30. Synthesis of Potential Inhibitors of Ethylene Biosynthesis: The Diastereoisomers of 1-Amino-2-bromocyclopropanecarboxylic Acid

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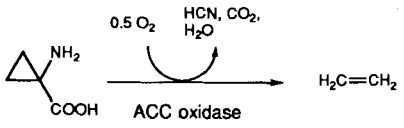
The preparation of the diastereoisomers of 1-amino-2-bromocyclopropanecarboxylic acid is described using the methyl (1*RS*,5*SR*)-2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate **5** as starting material. The key step is the oxidation of **9** with subsequent radical introduction of bromine according to the *Barton* procedure. The 2-bromocyclopropanecarboxylates *cis*-**11** and *trans*-**11** were obtained as diastereoisomer mixture in a ratio of 3:1. They were converted into *cis*- and *trans*-esters **12** and the acids **13**.

Introduction. – The phytohormone ethylene is an important regulator of plant growth and development [1] [2], promoting germination, fruit ripening, senescence of flowers, and abscission of leaves [2]. It also induces several defense-related reactions [3]. The biosynthesis of ethylene (**2**) has been studied extensively in the course of the last decade [4]. It proceeds by way of the intermediate 1-aminocyclopropanecarboxylic acid (ACC, **1**), a compound recognized as a constituent of plant fruit saps as early as 1957 [5] (*Scheme 1*). ACC is formed in two steps from L-methionin *via* adenosyl-*S*-methionine, and is further converted by ACC oxidase [4] into ethylene (**2**). The great importance of

Scheme 1



ethylene and its precursor ACC for plant biology has caused considerable interest in the development of ACC analogues which might help in analyses of mechanism of ACC oxidase. Such analogues also might induce inhibition of the ethylene production and, therefore, could act as regulators of plant growth and development. The chemical and enzymatic degradation of ACC has been studied using alkylated [6] and isotopically labeled derivatives [7]. Some chemical models have also been proposed, supporting the view the ACC is cleaved by a stepwise and homolytic mechanism in which the topology of the active site of ACC oxidase directs the stereochemical course of the process [8]

resulting *e.g.* in the preferential conversion of *cis*-substituted ethyl ACC derivatives, especially the (1*R*,2*S*)-derivative ((+)-allocoronamic acid) [9]. Various syntheses of ACC derivatives carrying alkyl (Me, Et, cyclopropyl ...) and Ph substituents at the cyclopropane ring were published [10]. Several of these ACC derivatives also occur naturally either in free form or peptide-bound [11] (*e.g.* coronamic acid as a substructure of the plant toxin coronatin). The interest for this unique class of conformationally constrained amino acids and their synthesis has grown in the past years and is still growing [12].

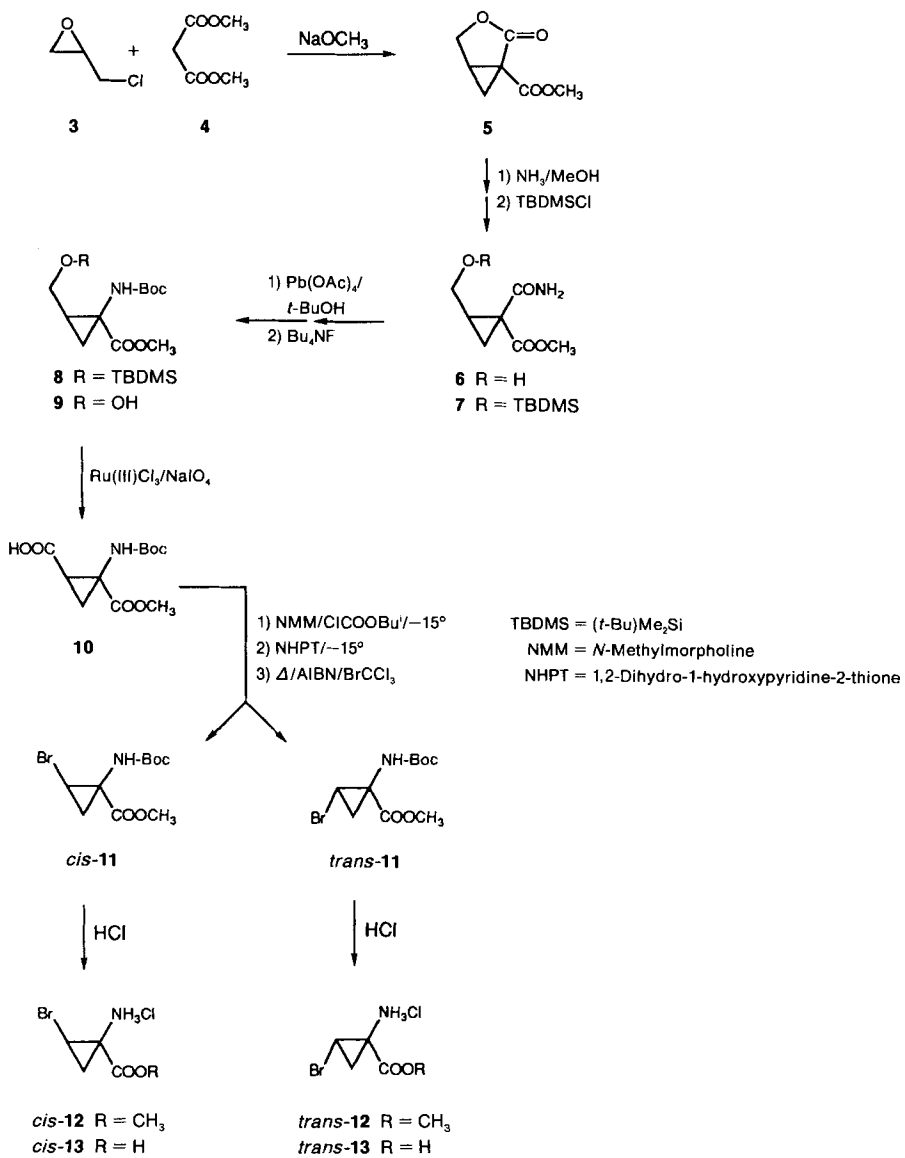
Concept and Synthesis of a New Potential Inhibitor. – To gain deeper insight into the biosynthesis of ethylene and its regulation, we became interested in the synthesis of specifically monochlorinated and monobrominated ACC derivatives as potential substrates and/or inhibitors of ACC oxidase. This type of compounds was chosen for the following reasons: *1*) The halogen atom introduces a further polar reactive group into the ACC moiety, providing a potential substrate/active-site interaction. To the best of our knowledge, these ACC derivatives never have been tested before on their activity of the ACC oxidase. *2*) A comparison of the *van der Waals* radii of the halogen atoms (Cl: 180 pm and Br: 195 pm) and the Me group (200 pm) shows an interesting steric relationship. Moreover, Me-substituted ACC derivatives belong to the best competitive inhibitors of the ACC oxidase [13]. *3*) The halogen–C, in particular, the Br–C bonding is sensitive to radical processes. This fact was expected to lead to new insights into the enzymatic mechanism of the ACC degradation *in vivo*.

Although considerable information concerning the synthesis of alkylated and isotopically labeled ACC derivatives has been accumulated, only one derivative of a mono-halogenated ACC derivative (1-amino-2-chlorocyclopropanecarboxlic acid) is known [14]. In this paper, we describe the principles of a new and general approach towards the synthesis of monohalogenated (Cl, Br, I) ACC derivatives: the idea is based on the introduction of the halogen atom into the cyclopropyl-amino acid (as a formal 'methanologue' of aspartic acid [11]) according to *Barton*'s procedure *via* radicals [15] starting from the suitably protected 1-amino-2-carboxycyclopropanecarboxylic acid. It was first applied to the preparation of *cis*- and *trans*-1-amino-2-bromocyclopropanecarboxylic acids.

Results and Discussion. – The synthesis of cyclopropyl-amino acids is based on the classical route using a *Hofmann* rearrangement of a suitably protected cyclopropane-1,1-dicarboxylate [16]. As reported earlier, the carbamoyl ester **6** was readily synthesized by condensation of the epichlorohydrine (**3**) and dimethyl malonate (**4**) with freshly generated NaOMe as base and subsequent aminolysis of the bicyclic lactone intermediate **5** [17] (*Scheme 2*).

The free OH group of **5** was first protected by treatment with (*t*-Bu)Me_2SiCl and imidazole (yield: 81%) and then subjected to the *Hofmann* rearrangement with $Pb(OAc)_4$ in *t*-BuOH as the oxidizing agent [18]. Removal of the (*t*-Bu)Me_2Si group from the resulting Boc-protected amino acid **7** was achieved with Bu_4NF following a standard procedure yielding the alcohol **9** (85% yield). The next step consisted in the mild oxidation under neutral conditions of the primary alcohol in presence of cyclopropane ring and the protected amino-acid functions. Whereas current oxidation methods, *e.g.* pyridinium dichromate in DMF [19], gave only very small yields of product **10**, the RuO_4-catalyzed

Scheme 2



oxidation according to *Sharpless* and coworkers [20] yielded the desired carboxylic acid **10** (60% yield).

For the subsequent introduction of halogen, the radical decarboxylation method of amino acids was followed by capturing the cyclopropyl radical with bromine as reported earlier by *Barton et al.* [15]. The free carboxy function of the protected amino acid **10** was converted at −15° to the corresponding thiohydroxamate. The subsequent radical chain

reaction was induced in inert atmosphere by two different methods in presence of CCl_3Br as the radical trap: *1*) irradiation of the thiohydroxamate with a tungsten lamp (100 W) or an UV lamp led to a diastereoisomer mixture of *cis*-**11** and *trans*-**11** in less than 10% yield. Moreover, NMR analysis of the other ninhydrine-active spots of TLC pointed to ring-opened olefines as major products. *2*) Thermal radical decomposition at 90° of the 'activated ester' in the presence of 10 mol-% α,α'-azoisobutyronitrile (AIBN) was more successful. A mixture of both diastereoisomers *cis*-**11** and *trans*-**11** could be achieved in 52% yield. The resulting mixture of the isomers was subsequently separated and purified chromatographically on silica gel. The addition of the Br-atom to the cyclopropyl radical gave a 3:1 mixture *cis*-**11**/*trans*-**11**. This fact is surprising, because a favored addition of the bulky bromine radical would have been expected to occur on the less hindered side of the methyl-ester group of the cyclopropane ring. (Preliminary experiments of the iodination with CHI_3 as the radical trap under thermal decomposition of the thiohydroxamate gave a 2.5:1 diastereoisomer mixture of the *cis*- and *trans*-isomers.) The diastereoisomer ratio *cis*-**11**/*trans*-**11** was determined by GC and ^{1}H-NMR analysis of the integrals of the MeO *singlets* of *cis*-**11** and *trans*-**11** at 3.73 ppm and 3.79 ppm, respectively. The chemical shifts in the ^{13}C-NMR of the carbonyl C-atom of the methyl ester provided the relative configuration of both products synthesized. ^{13}C-NMR Analysis based on the known γ-effect [21] which could be easily applied to the rigid cyclopropane system demonstrated that *trans*-substitution of the Br-atom has led to a *syn*-conformation and consequently to a high-field shift of the MeO C-atom of *trans*-**11** (169.2 ppm of *trans*-**11** *vs.* 171.0 ppm of *cis*-**11**). For *cis*-**11**, the X-ray diffraction (*Fig.*) clearly confirmed the results of the NMR analysis[1]).

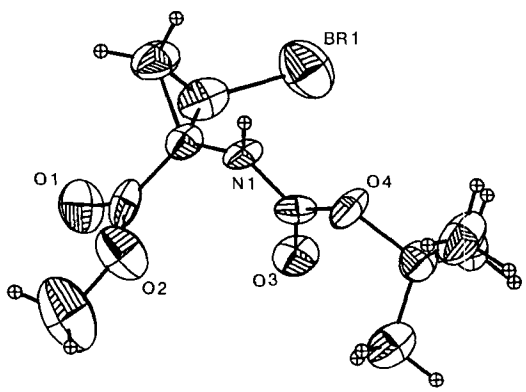


Figure. *X-Ray structure of* cis-**11**

Removal of the protecting groups was easily achieved by hydrolysis with diluted HCl leading to the hydrochlorides of the specifically monobrominated ACC derivatives of *cis*-**12** and *trans*-**12**. The Boc-group could selectively be cleaved in presence of the methyl ester with 6N HCl at room temperature yielding *cis*-**13** and *trans*-**13**, respectively.

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[1]) We thank Prof. *M. Zehnder* and *M. Neuburger*, Institut für Anorganische Chemie der Universität Basel, Spitalstrasse 51, CH–4056 Basel, for having resolved the X-ray structure of *cis*-**11**.

As was shown by preliminary experiments, the I- or Cl-analogues are obtained as well. Moreover, it is possible to prepare isomers of defined absolute configuration of the ACC derivatives by the method described starting from optical by pure epichlorohydrine according to [17].

Work on the biological activities of the ACC analogues mentioned here is in progress and will be published elsewhere.

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Experimental Part

General. All chemicals were purchased from *Fluka AG* or *Merck GmbH* in *purum* or *puriss. p.a.* quality. Reactions under anh. conditions were performed under N_2 or Ar if not stated otherwise. Solvents used in reactions were distilled and dried whenever necessary. THF was passed through a basic Al_2O_3 column and freshly distilled over K/Na alloy. Solvents used for column chromatography (industrial grade) were distilled once. The org. extracts were dried over Na_2SO_4 and the solvents removed on a rotary evaporator ($\leq 40°$/≥ 14 Torr) and dried under high vacuum (≥ 0.1 Torr). Reagents were purified as follows: *t*-BuOH, Et_3N, and *N*-methylmorpholine were distilled from CaH_2. $Pb(OAc)_4$ was washed with dry Et_2O under dry Ar and dried at r.t./0.3 Torr for 3 d prior to use. TLC: precoated glass plates (0.25 mm silica gel *60 F_{254}, Merck*), detection by UV light and/or spraying with a soln. of aq. 2% $KMnO_4$, 4% $NaHCO_3$ soln., respectively, a soln. of 3% ninhydrine in PrOH for amino acids followed by heating. Column chromatography (CC): *Merck* silica gel *60*, 63–200 μm. Flash chromatography (FC): overpressure *ca.* 0.3 bar; *Merck* silica gel *60*, 40–63 μm. Anal. GC: an *HP 5890 A* gas chromatograph equipped with a flame ionization detector and a 'fused-silica'-capillary (25 m × 0.2 mm) coated with a 0.33-μm 5% cross-linked (phenylmethyl)silicon layer. HPLC: *Waters delta prep. 3000* with UV detector (215 nm); column: *Knauer* 3.2 × 50 cm, silica gel *60* (10 μm); Et_2O/pentane 3:7 (40 ml/min). M.p.: on a *Kofler* block and are corrected. IR [cm^{-1}]: *Perkin-Elmer-781* spectrometer. NMR: *Varian Gemini-300* spectrometer (^1H: 300 MHz; ^{13}C: 75 MHz; δ in ppm rel. to internal TMS ($= 0$ ppm)) or sodium 3-(trimethylsilyl)propionat (^1H: 0.00 ppm; ^{13}C: 1.70 ppm); digital resolution for coupling constants 0.25 Hz/point; MS (*m*/*z* (%)): *VG-70-250* spectrometer.

*Methyl (1*RS,*2*RS*)-1-Carbamoyl-2-{[(*tert*-butyl)dimethylsilyloxy]methyl}cyclopropanecarboxylate* (**7**). To a soln. of 200 mg (1.156 mmol) of *methyl (1*RS,*2*RS*)-1-carbamoyl-2-(hydroxymethyl)cyclopropanecarboxylate* (**6**) in 4 ml of dry DMF, 697 mg (4.624 mmol) of (*t*-Bu)Me_2SiCl, 173 mg (2.312 mmol) of imidazole, and a few pellets of molecular sieve (4 Å) were added, and the mixture was stirred at r.t. for 15 h. After filtration, the soln. was diluted with Et_2O (20 ml) and crushed ice (25 g) was added. Then, the org. layer was washed successively twice with sat. NH_4Cl soln. and NaCl soln. The combined org. phases were dried and evaporated. The product was purified by CC (Et_2O) to afford 260 mg (81%) of **7** as pure colorless crystals. M.p. 82–84°. TLC: R_f 0.42 (Et_2O/pentane 1:1). IR (KBr): 3480, 3130 (NH); 2930, 2830, 1695 (CO); 1655 (CO); 1570, 1385, 825. ^1H-NMR (300 MHz, $CDCl_3$): 8.05 (br. *s*, NH); 5.65 (br. *s*, NH); 3.93 (*dd*, $J = 5.3, 11.3$, H–C(1′)); 3.71 (*s*, MeO); 3.64 (*dd*, $J = 8.5, 11.3$, H–C(1′)); 2.11 (*m*, H–C(2)); 1.74 (*m*, H–C(3)); 0.88 (*s*, *t*-Bu); 0.05, 0.04 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.65 (CO); 168.58 (CO); 60.98 (C(1′)); 52.43 (MeO); 34.98 (C(2)); 31.98 (C(1)); 25.84 (Me_3C); 19.29 (C(3)); 18.24 (Me_3C); −5.37, −5.41 (Me_2Si). CI-MS (NH_3): 288 (100, $[M + 1]^+$), 230 (14.8), 186 (3.8), 156 (74.3).

*Methyl (1*RS,*2*SR*)-2-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-1-{N-[(*tert*-butoxy)carbonyl]amino}cyclopropanecarboxylate* (**8**). To a soln. of 1.5 g (5.22 mmol) **7** in abs. *t*-BuOH (20 ml) at 70° under dry N_2, 4.63 g (10.44 mmol, 2 equiv.) $Pb(OAc)_4$ were added at once and the red brown mixture heated to reflux for another 90 min and cooled to r.t. Et_2O (300 ml) and $NaHCO_3$ (2.50 g) were added, the mixture was evaporated, and the residue taken up in Et_2O (100 ml). The brown suspension was filtered through 1 cm of silica gel in a *Büchner* funnel with another 200 ml of Et_2O. The filtrate was evaporated to yield a yellow oil which was purified by FC (Et_2O/pentane, (1.5:8.5)) to afford 550 mg (62%) of **8** as a yellow oil. TLC: R_f 0.42 (Et_2O/pentane 1.5:8.5). IR (film): 3400, 3330 (NH); 2925, 2900, 2860, 2830, 1710 (CO); 1480, 1350, 1240, 1155, 1080, 830, 770. ^1H-NMR (300 MHz, $CDCl_3$): 5.30 (br. *s*, NH); 3.95 (*dd*, $J = 5.3, 11.4$, H–C(1′)); 3.67 (*s*, MeO); 3.45 (br. *t*, $J = 10.1$, H–C(1′)); 1.89 (*m*, H–C(2)); 1.73 (br. *m*, H–C(3)); 1.43 (*s*, Me_3CO); 1.15 (br. *m*, H–C(3)); 0.87 (*s*, 9H, Me_3CSi); 0.04 and 0.03 (2*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.12 (CO); 156.32 (CO); 79.73 (Me_3CO); 62.84 (C(1′)); 52.32 (MeO); 37.83 (C(1)); 29.56 (C(2)); 28.22 (Me_3CO); 25.81 (Me_3CSi); 21.91 (Me_3CSi); 18.16 (C(3)); 5.37 (Me_2Si). CI-MS (NH_3): 360 (7.8, $[M + 1]^+$), 304 (76.9), 286 (25.5), 260 (100), 246 (6.0), 228 (5.3), 202 (20.3), 172 (6.0), 142 (6.2), 106 (5.3).

Methyl (1RS,2SR)-1-{N-[(tert-Butoxy)carbonyl]amino}-2-(hydroxymethyl)cyclopropanecarboxylate (**9**). To a soln. of 930 mg (5.22 mmol) of **8** dissolved in 50 ml of THF, 2.28 ml (15.66 mmol) of $Bu_4NF \cdot 3H_2O$ were added portionwise, and the mixture was stirred at r.t. for 10 h. Then, 50 ml of a sat. $NaHCO_3$ soln. was added and stirred for further 10 min. The org. phase was separated, washed with H_2O and brine, dried, and evaporated. The crude product was purified with FC (Et_2O/pentane (1:1)) to afford 550 mg (85%) of a slight yellow oil which solidified partially upon standing. M.p. 70–71°. TLC: R_f 0.20 (Et_2O/pentane 1:1). IR (film): 3600–3100 (NH, OH); 2980, 2930, 2910, 2880, 1715 (CO); 1680 (CO); 1300, 1160, 1020. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.28 (br. *s*, NH); 3.94 (br. *d*, J = 9.5, H–C(1′)); 3.77 (br. *s*, OH); 3.69 (*s*, MeO); 3.18 (br. *t*, J = 11.3, H–C(1′)); 2.24 (*m*, H–C(2)); 1.54 (*dd*, J = 5.0, 9.8, H–C(3)); 1.45 (*s*, *t*-Bu); 0.79 (*dd*, 5.0, 7.5, H–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.57 (CO); 158.04 (CO); 81.17 (Me_3C); 61.38 (C(1′)); 52.57 (MeO); 32.38 (C(1)); 31.09 (C(2)); 28.22 (Me_3C); 19.24 (C(3)). CI-MS (NH_3): 246 (2.5, $[M + 1]^+$), 207 (6.9), 190 (7.5), 189 (5.3), 172 (19.1), 146 (100), 128 (20.3), 114 (2.3), 74 (9.4).

Methyl (1RS,2SR)-2-{N-[(tert-Butoxy)carbonyl]amino}-2-(methoxycarbonyl)cyclopropanecarboxylic Acid (**10**). To a soln. of 266 mg (1.086 mmol) of **9** in 2 ml of CCl_4, 2 ml of MeCN and 3 ml of H_2O, 698 mg (3.258 mmol) of $NaIO_4$ and then 5.4 mg (2.2 mol-%) of $Ru^{III}Cl_3 \cdot H_2O$ were added, and the entire biphasic soln. was stirred vigorously for 3 h at r.t. CH_2Cl_2 (15 ml) was added, and the phases were separated. The upper aq. phase was extracted with CH_2Cl_2 (3 × 15 ml). The combined org. extracts were dried and evaporated to dryness. The resulting residue was diluted with 20 ml of Et_2O, filtered through a *Celite* pad, and evaporated. The residue was dissolved in 15 ml of $CHCl_2$ and extracted with sat. $NaHCO_3$ (3 × 10 ml). The pH of the aq. phase was adjusted to pH 4.0 with 2N HCl/sat. NaCl. The soln. was extracted with CH_2Cl_2 (5 × 15 ml), the pH being adjusted after every extraction. The combined org. phases were dried and evaporated to afford 200 mg of a pale yellow solid which was crystallized from CH_2Cl_2/pentane: 174 mg (62%) of **10** as crystals. M.p. 112–114°. TLC: R_f 0.36 (tailing) (Et_2O). IR (KBr): 3700–2380 (OH); 3300 (NH); 1695 (CO); 1650 (CO); 1500, 1260, 1160, 1070, 720. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.6 (br. *s*, COOH); 6.7 (br. *s*, NH); 3.69 (*s*, MeO); 2.51 (*m*, H–C(1)); 1.90 (*dd*, J = 5.0, 9.0, H–C(3)); 1.65 (*m*, H–C(3)); 1.43 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.11 (CO); 171.10 (CO); 158.12 (NHCO); 82.02 (Me_3C); 52.90 (MeO); 40.56 (C(1)); 29.00 (C(2)); 28.11 (Me_3C); 22.84 (C(3)). CI-MS (NH_3): 277 (2.1, $[M + NH_4]^+$), 260 (7.1, $[M + 1]^+$), 221 (15.5), 204 (15.0), 160 (100), 144 (25.1), 142 (19.1), 114 (5.3).

*Methyl (1RS,2SR)- and (1RS,2RS)-2-Bromo-1-{N-[(tert-butoxy)carbonyl]amino}cyclopropanecarboxylate (trans-***11** and *cis-***11**, resp.). To a soln. of 156 mg (0.602 mmol) **10** in dry THF (10 ml), under Ar at −15°, 1 equiv. each of *N*-methylmorpholine (NMM) and isobutyl chloroformate were dropwise added, and stirred for 10 min. A soln. of 1.2 equiv. of 1,2-dihydro-1-hydroxypyridine-2-thione (NHPT) and Et_3N was prepared in appropriate amount of dry THF and was added to the mixture in the dark. The stirring was continued at −15° for further 2.5 h in the dark (the required formation of the *Barton* ester can be followed as yellow spot on TLC (AcOEt/pentane 1:1)). After filtration of precipitated NMM hydrochloride, THF was removed *in vacuo* at r.t. with protection from light. The oily yellow residue was taken up in a soln. of 10 mg (0.1 equiv.) α,α′-azoisobutyronitrile (AIBN) in $CBrCl_3$, and added dropwise over a period of 30 min to 1 ml of $CBrCl_3$ at 90° and heated for another 30 min. After cooling, the solvent was removed *in vacuo* and the product purified by FC (Et_2O/pentane 3:7) to afford 93 mg (52%) of a mixture of crystals of both diastereoisomers in a *cis*/*trans* ratio of 3:1, which was further separated on silica gel by prep. HPLC (Et_2O/pentane 3:7).

Data of cis-**11**. TLC: R_f 0.51 (Et_2O/pentane 1:1). M.p. 89–90°. IR (CCl_4): 3410 (NH); 2960, 2920, 1710 (CO); 1470, 1290, 1350, 1230, 1150, 1060, 1040, 910. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.29 (br. *s*, NH); 3.73 (*s*, MeO); 3.60 (*dd*, J = 6.3, 8.6, H–C(2)); 2.26 (*t*, J = 7.0, H–C(3)); 1.55 (br. *t*, H–C(3)); 1.47 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.96 (CO); 155.62 (NHCO); 80.55 (Me_3C); 52.90 (MeO); 37.22 (C(1)); 28.24 (Me_3C); 27.26 (C(2)); 26.45 (C(3)). FAB-MS (NBA): 296 (11.1, $[M + 1]^+$), 294 (11.9, $[M + 1]^+$), 240 (49.70), 238 (51.6), 196 (20.7), 194 (22.5), 114 (25.3), 57 (100), 41 (15.21). FAB-MS (NBA + KCl): 334 (22.0, $[M + K]^+$), 332 (21.4, $[M + K]^+$), 296 (11.2, $[M + 1]^+$), 294 (11.7, $[M + 1]^+$), 240 (47.0), 238 (46.7), 196 (22.1), 194 (22.1), 114 (24.0), 57 (100), 41 (26.3).

Data of trans-**11**. M.p. 88–89°. TLC: R_f 0.50 (Et_2O/pentane 1:1). IR (CCl_4): 3400 (NH); 2940, 2920, 1710 (CO); 1460, 1230, 1040, 890. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.20 (br. *s*, NH); 3.79 (*s*, MeO); 3.32 (*dd*, J = 6.8, 8.6, H–C(2)); 2.11 (*t*, J = 6.7, H–C(3)); 1.79 (br. *t*, H–C(3)); 1.45 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.23 (CO); 155.26 (NHCO); 80.83 (Me_3C); 52.68 (MeO); 40.26 (C(1)); 28.23 (Me_3C); 26.01 (C(2)); 24.69 (C(3)).

*(1RS,2RS)-1-Amino-2-bromocyclopropanecarboxylic Acid Hydrochloride (cis-***13**). A soln. of 14 mg (0.048 mmol) of *cis-***11** in 4 ml of 6N HCl was heated to 80° for 6 h, and the solvent removed *in vacuo* to afford a slight yellow solid which was crystallized from MeOH/AcOEt: 7 mg (68%) of *cis-***13**. M.p. > 120° (slow dec.). IR (KBr): 3350 (br., NH); 3500–2500 (br., OH); 1710 (CO); 1380, 1180. ^{1}H-NMR (300 MHz, D_2O): 3.92 (*dd*, J = 6.5, 8.7, H–C(2)); 2.33 (*t*, J = 8.6, H–C(3)); 1.89 (*dd*, J = 6.5, 8.4, H–C(3)). ^{13}C-NMR (75 MHz, D_2O): 174.81 (CO); 41.93

(C(1)); 26.69, 26.54 (C(2)/C(3)). FAB-MS (glycerine/H_2O): 182 (62.0, $[M + 1]^+$), 180 (63.8, $[M + 1]^+$), 102 (64.2), 75 (45.4), 57 (91.0), 45 (82.8).

(1RS,2SR)-1-Amino-2-bromocyclopropanecarboxylic Acid Hydrochloride (*trans*-**13**). A soln. of 12 mg (0.041 mmol) of *trans*-**11** in 4 ml of 6N HCl was heated to 80° for 6 h, and the solvent removed *in vacuo* to afford a slight yellow solid which was crystallized from MeOH/AcOEt: 5.5 mg (75%) of *trans*-**13**. M.p. > 120° (slow dec.). IR (KBr): 3350 (br., NH); 3500–2500 (br., OH); 1710 (CO); 1370, 1160. ^{1}H-NMR (300 MHz, D_2O): 3.67 (*t*, $J = 8.0$, H–C(2)); 1.98 (*d*, $J = 8.0$, H–C(3)). ^{13}C-NMR (75 MHz, D_2O): 174.11 (CO); 44.23 (C(1)); 25.00; 24.74 (C(2)/C(3)).

X-Ray Structure Analysis of cis-**11**. The X-ray structure of *cis*-**11** is shown in the *Figure*. Crystal data and parameters of the data collection are compiled in the *Table*. Unit cells parameters were determined by accurate centering of 25 strong independent reflections by the least-square method. Reflection intensities were collected at r.t. on a four-circle diffractometer *Enraf Nonius CAD 4* equipped with a graphite monochromated MoK_α radiation. The structure was solved by direct methods using SHELXS-86 [22]. Anisotropic least-squares refinement was carried out on all non-H-atoms using the program CRYSTALS [23]. Position of the H-atoms were calculated. Scattering factors were taken from International Tables of Crystallography, Vol. IV. Fractional coordinates are deposited with the Cambridge *Crystallographic Data Centre*.

Table. *Crystal Data and Parameters of Data Collection for* cis-**11**

Molecular formula	$C_{10}H_{16}NO_4Br$	Crystal dimensions [mm]	0.16 × 0.18 × 0.50
Crystal system	tricline	Temp. [K]	298
Space group	$P\bar{1}$	Θ_{max} [°]	24.66
a [Å]	5.129(1)	Radiation	MoK_α, $\lambda = 0.71069$ Å
b [Å]	10.292(2)	Scan type	$\omega/2\Theta$
c [Å]	13.679(1)	No. of independent refl.	2520
α [°]	74.040(11)	No. of refl. in refinement	1036
β [°]	79.071(10)	No. of variables	145
γ [°]	77.443(15)	Final R	6.64
V [Å^3]	671.01(19)	Final R_w	6.07
Z	2	Weighting scheme	weight·$[1 - (\Delta F/6\sigma F)^2]^2$

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