. t, *J* = 8.8 Hz, 1H), 2.33-2.22 (m, 1H), 2.06-1.82 (m, 1H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR

(75 MHz, $CDCl_3$) δ 174.1, 154.5, 80.1, 60.9, 52.4, 52.2, 39.5, 28.3 (3C), 25.9; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{18}N_4NaO_4^+$: 293.1220; Found: 293.1212.

(±)-*trans*-*trans*-Methyl 3-azido-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 7c. Followed the general procedure **B**, using methyl ester **5** (245 mg, 1.0 mmol), PPh_3 (0.79 g, 3.0 mmol), DIAD (0.60 mL, 3.0 mmol) and DPPA (0.65 mL, 3.0 mmol). The reaction was performed at 50 °C for 3 h (using an oil bath). Flash chromatography (EtOAc/petroleum ether, 20/80) afforded the desired product **7c** (0.25 g, 93 %) as a white solid. R_f (EtOAc/petroleum ether, 25/75): 0.40; Mp: 94-95 °C; IR *v* 3362, 2983, 2082, 1728, 1681, 1526, 1254, 1228, 1155; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.95-5.68 (m, 0.3H), 5.56-5.14 (m, 0.7H), 4.12-3.82 (m, 1.7H), 3.72-3.50 (m, 0.3H), 3.66 (s, 3H), 3.05-2.83 (m, 0.7H), 2.73-2.50 (m, 0.3H), 2.33 (dt, *J* = 11.2, 8.1 Hz, 1H), 1.86 (app. q, *J* = 10.2 Hz, 1H), 1.39 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 172.7, 154.9, 80.1, 57.4, 55.8, 52.2, 38.4, 28.3 (3C), 25.6; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{18}N_4NaO_4^+$: 293.1220; Found: 293.1211.

(±)-*cis*-*trans*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-hydroxycyclobutane-1-carboxylate 8a. Followed the general procedure **C**, using racemic methyl ester **6a** (976 mg, 2.48 mmol), K_2CO_3 (171 mg, 1.24 mmol). Flash chromatography (EtOAc/petroleum ether, 50/50) afforded the desired product **8a** (571 mg, 94 %) as a white solid. R_f (EtOAc/petroleum ether, 50/50): 0.30; Mp: 85-86 °C; IR *v* 3368, 2979, 1692, 1511, 1364, 1250, 1160, 1046; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85-5.20 (m, 1H), 4.32 (app. q, *J* = 8.2 Hz, 1H), 4.23-4.07 (m, 1H), 4.06-3.90 (m, 1H), 3.65 (s, 3H), 3.16 (app. br. t, *J* = 8.7 Hz, 1H), 2.28 (app. br. t, *J* = 10.1 Hz, 1H), 1.84 (app. q, *J* = 10.1 Hz, 1H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 174.7, 155.4, 79.9, 72.0, 55.8, 51.9, 36.9, 29.4, 28.3 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_5^+$: 268.1155; Found: 268.1151.

(±)-*trans*-*trans*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-hydroxycyclobutane-1-carboxylate 9a. Followed the general procedure **C**, using methyl ester **7a** (58 mg, 0.15 mmol), K_2CO_3 (10 mg, 0.07 mmol). Flash chromatography (EtOAc/petroleum ether, 60/40) afforded the alcohol **9a** (33 mg, 90 %) as a white solid. R_f (EtOAc/petroleum ether, 60/40): 0.35; Mp: 114-115 °C; IR *v* 3360, 1729, 1681, 1521, 1369, 1153, 1015; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.62-5.42 (m, 0.2H), 5.26-4.95 (m, 0.8H), 4.05 (app. q, *J* = 7.5 Hz, 1H); 3.96-3.78 (m, 1H), 3.69 (s, 3H), 3.49-2.95 (m, 1H), 2.61-2.29 (m, 2H), 1.88 (dd, *J* = 19.2, 9.9 Hz, 1H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$) δ 173.4, 155.7, 80.2, 69.4, 59.0, 52.2, 36.2, 29.3, 28.5 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_5^+$: 268.1155; Found: 268.1150.

(±)-*cis*-*trans*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-mercaptocyclobutane-1-carboxylate 8b. Followed the general procedure **C**, using methyl ester **6b** (73 mg, 0.20 mmol), K_2CO_3 (41 mg, 0.30 mmol). Flash chromatography (EtOAc/petroleum ether, 20/80) afforded the desired product **8b** (49 mg, 95 %) as a white solid. R_f (EtOAc/petroleum ether, 20/80): 0.40; Mp: 114-115 °C; IR *v* 3316, 2979, 1725, 1687, 1526, 1345, 1198, 1155, 1060; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.57-4.97 (m, 1H), 4.35-3.99 (m, 1H), 3.70 (s, 3H), 3.64-3.48 (m, 1H), 3.41 (app. t, *J* = 8.7 Hz, 1H), 2.44 (app. td, *J* = 10.5, 1.6 Hz, 1H), 1.97-1.74 (m, 2H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 174.2, 154.8, 79.9, 56.8, 52.1, 42.9, 39.9, 31.0, 28.3 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_4S^+$: 284.0927; Found: 284.0921.

(±)-*trans*-*trans*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-mercaptocyclobutane-1-carboxylate 9b. Followed the general procedure **C**, using methyl ester **7b** (100 mg, 0.27 mmol), K_2CO_3 (57 mg, 0.41 mmol). Flash chromatography (EtOAc/petroleum ether, 20/80) afforded the title compound **9b** (65 mg, 91 %) as a white solid. R_f (EtOAc/petroleum ether, 25/75): 0.40; Mp: 99-101 °C; IR *v* 3349, 2983, 1724, 1681, 1526, 1371, 1228, 1155; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 5.60-4.97 (m, 1H), 4.00-3.75 (m, 1H), 3.65 (s, 3H), 3.47-3.23 (m, 0.8H), 3.20-2.95 (m, 1H), 3.92-2.69 (m, 0.2H), 2.46 (dd, *J* = 19.5, 8.8 Hz, 1H), 1.85 (d, *J* = 9.3 Hz, 1H), 1.79 (app. q, *J* = 10.6 Hz, 1H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 172.7, 154.9, 79.9, 60.4, 52.0, 42.7, 36.6, 30.5, 28.3 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{19}NNaO_4S^+$: 284.0927; Found: 284.0913.

(±)-*cis*-*trans*-Methyl 3-amino-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 8c. Followed the general procedure **D**, using methyl ester **6c** (195 mg, 0.72 mmol), Pd/C (10 %) (77 mg, 0.072 mmol). Compound **8c** (168 mg, 96 %) was obtained as a colorless sticky oil. R_f (EtOAc): 0.12; IR *v* 3372, 2979, 1704, 1501, 1364, 1246, 1161; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 5.56-5.35 (m, 1H), 3.94 (app. q, *J* = 8.6 Hz, 1H), 3.64 (s, 3H), 3.52 (app. q, *J* = 8.9 Hz, 1H), 3.15 (br. t, *J* = 8.6 Hz, 1H), 2.25 (br. t, *J* = 9.7 Hz, 1H), 1.73 (br. s, 2H), 1.59 (app. q, *J* = 9.7 Hz, 1H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 174.8, 155.2, 79.6, 56.6, 55.1, 51.9, 38.5, 30.0, 28.4 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{20}N_2NaO_4^+$: 267.1315; Found: 267.1309.

(±)-*trans*-*trans*-Methyl 3-amino-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 9c. Followed the general procedure **D**, using methyl ester **7c** (100 mg, 0.37 mmol), Pd/C (10 %) (39 mg, 0.037 mmol). Methyl ester **9c** (89 mg, 98 %) was obtained as a colorless sticky oil. R_f (EtOAc): 0.08; IR *v* 3355, 2979, 1694, 1521, 1365, 1253, 1162, 1023; ^{1}H NMR (360 MHz, $CDCl_3$) *δ* 6.45-6.25 (m, 0.3H), 6.08-5.82 (m, 0.7H), 5.27 (br. s, 2H), 4.05-3.75 (m, 1H), 3.58 (s, 3H), 3.67-3.30 (m, 1H), 2.90-2.45 (m, 1H), 2.43-2.16 (m, 1H), 1.95-1.60 (m, 1H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (90 MHz, $CDCl_3$) *δ* 173.3, 155.4, 79.6, 56.6, 51.9, 50.1, 39.1, 28.3 (3C), 27.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{20}N_2NaO_4^+$: 267.1315; Found: 267.1303.

(±)-*cis*-*trans*-2-Amino-3-hydroxycyclobutane-1-carboxylic acid 10a. Followed the general procedure **E** using methyl ester **8a** (380 mg, 1.55 mmol), LiOH monohydrate (65 mg, 1.55 mmol), TFA (3.7 mL, 48.2 mmol). Free amino acid **10a** (180 mg, 88 %) was obtained as a white solid. Mp: 102-103 °C (degradation); IR *v* 2951, 1520, 1387, 1113; ^{1}H NMR (360 MHz, D_2O) *δ* 4.43-4.34 (m, 1H), 3.59 (t, *J* = 8.1 Hz, 1H), 2.94-2.85 (m, 1H), 2.25 (ddd, *J* = 11.1, 9.0, 1.9 Hz, 1H), 2.01 (td, *J* = 11.1, 9.0 Hz, 1H), COOH, OH and NH_2 are not observed; ^{13}C{^{1}H} NMR (90 MHz, D_2O (with one drop of dioxane)) *δ* 180.5, 68.0, 53.3, 33.6, 31.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_5H_{10}NO_3^+$: 132.0655; Found: 132.0658.

(±)-*trans*-*trans*-2-Amino-3-hydroxycyclobutane-1-carboxylic acid 11a. Followed the general procedure **E**, using methyl ester **9a** (153 mg, 0.62 mmol), LiOH monohydrate (26 mg, 0.62 mmol), TFA (1.59 mL, 20.8 mmol). Free amino acid **11a** (74 mg, 91 %) was obtained as a white solid. Mp: 116-118 °C degradation; IR *v* 3373, 3035, 2490, 2235, 1560, 1400; ^{1}H NMR (360 MHz, D_2O) *δ* 4.10-3.95 (m, 1H), 3.58-3.45 (m, 1H), 2.55-2.40 (m, 2H), 1.76-7.63 (m, 1H), COOH, OH and NH_2 are not observed; ^{13}C{^{1}H} NMR (90 MHz, D_2O (with one drop of dioxane)) *δ* 179.5, 65.2, 56.2, 36.6, 30.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_5H_{10}NO_3^+$: 132.0655; Found: 132.0657.

(±)-*cis-trans*-2,3-Diaminocyclobutane-1-carboxylic acid 10c. Followed the general procedure **E**, using methyl ester **8c** (46 mg, 0.19 mmol), LiOH monohydrate (8.0 mg, 0.19 mmol), TFA (0.5 mL, 6.5 mmol). After the saponification step, solvent was removed and the residue was used for the deprotection step directly. Free amino acid **10c** (23 mg, 95 %) was obtained as a pale yellow solid. Mp: 119-120 °C (degradation); IR *v* 2947, 1534, 1383, 1113; ^{1}H NMR (300 MHz, D_2O) *δ* 3.86 (app. q, *J* = 8.6 Hz, 1H), 3.73 (t, *J* = 8.4 Hz, 1H), 3.11 (app. br. t, *J* = 8.6 Hz, 1H), 2.33 (app. br. t, *J* = 10.3 Hz, 1H), 2.06 (app. q, *J* = 9.7 Hz, 1H), COOH and both NH_2 are not observed; ^{13}C{^{1}H} NMR (75 MHz, D_2O (with one drop of dioxane)) *δ* 180.1, 52.0, 51.1, 39.2, 26.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_5H_{11}N_2O_2^+$: 131.0815; Found: 131.0817.

(±)-*trans-trans*-2,3-Diaminocyclobutane-1-carboxylic acid 11c. Followed the general procedure **E**, using methyl ester **9c** (100 mg, 0.41 mmol), LiOH monohydrate (17.2 mg, 0.41 mmol), TFA (1.05 mL, 13.7 mmol). After the saponification step, the solvent was removed and the residue was used for the deprotection step directly. Free amino acid **11c** (50 mg, 94 %) was obtained as a white solid. Mp: 133-135 °C degradation; IR v 2914, 2170, 1543, 1391; ^{1}H NMR (360 MHz, D_2O) *δ* 3.45 (t, *J* = 8.2 Hz, 1H), 3.34 (dd, *J* = 17.1, 8.2 Hz, 1H), 2.56 (dt, *J* = 9.9, 8.6 Hz, 1H), 2.41 (dt, *J* = 10.7, 8.6 Hz, 1H), 1.71 (ddd, *J* = 11.1, 10.1, 9.3 Hz, 1H), COOH and both NH_2 are not observed; ^{13}C{^{1}H} NMR (90 MHz, D_2O (with one drop of dioxane)) *δ* 180.4, 55.8, 48.9, 42.7, 26.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_5H_{11}N_2O_2^+$: 131.0815; Found: 131.0818.

(±)-*cis-trans*-2-Amino-3-azidocyclobutane-1-carboxylic acid 10d. Followed the general procedure **E**, using methyl ester **6c** (200 mg, 0.74 mmol), LiOH monohydrate (31 mg, 0.74 mmol), TFA (1.9 mL, 24.8 mmol). Free amino acid **10d** (96 mg, 83 %) was obtained as a white solid. Mp: 101-102 °C (degradation); IR *v* 2705, 2105, 1558, 1406, 1255; ^{1}H NMR (300 MHz, D_2O) *δ* 4.33 (app. q, *J* = 8.7 Hz, 1H), 3.83 (t, *J* = 8.4 Hz, 1H), 3.13-3.01 (m, 1H), 2.42 (ddd, *J* = 11.7, 9.0, 2.6 Hz, 1H), 2.29 (dt, *J* = 11.7, 9.7 Hz, 1H), COOH and NH_2 are not observed; ^{13}C{^{1}H} NMR (75 MHz, D_2O (with one drop of dioxane)) *δ* 179.8, 57.3, 50.4, 35.8, 28.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_5H_9N_4O_2^+$: 157.0720; Found: 157.0720.

(±)-*trans-trans*-2-Amino-3-azidocyclobutane-1-carboxylic acid 11d. Followed the general procedure **E**, using methyl ester **7c** (54 mg, 0.20 mmol), LiOH monohydrate (8.4 mg, 0.20 mmol), TFA (0.82 mL, 10.8 mmol). Free amino acid **11d** (28 mg, 92 %) was obtained as a white solid. Mp: 178-179 °C (degradation); IR v 2594, 2096, 1556, 1413, 1244; ^{1}H NMR (360 MHz, D_2O) *δ* 3.94 (dd, *J* = 16.8, 8.4 Hz, 1H), 3.74 (t, *J* = 8.6 Hz, 1H), 2.77 (dd, *J* = 19.1, 9.0 Hz, 1H), 2.67-2.56 (m, 1H), 1.93 (ddd, *J* = 11.1, 10.2, 9.0 Hz, 1H), COOH and NH_2 are not observed; ^{13}C{^{1}H} NMR (90 MHz, D_2O and CD_3OD (with one drop of dioxane)) *δ* 178.7, 54.2, 53.6, 38.8, 27.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_5H_8N_4NaO_2^+$: 179.0539; Found: 179.0537.

(±)-*trans-cis*-2-amino-3-hydroxycyclobutane-1-carboxylic acid 12a. Followed the general procedure **E**, using methyl ester **4** (150 mg, 0.50 mmol), LiOH monohydrate (21 mg, 0.5 mmol), TFA (1.25 mL, 16.5 mmol), 15 hours was needed instead of 30 min after addition of TFA. Free amino acid **12a** (62 mg, 95 %) was obtained as a white solid. Mp: 126-128 °C (degradation); IR *v* 3099, 2853, 2325, 1536, 1400; ^{1}H NMR (300 MHz, D_2O) *δ* 4.49-3.37 (m, 1H), 3.87 (t, *J* = 6.3 Hz, 1H), 3.19 (dd, *J* = 17.7, 8.5 Hz, 1H), 2.38-2.12 (m, 2H),

COOH, OH and NH_2 are not observed; $^{13}C\{^1H\}$ NMR (90 MHz, D_2O (with one drop of dioxane)) δ 180.5, 64.2, 51.2, 43.0, 31.0; HRMS (ESI-TOF) m/z: $[M-H]^-$ calcd for $C_5H_8NO_3^-$: 130.0510; Found: 130.0507.

(±)-*cis*-*trans*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-iodocyclobutane-1-carboxylate 14e. Followed the general procedure **F**, using methyl ester **3** (0.98 g, 4.0 mmol), I_2 (1.52 g, 6.0 mmol), imidazole (0.82 g, 12 mmol) and PPh_3 (2.1 g, 8.0 mmol). Flash chromatography (Et_2O/petroleum ether, 25/75) afforded the desired product **14e** (0.49 g, 34 %) as a white solid. R_f (Et_2O/petroleum ether, 25/75): 0.35; Mp: 141-143 °C; IR *v* 3311, 2984, 1730, 1682, 1526, 1340, 1283, 1198, 1169; ^1H NMR (360 MHz, $CDCl_3$) δ 5.56-5.15 (m, 1H), 4.74-4.58 (m, 1H), 4.51 (app. q, *J* = 9.2 Hz, 1H), 3.69 (s, 3H), 3.52-3.38 (m, 1H), 2.64-2.43 (m, 1H), 2.36 (app. dd, *J* = 21.6, 9.8 Hz, 1H), 1.41 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 173.9, 154.4, 80.2, 56.7, 52.3, 47.6, 31.2, 28.3 (3C), 17.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{18}INNaO_4^+$: 378.0173; Found: 378.0159.

(±)-*trans*-*trans*-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-iodocyclobutane-1-carboxylate 15e. Followed the general procedure **F**, using methyl ester **5** (245 mg, 1.0 mmol), I_2 (381 mg, 1.5 mmol), imidazole (204 mg, 3.0 mmol) and PPh_3 (524 mg, 2.0 mmol). Flash chromatography (EtOAc/petroleum ether, 10/90) afforded the desired product **15e** (285 mg, 80 %) as a white solid. R_f (Et_2O/petroleum ether, 50/50): 0.4; Mp: 120-121 °C; IR *v* 3346, 2986, 1726, 1678, 1527, 1370, 1280, 1254, 1154, 1137; ^1H NMR (360 MHz, $CDCl_3$) δ 5.55-5.35 (m, 0.3H), 5.32-5.15 (m, 0.7H), 4.47-4.35 (m, 0.7H), 4.35-4.13 (m, 1H), 4.12-3.95 (m, 0.3H), 3.68 (s, 3H), 3.50-3.30 (m, 0.7H), 3.12-2.85 (m, 0.3H), 2.63 (app. dd, *J* = 18.9, 8.8 Hz, 1H), 2.31 (dd, *J* = 21.4, 10.0 Hz, 1H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 171.3, 154.7, 80.3, 60.4, 52.3, 46.4, 30.9, 28.4 (3C), 13.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{18}INNaO_4^+$: 378.0173; Found: 378.0166.

(±)-*cis*-*trans*-Methyl 3-bromo-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 14f. Followed the general procedure **G**, using methyl ester **3** (122 mg, 0.50 mmol), CBr_4 (332 mg, 1.0 mmol), PPh_3 (262 g, 1.0 mmol), and TBAB (10 mg). Flash chromatography (Et_2O/petroleum ether, 25/75) afforded the product **14f** (100 mg, 65 %) as a white solid. R_f (Et_2O/petroleum ether, 25/75): 0.35; Mp: 134-135 °C; IR *v* 3310, 2984, 1732, 1690, 1529, 1340, 1288, 1198, 1170; ^1H NMR (250 MHz, $CDCl_3$) δ 5.55-5.30 (m, 0.8H), δ 5.25-5.05 (m, 0.2H), 4.75-4.57 (m, 1H), 4.52 (app. q, *J* = 8.8 Hz, 1H), 3.71 (s, 3H), 3.53 (td, *J* = 9.5, 2.4 Hz, 1H), 2.57 (ddd, *J* = 11.0, 8.4, 2.4 Hz, 1H), 2.30 (dt, *J* = 12.1, 9.5 Hz, 1H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (63 MHz, $CDCl_3$) δ 173.8, 154.5, 80.4, 56.2, 52.3, 44.8, 44.2, 30.8, 28.4 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{18}N^{79}BrNaO_4^+$: 330.0311; Found: 330.0298.

(±)-*trans*-*trans*-Methyl 3-bromo-2-((*tert*-butoxycarbonyl)amino)cyclobutane-1-carboxylate 15f. Followed the general procedure **G**, using methyl ester **5** (122 mg, 0.50 mmol), CBr_4 (332 mg, 1.0 mmol), PPh_3 (262 g, 1.0 mmol), and TBAB (10 mg). Flash chromatography (Et_2O/petroleum ether, 25/75) afforded the product **15f** (47 mg, 30 %) as a white solid. R_f (Et_2O/petroleum ether, 50/50): 0.45; Mp: 116-117 °C; IR *v* 3346, 2984, 1727, 1684, 1529, 1374, 1284, 1258, 1146; ^1H NMR (360 MHz, $CDCl_3$) δ 5.18 (br. s, 1H), 4.67-4.22 (m, 1H), 4.20-4.01 (m, 1H), 3.70 (s, 3H), 3.44-3.15 (m, 0.8H), 3.05-2.75 (m, 0.2H), 2.64 (dd, *J* = 19.6, 8.6 Hz, 1H), 2.23 (dd, *J* = 21.1, 9.9 Hz, 1H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (90 MHz, $CDCl_3$) δ 172.0, 154.8, 80.4, 59.9, 52.3, 42.6, 41.3, 30.4, 28.4 (3C); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{11}H_{18}N^{79}BrNaO_4^+$: 330.0311; Found: 330.0300.

ASSOCIATED COMMENT

Supporting Information

Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, and crystallographic data for **6a** and **7a** (CCDC 1898946 and 1898947, respectively) are presented in the Electronic Supporting Information. The ESI and crystallographic data in CIF are available free of charge on the ACS Publications website at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Z.C. is grateful to the China Scholarship Council for the award of a PhD grant. The authors thank Mr J.-P. Baltaze (ICMMO) for assistance with NMR studies.

REFERENCES

[1] (a) Anslyn, E. V.; Dougherty, D. A. Strain and Stability. In *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; pp 65-145. (b) *The Chemistry of Cyclobutanes*; Rappoport, Z.; Liebman, J. F., Eds.; Wiley: Chichester, UK, 2005.

[2] (a) Hanson, J. R. Diterpenoids of Terrestrial Origin. *Nat. Prod. Rep*. **2017**, *34*, 1233−1243 and previous reviews in this annual series. (b) Fan, Y.-Y.; Gao, X.-H.; Yue, J.-M. Attractive Natural Products with Strained Cyclopropane and/or Cyclobutane Ring Systems. *Sci. China Chem*. **2016**, *59*, 1126-1141. (c) Hong, Y. J.; Tantillo, D. J. How Cyclobutanes Are Assembled In Nature - Insights from Quantum Chemistry. *Chem. Soc. Rev.* **2014**, *43*, 5042-5050. (d) Crews, C.; Driffield, M.; Thomas, C. Analysis of 2-Alkylcyclobutanones for Detection of Food Irradiation: Current Status, Needs and Prospects. *J. Food Compos. Anal.* **2012**, *26*, 1-11. (e) Dembitsky V. M. Bioactive Cyclobutane-Containing Alkaloids. *J. Nat. Med.* **2008**, *62*, 1-33.

[3] (a) Xu, Y.; Conner, M. L.; Brown, M. K. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2+2] Cycloadditions. *Angew. Chem., Int. Ed.* **2015**, *54*, 11918-11928. (b) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. Cyclobutanes in Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740-7752. (c) Leemans, E.; D'hooghe, M.; De Kimpe, N. Ring Expansion of Cyclobutylmethylcarbenium Ions to Cyclopentane or Cyclopentene Derivatives and Metal-Promoted Analogous Rearrangements. *Chem. Rev.* **2011**, *111*, 3268-

3333. (d) Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1485-1537.

[4] (a) Wu, Q.-F.; Wang, X.-B.; Shen, P.-X; Yu, J.-Q. Enantioselective C-H Arylation and Vinylation of Cyclobutyl Carboxylic Amides. *ACS Catal*. **2018**, *8*, 2577-2581. (b) Wang, M.; Lu, P. Catalytic Approaches to Assemble Cyclobutane Motifs in Natural Product Synthesis. *Org. Chem. Front.* **2018**, *5*, 254-259. (c) Gutekunst, W. R.; Baran, P. S. Applications of C-H Functionalization Logic to Cyclobutane Synthesis. *J. Org. Chem.* **2014**, *79*, 2430-2452. (d) Frébault, F.; Maulide, N. Total Synthesis and Structural Revision of the Piperarborenines: When Photochemistry Meets C-H Activation. *Angew. Chem., Int. Ed.* **2012**, *51*, 2815-2817.

[5] (a) Secci, F.; Frongia, A.; Piras, P. P. Stereocontrolled Synthesis and Functionalization of Cyclobutanes and Cyclobutanones. *Molecules* **2013**, *18*, 15541-15572. (b) Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. Y. Cyclobutane Biomolecules: Synthetic Approaches to Amino Acids, Peptides and Nucleosides. *Curr. Org. Chem.* **2005**, *9*, 237-259. (c) Salaün, J. Product Class 2: Cyclobutanones and Their Precursors. *Science of Synthesis* **2004**, *26*, 557-606. (d) Lee-Ruff, E.; Mladenova, G. Enantiomerically Pure Cyclobutane Derivatives and Their Use in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1449-1484.

[6] (a) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions. *Chem. Rev.* **2016**, *116*, 9748-9815. (b) Bach, T.; Hehn, J. P. Photochemical Reactions as Key Steps in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000-1045. (c) Hoffmann, N. Photochemical Reactions as Key Steps in Organic Synthesis. *Chem. Rev.* **2008**, *108*, 1052-1103.

[7] Kiss, L.; Fülöp, F. Synthesis of Carbocyclic and Heterocyclic β-Aminocarboxylic Acids. *Chem. Rev.* **2014**, *114*, 1116-1169.

[8] (a) Kiss, L.; Mándity, I. M.; Fülöp, F. Highly Functionalized Cyclic β-Amino Acid Moieties as Promising Scaffolds in Peptide Research and Drug Design. *Amino Acids* **2017**, *49*, 1441-1455. (b) Cabrele, C.; Martinek, T. A.; Reiser, O.; Berlicki, L. Peptides Containing β-Amino Acid Patterns: Challenges and Successes in Medicinal Chemistry. *J. Med. Chem.* **2014**, *57*, 9718-9739.

[9] (a) Vasudev, P. G.; Chatterjee, S.; Shamala, N.; Balaram, P. Structural Chemistry of Peptides Containing Backbone Expanded Amino Acid Residues: Conformational Features of β, γ, and Hybrid Peptides. *Chem. Rev.* **2011**, *111*, 657-687. (b) Seebach, D.; Gardiner, J. β-Peptidic Peptidomimetics. *Acc. Chem. Res.* **2008**, *41*, 1366-1375. (c) Cheng, R. P.; Gellman S. H.; DeGrado, W. F. β-Peptides: From Structure to Function. *Chem. Rev.* **2001**, *101*, 3219‑3232.

[10] For cyclobutane-based β-peptide foldamers studied in our group, see: Declerck, V.; Aitken, D. J. Strategic C to N Replacement in β-Peptides: Atomic Level Control of Helical Folding. *J. Org. Chem.*, **2018**, *83*, 8793-8800 and references cited therein.

[11] (a) Chang, Z.; Boyaud, F.; Guillot, R.; Boddaert, T.; Aitken, D. J. A Photochemical Route to 3- and 4-Hydroxy Derivatives of 2-Aminocyclobutane-1-carboxylic Acid with an *all-cis* Geometry. *J. Org. Chem.* **2018**, *83*, 527-534. (b) Hernvann, F.; Rasore, G.; Declerck V.; Aitken, D. J. Stereoselective Intermolecular [2+2]-

Photocycloaddition Reactions of Maleic Anhydride: Stereocontrolled and Regiocontrolled Access to 1,2,3-Trifunctionalized Cyclobutanes. *Org. Biomol. Chem.* **2014**, *12*, 8212-8222. (c) Mondière, A.; Peng, R.; Remuson, R.; Aitken, D. J. Efficient Synthesis of 3-Hydroxymethylated *cis*- and *trans*-Cyclobutane β-Amino Acids using an Intramolecular Photocycloaddition Strategy. *Tetrahedron* **2008**, *64*, 1088-1093. (d) Gauzy, C.; Saby, B.; Pereira, E.; Faure, S.; Aitken, D. J. The [2+2] Photocycloaddition of Uracil Derivatives with Ethylene as a General Route to *cis*-Cyclobutane β-Amino Acids. *Synlett* **2006**, 1394-1398.

[12] For photochemical approaches for the parent cyclobutane β-amino acid, see: (a) Declerck, V.; Aitken, D. J. A Refined Synthesis of Enantiomerically Pure 2-Aminocyclobutane Carboxylic Acids. *Amino Acids* **2011**, *41*, 587-595. (b) Fernandes, C.; Pereira, E.; Faure, S.; Aitken, D. J. Expedient Preparation of All Isomers of 2-Aminocyclobutane-1-carboxylic Acid in Enantiomerically Pure Form. *J. Org. Chem.* **2009**, *74*, 3217-3220. (c) Fernandes, C.; Gauzy, C.; Yang, Y.; Roy, O.; Pereira, E.; Faure, S.; Aitken, D. J. [2+2] Photocycloadditions with Chiral Uracil Derivatives: Access to All Four Stereoisomers of 2-Aminocyclobutanecarboxylic Acid. *Synthesis* **2007**, 2222-2230.

[13] For 3- or 4-substituted ACBCs prepared using other approaches but with limited scope, see: (a) de Nanteuil, F.; Waser, J. Synthesis of Aminocyclobutanes via Iron-Catalyzed [2+2] Cycloaddition. *Angew. Chem., Int. Ed.* **2013**, *52*, 9009-9013. (b) Charnay-Pouget, F.; Frank, M.; Baltaze, J.-P.; Pereira, E.; Aitken, D. J. Evaluation of an Aza-Michael Approach for the Synthesis of 3,3-Dimethyl-2-aminocyclobutane-1-carboxylic Acid. *ARKIVOC* **2012**, 80-93. (c) Hazelard, D.; Fadel, A.; Guillot, R. First Synthesis of Enantiomerically Pure (1S,2S)- and (1R,2R)-1,2-Diaminocyclobutanecarboxylic Acid - Ornithine Derivative -, from Racemic 2-Aminocyclobutanone. *Tetrahedron: Asymmetry* **2008**, *19*, 2063-2067. (d) Mittendorf, J.; Kunisch, F.; Matzke, F.; Militzer, H.-C.; Schmidt, A.; Schönfeld, W. Novel Antifungal β-Amino acids: Synthesis and Activity Against *Candida Albicans*. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433-436. (e) Yuan, P.; Driscoll, M. R.; Raymond, S. J.; Hansen, D. E.; Blatchly, R. A. The Synthesis of Cyclobutanol-Containing Dipeptide Analogues. *Tetrahedron Lett.* **1994**, *35*, 6195-6198. (f) Mitsudo, T.-A.; Zhang, S.-W.; Satake, N.; Kondo, T.; Watanabe, Y. Selective Syntheses of Cyclobutane-β-Aminocarboxylic Acid Derivatives by the Ruthenium Complex-Catalyzed Reaction of Allylamines with Acrylic Compounds. *Tetrahedron Lett.* **1992**, *33*, 5533-5536. (g) Katagiri, N.; Sato, H.; Kaneko, C. Highly Stereoselective Synthesis of Carbocyclic Analogues of Oxetanocin. *Chem. Pharm. Bull.* **1990**, *38*, 288-290. (h) Brannock, K. C.; Bell, A.; Burpitt, R. D.; Kelly, C. A. Reactions of Isobutenylamines. I. Cyclobutane Formation. *J. Org. Chem.* **1961**, *26*, 625-626.

[14] (a) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. Mitsunobu and Related Reactions: Advances and Applications. *Chem. Rev.* **2009**, *109*, 2551-2651. (b) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1-28.

[15] (a) de Andrade, V. S. C.; de Mattos, M. C. S. New Reagents and Synthetic Approaches to the Appel Reaction. *Curr. Org. Synth.* **2015**, *12*, 309-327. (b) Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P-N Linkage. *Angew. Chem., Int. Ed.* **1975**, *14*, 801-811.