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PII: S0040-4039(14)00637-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.038
Reference: TETL 44500

To appear in: *Tetrahedron Letters*

Received Date: 18 January 2014
Revised Date: 29 March 2014
Accepted Date: 10 April 2014

Please cite this article as: Tymtsunik, A.V., Ivon, Y.M., Komarov, I.V., Grygorenko, O.O., Synthesis of Boc-protected 4,5-methano-β-proline, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.038

Graphical Abstract

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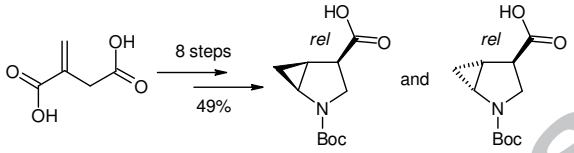

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Synthesis of Boc-protected 4,5-methano-β-proline

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
β-Amino acids;
Proline analogues;
Cyclopropane;
Bicyclic compounds;
Simmons–Smith reaction

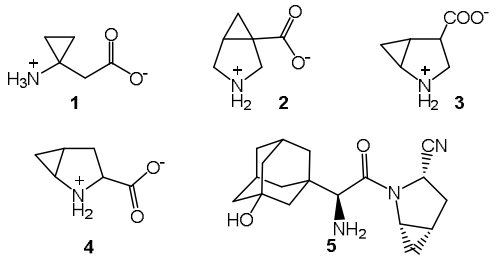
ABSTRACT

An efficient method for the preparation of Boc-protected 4,5-methano-β-proline – a novel bicyclic cyclopropane-containing β-amino acid – was developed, starting from readily available itaconic acid. A modified Simmons–Smith reaction was used for the construction of the cyclopropane ring. The method allowed for the synthesis of both *cis* and *trans* isomers of the title compound in 49% total yield and can be employed for gram-scale preparations. An approach to the preparation of methyl 5-oxopyrrolidine-3-carboxylate, which is one of the key intermediates in the synthetic scheme, on a multigram scale was also developed.

β-Amino acids are of significant importance among tailor-made amino acids; their residues are also found in small natural peptides.[1] Peptides constructed from β-amino acids were shown to adopt a number of intrinsic secondary structures, including helices, hairpins and reverse turns.[2] Notably, many of these structures were obtained by imposing conformational restrictions onto the residues of β-amino acids by a number of methods, which are widely recognized in model studies of peptides, proteins and other biologically relevant molecules.[3] Incorporation of a cyclopropane ring into the amino acid residues is one such method, which might severely alter the conformational behavior and electronic properties of the compounds by minimal structural changes to the parent scaffolds.[4] This can be advantageous in medicinal chemistry in the search for potential drug candidates, as well as for model studies of conformational and biological properties in the field of peptides.

Modification of β-amino acid molecules with a cyclopropane ring has been reported previously in the literature. In particular, one of the first simple representatives, **1**, was described in a patent in 1973.[5] Bicyclic cyclopropane-containing β-amino acids are much rarer. The preparation of a Boc-protected bicyclic cyclopropane-containing β-amino acid, 3,4-methano-β-proline (**2**), has also been documented.[6]

In this paper, we report a scalable synthesis of a novel, cyclopropane-modified β-proline analogue, 2-azabicyclo-[3.1.0]hexane-4-carboxylic acid (**3**) (4,5-methano-β-proline). Notably, derivatives of 4,5-methano(-α-)proline (**4**) – a close analogue of **3** – were used in the design and synthesis of saxagliptin (**5**), an oral anti-diabetic drug approved by the FDA in 2009,[7] as well as captopril analogs.[8]



Our retrosynthetic approach to **3** relied on disconnection of the cyclopropane ring, which led to the corresponding enamine derivative **6** (Scheme 1). Many synthetic methods could be used to implement this approach, but in this work, we relied on the Simmons–Smith reaction, which was recently applied by our group for the synthesis of a Boc-protected cyclopropane-containing proline analogue.[9] Compound **6** can be obtained from methyl 5-oxopyrrolidine-3-carboxylate (**7**) analogously to

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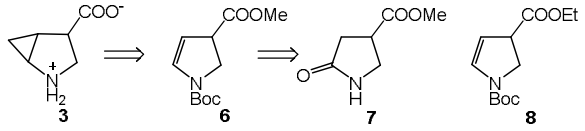
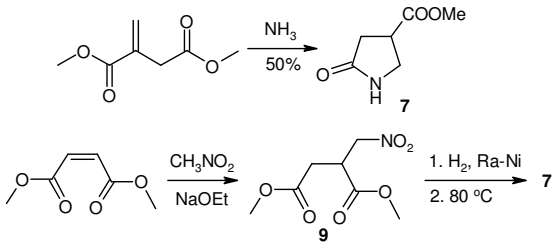
4,5-dehydroproline derivative **8**, which was prepared from pyroglutamic acid.[8]



Scheme 1. Retrosynthetic analysis of amino acid **3**



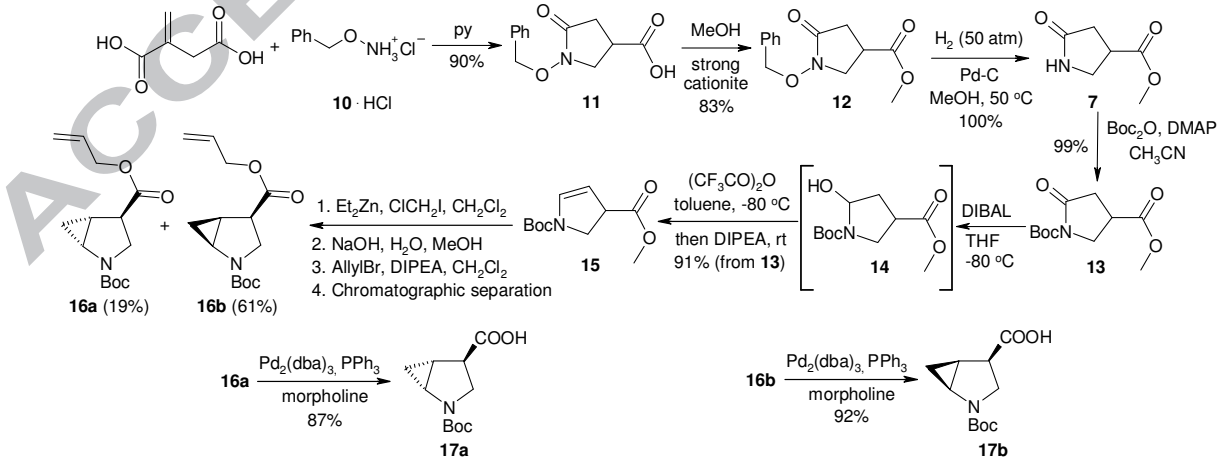
Scheme 2. Selected literature syntheses of **7**

Although compound **7** was described in the literature, none of the methods reported for its synthesis was suitable for large scale preparation. In our hands, scale-up of the procedure employing the reaction of dimethyl itaconate and ammonia (Scheme 2)[10] led to the formation of the target product with insufficient purity and in moderate non-reproducible yields. The method relying on a Michael addition of nitromethane to dimethyl maleate[11] included another step which was problematic for scale-up, namely, reduction of an aliphatic nitro group in the Michael adduct **9**. Other procedures involved the use of expensive organocatalysts[12] or potentially explosive reagents such as azides[13] or diazoalkanes.[14]

Our approach to **7** relied on a transformation used since the 1960s, namely, reaction of itaconic acid or its derivatives with *N*-nucleophiles. In order to simplify the isolation and purification of the intermediate products in the reaction sequence, we decided to increase their lipophilicity by using *O*-benzylhydroxylamine (**10**) as the nucleophile in the first step. This reagent is superior to other analogous *N*-nucleophiles (*e.g.*, benzylamine[15]) as the benzyloxy group can be readily removed under mild conditions. Reaction of itaconic acid and **10**·HCl was performed by heating the starting materials in pyridine (Scheme 3). Owing to the low aqueous solubility of **11**, isolation of the product was very simple and involved evaporation of the solvent, trituration of the residue with 4 M HCl and filtration. This gave carboxylic acid **11** (90%), which was pure enough for the next step.[16] Esterification of **11** was achieved by treatment of its methanolic solution with strong cationite, which led to the formation of ester **12** in 83% yield.[17] Deprotection of the nitrogen atom in **12** by catalytic hydrogenation using palladium on charcoal as the catalyst occurred at 20 atm of hydrogen. In order to increase the conversion rate on large scale, the reaction was carried out at 50 atm to give ester **7** quantitatively.[18] For both steps (**11** → **12** and **12** → **7**), isolation of the product included filtration of the catalyst and evaporation to dryness. It should be noted that up to 100 g of **7** of more than 95% purity was obtained in a single run using this reaction sequence without any chromatographic separations.

Compound **7** was transformed into the corresponding Boc derivative **13** in 99% yield by reaction with Boc_2O and DMAP.[19] Selective reduction of the pyrrolidone moiety in **13** was achieved using a stoichiometric amount of DIBAL-H; under these conditions, cyclic hemiaminal derivative **14** was obtained. Compound **14** was treated with trifluoroacetic anhydride in toluene at –80 °C, and the *in situ* formed trifluoroacetate was subjected to elimination upon treatment with *N*,*N*-diisopropylethylamine (DIPEA) to give enamine derivative **15** (91% over 2 steps), which was purified chromatographically.[20]

For the cyclopropanation of **15**, we used a slightly modified Furukawa variation of the Simmons–Smith reaction [Et_2Zn (2.5 mol), $ClCH_2I$ (2.55 mol), CH_2Cl_2, –50 °C to rt, overnight].[21] The reaction showed moderate diastereoselectivity and led to a *ca.* 1:3 mixture of the corresponding methyl esters, which were hydrolyzed with alkali to give a mixture of the carboxylic acids in 94% yield (over 2 steps). Since neither the methyl esters nor carboxylic acids could be separated chromatographically, the latter were transformed into allyl esters **16a** and **16b** (in order to simplify the detection of the



Scheme 3. Synthesis of Boc-protected 4,5-methano-β-prolines **17a,b** (relative configurations are shown)

diastereomers during TLC analysis of the fractions). This approach was fruitful, and the compounds **16a** and **16b** were separated smoothly using column chromatography (19% and 61% yields from **15**, respectively).[22] In the last step of the synthesis, deprotection of **16a** and **16b** with *in situ* generated $Pd(PPh_3)_4$ gave Boc-protected amino acids **17a** and **17b** in 87% and 92% yields, respectively.[23, 24]

The relative stereochemistry of the products was established using NOESY experiments with Boc derivatives **17a** and **17b** (Figure 1). Thus, the *cis* diastereomer was formed predominantly upon Simmons–Smith cyclopropanation of alkene **15**, which can be rationalized by coordination of the intermediate zinc species with the ester moiety of **15**.

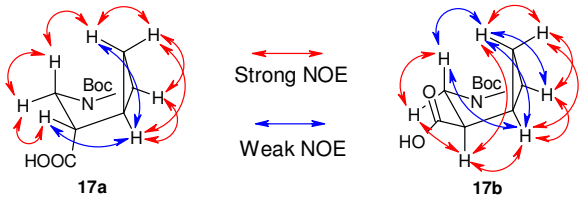


Figure 1. Correlations in the NOESY spectra of **17a** and **17b**

In conclusion, an efficient method for the preparation of the novel, bicyclic, cyclopropane-containing β-amino acid derivative, Boc-protected 4,5-methano-β-proline, has been developed. The synthesis commenced from itaconic acid and allowed for the preparation of both the *cis* and *trans* isomers of the title compound in 11% and 38% total yields, respectively.

Acknowledgments

The authors thank Mr. Vitaliy Polovinko for NMR experiments and Prof. Andrey A. Tolmachev for his encouragement and support.

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16. Procedure for the preparation of **11**: *O*-benzylhydroxylamine hydrochloride (**10**·HCl) (163.4 g, 1.02 mol) was added to a solution of of itaconic acid (133.2 g, 1.02 mol) in dry pyridine (900 mL) with stirring, and the resulting mixture was refluxed for 20 h. The solvent was evaporated in vacuo, and the residue triturated with 4 M aq HCl (1 L) at ambient temperature (external cooling bath!). The mixture was stirred vigorously for 1 h and filtered. The precipitate was washed thoroughly with H_2O (1 L) and dried in air for 3 d to give **11** as pale yellow crystals (217.9 g, 90%). Mp 127–128 °C. MS (*m/z*, CI): 236 (MH^+), 91 ($C_7H_7^+$). Anal. Calcld. for $C_{12}H_{13}NO_4$ C 61.27, H 5.57, N 5.95. Found C 61.04, H 5.80, N 6.21. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.74 (br s, 1H), 7.52 – 7.19 (m, 5H), 4.90 (s, 2H), 3.62 (t, *J* = 8.3 Hz, 1H), 3.53 (t, *J* = 8.2 Hz, 1H), 3.22 – 3.13 (m, 1H), 2.54 – 2.38 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.1 (*C*), 169.1 (*C*), 135.8 (*C*), 129.6 (*CH*), 129.0 (*CH*), 128.8 (*CH*), 76.1 (CH_2), 48.3 (CH_2), 33.4 (*CH*), 30.9 (CH_2).
17. Procedure for the preparation of **12**: strong cationite (KY-2) (*ca.* 30 g) was added to a stirred solution of the acid **11** (58.3 g, 0.248 mol) in absolute MeOH (1 L). The mixture was refluxed for 2 d, filtered through silica and washed thoroughly with MeOH (0.6 L). The filtrate was evaporated to dryness to give **12** (51.2 g, 83%) as a colourless oil, which crystallized upon standing. Mp 42–43 °C. MS (*m/z*, CI): 250 (MH^+), 91 ($C_7H_7^+$). Anal. Calcld. for $C_{13}H_{15}NO_4$ C 62.64, H 6.07, N 5.62. Found C 62.78, H 6.09, N 5.85. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.49 – 7.35 (m, 5H), 4.91 (s, 2H), 3.68 – 3.56 (m, 1H), 3.65 (s, 3H), 3.54 – 3.48 (m, 1H), 3.32 – 3.24 (m, 1H), 2.57 – 2.39 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.0, 168.8, 135.8, 129.6, 129.0, 128.8, 76.2, 52.6, 48.2, 33.3, 30.8.

18. Procedure for the preparation of **7**: an autoclave was charged with **12** (51.0 g, 0.205 mol), 10% Pd-C (9.0 g) and MeOH (400 mL). The mixture was stirred vigorously at 50 atm of hydrogen at 50 °C for 24 h. The suspension was filtered, and the slurry of catalyst was washed with MeOH (2×100 mL). The filtrate was evaporated to dryness in vacuo and the product **7** (29.2 g, 100%) was obtained as colourless oil, which crystallized upon standing. Mp 55–58 °C (lit.[10b] 61–62 °C). MS (*m/z*, CI): 287 (M_2H^+), 144 (MH^+). Anal. Calcd. for $C_6H_9NO_3$ C 50.35, H 6.34, N 9.79. Found C 50.13, H 6.47, N 10.02. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67 (s, 1H), 3.64 (s, 3H), 3.46 (t, J = 11.1 Hz, 1H), 3.39 – 3.31 (m, 2H), 2.43 – 2.28 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.4, 174.0, 52.4, 44.0, 38.4, 33.4.
19. Procedure for the preparation of **13**: lactam **7** (29.2 g, 0.204 mol) and DMAP (12.5 g, 0.102 mol) were dissolved in MeCN (300 mL). A solution of Boc_2O (66.8 g, 0.306 mol) in MeCN (60 mL) was added to the reaction mixture with stirring over *ca.* 3 h. The solution was stirred overnight, and the solvent was evaporated in vacuo. The residue was carefully acidified with 1 M aq $NaHSO_4$ to pH=2 and extracted with EtOAc (2×300 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo. Dry THF (200 mL) was added and the solution evaporated to dryness to give **13** (49.2 g, 99%) as a brownish-red oil which crystallized upon standing. Mp 41–42 °C. MS (*m/z*, CI): 188 (MH^+–C_4H_8). Anal. Calcd. for $C_{11}H_{17}NO_5$ C 54.31, H 7.04, N 5.76. Found C 54.63, H 7.19, N 5.44. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.88 (t, J = 9.5 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.67 (s, 3H), 3.38 – 3.28 (m, 1H), 2.76 – 2.61 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.2, 171.8, 149.8, 82.3, 52.6, 48.1, 35.6, 34.6, 28.1.
20. Procedure for the preparation of **15**: DIBAL-H (45 mL, 0.252 mol) was added dropwise to the solution of **13** (49.2 g, 0.202 mol) in absolute THF (600 mL) at –80 °C under an argon atmosphere. The solution was stirred at –80 °C for 1 h. Saturated aq NH_4Cl (300 mL) was added dropwise with vigorous stirring while the temperature rose from –80 °C to 10°C (**CAUTION!** A violent reaction occurs above 10 °C, such that external cooling is nessesary in order not to allow the temperature to exceed 25 °C). The mixture was stirred vigourously for 15 min and filtered immediately (it should not be left for a long period of time!). The slurry was washed with THF (3×200 mL). The filtrate was evaporated in vacuo at a bath temperature below 40 °C. The resulting oil was quenched with H_2O (200 mL) and extracted with Et_2O (2×200 ml). The combined extracts were dried over $MgSO_4$ and evaporated to give crude **14** (47.3 g) as a yellowish oil, which was used without further purification. The crude product should be stored at –20 °C; it is preferrable to use it in the next step as soon as possible.
    Compound **14** (47.3 g) was dissolved in absolute toluene and cooled to –80 °C under an argon atmosphere with vigourous stirring. $(CF_3CO)_2O$ (27.7 mL, 0.199 mol) was added dropwise at that temperature. After 20 min, DIPEA (132 mL, 0.758 mol) was added at –80 °C and the mixture was allowed to warm to rt overnight with stirring. The solution was cooled to 0 °C, and H_2O (100 mL) was added. The mixture was acidified carefully with 10% aq citric acid to pH = 6. The toluene layer was separated, washed with H_2O (600 mL), dried over Na_2SO_4 and evaporated in vacuo at a bath temperature below 60 °C to give a crude residue (48.7 g), wich was purified chromatographically on silica using hexane–EtOAc (8:1) as the eluent to give **15** as a yellowish oil (41.3 g, 91% over 2 steps). The pure product can be stored at 4 °C for several months. R_f = 0.33 [hexanes – EtOAc (8:1)]. MS (*m/z*, EI): 227 (M^+), 171 (M^+–C_4H_8), 57 ($C_4H_9^+$). Anal. Calcd. for $C_{11}H_{17}NO_4$ C 58.14, H 7.54, N 6.16. Found C 57.83, H 7.50, N 6.37. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 0.5H), 6.57 (s, 0.5H), 5.06 (s, 0.5H), 5.01 (s, 0.5H), 4.17 – 4.06 (m, 1H), 3.93 – 3.79 (m, 2H), 3.74 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 151.7 and 151.0, 131.7, 104.8, 80.7, 80.6, 55.2, 47.7, 47.4, 47.1, 46.6, 28.3.
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22. Procedure for the preparation of **16a,b**: to a solution of enamide **15** (0.62 g, 2.73 mmol) in absolute CH_2Cl_2 (15 mL), 15% (0.87 M) $ZnEt_2$ in hexane (7.8 ml, 6.79 mmol) was added in one portion at –40 °C under an argon atmosphere. After 5 min, the solution was cooled to –55 °C, and $ClCH_2I$ (0.51 ml, 7.00 mmol) was added in one portion. As a result, the temperature of the mixture increased to –50 °C. The mixture was stirred for 21 h with slow warming from –50 °C to 10 °C, then cooled to 0 °C, and 5% aq $NaHCO_3$ (50 mL) was added. The suspension was stirred for an additional 10 min and filtered. The slurry was washed with CH_2Cl_2 (2×10 mL), the organic layer was separated, and the aqueous phase extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated. The crude product (0.74 g) was dissolved in MeOH (30 mL), and a solution of NaOH (0.33 g, 8.19 mmol) in H_2O (3 mL) was added. The mixture was stirred at rt for 2 d, after which the MeOH was evaporated, and the residue was quenched with H_2O (20 mL), washed with Et_2O (2×15 mL), acidified with 1 M aq $NaHSO_4$ to pH = 2 and extracted with $CHCl_3$ (3×20 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give a *ca.* 1:3 mixture of **17a** and **17b** (0.58 g).
    The mixture of acids **17** (0.56 g, 2.46 mmol) was dissolved in CH_2Cl_2 (40 mL). DIPEA (0.86 mL, 4.93 mmol) and allyl bromide (0.32 mL, 3.70 mmol) were added to the solution. The mixture was refluxed for 2 d, cooled to rt, washed with 10% aq citric acid (30 mL), 5% aq $NaHCO_3$ (20 mL), and H_2O (20 mL), dried over Na_2SO_4, and evaporated to give a mixture of **16a** and **16b** (0.64 g). The diastereomers were separated by column chromatography on silica gel, using hexane – EtOAc (5:1) as eluent. The *trans*-isomer **16a** was obtained as pale yellow oil (0.13 g, 19% from **15**). R_f = 0.29 [hexane – EtOAc (5:1)]. MS (*m/z*, EI) 194 (M^+–OC_4H_9), 167 (M^+–CO_2–C_4H_8), 126 (M^+–CO_2–C_4H_8–C_3H_5), 57 ($C_4H_9^+$), 41 ($C_3H_5^+$). Anal. Calcd. for $C_{14}H_{21}NO_4$ C 62.90, H 7.92, N 5.24. Found C 63.06, H 7.69, N 5.21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 – 5.85 (m, 1H), 5.34 (d, J = 17.3 Hz, 1H), 5.26 (d, J = 10.6 Hz, 1H), 4.64 (s, 2H), 3.97 (s, 1H), 3.65 – 3.45 (m, 1H), 3.23 – 3.06 (m, 2H), 1.92 – 1.83 (m, 1H), 1.47 (s, 9H), 0.90 – 0.73 (m, 1H), 0.62 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 154.5, 131.4, 118.0, 79.4, 65.2, 46.4, 44.2, 43.3, 35.1, 28.0, 18.1, 17.4, 10.0.
    The *cis*-isomer **16b** was obtained as a colourless oil which crystallized upon standing (0.43 g, 61% from **15**). R_f = 0.37 [hexane – EtOAc (5:1)]. Mp 52–53 °C. MS (*m/z*, EI) 194 (M^+–OC_4H_9), 167 (M^+–CO_2–C_4H_8), 126 (M^+–CO_2–C_4H_8–C_3H_5), 57 ($C_4H_9^+$), 41 ($C_3H_5^+$). Anal. Calcd. for $C_{14}H_{21}NO_4$ C 62.90, H 7.92, N 5.24. Found C 62.63, H 8.08, N 5.60. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 – 5.80 (m, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.22 (d, J = 10.3 Hz, 1H), 4.60 (d, J = 5.2 Hz, 2H), 3.89 – 3.63 (m, 1H), 3.60 – 3.41 (m, 1H), 3.35 – 3.26 (m, 1H), 3.26 – 3.16 (m, 1H), 1.89 – 1.77 (m, 1H), 1.44 (s, 9H), 0.82 (s, 1H), 0.67 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 154.4, 131.5, 118.0, 79.4, 65.1, 44.7, 42.6, 42.0, 35.6, 28.0, 18.4, 17.9, 8.5.
23. Procedure for the preparation of **17a**: a solution of allyl ester **16a** (70 mg, 0.26 mmol) in absolute THF (4 mL) was degassed by refluxing under an argon flow. $Pd_2(dba)_3$ (14 mg, 0.015 mmol) and PPh_3 (8 mg, 0.03 mmol) were added to the solution sequentially at rt under an argon atmosphere. After 5 min, morpholine (0.22 ml, 2.6 mmol) was added. The mixture was stirred at rt for 2 d, then diluted with EtOAc (30 mL) and extracted with H_2O (2×25 mL). The combined aqueous extracts were washed with EtOAc (15 mL), acidified with 1 M aq $NaHSO_4$ to pH = 2, and extracted with $CHCl_3$ (2×15 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to give the product **17a** as a yellowish glass (52 mg, 87%). MS (*m/z*, CI): 226 (M–H^+). Anal. Calcd. for $C_{11}H_{17}NO_4$ C 58.14, H 7.54, N 6.16. Found C 58.51, H 7.33, N 5.89. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (br s, 1H), 4.05 – 3.87 (m, 1H), 3.65 – 3.39 (m, 1H), 3.19 – 3.00 (m, 2H), 1.91 – 1.79 (m, 1H), 1.44 (s, 9H), 0.89 – 0.66 (m, 1H), 0.60 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 154.8, 79.6, 46.4, 44.3, 43.4, 35.1, 28.0, 18.2, 17.5, 10.1.
24. Acid **17b** was prepared from **16b** analogously to **17a**. The product was obtained as a colourless viscous oil, which solidified

upon standing. Yield 92%. Mp 107–110 °C. MS (*m/z*, CI): 226 ($M–H^+$). Anal. Calcd. for $C_{11}H_{17}NO_4$ C 58.14, H 7.54, N 6.16. Found C 58.03, H 7.74, N 6.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 3.85 – 3.68 (m, 1H), 3.63 – 3.42 (m, 1H), 3.38 – 3.26 (m, 1H), 3.25 – 3.14 (m, 1H), 1.92 – 1.79 (m, 1H), 1.45 (s, 9H), 0.90 – 0.79 (m, 1H), 0.76 – 0.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 154.6, 79.8, 44.7, 42.4, 41.7, 35.6, 28.0, 18.5, 17.8, 8.6.