Titanium-Catalyzed Cyclopropanation of Boc-Protected Cyanohydrins: A Short Access to Aminocyclopropanecarboxylic Acid Derivatives

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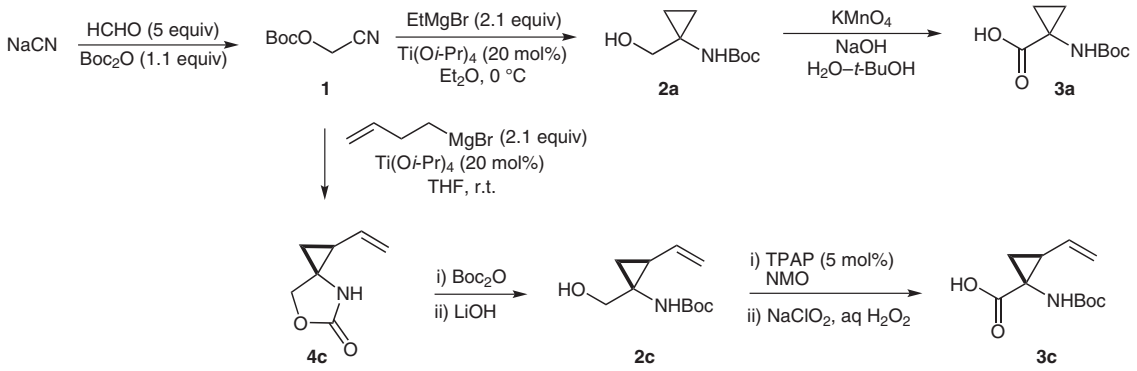
Abstract: The preparation of protected 1-aminocyclopropanecarboxylic acid was performed from readily available and inexpensive starting materials, using titanium-catalyzed cyclopropanation as the key step. As an extension of this methodology, a diastereoselective synthesis of the *cis*-2-vinyl-substituted analogue is presented.

Key words: amino acids, cyanohydrins, cyclopropane, organometallic reagents, titanium



Scheme 1

1-Aminocyclopropanecarboxylic acid (ACC) is a non-proteogenic α-amino acid that displays important biological activity.[1] It is the direct precursor of the plant hormone ethylene, and, thus, has been studied extensively in agrochemistry.[2] In addition, 1-aminocyclopropanecarboxylic acid mimics the effects of glycine on the NMDA receptor ion channel[3] and shows antidepressant and anxiolytic activity.[4] Its incorporation into peptides led to unusual conformations, which are useful for structurally defined peptides[5] and some of these peptides possess biological activity.[6] 1-Aminocyclopropanecarboxylic acid has also been used as a building block for the synthesis of many aminocyclopropane-containing biologically active compounds.[1] 2-Substituted analogues of 1-aminocyclopropanecarboxylic acid, the so-called 2,3-methanoamino acids, are generally used as configurationally constrained analogues of natural α-amino acids and they present interesting biological activity alone or when incorporated into peptides or cyclopeptides.[7] A remarkable example is BILN 2061, a potent HCV protease inhibitor, which displays a 1-amino-2-vinylcyclopropanecarboxylic acid unit.[8]

Since the first synthesis of 1-aminocyclopropanecarboxylic acid in 1922,[9] many approaches to 1-aminocyclopropanecarboxylic acid or its protected form have been published,[1,10] including cyclopropanation of α,β-dehydroamino acids,[10a,b] cyclization of glycine anion equivalents,[10c,d] or Curtius rearrangement of substituted cyclopropanecarboxylic acid derivatives.[10e,f] Despite their efficiency, these methods require several steps and/or relatively expensive starting materials. Recently, new reported routes to *N*-Boc-protected 1-aminocyclopropanecarboxylic acid **3a** from *N*,*N*-dialkylamides[11] or nitriles[12] used titanium-mediated cyclopropanations.[13] Particularly, a short synthesis of **3a** in only three steps from easily available and inexpensive starting materials was described by our group. 1-Aminocyclopropanecarboxylic acid has been extensively used in research, however, despite the numerous syntheses reported, it remains relatively expensive.[14] In this paper, we present an optimized multigram-scale synthesis of **3a**, as well as the synthesis of its synthetically useful *cis*-2-vinyl-substituted analogue

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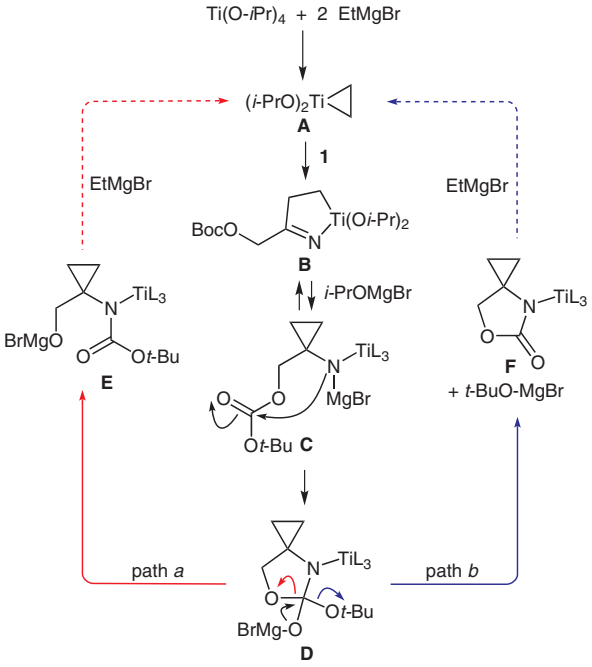
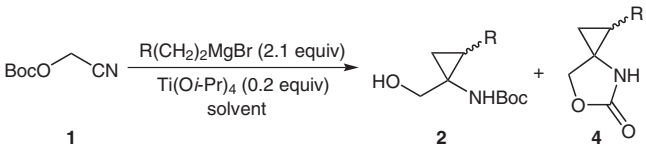
3c, using the titanium-catalyzed cyclopropanation of the Boc-protected cyanohydrin **1** as the key step (Scheme 1).

The first step in the synthesis of **3a** involves the in situ formation of glycolonitrile from sodium cyanide and aqueous formaldehyde in methanol, followed by trapping with di-*tert*-butyl dicarbonate, to afford **1**. A careful study of the reaction showed that a large excess of aqueous formaldehyde (37–41% in water) and a slight excess of di-*tert*-butyl dicarbonate (1.1 equiv) minimize the formation of byproducts. The synthesis was performed on 0.25-mole scale and the crude Boc-protected cyanohydrin obtained was purified by chromatography (78% yield) or used directly in the next step (*vide infra*). The key reaction, namely the titanium-catalyzed cyclopropanation of **1**, was undertaken with 0.2 equivalents of titanium(IV) isopropoxide and 2.1 equivalents of ethylmagnesium bromide in diethyl ether to provide **2a** in 65% yield. As shown in Scheme 2, the contraction of the first azatitanacycle intermediate **B** affords the dimetalated cyclopropylamine **C**, which in turn undergoes Boc transfer from the alkoxy to the amine moiety, giving **E** through **D** (path a) and releasing the hydroxy moiety. Interestingly, the nature of the solvent is very important. When using tetrahydrofuran instead of diethyl ether, the spirocyclopropane oxazolidinone **4a** was obtained as the main product in 35% yield (Table 1, entry 2 vs. 1), following an alternative path (Scheme 2, path b). The reason for this solvent-dependent outcome is not clear at present. The alcohol **2a** was isolated as a white solid, mp 85.2–86.2 °C after recrystallization from toluene–cyclohexane. Interestingly, the reaction can also be performed from crude **1** to afford **2a** in a slightly lower yield (45–50% over 2 steps), avoiding the need to purify **1**. The last step, i.e. the oxidation of the primary alcohol, was undertaken with potassium permanganate as oxidant following a procedure inspired by de Meijere's work.[11] The crude acid was purified by recrystallization (toluene), providing the Boc-protected 1-aminocyclopropanecarboxylic acid **3a** as a white crystalline powder in 92% yield. Unprotected 1-aminocyclopropanecarboxylic acid can easily be obtained by heating **3a** at reflux in distilled water for eight hours.[10f]



Scheme 2

Table 1 Scope of the Reaction of Boc-Protected Cyanohydrin **1** with Grignard Reagents



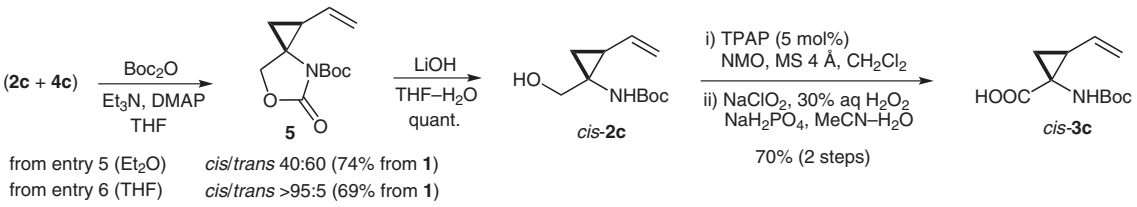
Entry	R	Solvent	Product(s) (yield)
1	H	Et_2O	**2a** (65%) + **4a** (0%)
2	H	THF	**2a** (29%) + **4a** (35%)
3	Et	Et_2O	**2b** (40%)[a] + **4b** (0%)
4	Et	THF	**2b** + **4b** (35:65) (26%)
5	$CH=CH_2$	Et_2O	**2c** + **4c** (70:30) (74%)[b]
6	$CH=CH_2$	THF	**2c** + **4c** (15:85) (69%)[b]

[a] Diastereoselectivity 2:1.
[b] Yield of **5**, see text.

Scope and Limitations

Following this strategy, the use of substituted ethyl Grignard reagents would generate 2-substituted 1-aminocyclopropanecarboxylic acids from the Boc-protected cyanohydrin **1** (Table 1). Unfortunately, despite numerous attempts, the reaction was not selective and generally led to inseparable mixtures of *N*-Boc-protected amino alcohols **2** and oxazolidinones **4**, both existing as mixtures of diastereoisomers. The use of butylmagnesium bromide is representative: alcohol **2b** was obtained in 40% yield in diethyl ether as a 2:1 mixture of isomers (entry 3) and an even lower combined yield of **2b** and **4b** was observed in tetrahydrofuran (entry 4).

An outstanding exception to this general trend was observed when using homoallylmagnesium bromide.[15] When the reaction was performed in diethyl ether, an inseparable mixture of the amino alcohol **2c** and the oxazolidinone **4c** was obtained (entry 5). The crude mixture was directly treated with di-*tert*-butyl dicarbonate to give the unique Boc-oxazolidinone **5**, isolated in pure form in 74% yield for the two-step process, but with a poor diastereomeric ratio (*cis*/*trans* 40:60). In contrast, when the reaction was performed in tetrahydrofuran and subjected to the same conditions (cyclopropanation, followed by Boc_2O), the oxazolidinone **5** was obtained in diastereomerically pure form (*cis*/*trans* >95:5) in 69% yield (entry



Scheme 3

6), underlining the importance of the solvent in the cyclopropanation step.[16] Subsequent quantitative hydroxide-mediated ring opening of the oxazolidinone **5** gave the alcohol **2c** (Scheme 3).

Finally, in order to preserve the alkene moiety, the oxidation of the primary alcohol was performed in two steps to furnish the Boc-protected *cis*-amino acid **3c** in 70% overall yield.[17] Whereas the large-scale preparation of the *trans*-isomer was well described as a part of the synthesis of BILN 2061,[17b] the preparation of the *cis*-isomer was less documented.[18] Since a double bond can be easily transformed by many established procedures, this amino acid would be a template for the synthesis of various constrained 1-aminocyclopropanecarboxylic acid derivatives.

In summary, we have presented a multigram-scale synthesis of the Boc-protected aminocyclopropanecarboxylic acid (Boc-ACC) **3a**. Based on inexpensive starting materials, this procedure requires only three steps without the need for chromatographic purification. In addition, we have developed the synthesis of the *cis*-2-vinyl-substituted 1-aminocyclopropanecarboxylic acid analogue **3c** in diastereomerically pure form.

Analytical TLC were performed on Alugram SIL G/UV_{254} silica gel sheets (Macherey-Nagel) with detection by 0.5% phosphomolybdic acid soln in 95% EtOH or vanillin. Column chromatography was carried out using silica gel 60 (0.040–0.063 mm) from Merck. Melting points were determined with a Büchi B-540 melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer on a single-reflection diamond ATR unit. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX-200 or Bruker AC-400 spectrometer, relative to the residual solvent peak. HRMS were recorded on a Waters Micromass GCT Premier spectrometer.

***tert*-Butyl Cyanomethyl Carbonate (1)**

To a soln of NaCN (12.24 g, 0.25 mol) in MeOH (200 mL) at 0 °C was slowly added 37–41% aq HCHO soln (100 mL). The addition rate was maintained in order to keep the temperature inside the reaction media below 10 °C. The mixture was stirred for 30 min, and then solid Boc_2O (60 g, 0.275 mol) was added. A white precipitate appeared rapidly, and the soln became viscous. The mixture was stirred for 2 h, and H_2O (0.5 L) and EtOAc (100 mL) were added to dissolve the precipitate. The mixture was transferred into a separatory funnel and extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with sat. aq NaCl soln (50 mL), dried ($MgSO_4$), and the solvent was evaporated. The resulting oil was purified by flash chromatography (cyclohexane–EtOAc, 90:10 then 80:20) to remove the slight excess Boc_2O and the cyano ester **1** (30.65 g, 78%) was isolated as a colorless oil; R_f = 0.36 (cyclohexane–EtOAc, 8:2).

IR (neat): 1750, 1371, 1274, 1254, 1104 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, CH_3), 4.65 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 50.7, 84.7, 114.4, 151.8.

HRMS (CI-CH_4): *m*/*z* [M + H]$^+$ calcd for $C_7H_{12}NO_3$: 158.0817; found: 158.0819.

***tert*-Butyl 1-(Hydroxymethyl)cyclopropylcarbamate (2a)**

To a soln of the nitrile **1** (7.85 g, 0.05 mol) and Ti(O*i*-Pr)$_4$ (3 mL, 10 mmol) in Et_2O (150 mL) under argon at 0 °C was added dropwise 2.5 M EtMgBr in Et_2O (42 mL, 105 mmol). The soln turned gradually from clear yellow to brown with a yellow precipitate. At the end of the addition (ca. 2 h), TLC analysis (cyclohexane–EtOAc 7:3, vanillin development) showed the disappearance of the starting material. H_2O (ca. 50 mL) was slowly added at 0 °C, followed by EtOAc (100 mL) and 1 M HCl until the two layers became clear (ca. 100 mL). The mixture was transferred into a separatory funnel and the two phases were separated. The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated. The resulting pale-yellow solid was purified by flash chromatography (cyclohexane–EtOAc, 7:3) to provide **2a** (6.11 g, 65%) as a white crystalline solid. The crude solid can alternatively be recrystallized (toluene–cyclohexane) to afford a white crystalline powder (5.39 g, 58%); when the same reaction was performed with crude **1**, the alcohol **2a** was isolated in 45–50% yield after recrystallization; mp 85.2–86.2 °C; R_f = 0.27 (cyclohexane–EtOAc, 5:5).

IR (neat): 3340, 3270, 1692, 1504, 1162 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (s, 4 H, CH_2), 1.41 (s, 9 H, CH_3), 3.54 (s, 2 H, CH_2), 3.60 (br s, 1 H, OH), 5.22 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 28.4, 35.3, 69.5, 80.2, 157.6.

HRMS (CI-CH_4): *m*/*z* [M + H]$^+$ calcd for $C_9H_{18}NO_3$: 188.1287; found: 188.1288.

1-(*tert*-Butoxycarbonylamino)cyclopropanecarboxylic Acid (3a)

To a soln of the alcohol **2a** (4.67 g, 25 mmol) in *t*-BuOH (100 mL) was added a soln of $KMnO_4$ (11.85 g, 75 mmol) and NaOH (8 g, 0.2 mol) in H_2O (200 mL). The mixture was stirred for 2 h, and then Na_2SO_3 and 1 M HCl were added to the dark soln until the soln became colorless and the pH was below 2. The mixture was extracted with EtOAc (5 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting white solid was recrystallized (toluene) to afford **3a** (4.62 g, 92%) as a white crystalline powder; mp 174.4–175.3 °C; R_f = 0.23 (cyclohexane–EtOAc, 5:5).

IR (neat): 3240, 2563, 1694, 1647, 1399, 1159 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.92–0.97 (m, 2 H, CH_2), 1.23–1.28 (m, 2 H, CH_2), 1.37 (s, 9 H, CH_3), 7.35 (br s, 1 H, NH), 12.18 (br s, 1 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.6, 28.2, 33.2, 77.8, 155.7, 174.4.

HRMS (CI-CH_4): *m/z* [M + H]$^+$ calcd for $C_9H_{16}NO_4$: 202.1079; found: 202.1082.

***tert*-Butyl *cis*-5-Oxo-1-vinyl-6-oxa-4-azaspiro[2.4]heptane-4-carboxylate (5)**

To a soln of the nitrile **1** (2.10 g, 13.36 mmol) and Ti(O*i*-Pr)$_4$ (800 μL, 2.68 mmol) in THF (100 mL) under argon at 50 °C was added dropwise 1.2 M EtMgBr in THF (24.4 mL, 29.4 mmol). The soln turned gradually from clear yellow to brown. At the end of the addition (ca. 30 min), TLC analysis (cyclohexane–EtOAc, 7:3, vanillin development) showed the disappearance of the starting material. H_2O (ca. 40 mL) was slowly added, followed by EtOAc (40 mL) and 1 M HCl until the two layers became clear (acidic pH). The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a crude mixture of amino alcohol **2c** and oxazolidinone **4c**.[15]

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (m, 1 H, **2c**-CH_2), 1.05 (m, 2 H, **4c**-CH_2), 1.17 (m, 1H, **2c**-CH_2), 1.40 (s, 9 H, **2c**-CH_3), 1.64 (m, 1 H, **4c**-CH), 1.74 (m, 1 H, **2c**-CH), 3.50–3.78 (m, 3 H, **2c**-OH, **2c**-CH_2), 4.34 (d, *J* = 8.3 Hz, 1 H, **4c**-CH_2), 4.37 (d, *J* = 8.3 Hz, 1 H, **4c**-CH_2), 4.90–5.30 (m, 3 H, **2c**-NH, **2c**-CH_2), 5.15 (ddd, *J* = 10.1, 1.6, 0.6 Hz, 1 H, **4c**-CH_2), 5.17 (ddd, *J* = 17.2, 1.6, 0.7 Hz, 1 H, **4c**-CH_2), 5.40–5.60 (m, 1 H, **2c**-CH), 5.56 (ddd, *J* = 17.2, 10.1, 7.9 Hz, 1 H, **4c**-CH), 6.90 (s, 1 H, **4c**-NH).

To a soln of the crude mixture of **2c** and **4c** in THF (30 mL) was added successively Boc_2O (3.50 g, 16.0 mmol), Et_3N (2.42 mL, 17.4 mmol), and DMAP (328 mg, 2.68 mmol). The soln was stirred at r.t. for 1 h then sat. aq NH_4Cl soln (30 mL) was added. The aqueous phase was extracted with Et_2O (3 × 25 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the crude product was purified by flash chromatography (silica gel, cyclohexane–EtOAc, 7:3, vanillin development) to afford the pure *cis*-Boc-oxazolidinone **5** (2.20 g, 69% yield over two steps) as a colorless oil; R_f = 0.30 (cyclohexane–EtOAc, 7:3).

IR (neat): 2981, 1790, 1724, 1636, 1477, 1457, 1332, 1154, 1069 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (dd, *J* = 10.0, 7.0 Hz, 1 H, CH_2), 1.52 (s, 9 H, CH_3), 1.68 (m, 1 H, CH), 2.51 (t, *J* = 7.0 Hz, 1 H, CH_2), 3.90 (d, *J* = 8.3 Hz, 1 H, CH_2), 4.36 (d, *J* = 8.3 Hz, 1 H, CH_2), 5.08 (ddd, *J* = 10.4, 1.6, 0.6 Hz, 1 H, CH_2), 5.21 (ddd, *J* = 17.2, 1.6, 0.7 Hz, 1 H, CH_2), 5.66 (ddd, *J* = 17.2, 10.4, 8.6 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 28.1, 29.9, 46.4, 71.2, 84.2, 118.0, 133.7, 149.9, 152.9.

HRMS (CI-NH_3): *m/z* [M + NH_4]$^+$ calcd for $C_{12}H_{21}N_2O_4$: 257.1501; found: 257.1499.

***tert*-Butyl *cis*-1-(Hydroxymethyl)-2-vinylcyclopropylcarbamate (2c)**

To a soln of Boc-oxazolidinone **5** (710 mg, 2.97 mmol) in THF (15 mL) was added aq 2 M LiOH (15 mL, 29.7 mmol). The mixture was stirred at r.t. for 1 h and H_2O (15 mL) was added. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (cyclohexane–EtOAc, 1:1, vanillin development) to provide amino alcohol **2c** (633 mg, quantitative yield) as a white solid; mp 44–45 °C; R_f = 0.25 (cyclohexane–EtOAc, 1:1).

IR (neat): 3332, 2977, 2934, 1689, 1638, 1496, 1455, 1366, 1250, 1163 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (m, 1 H, CH_2), 1.17 (m, 1 H, CH_2), 1.40 (s, 9 H, CH_3), 1.74 (m, 1 H, CH), 3.47–3.66 (m, 2 H, CH_2), 3.74 (br s, 1 H, OH), 5.02–5.10 (m, 2 H, NH, CH_2), 5.15 (d, *J* = 17.2 Hz, 1 H, CH_2), 5.55 (ddd, *J* = 17.2, 10, 8.5 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 27.0, 28.4, 40.7, 69.9, 80.3, 116.4, 135.0, 157.7.

HRMS (CI-NH_3): *m/z* [M + H]$^+$ calcd for $C_{11}H_{20}NO_3$: 214.1443; found: 214.1445.

***cis*-1-(*tert*-Butoxycarbonylamino)-2-vinylcyclopropanecarboxylic Acid (3c)**

To a soln of alcohol **2c** (633 mg, 2.97 mmol) in CH_2Cl_2 (6 mL) under argon were successively added NMO (522 mg, 4.46 mmol), powdered 4Å molecular sieves (1.50 g), and TPAP (52 mg, 5 mol%). The mixture was stirred at r.t. until TLC showed complete consumption of the starting material (1 h). Filtration through a pad of silica gel (100% EtOAc) afforded the pure corresponding aldehyde (625 mg, quantitative yield) as a colorless oil which was used directly in the next step; R_f = 0.75 (cyclohexane–EtOAc, 1:1).

IR (neat): 3357, 3088, 2979, 2933, 1702, 1639, 1500, 1456, 1366, 1162 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 16:1 mixture of rotamers): δ = 1.38–1.48 (m, 10 H, CH_2, CH_3), 1.83 (br m, 1 H, CH_2), 2.33 (q, *J* = 8.3 Hz, 1 H, CH), 5.11 (m, 1 H, NH), 5.20 (m, 1 H, CH_2), 5.26 (d, *J* = 17.2 Hz, 1 H, CH_2), 5.55 (ddd, *J* = 17.2, 9.8, 8.0 Hz, 0.94 H, CH), 5.77 (m, 0.06 H, CH), 9.30–9.50 (br s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$, 16:1 mixture of rotamers): δ = 22.7 (0.94 C), 23.6 (0.06 C), 28.3 (3 × 0.94 C), 28.4 (3 × 0.06 C), 32.0 (0.94 C), 33.2 (0.06 C), 47.2, 80.6, 119.0, 132.8, 156.2, 200.0.

HRMS (CIN-NH_3): *m/z* [M$^-$] calcd for $C_{11}H_{17}NO_3$: 211.1208; found: 211.1205.

To a soln of the aldehyde in MeCN (10 mL) cooled to 0 °C was added successively a soln of NaH_2PO_4 (232 mg, 1.49 mmol) in H_2O (4 mL), 37% aq H_2O_2 soln (0.34 mL, 2.97 mmol), and a soln of $NaClO_2$ (403 mg, 4.46 mmol) in H_2O (6 mL). The mixture was allowed to warm up to r.t. and vigorously stirred at this temperature until TLC showed complete consumption of the starting material (1 h). Na_2SO_3 (300 mg, 2.38 mmol) was added to destroy the excess of $NaClO_2$ and the soln was stirred for an additional 1 h. After the addition of 1 M aq $KHSO_4$ (2 mL), the aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with sat. $NaHCO_3$ soln (2 × 10 mL). The combined basic aqueous extracts were acidified by addition of aq 1 M HCl and the resulting aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), the organic fraction was concentrated under reduced pressure, and the crude oil was filtered through a pad of silica gel (cyclohexane–EtOAc, 1:1, vanillin development) to afford pure acid (440 mg, 70% yield) as a colorless oil; R_f = 0.20 (cyclohexane–EtOAc, 1:1).

IR (neat): 3321, 3087, 2977, 2929, 2852, 2568, 1698, 1498, 1478, 1450, 1367, 1258, 1159 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 5:1 mixture of rotamers): δ = 1.24–1.30 (m, 1 H, CH_2), 1.43 (s, 9 × 0.83 H, CH_3), 1.44 (s, 9 × 0.17 H, CH_3), 1.80 (br s, 0.17 H, CH_2), 1.94 (br s, 0.83 H, CH_2), 2.42 (br q, *J* = 7.9 Hz, 1 H, CH), 4.99 (br s, 0.83 H, NH), 5.07–5.33 (m, 2 H, CH_2), 5.77 (m, 0.17 H, CH), 5.87 (br s, 0.17 H, NH), 8.95–9.61 (br s, 1 H, COOH).

^{13}C NMR (100 MHz, $CDCl_3$, 5:1 mixture of rotamers): δ = 23.4 (0.83 C), 23.6 (0.17 C), 28.3 (3 × 0.83 C), 28.4 (3 × 0.17 C), 32.0 (0.83 C), 32.3 (0.17 C), 39.4 (0.83 C), 39.8 (0.17 C), 80.5 (0.83 C), 81.2 (0.17 C), 118.6, 133.8, 156.3, 177.8.

HRMS (CI-NH_3): *m/z* [M + H]$^+$ calcd for $C_{11}H_{18}NO_4$: 228.1236; found: 228.1238.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0006th.

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References

(1) Reviews for ACC and derivatives: (a) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (c) Burgess, K.; Ho, K. K.; Moye-Sherman, D. *Synlett* **1994**, 575. (d) Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5.

(2) (a) Yang, S. F.; Hoffman, N. E. *Annu. Rev. Plant Physiol.* **1984**, *35*, 155. (b) Pirrung, M. C. *Acc. Chem. Res.* **1999**, *32*, 711.

(3) Nadler, V.; Kloog, Y.; Sokolovsky, M. *Eur. J. Pharmacol.* **1988**, *157*, 115.

(4) Trullas, R.; Folio, T.; Young, A.; Miller, R.; Boje, K.; Skolnick, P. *Eur. J. Pharmacol.* **1991**, *203*, 379.

(5) See for instance: (a) Crisma, M.; Bonora, G. M.; Toniolo, C.; Barone, V.; Benedetti, E.; Di Blasio, B.; Pavone, V.; Pedone, C.; Santini, A.; Fraternali, F.; Bavoso, A.; Lelj, F. *Int. J. Biol. Macromol.* **1989**, *11*, 345. (b) Evans, M. C.; Pradhan, A.; Venkatraman, S.; Ojala, W. H.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 1441. (c) Zanuy, D.; Ballano, G.; Jiménez, A. I.; Casanovas, J.; Haspel, N.; Cativiela, C.; Curcó, D.; Nussinov, R.; Alemán, C. *J. Chem. Inf. Model.* **2009**, *49*, 1623.

(6) See for instance: (a) Husbands, S.; Suckling, C. A.; Suckling, C. J. *Tetrahedron* **1994**, *50*, 9729. (b) Fink, C. A.; Qiao, Y.; Berry, C. J.; Sakane, Y.; Ghai, R. D.; Trapani, A. J. *J. Med. Chem.* **1995**, *38*, 5023. (c) Poupart, M.-A.; Cameron, D. R.; Chabot, C.; Ghiro, E.; Goudreau, N.; Goulet, S.; Poirier, M.; Tsatrizos, Y. S. *J. Org. Chem.* **2001**, *66*, 4743.

(7) See for instance: (a) Moye-Sherman, D.; Jin, S.; Ham, I.; Lim, D.; Scholtz, J. M.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9435. (b) Jiménez, A. I.; Marraud, M.; Cativiela, C. *Tetrahedron Lett.* **2003**, *44*, 3147.

(8) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P. R.; Bös, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Coudreau, N.; Kawai, S. H.; Kukolj, G.; Lagacé, L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinàs-Brunet, M. *Nature* **2003**, *426*, 186.

(9) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1922**, *121*, 1177.

(10) Some representative examples for the synthesis of ACC: (a) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270. (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Jimenez, A. I. *Tetrahedron* **1994**, *50*, 9157. (c) Adlington, R. M.; Aplin, R. T.; Baldwin, J. E.; Rawlings, B. J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086. (d) Allwein, S. P.; Secord, E. A.; Martins, A.; Mitten, J. V.; Nelson, T. D.; Kress, M. H.; Dolling, U. H. *Synlett* **2004**, 2489. (e) Hill, R. K.; Prakash, S. R.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Liu, H. W.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 795. (f) Wheeler, T. N.; Ray, J. A. *Synth. Commun.* **1988**, *18*, 141. (g) Salaün, J.; Marguerite, J.; Karkour, B. *J. Org. Chem.* **1990**, *55*, 4276. (h) Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 192. (i) Fadel, A. *Tetrahedron* **1991**, *47*, 6265.

(11) Kordes, M.; Winsel, H.; de Meijere, A. *Eur. J. Org. Chem.* **2000**, 3235.

(12) (a) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965. (b) Laroche, C.; Harakat, D.; Bertus, P.; Szymoniak, J. *Org. Biomol. Chem.* **2005**, *3*, 3482.

(13) For the synthesis of cyclopropylamines from amides or nitriles, see for amides: (a) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413. (b) de Meijere, A.; Kozhushkov, S. I.; Savchenko, A. I. *J. Organomet. Chem.* **2004**, *689*, 2033. For nitriles, see: (c) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792. (d) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2003**, *68*, 7133. (e) Bertus, P.; Szymoniak, J. *Synlett* **2007**, 1346.

(14) Respectively € 400 and € 300 for 1 g of ACC and Boc-ACC (Aldrich, 2010).

(15) For the titanium-mediated use of homoallylmagnesium bromide with nitriles, see: Bertus, P.; Menant, C.; Tanguy, C.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 777.

(16) The relative configuration of **4c** was established by NOESY 2D NMR analysis of the two diastereomers of **5**.

(17) The carboxylic acid **3c** was subjected to quantitative esterification using $TMSCH=N_2$ to provide the corresponding methyl ester which showed ^1H and ^{13}C NMR signals identical to those reported in the literature and proved the unique *cis* conformation: (a) For *cis*-methyl ester, see: Zeng, X.; Wei, X.; Farina, V.; Napolitano, E.; Xu, Y.; Zhang, L.; Haddad, N.; Yee, N. K.; Grinberg, N.; Shen, S.; Senanayaka, C. H. *J. Org. Chem.* **2006**, *71*, 8864. (b) For *trans*-methyl ester, see: Beaulieu, P. L.; Gillard, J.; Bailey, M. D.; Boucher, C.; Duceppe, J.-S.; Simoneau, B.; Wang, X.-J.; Zhang, L.; Grozinger, K.; Houpis, I.; Farina, V.; Heimroth, H.; Krueger, T.; Schnaubelt, J. *J. Org. Chem.* **2005**, *70*, 5869.

(18) (a) Jiménez, J. M.; Casas, R.; Ortuño, R. M. *Tetrahedron Lett.* **1994**, *35*, 5945. (b) Fliche, C.; Braun, J.; Le Goffic, F. *Synth. Commun.* **1994**, *24*, 2873.