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Synthesis of 2-methyl- and 2-methylenecyclobutane amino acids

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Abstract—An efficient and easy formal [2+2] cycloaddition (Michael–Dieckmann-type reaction) on methyl 2-acetamidoacrylate with ketene diethyl acetal gave the cyclobutane core. Two kinds of 2-substituted cyclobutane amino acids have been obtained from this compound by means of stereocontrolled interconversion of functional groups: 1-amino-2-methylcyclobutane-1-carboxylic acids (2,4-methanovalines) and 1-amino-2-methylenecyclobutane-1-carboxylic acid. The latter amino acid can be regarded as a restricted α-methyl-α-vinylglycine.

1. Introduction

1-Aminocycloalkane-1-carboxylic acids,[1] especially those with three-, five-, or six-membered rings, have attracted considerable attention, mainly due to the conformational restriction produced when they are incorporated into peptides.[2] Despite this interest, 1-aminocyclobutane-1-carboxylic acids received very little attention until 1980.[3] Since then, a number of naturally occurring cyclobutane amino acids were discovered and several derivatives were found to be potent neurotransmitters.[4] Synthetic efforts have since been extended to a whole range of cyclobutane amino acids of potential biological interest.[5]

Nevertheless, the synthesis of 2-substituted cyclobutane amino acids has not received the same attention as the preparation of other substituted cyclobutane α-amino acids[5] and, to the best of our knowledge, only a few methods for the synthesis of 1-amino-2-alkylcyclobutane-1-carboxylic acids have been described.[6] In particular, (1*S**,2*S**)-1-amino-2-methylcyclobutane-1-carboxylic acid (**1**) (2,4-methanovaline) was first synthesized by Gaoni in 1995 by the azidation of methyl 2-methyl-3-(phenylsulfonyl)bicyclo[1.1.0]butane-1-carboxylate, followed by hydrogenation, desulfonylation and hydrolysis.[5c] Later, Frahm and co-workers[7] obtained the four stereoisomers in enantiopure form by an asymmetric Strecker synthesis starting from racemic 2-methylcyclobutanone and (*R*)-phenylethylamine as a chiral auxiliary, which gave poor diastereoselectivity, followed by separation by column chromatography (Fig. 1).

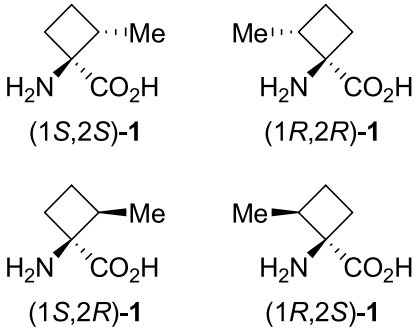
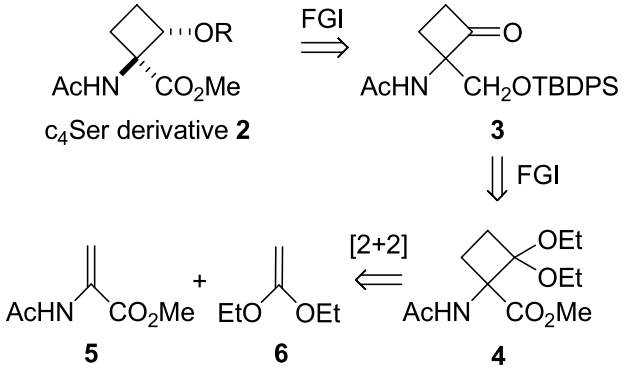


Figure 1. The all four stereoisomers of 2,4-methanovalines **1**.

As part of our research programme on the synthesis of cyclic amino acids,[8] we recently described the synthesis of the serine analogue derivative **2**, which incorporates the cyclobutane skeleton (c_4Ser).[8h] The key step in this synthesis involves a reaction of methyl 2-acetamidoacrylate **5** with ketene diethyl acetal **6** in a formal [2+2] cycloaddition (Scheme 1).



Scheme 1. Retrosynthesis of a c_4Ser derivative from methyl 2-acetamidoacrylate **5** by a [2+2] cycloaddition.

Keywords: Amino acid; Cyclobutane; Hydrogenation; Valine.
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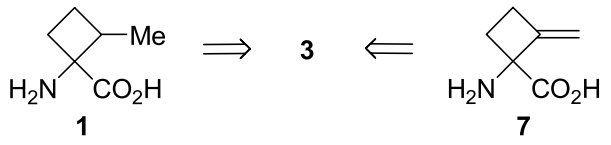
In this way, the cyclobutane skeleton was obtained by a tandem Michael–Dieckmann-type process that gave compound **4**, which was then transformed into the intermediate **3** (Scheme 1).

This pathway opens the door to important 2-substituted cyclobutane amino acids. In an effort to exemplify this feature, we decided to explore the reactivity of intermediate **3** as a building block in stereocontrolled organic synthesis in order to obtain both stereoisomers of 2,4-methanovaline **1** as well as 2-methylenecyclobutane amino acid **7** in racemic forms (Scheme 2).



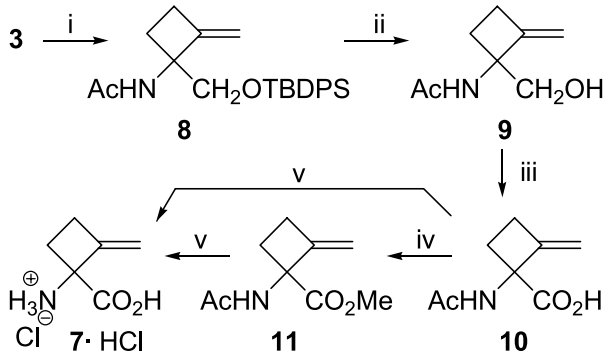
Scheme 2. Retrosynthesis of 2-substituted cyclobutane amino acids from intermediate **3**.

β,γ-Unsaturated amino acid derivatives have received a great deal of attention because they are important enzyme inhibitors.[9] For example, α-vinyl amino acids are known to inhibit pyridoxal phosphate-dependent enzymes and, in particular, amino acid decarboxylases.[10] Given this background, the interesting amino acid **7** can be regarded as a particularly restricted analogue of α-vinylalanine.[11] Moreover, it has only been synthesized on one occasion and this involved isomerization of a spiranic amino acid derivative.[12]

2. Results and discussion

2.1. Synthesis of 2-methylenecyclobutane amino acid 7

Racemic 2-methylenecyclobutane amino acid **7** was obtained as the hydrochloride salt in 22% overall yield from a four-step synthesis starting from intermediate **3** (Scheme 3). The initial step involved Wittig methylenation[13] of **3** and was carried out under salt-free Wittig conditions using methyltriphenylphosphonium bromide ($Ph_3PMe^+Br^-$) with several bases tested. The use of 2.0 equiv of potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C gave 67% yield of alkene **8** but the best result was achieved with 3.0 equiv of this base, which afforded alkene **8** in 86% yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) KHMDS (3.0 equiv), $Ph_3PMe^+Br^-$, THF, rt, 5 h, 86%; (ii) TBAF, THF, rt, 1 h, 91%; (iii) Jones reagent, acetone, 0 °C, 4 h, 64%; (iv) CH_2N_2, ethyl ether, rt, 30 min, 85%; (v) 3 N HCl, reflux, 3 h, 51%.

The structure of compound **8** was confirmed by X-ray analysis[†] of monocrystals and is shown in the ORTEP representation Figure 2.

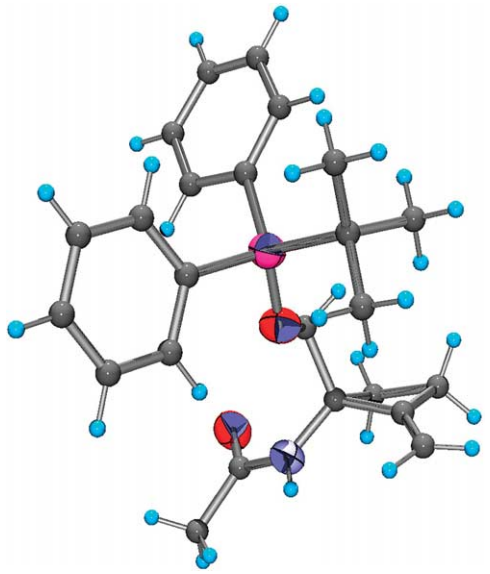


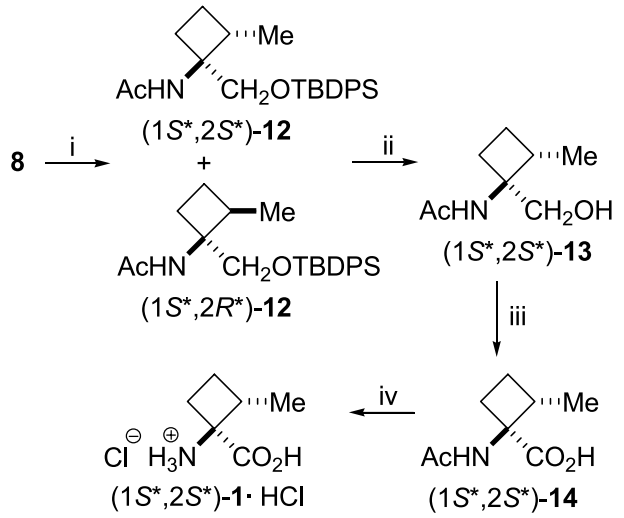
Figure 2. ORTEP representation of compound **8**.

Subsequent cleavage of the silyl group in compound **8** with tetrabutylammonium fluoride (TBAF) in THF at room temperature gave the corresponding primary alcohol **9** in excellent yield. This compound was subjected to oxidation in the presence of Jones reagent[14] to give the carboxylic acid derivative **10**. The required amino acid **7** was obtained as the hydrochloride salt by acid hydrolysis of **10** using 3 N HCl at reflux. In order to purify carboxylic acid derivative **10**, an aliquot was converted into the corresponding methyl ester by addition of diazomethane in ethyl ether at room temperature. Acid hydrolysis of compound **11** gave amino acid **7** as the hydrochloride salt with a similar yield (Scheme 3).

2.2. Synthesis of racemic 2-methylcyclobutane amino acids (1*S**,2*S**)-1

Starting from compound **8**, which in turn comes from the intermediate **3**, we envisioned a synthetic route to the

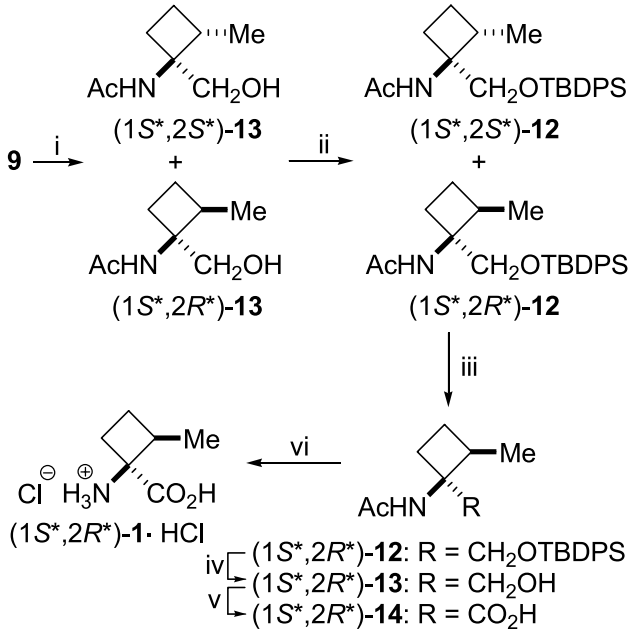
[†] The monocrystals were obtained by slowly adding octane to a solution of compound **8** in dichloromethane to form an interface. The crystal grew at the border of the two solvents. Crystal data: $C_{48}H_{62}N_2O_4Si_2$, M_w=787.18, colourless prism of 0.50×0.42×0.20 mm^3, T=223(2) K, triclinic, space group P-1, Z=2, a=9.6181(4) Å, b=14.6066(6) Å, c=16.5421(8) Å, α=79.3829(17), β=82.0665(17), γ=90.0352(13), V=2261.51(17) Å^3, d_{calc}=1.156 g cm^{-3}, $F(000)$=848, λ=0.71073 Å (Mo Kα), μ=0.12 mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.26–28.00°, 28,939 collected reflections, 10,432 unique (R_{int}=0.1694), full-matrix least-squares (SHELXL97),[15] R_1=0.1156, wR_2=0.2618, (R_1=0.2373, wR_2=0.3537 all data), goodness of fit=1.601, residual electron density between 0.870 and −1.034 e Å^{-3}. Hydrogen atoms were located from mixed methods. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 239349.



Scheme 4. Reagents and conditions: (i) H_2, Pd–C, CH_2Cl_2, rt, 17 h, 96%; (ii) TBAF, THF, rt, 1 h, 76%; (iii) Jones reagent, acetone, 0 °C, 2 h, 73%; (iv) 3 N HCl, reflux, 6 h, 90%.

2-methylcyclobutane amino acid (1*S**,2*S**)-**1**. The reaction sequence on compound **8** starts with a selective hydrogenation followed by deprotection by removing the silyl group, oxidation and hydrolysis (Scheme 4).

Hydrogenation of the exocyclic double bond in compound **8** using palladium–carbon as a catalyst was studied in two solvents. Ethyl acetate gave an excellent yield (97%) of the mixture of hydrogenation products (1*S**,2*S**)-**12** and (1*S**,2*R**)-**12** and a stereoselectivity of 89:11 in favour of (1*S**,2*S**)-**12**. Fortunately, dichloromethane gave a similar yield (96%) but the stereoselectivity was increased to 93:7. Once separated by column chromatography, (1*S**,2*S**)-**12** was desilylated by the action of TBAF to give primary alcohol (1*S**,2*S**)-**13**, which was treated with Jones reagent to give the carboxylic acid (1*S**,2*S**)-**14**. Acid hydrolysis of this compound furnished the racemic 2,4-methanovaline (1*S**,2*S**)-**1**, as its hydrochoride salt, in which the carboxylic acid group and methyl substituent are in a *cis* disposition. This stereochemistry was confirmed by ROE experiments on compound (1*S**,2*S**)-**13** (see Section 2.4).



Scheme 5. Reagents and conditions: (i) H_2, $Pd(OH)_2$–C, CH_2Cl_2, rt, 17 h; (ii) TBDPSCl, imidazole, DMF, 50 °C, 17 h; (iii) column chromatography: hexane/ethyl acetate 65:35; 32% from **9**; (iv) TBAF, THF, rt, 1 h, 95%; (v) Jones reagent, acetone, 0 °C, 2 h, 63%; (vi) 3 N HCl, reflux, 6 h, 70%.

2.3. Synthesis of racemic 2-methylcyclobutane amino acids (1*S**,2*R**)-1

Racemic 2,4-methanovaline (1*S**,2*R**)-**1** was obtained following the same strategy as described above for 2,4-methanovaline (1*S**,2*S**)-**1**, but starting from compound **9**, which was obtained by desilylation of compound **8** (Scheme 5). The structure of the new starting compound **9** was determined by X-ray analysis[‡] in the same way as for compound **8** (Fig. 3).

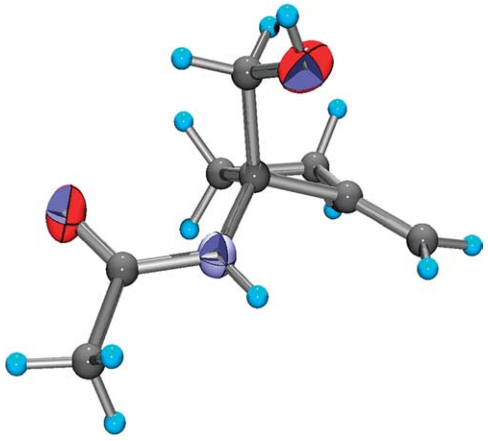


Figure 3. ORTEP structure of compound **9**.

Hydrogenation of the double bond in compound **9** was investigated under several sets of conditions. Initially, the homogeneous hydrogenation was attempted with $(Ph_3P)_3RhCl$ and after 24 h at 55 °C only a 16% of hydrogenation products (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** was obtained without selectivity. Therefore, the heterogeneous hydrogenation was assayed using palladium–carbon in three different solvents; methanol, ethyl acetate and dichloromethane. In all cases the yield was excellent (98, 96 and 95%, respectively) and the stereoselectivity of hydrogenated products (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** was as follows, 45:55, 38:62 and 37:63, respectively, always in favour of (1*S**,2*R**)-**13**. The change in the catalyst for the hydrogenation only led to a slight increase in the

[‡] Crystal data: $C_8H_{13}NO_2$, $M_w=155.19$, colourless prism of 0.50×0.37×0.25 mm^3, $T=223(2)$ K, monoclinic, space group $P\,21/c$, $Z=4$, $a=8.5399(3)$ Å, $b=10.0205(4)$ Å, $c=10.3072(4)$ Å, $\alpha=90$, $\beta=104.454(2)$, $\gamma=90$, $V=854.11(6)$ Å^3, $d_{calc}=1.207$ g cm^{-3}, $F(000)=336$, $\lambda=0.71073$ Å (Mo Kα), $\mu=0.087$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 2.03–27.88°, 6840 collected reflections, 2009 unique ($R_{int}=0.0755$), full-matrix least-squares (SHELXL97),[15] $R_1=0.0687$, w$R_2=0.2038$, ($R_1=0.0812$, w$R_2=0.2174$ all data), goodness of fit=1.068, residual electron density between 0.425 and −0.352 e Å^{-3}. Hydrogen atoms were located from mixed methods. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 239348.

stereoselectivity; indeed, when the hydrogenation was carried out in the presence of palladium hydroxide supported on carbon and using dichloromethane as solvent, the stereoselectivity was 34:66 with a yield of 95%. This mixture of products could not be separated by column chromatography, so it was transformed into the corresponding silylated derivatives (1*S**,2*S**)-**12** and (1*S**,2*R**)-**12** with *tert*-butyldiphenylsilyl chloride (TBDPSCl). Once separated, (1*S**,2*R**)-**12** was desilylated to give pure (1*S**,2*R**)-**13**, which was oxidized to carboxylic acid (1*S**,2*R**)-**14** and hydrolysed to give the desired racemic 2,4-methanovaline (1*S**,2*R**)-**1** as its hydrochloride salt (Scheme 5).

2.4. Stereochemical outcome of the hydrogenation

The stereochemistry of the minor product (1*S**,2*S**)-**13** obtained in the heterogeneous hydrogenation reaction of compound **9** was assigned on the basis of selective gradient-enhanced 1D ROESY experiments.[16] Therefore, once the signals of the ^{1}H NMR spectra of this compound were assigned by COSY and HSQC experiments, the signal at 6.30 ppm, corresponding to the NH proton, was presaturated using a mixing time of 500 ms. As a consequence, a ROE enhancement of 2% was observed in the signal at 2.53 ppm, corresponding to proton H-2, indicating that the NHAc group is in a *cis* disposition with respect to the H-2 proton attached to C-2 of the cyclobutane ring. When the same experiment was performed on the major product (1*S**,2*R**)-**13**, a ROE enhancement was not observed on proton H-2 (Fig. 4).

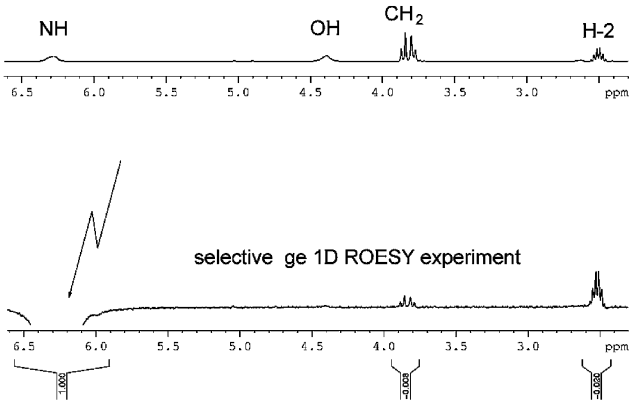


Figure 4. Selective 1D ROESY on compound (1*S**,2*S**)-**13**.

A number of calculations were performed in an effort to explain the stereochemical outcome obtained in the hydrogenation of compound **8**. First, and in order to obtain the conformational preferences of compound **8**, the initial geometry extracted from the X-ray structure of this compound was optimised by the semi-empirical PM3 method[17] with the CS MOPAC Pro 8.0 program based on MOPAC 2000, as implemented in Chem3D Ultra 8.0 software. Once other variables had been properly evaluated, the relaxed potential-energy surface (PES) scan was performed by varying the CH_2–O–Si–$C(CH_3)_3$ dihedral angle with step-sizes of 5° (Fig. 5). The global minimum was located at 290°.

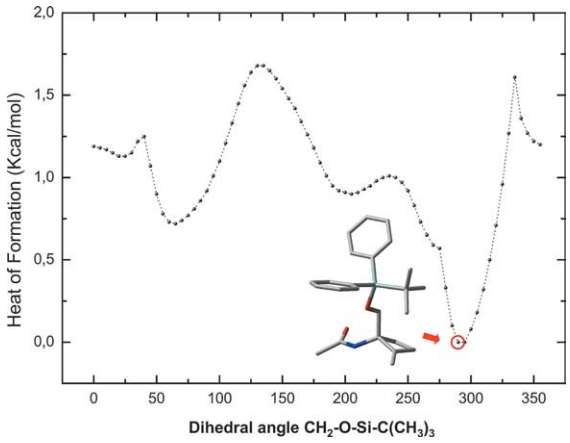


Figure 5. PES scans with PM3 method on compound **8**.

The lowest energy structure found in these preliminary calculations was fully optimised and characterised by a frequency calculation that took into account the solvent effects using the Onsager SCRF method[18] implemented in Gaussian 98. A dielectric constant of 8.93 (dichloromethane) was used in order to be consistent with the experimental conditions. The calculations were carried out at the B3LYP/6-31G(d) level[19] with the Gaussian 98 package[20] (Fig. 6).

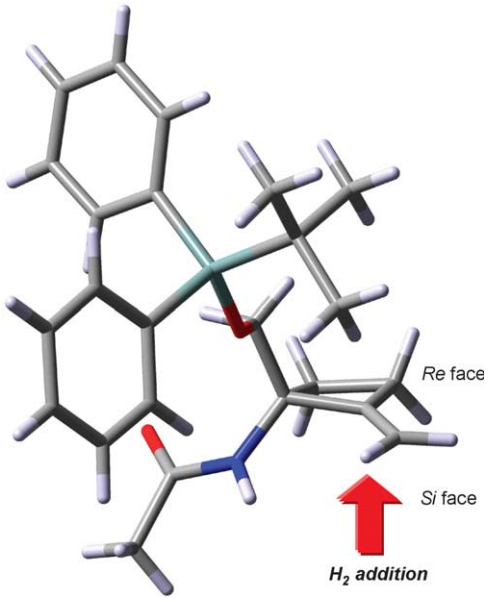


Figure 6. Optimized structure at B3LYP/6-31G(d) level considering solvent effects (Onsager) for compound **8**.

The geometry obtained from the calculations that considered the solvent effects was very similar to that obtained from the solid state. In order to confirm this feature a gradient-enhanced 2D NOESY experiment,[21] using a mixing time of 500 ms, was performed on compound **8** and a small NOE enhancement between vinylic protons and the protons of the *tert*-butyl group was observed. Therefore, it can be concluded that the conformation obtained in both the calculation and the solid state also exists in solution (Fig. 6).

In this situation the *tert*-butyl group probably shields the *re*

face of the double bond of compound **8** in such a way that the olefinic bond is forced to coordinate to the catalyst surface by the *Si* face. Consequently, the addition of hydrogen occurs at this face to give a remarkably stereochemically controlled hydrogenated product (1*S**,2*S**)-**12** (Fig. 6). In contrast, when the hydrogenation is carried out on olefin **9**, we believe that the opposite selectivity obtained is due to the presence of a coordinating function, that is, the primary alcohol, in the olefinic molecule. This group anchors itself on the catalyst surface and forces the addition of hydrogen to its own side of the molecule (*Re* face). There are numerous examples in the literature of such an anchoring effect.[22]

3. Conclusions

In summary, we have developed a new stereoselective synthetic route for 2-substituted cyclobutane-α-amino acids from the cycloadduct obtained in the formal [2+2] cycloaddition of methyl 2-acetamidoacrylate and ketene diethyl acetal. Two kinds of α-amino acid could be synthesised, 2-alkyl- and 2-alkylidenecyclobutane-α-amino acids. As an example of the first type, both stereoisomers of the well-known 2,4-methanovaline were obtained in racemic form by stereocontrolled reactions on the aforementioned cyclobutane derivative. The key step is the hydrogenation of an exocyclic double bond. This reaction is controlled by the functional groups attached to the cyclobutane skeleton. The second type of amino acid was exemplified by the synthesis of 1-amino-2-methylene-cyclobutane-1-carboxylic acid, which can be considered as a conformationally restricted analogue of an important β,γ-unsaturated α-amino acid (α-vinylalanine).

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer using $CDCl_3$ with TMS as the internal standard or using CD_3OD or D_2O with TMS as the external standard with a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, proton–proton COSY experiments and proton–carbon HETCOR experiments on a Bruker AVANCE 400 spectrometer. This spectrometer was also used for the selective gradient-enhanced 1D ROESY and 2D NOESY experiments described in the text. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values.

4.1.1. *N*-[1-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylenecyclobutyl]acetamide 8. Methyltriphenylphosphonium bromide (1.36 g, 3.80 mmol) was suspended in THF (20 mL) at 25 °C and KHMDS (0.5 M in toluene, 7.6 mL, 3.80 mmol) was added. The resulting yellow suspension was stirred at 25 °C for 1 h, then cooled to −78 °C and a solution of ketone **3** (500 mg, 1.27 mmol) in THF (10 mL) was added dropwise. The cooling bath was removed and the mixture allowed to reach 25 °C over 5 h. The reaction was quenched with MeOH (2 mL) and the resulting mixture was poured into a saturated solution of potassium sodium tartrate and H_2O (1:1, v/v, 30 mL). Extraction with ethyl ether (2×15 mL), drying and evaporation of the solvent gave a pale yellow syrup, which was purified by column chromatography (hexane/ethyl acetate, 7:3) to give **8** (430 mg, 86%) as a white solid. Mp 114–116 °C. ^{1}H NMR ($CDCl_3$): δ 1.08 [s, 9H, $C(CH_3)_3$], 1.92 (s, 3H, CH_3CO), 1.97–2.08 (m, 1H, CH_2C–N), 2.40–2.72 (m, 3H, CH_2C–N, $CH_2C{=}CH_2$), 3.76 (d, 1H, J=9.9 Hz, CH_2O), 3.87 (d, 1H, J=10.2 Hz, CH_2O), 4.91 (s, 1H, C=CH_2), 5.05 (s, 1H, C=CH_2), 5.88 (br s, 1H, NH), 7.36–7.47 (m, 6H, Arom.), 7.64–7.68 (m, 4H, Arom.); ^{13}C NMR ($CDCl_3$): δ 19.3 [$C(CH_3)_3$], 23.9 (CH_3CO), 25.7 (CH_2C–N), 26.8 [$C(CH_3)_3$], 27.0 ($CH_2C{=}CH_2$), 63.1 (CCH_2O), 66.7 (CCH_2O), 106.5 (C=CH_2), 127.8, 129.7 (Arom.), 133.2 (C=CH_2), 135.6, 151.1 (Arom.), 169.2 (CONH); ESI$^+$ (m/z)=393.9. Anal. Calcd for $C_{24}H_{31}NO_2Si$: C, 73.24; H, 7.94; N, 3.56. Found: C, 73.54; H, 7.90; N, 3.50.

4.1.2. *N*-[1-(Hydroxymethyl)-2-methylenecyclobutyl]-acetamide 9. TBAF (1.53 mL, 1 M in THF) was added to a solution of compound **8** (500 mg, 1.53 mmol) in dry THF (15 mL) at 25 °C under an inert atmosphere and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the organic material was extracted with $CHCl_3$/^{i}PrOH (4:1) (2×20 mL). The organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (5:95), to give 180 mg (91%) of **9** as a white solid. Mp 85–87 °C. ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, CH_3CO), 2.17–2.24 (m, 1H, CH_2C–N), 2.30–2.39 (m, 1H, CH_2C–N), 2.54–2.63 (m, 2H, $CH_2C{=}CH_2$), 3.65–3.77 (m, 2H, CH_2O), 4.86 (s, 1H, C=CH_2), 4.99 (s, 1H, C=CH_2), 6.44 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.5 ($CH_2C{=}CH_2$), 25.8 (CH_3CO), 28.1 (CH_2C–N), 64.7 (CCH_2O), 67.0 (CCH_2O), 106.6 (C=CH_2), 151.1 (C=CH_2), 171.2 (CONH); ESI$^+$ (m/z)=156.1. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.97; H, 8.47; N, 9.07.

4.1.3. 1-Acetamido-2-methylenecyclobutane-1-carboxylic acid 10. To a solution of compound **9** (120 mg, 0.77 mmol) in acetone (15 mL) at 0 °C was added a 2.0-fold excess of Jones reagent (0.77 mL, 2 M in water) dropwise over 5 min. The mixture was stirred at 0 °C for 4 h. The excess Jones reagent was destroyed with ^{i}PrOH. The mixture was then diluted with water (10 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3×15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 77 mg (64%) of compound **10** as a white solid. This compound was used in the next step without further purification. Mp >200 °C (decomp.). ^{1}H NMR (CD_3OD): δ 1.96 (s, 3H, CH_3CO), 2.04–2.13 (m, 1H), 2.67–2.79 (m, 2H), 2.86–2.95 (m, 1H), 5.00 (s, 1H, C=CH_2), 5.23 (s, 1H, C=CH_2); ^{13}C NMR (CD_3OD): δ 21.5, 26.4, 28.7, 64.4 ($CCOO$), 109.9 (C=CH_2), 147.0

(C=CH_2), 173.9, 175.0 (COO, CONH); ESI^+ (m/z)= 170.1.

4.1.4. 1-Acetamido-2-methylenecyclobutane-1-carboxylic acid methyl ester 11. Compound **10** was purified by transforming the carboxylic acid group into the corresponding methyl ester by addition of an excess of an ethereal solution of diazomethane to a solution of the carboxylic acid **10** (12 mg, 0.07 mmol) in ethyl ether (3 mL). The mixture was stirred for 10 min, then anhydrous $CaCl_2$ was added and the solution was filtered, the solvent evaporated and the residue purified by silica gel column chromatography, eluting with hexane/ethyl acetate (3:7), to give 9 mg (85%) of methyl ester **11** as a colourless oil. ^1H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3CO), 2.27–2.37 (m, 1H, CH_2CCOO), 2.72–2.79 (m, 2H, CH_2C=CH_2), 2.85–2.91 (m, 1H, CH_2CCOO), 3.75 ($COOCH_3$), 4.96 (s, 1H, C=CH_2), 5.09 (s, 1H, C=CH_2), 6.38 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.0 (CH_3CO), 26.3 (CH_2C=CH_2), 28.8 (CH_2CCOO), 52.8 ($COOCH_3$), 64.4 ($CCOO$), 108.4 (C=CH_2), 148.2 (C=CH_2), 169.4, 171.3 (COO, CONH); ESI^+ (m/z)=184.0. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.91; H, 7.22; N, 7.58.

4.1.5. 1-Amino-2-methylenecyclobutane-1-carboxylic acid hydrochloride salt 7·HCl. The white solid corresponding to carboxylic acid **10** (77 mg, 0.46 mmol) was dissolved in aqueous 3 N HCl (5 mL) and heated at 100 °C for 3 h. The solution was concentrated to give a residue, which was eluted through a C18 reverse-phase Sep-pak cartridge to give, after removal of the water, 39 mg of a white solid; yield: 51%. Mp >200 °C (decomp.). ^1H NMR (D_2O): δ 2.31–2.41 (m, 1H), 2.66–2.75 (m, 2H), 2.84–2.92 (m, 1H), 5.21–5.24 (m, 1H, C=CH_2), 5.27–5.29 (m, 1H, C=CH_2); ^{13}C NMR (D_2O): δ 25.1 (CH_2C=CH_2), 27.5 (CH_2CCOO), 63.5 ($CCOO$), 113.1 (C=CH_2), 144.8 (C=CH_2), 173.1 (COO). Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.18; H, 6.20; N, 8.61.

4.1.6. (1*S,2*S**)-*N*-[1-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*S**)-12.** A solution of olefin **8** (200 mg, 0.51 mmol) in dichloromethane (40 mL) was hydrogenated at 20 °C for 15 h with 10% palladium–carbon (40 mg) as a catalyst. Removal of the catalyst and the solvent gave a white solid corresponding to a mixture of compounds (1*S**,2*S**)-**12** and (1*S**,2*R**)-**12** in a ratio of 93:7 in favour of (1*S**,2*S**)-**12** and in 96% yield. The major compound was purified by column chromatography (hexane/ethyl acetate, 65:35) to give (1*S**,2*S**)-**12** (179 mg, 89%) as a white solid. Mp 116–117 °C. ^1H NMR ($CDCl_3$): δ 1.05–1.08 [m, 12H, CH_3CH, $C(CH_3)_3$], 1.25–1.38 (m, 1H, CH_2CH), 1.86 (s, 3H, CH_3CO), 1.91–2.04 (m, 2H, CH_2CH, CH_2C), 2.19–2.29 (m, 1H, CH_2C), 2.74–2.87 (m, 1H, CH_3CH), 3.82 (d, 1H, J=10.2 Hz, CH_2O), 3.95 (d, 1H, J=10.2 Hz, CH_2O), 5.69 (br s, 1H, NH), 7.37–7.47 (m, 6H, Arom.), 7.66–7.86 (m, 4H, Arom.); ^{13}C NMR ($CDCl_3$): δ 15.6 (CH_3CH), 19.4 [$C(CH_3)_3$], 23.0 (CH_2CH), 24.0 (CH_3CO), 26.9 [$C(CH_3)_3$], 27.1 (CH_2C), 37.9 (CH_3CH), 59.8 (CH_2C), 64.0 (CH_2O), 127.8, 129.8, 133.5, 135.6 (Arom.), 169.3 (CONH); ESI^+ (m/z)=396.4. Anal. Calcd for $C_{24}H_{33}NO_2Si$: C, 72.86; H, 8.41; N, 3.54. Found: C, 72.94; H, 8.48; N, 3.58.

4.1.7. (1*S,2*S**)-*N*-[1-(Hydroxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*S**)-13.** TBAF (0.52 mL, 1 M in THF) was added to a solution of (1*S**,2*S**)-**12** (170 mg, 0.43 mmol) in dry THF (15 mL) at 20 °C under an inert atmosphere and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the organic material was extracted with $CHCl_3$/^{i}PrOH (4:1) (2×15 mL). The combined organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (5:95), to give 52 mg (76%) of (1*S**,2*S**)-**13** as a white solid. Mp 112–113 °C. ^1H NMR ($CDCl_3$): δ 1.08 (d, 3H, J=7.0 Hz, CH_3CH), 1.40–1.53 (m, 1H, CH_2CH), 1.87–2.10 (m, 5H, CH_3CO, CH_2CH, CH_2C), 2.21–2.29 (m, 1H, CH_2C), 2.46–2.54 (m, 1H, CH_3CH), 3.77–3.88 (m, 2H, CH_2O), 4.38 (br s, 1H, OH), 6.22 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 15.0 (CH_3CH), 23.1 (CH_2CH), 23.6 (CH_3CO), 28.4 (CH_2C), 39.8 (CH_3CH), 60.4 (CH_2C), 65.0 (CH_2O), 171.5 (CONH); ESI^+ (m/z)=158.3. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.22; H, 9.56; N, 8.88.

4.1.8. (1*S,2*S**)-1-Acetamido-2-methylcyclobutane-1-carboxylic acid (1*S**,2*S**)-14.** To a solution of (1*S**,2*S**)-**13** (49 mg, 0.32 mmol) in acetone (10 mL) at 0 °C was added a 1.5-fold excess of Jones reagent (0.23 mL, 2 M in water) dropwise over 5 min. The mixture was stirred at 20 °C for 2 h. The excess Jones reagent was destroyed with ^{i}PrOH. The mixture was then diluted with water (10 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3×15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 40 mg (73%) of (1*S**,2*S**)-**14** as a white solid. This compound was used in the next step without further purification. Mp >200 °C (decomp.). ^1H NMR (CD_3OD): δ 1.03 (d, 3H, J=5.4 Hz, CH_3CH), 1.63–1.75 (m, 1H, CH_2CH), 1.87–2.07 (m, 5H, CH_3CO, CH_2CH, CH_2C), 2.61–2.82 (m, 2H, CH_2C, CH_3CH); ^{13}C NMR (CD_3OD): δ 16.9 (CH_3CH), 22.5 (CH_3CO), 24.6 (CH_2CH), 30.6 (CH_2C), 39.7 (CH_3CH), 64.0 (CH_2C), 172.9, 175.9 (COO, CONH); ESI^+ (m/z)=172.2.

4.1.9. (1*S,2*S**)-1-Amino-2-methylcyclobutane-1-carboxylic acid hydrochloride salt (1*S**,2*S**)-1·HCl.** The white solid corresponding to carboxylic acid (1*S**,2*S**)-**14** (20 mg, 0.12 mmol) was dissolved in aqueous 3 N HCl (3 mL) and heated at 100 °C for 6 h. The solution was concentrated to give 18 mg of a white solid; yield: 90%. Mp >200 °C (decomp.). Spectral data in CD_3OD agree with those published in the literature[7] for the corresponding enantiopure forms; the spectral data in D_2O are given below. ^1H NMR (D_2O): δ 1.04 (d, 3H, J=6.3 Hz, CH_3CH), 1.75–1.87 (m, 1H, CH_2CH), 2.04–2.27 (m, 2H, CH_2CH, CH_2C), 2.49–2.56 (m, 1H, CH_2C), 2.81–2.88 (m, 1H, CH_3CH); ^{13}C NMR (D_2O): δ 15.9 (CH_3CH), 23.5 (CH_2CH), 27.2 (CH_2C), 39.4 (CH_3CH), 62.5 (CH_2C), 173.7 (COO). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.43; H, 7.37; N, 8.51.

4.1.10. (1*S,2*R**)-*N*-[1-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*R**)-12.** A solution of olefin **9** (120 mg, 0.78 mmol) in dichloromethane (60 mL) was hydrogenated at 20 °C for 17 h with 10% palladium hydroxide–carbon (12 mg) as a catalyst. Removal of the catalyst and the solvent gave a white solid

corresponding to a mixture of compounds (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** in a 35:65 ratio in favour of (1*S**,2*R**)-**13** and in 95% yield. This mixture could not be separated by column chromatography and therefore the compounds were transformed into the corresponding silylated derivatives. To a solution of the mixture of (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** (90 mg, 0.57 mmol) in DMF (5 mL) were added imidazole (117 mg, 1.70 mmol) and TBDPSCl (0.43 mL, 1.80 mmol) and the mixture was stirred at 50 °C for 17 h. The solvent was evaporated under reduced pressure and 5% aqueous $NaHCO_3$ (10 mL) and ethyl acetate (15 mL) were added. The organic layer was separated and the aqueous layer was washed with ethyl acetate (3×10 mL). The combined organic layers were dried, filtered and the solvent evaporated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (65:35), to give 50 mg of (1*S**,2*R**)-**12** (32% from **9**) as a white solid. Mp 146–147 °C. ^{1}H NMR ($CDCl_3$): δ 1.07–1.12 [m, 12H, CH_3CH, C(CH_3)$_3$], 1.43–1.51 (m, 1H, CH_2CH), 1.86–1.99 (m, 4H, CH_2CH, CH_3CO), 2.09–2.13 (m, 1H, CH_2C), 2.19–2.29 (m, 1H, CH_2C), 2.40–2.44 (m, 1H, CH_3C*H*), 3.87 (d, 1H, J=10.0 Hz, CH_2O), 3.97 (d, 1H, J=10.0 Hz, CH_2O), 5.50 (br s, 1H, NH), 7.36–7.45 (m, 6H, Arom.), 7.63–7.74 (m, 4H, Arom.); ^{13}C NMR ($CDCl_3$): δ 15.8 (*C*H_3CH), 19.4 [*C*(CH_3)$_3$], 23.6 (*C*H_2CH), 23.8 (*C*H_3CO), 26.6 (*C*H_2C), 26.9 [C(*C*H_3)$_3$], 34.8 (CH_3*C*H), 59.8 (CH_2*C*), 67.0 (CH_2O), 127.7, 129.6, 129.7, 133.7, 133.8, 134.8, 135.6, 135.7 (Arom.), 169.5 (CONH); ESI$^+$ (m/z)=396.4. Anal. Calcd for $C_{24}H_{33}NO_2Si$: C, 72.86; H, 8.41; N, 3.54. Found: C, 72.92; H, 8.45; N, 3.61.

4.1.11. (1*S,2*R**)-*N*-[1-(Hydroxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*R**)-13.** TBAF (0.15 mL, 1 M in THF) was added to a solution of (1*S**,2*R**)-**12** (50 mg, 0.13 mmol) in dry THF (10 mL) at 20 °C under an inert atmosphere and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and the organic material was extracted with $CHCl_3$/^{i}PrOH (4:1) (2×10 mL). The organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (5:95), to give 20 mg (95%) of (1*S**,2*R**)-**13** as a white solid. Mp 94–95 °C. ^{1}H NMR ($CDCl_3$): δ 1.10 (d, 3H, J=7.2 Hz, CH_3CH), 1.43–1.50 (m, 1H, CH_2CH), 1.91–2.09 (m, 6H, CH_3CO, CH_2CH, CH_2C), 2.60–2.67 (m, 1H, CH_3C*H*), 3.79 (s, 2H, CH_2O), 4.79 (br s, 1H, OH), 5.83 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.0 (*C*H_3CH), 22.9 (*C*H_2CH), 23.4 (*C*H_3CO), 29.2 (*C*H_2C), 34.5 (CH_3*C*H), 60.4 (CH_2*C*), 69.2 (CH_2O), 171.7 (CONH); ESI$^+$ (m/z)=158.3. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.25; H, 9.70; N, 8.96.

4.1.12. (1*S,2*R**)-1-Acetamido-2-methylcyclobutane-1-carboxylic acid (1*S**,2*R**)-14.** To a solution of (1*S**,2*R**)-**13** (20 mg, 0.14 mmol) in acetone (7 mL) at 0 °C was added a 2.0-fold excess of Jones reagent (0.14 mL, 2 M in water) dropwise over 5 min. The mixture was stirred at 20 °C for 2 h. The excess Jones reagent was destroyed with ^{i}PrOH. The mixture was then diluted with water (10 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3× 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 15 mg (63%) of (1*S**,2*R**)-**14** as a white solid. This compound was used in the next step without further purification. Mp > 200 °C (decomp.). ^{1}H NMR (CD_3OD): δ 1.03 (d, 3H, J= 7.2 Hz, CH_3CH), 1.44–1.54 (m, 1H, CH_2CH), 1.97 (s, 3H, CH_3CO), 2.12–2.31 (m, 3H, CH_2CH, CH_2C), 3.04–3.11 (m, 1H, CH_3C*H*); ^{13}C NMR (CD_3OD): δ 16.3 (*C*H_3CH), 22.2 (*C*H_3CO), 24.4 (*C*H_2CH), 29.9 (*C*H_2C), 37.0 (CH_3*C*H), 61.8 (CH_2*C*), 173.5, 177.4 (COO, CONH); ESI$^+$ (m/z)=172.2.

4.1.13. (1*S,2*R**)-1-Amino-2-methylcyclobutane-1-carboxylic acid hydrochloride salt (1*S**,2*R**)-1·HCl.** The white solid corresponding to carboxylic acid (1*S**,2*R**)-**14** (10 mg, 0.06 mmol) was dissolved in aqueous 3 N HCl (2 mL) and heated at 100 °C for 6 h. The solution was concentrated to give 7 mg of a white solid; yield: 70%. Mp >200 °C (decomp.). Spectral data in CD_3OD agree with those published in the literature[7] for the corresponding enantiopure forms; the spectral data in D_2O are given below. ^{1}H NMR (D_2O): δ 1.14 (d, 3H, J=7.5 Hz, CH_3CH), 1.75–1.88 (m, 1H, CH_2CH), 2.17–2.35 (m, 2H, CH_2CH, CH_2C), 2.61–2.71 (m, 1H, CH_2C), 3.03–3.15 (m, 1H, CH_3C*H*); ^{13}C NMR (D_2O): δ 15.4 (*C*H_3CH), 24.1 (*C*H_2CH), 27.9 (*C*H_2C), 37.0 (CH_3*C*H), 62.3 (CH_2*C*), 175.2 (COO). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.41; H, 7.41; N, 8.53.

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