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Asymmetric Synthesis via Heterocyclic Intermediates, XLVII[1]

Asymmetric Synthesis of (+)-(1*R*,2*S*)-*allo*-Coronamic Acid[1]

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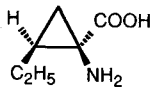
allo-Coronamic acid (**1**) was synthesized in five steps enantiomerically and diastereomerically virtually pure by starting from the bislactim ethers of cyclo(-L-Val-Gly-) (**3a**) or cyclo(-L-*tert*-Leu-Gly-) (**3b**) in an overall yield of 31%. The key step of this synthesis is the intramolecular alkylation of the lithium azaenolate derived from the allylic chloride **4**.

During the last several years 1-amino-1-cyclopropanecarboxylic acid (AAC) and its derivatives have attracted special attention due to their biological activity[2]. The outstanding reactivity of the cyclopropyl group seems to be responsible for the selective inhibition of enzymes by many cyclopropyl amino acids. The best known cyclopropyl amino acid is the achiral 1-amino-1-cyclopropanecarboxylic acid itself, the biosynthetic precursor of ethylene, which is responsible for the ripening of fruits[3]. Another cyclopropyl amino acid – *allo*-coronamic acid (**1**) – is converted into 1-butene by plant tissues and promises the control of enzymatic processes for plant growth and fruit ripening[4]. The isomeric coronamic acid (**2**) is a constituent of coronatin which, as a vivotoxin, induces the chlorosis of Italian rye-grass leaves[5].



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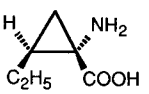

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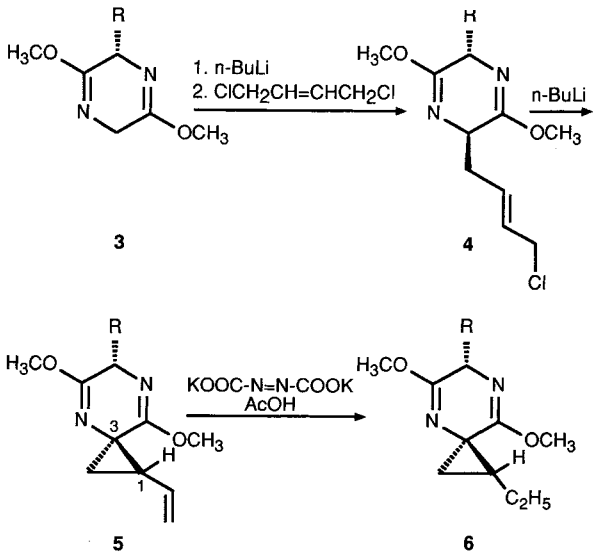
So far, most of the *allo*-coronamic acid syntheses have been the result of a resolution of racemic mixtures[4,6]. In 1987, Marco reported a seven step synthesis of (1*S*,2*R*)-*allo*-coronamic acid with an enantiomeric excess of 30% and an overall yield of <1%[7]. In 1991, a French group reported a more simple four-step synthesis of **1** employing a diastereoselective cyclopropanation to a chiral dehydro amino acid derivative[8]. Unfortunately, the last step of this synthesis yielded **1** in only 25%; therefore, the overall yield dropped down to 7% with an enantiomeric excess of 40%.

The successful synthesis of (+)-*allo*-coronamic acid (**1**) described herein is based on the bislactim ether method[9] and the asymmetric cyclopropanation of carbonyl derivatives, which was found by Quinkert et al. and successfully employed towards the synthesis of enantiomerically pure (3*S*)-2-methyl-3-vinyl-1-cyclopentanone[10].

The bislactim ethers of cyclo(-L-Val-Gly-) (**3a**) and of cyclo(-L-*tert*-Leu-Gly-) (**3b**) were lithiated with *n*-butyllithium and alkylated with *trans*-1,4-dichloro-2-butene to the allylic chlorides **4a** and **b**. In order to avoid a second alkylation



3 **4** **5** **6**

		yield (%) of			diastereomeric ratio of **5**			
3-6	R	**4**	**5**	**6**	(1R,3R)	(1R,3S)	(1S,3S)	(1S,3R)
a	i-Pr	82	84 (53)[a]	99	67	23	6	4
b	t-Bu	84	82 (62)[a]	99	83	9	5	3

[a] (1R,3R)-**5** after chromatographic separation of diastereomers.

of the lithium enolates of **3** with the allylic chlorides **4**, a large excess of *trans*-1,4-dichloro-2-butene (10 equivalents) was used. The allylic chlorides **4a** and **b** were obtained in 82% and 84% yield with diastereomeric excesses of 79% and 83%. Lithiation of **4a** and **b** with *n*-butyllithium and subsequent intramolecular alkylation afforded the vinyl-cyclopropyl derivatives **5a** and **b** in 84% and 82% yield. **5a** was obtained as a 67:23:6:4 mixture of diastereomeres, whereas **5b** was obtained as a 83:9:5:3 diastereomeric mixture. After column chromatography (1′*R*,2*R*,5*S*)-**5a** and (1′*R*,2′*R*,5*S*)-**5b** were isolated in 53% and 62% yield enan-

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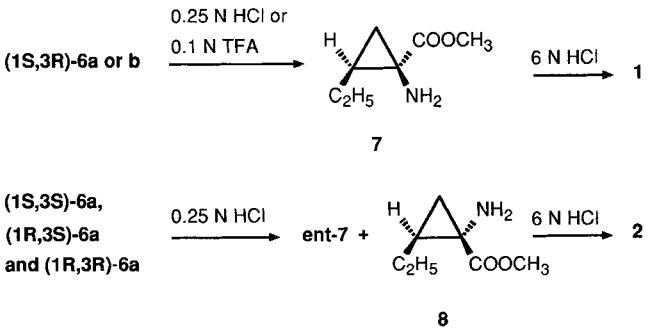
tiomerically and diastereomerically pure. The mechanism of a related cyclization as well as its stereochemical outcome have both been discussed in detail by Quinkert et al.[10b].

Our next concern was the reduction of the vinyl group in the presence of the cyclopropane unit. Since substituted cyclopropanes can be easily cleaved under the conditions of catalytic hydrogenation[11] diimide was tried as a reducing agent[12]. In a first attempt **5a** was treated with hydrazine/O_2 and catalytic or stoichiometric amounts of selenium as a diimide source[13]. In no case **6a** could be isolated. In a second experiment an excess of diimide (2.5 equivalents) was generated from potassium azadicarboxylate[14] and acetic acid in the presence of the olefines **5a** or **b**[15]. The reduction was completed within 1 h; the saturated cyclopropane derivatives **6a** and **b** were obtained in an almost quantitative yield analytically pure.



Acidic hydrolysis of **6a** (2 equivalents of 0.25 N HCl, room temp.) yielded methyl L-valinate (83%) – the chiral auxiliary in this synthesis – and *allo*-coronamic acid methyl ester (**7**) (77%), which were separated by flash chromatography. Upon hydrolysis of **6b** under identical conditions, only methyl L-*tert*-leucinate (30%) and a mixture of dipeptide esters were obtained. Once again the yield could be improved by using trifluoroacetic acid for the hydrolysis[16]. In this case **7** was obtained in 84% yield besides methyl L-*tert*-leucinate (79%).

In order to confirm the structure of (1*R*,2*S*)-**7**, a 70:80:12 mixture of the minor diastereomers of **6a** which was obtained by chromatographic purification of (1′*R*,2′*R*,5*S*)-**5a** and subsequent hydrogenation was hydrolyzed. (1*S*,2*R*)-*allo*-coronamic acid methyl ester (*ent*-**7**) (10%), (1*S*,2*S*)-coronamic acid methyl ester (**8**) (43%) and methyl L-valinate (67%) were obtained, which could be separated by flash chromatography.

Acidic hydrolysis of the amino acid methyl esters **7** and **8** with 6 N HCl afforded enantiomerically and diastereomerically virtually pure (1*R*,2*S*)-*allo*-coronamic acid (**1**) with an optical rotation of $[\alpha]_D^{20} = +55.9$ ($c = 0.56$, H_2O) as well as enantiomerically enriched (68% ee) (1*S*,2*S*)-coronamic acid (**2**) with an optical rotation of $[\alpha]_D^{20} = +30.8$ ($c = 0.51$, H_2O). The optical rotation of **1** is in agreement with the values reported previously[6a,f,8].

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Experimental

The bislactim ethers of cyclo(-L-Val-Gly-) and cyclo(-L-*tert*-Leu-Gly-) were prepared as described previously[17,18]. – IR spectra: Perkin-Elmer 298 spectrometer. – NMR spectra: Varian FT 80, XL 200 or a VXR 200 spectrometer for ^1H and ^{13}C NMR. Chemical shifts are given as δ values and are referenced to internal tetramethylsilane or dioxane. – Mass spectra: Varian MAT 731 or 311 A spectrometers. – Optical rotations: Perkin-Elmer Mod. 141 polarimeter. – TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (30–60 μm) from Baker was used for flash chromatography. – Combustion analyses were carried out by the microanalytical laboratory of the University of Göttingen. – All reactions were carried out under nitrogen or argon except those involving hydrolysis. – All reagents were purified and dried if necessary prior to use.

Alkylation of the Bislactim Ethers **3** *with trans-1,4-Dichloro-2-butene. – Bislactim Ethers* **4**. – *General Procedure:* A solution of *n*-butyllithium in hexane (1.6 N, 6.9 ml, 11 mmol) was added at −70 °C to a stirred solution of the bislactim ether **3** (10 mmol) in THF (50 ml). After 15 min *trans*-1,4-dichloro-2-butene (12.5 g, 0.1 mol) was added within 10 min. After stirring was continued for 4 h a saturated NH_4Cl solution (25 ml) was added and the solution was allowed to warm up to room temp. within 10 min. The organic volatile components were removed in vacuo (40 °C, 15 Torr) and the residue was dissolved in diethyl ether (100 ml) and H_2O (25 ml). The layers were separated, the organic layer was extracted four times with 25-ml portions of H_2O and dried with $MgSO_4$. After removal of the solvent in vacuo the residue was purified by bulb-to-bulb distillation.

(2S,5R)-5-[(E)-4-Chloro-2-butenyl]-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**4a**): 1.84 g of **3a** was used and 2.24 g (82%) of **4a** was obtained as a pale yellow oil. – Ratio of diastereomers 89:11, determined by ^{13}C-NMR spectroscopy. – B.p. 120–125 °C/0.01 Torr. – IR (film): $\tilde{\nu} = 1685\ cm^{-1}$ (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.67 [d, J = 7 Hz; 3H, $CH(CH_3)_2$], 1.04 [d, J = 7 Hz, 3H, $CH(CH_3)_2$], 2.27 [dsp, J = 3 and 7 Hz; 1H, $CH(CH_3)_2$], 2.46–2.70 (m; 2H, $CHCH_2$), 3.67 and 3.68 (2 s; 6H, OCH_3), 3.80–4.17 (m; 4H, CH_2Cl, 2-H and 5-H), 5.55–5.75 (m; 2H, CH=CH). – ^{13}C NMR (20 MHz, $CDCl_3$): (2*S*,5*R*)-**4a**: δ = 16.45 (CH_3), 18.92 (CH_3), 31.56 [$CH(CH_3)_2$], 36.70 ($CHCH_2$), 44.89 (CH_2Cl), 52.23 and 52.32 (OCH_3), 55.05 ($CHCH_2$), 60.68 [CH-$CH(CH_3)_2$], 129.14 and 130.81 (C=C), 162.76 and 163.92 (C=N). – (2*S*,5*S*)-**4a**: δ = 15.94 (CH_3), 18.92 (CH_3), 31.80 [$CH(CH_3)_2$], 36.45 ($CHCH_2$), 48.76 (CH_2Cl), 52.72 and 52.95 (OCH_3), 55.87 ($CHCH_2$), 60.53 [CH-$CH(CH_3)_2$], 129.29 and 129.46 (C=C), 162.59 (C=N), 164.06 (C=N). – MS (70 eV): *m/z* (%) = 274 and 272 (2 and 4) [M^+], 231 and 229 (1 and 2) [$M^+ - C_3H_7$].

$C_{13}H_{21}ClN_2O_2$ (272.8) Calcd. C 57.24 H 7.76
Found C 57.32 H 7.80

(2S,5R)-2-tert-Butyl-5-[(E)-4-chloro-2-butene-1-yl]-2,5-dihydro-3,6-dimethoxypyrazine (**4b**): 1.98 g of **3b** was used and 2.41 g (84%) of **4b** was obtained as a pale yellow oil. – Ratio of diastereomers 92:8, determined by GC-MS. – B.p. 120–125 °C/0.01 Torr. – IR (film): $\tilde{\nu} = 1685\ cm^{-1}$ (C=N). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.95 [s; 9H, $C(CH_3)_3$], 2.42–2.62 (m; 2H, $CHCH_2$), 3.68 and 3.71 (2 s; 6H, OCH_3), 3.78 [d, J = 3 Hz; 1H, $CHC(CH_3)_3$], 3.90–4.09 (m; 3H, CH_2Cl and $CHCH_2$), 5.60–5.76 (m; 2H, CH=CH). – MS (70 eV): *m/z* (%) = 288 and 286 (1 and 2) [M^+], 231 and 229 (1 and 2) [$M^+ - C_4H_9$].

$C_{14}H_{23}ClN_2O_2$ (286.8) Calcd. C 58.63 H 8.08
Found C 58.56 H 8.06

Cyclization of the Allylic Chlorides **4**. – *Cyclopropyl Compounds* **5**. – *General Procedure:* A solution of *n*-butyllithium in hexane (1.6 N, 3.8 ml, 6 mmol) was added at −70°C to a stirred solution of the bislactim ether **4** (5 mmol) in THF (50 ml). After stirring was continued for 6 h a saturated NH_4Cl solution (25 ml) was added and the solution was allowed to warm up to room temp. within 10 min. The organic volatile components were removed in vacuo (40°C, 15 Torr) and the residue was dissolved in diethyl ether (100 ml) and H_2O (25 ml). The layers were separated, the organic layer was extracted twice with 25-ml portions of H_2O and dried with $MgSO_4$. After removal of the solvent in vacuo the residue was purified by bulb-to-bulb distillation and subsequently by flash chromatography.

(1R,3R,6S)-3,6-Dihydro-6-isopropyl-5,8-dimethoxy-1-vinyl-4,7-diazaspiro[2.5]octane (**5a**): 1.36 g of **4a** was used and 0.99 g (84%) of **5a** was obtained as a pale yellow oil with b.p. 90°C/0.01 Torr; ratio of diastereomers: 67:23:6:4, determined by ^{13}C-NMR spectroscopy. – After flash chromatography on silica gel (160 g) with pentane/ethyl acetate (40:1) 0.63 g (53%) of (1*R*,3*R*,6*S*)-**5a** and 0.21 g (18%) of a mixture of (1*R*,3*S*,6*S*)-**5a**, (1*S*,3*S*,6*S*)-**5a**, (1*S*,3*R*,6*S*)-**5a** were obtained as colorless oils.

(1*R*,3*R*,6*S*)-**5a**: R_f = 0.27. – Diastereomeric purity: >95%, determined by ^{13}C-NMR spectroscopy. – IR (film): $\tilde{\nu}$ = 3070 (olefinic CH), 1660 (C=N), 1630 cm^{-1} (olefinic C=C). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.74 and 1.03 [2 d, *J* = 7 Hz; 6H, $CH(CH_3)_2$], 0.99–1.10 (m; 1H, cyclopropyl H), 1.65 (dd, *J* = 9 and 4.5 Hz; 1H, cyclopropyl H), 2.23 [dsp, *J* = 3.5 and 7 Hz; 1H, $CH(CH_3)_2$], 2.39 (ddd, *J* = 9, 9 and 7 Hz; 1H, $CHCH=CH_2$), 3.64 and 3.66 (2 s; 6H, OCH_3), 4.12 [d, *J* = 3.5 Hz; 1H, $CHCH(CH_3)_2$], 5.06 (ddd, J_{cis} = 10 Hz, *J* = 2 and <1 Hz; 1H, $CH=CH_2$), 5.21 (ddd, J_{trans} = 17.5 Hz, *J* = 2 and <1 Hz; 1H, $CH=CH_2$), 5.87 (ddd, J_{trans} = 17.5 Hz, J_{cis} = 10 Hz and *J* = 9 Hz; 1H, $CH=CH_2$). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 16.83 and 19.05 (CH_3), 23.21 (CH_2), 30.67 ($CHCH=CH_2$), 32.12 [$CH(CH_3)_2$], 43.71 (C-3), 52.35 and 52.47 (OCH_3), 61.50 (C-6), 114.91 ($CH=CH_2$), 136.94 ($CH=CH_2$), 162.71 and 163.88 (C=N). – MS (70 eV): *m/z* (%) = 236 (3) [M^+], 221 (4) [$M^+ - CH_3$], 193 (100) [$M^+ - C_3H_7$].

$C_{13}H_{20}N_2O_2$ (236.3) Calcd. C 66.08 H 8.53
Found C 66.06 H 8.60

(1*R*,3*S*,6*S*)-**5a**, (1*S*,3*S*,6*S*)-**5a**, (1*S*,3*R*,6*S*)-**5a**: R_f = 0.15. – Ratio of diastereomers: 70:18:12, determined by ^{13}C-NMR spectroscopy. – IR (film): $\tilde{\nu}$ = 3070 (olefinic CH), 1660 (C=N), 1630 cm^{-1} (olefinic C=C). – ^{1}H NMR (200 MHz, $CDCl_3$), major isomer of 3 diastereomers: δ = 0.77 [d, *J* = 7 Hz; 3H, $CH(CH_3)_2$], 0.98 [d, *J* = 7 Hz; 3H, $CH(CH_3)_2$], 1.43 (dd, *J* = 9 and 4.5 Hz; 1H, cycloproyl H), 1.72–2.0 (m; 2H, cyclopropyl H), 2.07 [dsp, *J* = 3.5 and 7 Hz; 1H, $CH(CH_3)_2$], 3.65, 3.72 (2 s; 6H, OCH_3), 4.17 [d, *J* = 3.5 Hz; $CHCH(CH_3)_2$], 5.01 (ddd, J_{cis} = 10.5 Hz, *J* = 2 and <1 Hz; 1H, $CH=CH_2$), 5.14 (ddd, J_{trans} = 17.5 Hz, *J* = 2 and <1 Hz; 1H, $CH=CH_2$), 5.73 (ddd, J_{trans} = 17.5 Hz, J_{cis} = 10.5 Hz and *J* = 9 Hz; 1H, $CH=CH_2$). – MS (70 eV): *m/z* (%) = 236 (7) [M^+], 221 (8) [$M^+ - CH_3$], 193 (100) [$M^+ - C_3H_7$].

$C_{13}H_{20}N_2O_2$ (236.3) Calcd. C 66.08 H 8.53
Found C 66.72 H 8.44

(1R,3R,6S)-6-tert-Butyl-3,6-dihydro-5,8-dimethoxy-1-vinyl-4,7-diazaspiro[2.5]octane (**5b**): 1.43 g of **4b** was used and 1.03 g (82%) of **5b** was obtained as a pale yellow oil with b.p. 100°C/0.01 Torr; ratio of diastereomers: 83:9:5:3, determined by ^{13}C NMR and GC-MS. – After flash chromatography on silica gel (160 g) with petroleum ether/ethyl acetate (20:1), 0.78 g (62%) of (1*R*,3*R*,6*S*)-**5b** was obtained as a colorless oil, diastereomerically pure. – R_f = 0.31. – IR (film): $\tilde{\nu}$ = 3070 (olefinic CH), 1670 (C=N), 1635 cm^{-1} (olefinic C=C). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 [s; 9H, $C(CH_3)_3$], 1.05 (dd, *J* = 7 and 4.5 Hz; 1H, cyclopropyl H), 1.60 (dd, *J* = 9.5 and 4.5 Hz; 1H, cyclopropyl H), 2.49 (ddd, *J* = 9.5, 9.5 and 7 Hz; 1H, $CHCH=CH_2$), 3.66 and 3.69 (2 s; 6H, OCH_3), 3.95 [s; 1H, $CH(CH_3)_3$], 5.10 (ddd, J_{cis} = 10 Hz, *J* = 2 and 0.5 Hz; 1H, $CH=CH_2$), 5.24 (ddd, J_{trans} = 17.5 Hz, *J* = 2 and 0.5 Hz; 1H, $CH=CH_2$), 5.92 (ddd, J_{trans} = 17.5 Hz, J_{cis} = 10 Hz and *J* = 9.5 Hz; 1H, $CH=CH_2$). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 23.41 (CH_2), 27.08 [$C(CH_3)_3$], 30.39 ($CHCH=CH_2$), 37.41 [$C(CH_3)_3$], 44.21 (C-3), 52.22 and 52.76 (OCH_3), 65.63 (C-6), 114.85 ($CH=CH_2$), 136.98 ($CH=CH_2$), 163.12 and 164.40 (C=N). – MS (70 eV): *m/z* (%) = 250 (2) [M^+], 235 (3) [$M^+ - CH_3$], 193 (24) [$M^+ - C_4H_9$], 57 (100) [C_4H_9].

$C_{14}H_{22}N_2O_2$ (250.3) Calcd. C 67.32 H 8.86
Found C 67.22 H 8.78

Hydrogenation of the Vinylcyclopropane Adducts **5**. – *Cyclopropyl Compounds* **6**. – *General Procedure:* To a suspension of potassium azodicarboxylate (0.97 g, 5 mmol) in methanol (5 ml) 2 mmol of the cyclopropyl compound **5** was added. Within 30 min acetic acid (0.54 g, 9 mmol) was added to this suspension at 0°C and stirring was continued for one additional hour at room temp. Diethyl ether (50 ml) and H_2O (10 ml) were added and the phases were separated. The aqueous phase was reextracted twice with ether (10 ml each) and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo and the crude products were purified by column filtration on silica gel (column length 5 cm) with petroleum ether/diethyl ether (10:1) if necessary.

(1S,3R,6S)-1-Ethyl-3,6-dihydro-6-isopropyl-5,8-dimethoxy-4,7-diazaspiro[2.5]octane (**6a**): 0.47 g (2 mmol) of (1*R*,3*R*,6*S*)-**5a** was used and 0.47 g (99%) of **6a** was obtained analytically pure. – Diastereomeric excess: >95%, determined by ^{13}C-NMR spectroscopy. – IR (film): $\tilde{\nu}$ = 1685 cm^{-1} (C=N). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.61–0.70 (m; 1H, cyclopropyl H), 0.77 and 1.04 [2 d, *J* = 7 Hz; 6H, $CH(CH_3)_2$], 0.96 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.14–1.36 (m; 1H, cyclopropyl H), 1.36–1.47 (m; 1H, cyclopropyl H), 1.50–1.69 (m; 2H, CH_2), 2.22 [dsp; *J* = 3.5 and 7 Hz; 1H, $CH(CH_3)_2$], 3.63 and 3.65 (2 s; 6H, OCH_3), 4.13 [d, *J* = 3.5 Hz; 1H, $CHCH(CH_3)_2$]. – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 13.56 (CH_2CH_3), 16.97 and 19.04 [$CH(CH_3)_2$], 21.19 (CH_2CH_3), 22.77 (cyclopropyl CH_2), 28.50 (C-1), 32.36 [$CH(CH_3)_2$], 41.60 (C-3), 52.22 and 52.38 (OCH_3), 61.68 (C-6), 163.52 and 164.42 (C=N). – MS (70 eV): *m/z* (%) = 238 (9) [M^+], 195 (100) [$M^+ - C_3H_7$].

$C_{13}H_{22}N_2O_2$ (238.3) Calcd. C 65.52 H 9.30
Found C 65.68 H 9.30

(1S,3S,6S)-, (1R,3S,6S)-, (1R,3R,6S)-1-ethyl-3,6-dihydro-6-isopropyl-5,8-dimethoxy-4,7-diazaspiro[2.5]octane (**6a**): 0.19 g (0.8 mmol) of a (1*R*,3*S*,6*S*)-, (1*S*,3*S*,6*S*)-, (1*S*,3*R*,6*S*)-**5a** mixture was used and 0.19 g (99%) of a (1*S*,3*S*,6*S*)-, (1*R*,3*S*,6*S*)-, (1*R*,3*R*,6*S*)-**6a** mixture was obtained. – R_f = 0.25. – IR (film): $\tilde{\nu}$ = 1685 cm^{-1} (C=N). – ^{1}H NMR (100 MHz, $CDCl_3$), major isomer of 3 diastereomers: δ = 0.62–2.32 [m; 6H, cyclopropyl H, CH_2CH_3 and $CH(CH_3)_2$], 0.83 [d, *J* = 7 Hz; 3H, $CH(CH_3)_2$], 0.95 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.02 (t, *J* = 7 Hz; 3H, CH_2CH_3), 3.63 and 3.69 (2 s; 6H, OCH_3), 4.14 [d, *J* = 3.5 Hz; 1H, $CHCH(CH_3)_2$], 4.16 [d, *J* = 3.5 Hz; 1H, $CHCH(CH_3)_2$]. – MS (70 eV): *m/z* (%) = 238 (7) [M^+], 195 (100) [$M^+ - C_3H_7$].

$C_{13}H_{22}N_2O_2$ (238.3) Calcd. C 65.52 H 9.30
Found C 65.57 H 9.32

(1S,3R,6S)-6-tert-Butyl-1-ethyl-3,6-dihydro-5,8-dimethoxy-4,7-diazaspiro[2.5]octane (**6b**): 0.50 g (2 mmol) of (1*R*,3*R*,6*S*)-**5b** was used and 0.50 g (99%) of **6b** was obtained. – R_f = 0.36. – Diastereomeric excess: >95%, determined by ^{13}C-NMR spectroscopy.

– IR (film): $\tilde{\nu}$ = 1670 cm^{-1} (C=N). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.65 (dd, *J* = 6.5 and 4 Hz; 1H, cyclopropyl H), 0.96 [s; 9H, $C(CH_3)_3$], 0.96 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.33 (dd, *J* = 9 Hz and 4 Hz; 1H, cyclopropyl H), 1.52–1.77 (m; 3H, $CHCH_2CH_3$), 3.64 and 3.67 (2 s; 6H, OCH_3), 4.94 [s; 1H, $CHC(CH_3)_3$]. – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 13.54 (CH_2CH_3), 21.20 (CH_2CH_3), 23.03 (cyclopropyl CH_2), 27.15 [$C(CH_3)_3$], 28.25 (C-1), 37.44 [$C(CH_3)_3$], 42.08 (C-3), 52.02 and 52.60 (OCH_3), 65.81 (C-6), 164.08 and 164.70 (C=N). – MS (70 eV): *m/z* (%) = 252 (3) [M^+], 237 (3) [$M^+ - CH_3$], 195 (100) [$M^+ - C_4H_9$].

$C_{14}H_{24}N_2O_2$ (252.4) Calcd. C 66.63 H 9.59
Found C 66.66 H 9.72

Hydrolysis of the Bislactim Ethers **6**. – *1-Amino-2-ethyl-1-cyclopropanecarboxylates* **7**, *ent*-**7** and **8**. – *General Procedure:* To a stirred suspension of **6** (2 mmol) in hydrochloric acid (0.25 N, 16 ml, 4 mmol) or trifluoroacetic acid (0.1 N, 40 ml, 4 mmol) THF was added until the mixture became homogeneous and stirring was continued at room temp. for 4 d. Volatile compounds were removed in vacuo (25°C/10 Torr) and the aqueous solution was extracted with diethyl ether (25 ml) in order to remove undesired non basic organic materials. Diethyl ether (25 ml) was added to the aqueous layer and the mixture was brought to pH 8–10 with conc. ammonia under stirring. The layers were separated and the aqueous layer was extracted twice with diethyl ether (25 ml each). The combined ethereal layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo (0°C/10 Torr). The residues – the crude compounds **7**, *ent*-**7**, **8** and methyl L-valinate or methyl L-*tert*-leucinate – were separated by chromatography (silica gel, 15 g, diethyl ether/pentane, 3:2).

Methyl (1R,2S)-(+)-1-Amino-2-ethyl-1-cyclopropanecarboxylate (**7**): 0.48 g (2 mmol) of **6a** was used and 0.22 g (77%) of (+)-**7** was obtained as a colorless oil. Starting from 0.50 g (2 mmol) of **6b** and trifluoroacetic acid (0.1 N, 40 ml, 4 mmol) 0.24 g (84%) of (+)-**7** was obtained. – R_f = 0.29. – $[\alpha]_D^{20}$ = +27.9 (*c* = 1.0, CH_3OH). – Enantiomeric excess: 96%, determined by ^1H-NMR spectroscopy with the chiral shift reagent $Eu(TFC)_3$[19]. – IR (film): $\tilde{\nu}$ = 3370, 3310 (NH_2), 1715 (C=O), 1620 cm^{-1} (NH_2). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.60–0.68 (m; 1H, cyclopropyl H), 1.00 (t, *J* = 7 Hz; 3H, CH_2CH_3), 1.30–1.60 (m; 4H, CH_2CH_3 and cyclopropyl H), 1.80 (br. s; 2H, NH_2), 3.70 (s; 3H, OCH_3). – MS (70 eV): *m/z* (%) = 143 (6) [M^+], 128 (19) [$M^+ - CH_3$], 114 (100) [$M^+ - CH_2CH_3$], 84 (24) [$M^+ - COOCH_3$].

$C_7H_{13}NO_2$ (143.2) Calcd. C 58.72 H 9.15
Found C 58.87 H 9.32

Methyl (1S,2S)-(–)- and (1S,2R)-(–)-1-Amino-2-ethyl-1-cyclopropanecarboxylate (**8** and *ent*-**7**): 0.36 g (1.5 mmol) of a (1*S*,3*S*,6*S*)-, (1*R*,3*S*,6*S*)-, (1*R*,3*R*,6*S*)-**6** mixture was used. 21 mg (10%) of (–)-*ent*-**7** and 92 mg (43%) of (–)-**8** were obtained as colorless oils.

Methyl (1S,2R)-(–)-1-Amino-2-ethyl-1-cyclopropanecarboxylate (*ent*-**7**): R_f = 0.29. – $[\alpha]_D^{20}$ = –27.2 (*c* = 0.5, CH_3OH). – Enantiomeric excess: 96%, determined by ^1H-NMR spectroscopy with the chiral shift reagent $Eu(TFC)_3$. – Spectroscopical data identical with those obtained for **7**.

$C_7H_{13}NO_2$ (143.2) Calcd. C 58.72 H 9.15
Found C 58.84 H 9.28

Methyl (1S,2S)-(–)-1-Amino-2-ethyl-1-cyclopropanecarboxylate (**8**): R_f = 0.15. – $[\alpha]_D^{20}$ = –8.3 (*c* = 1.24, CH_3OH). – Enantiomeric excess: 68%, determined by ^1H-NMR spectroscopy with the chiral shift reagent $Eu(TFC)_3$. – IR (film): $\tilde{\nu}$ = 3370, 3310 (NH_2), 1715 (C=O), 1620 cm^{-1} (NH_2). – ^1H NMR (100 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7 Hz, 3H, CH_2CH_3), 1.00–1.75 (m; 5H, CH_2CH_3 and cyclopropyl H), 2.01 (br. s; 2H, NH_2), 3.76 (s; 3H, OCH_3).

$C_7H_{13}NO_2$ (143.2) Calcd. C 58.72 H 9.15
Found C 58.96 H 9.39

Hydrolysis of the Amino Acid Methyl Esters **7** *and* **8**. – *(1S,2S)-(+)-1-Amino-2-ethyl-1-cyclopropanecarboxylic Acid* (**2**) and *(1R,2S)-(+)-1-Amino-2-ethyl-1-cyclopropanecarboxylic Acid* (**1**). – *General Procedure:* A solution of the amino acid methyl ester **7** or **8** (1 mmol) in hydrochloric acid (6 N, 10 ml) was refluxed for 1 h. Excess hydrochloric acid was removed in vacuo (50°C/10 Torr) and the dry residue was dissolved in ethanol (5 ml). Propylene oxide (2 ml) was added and the mixture was refluxed for 15 min. Upon cooling down to 0°C the amino acid precipitated. The suspension was filtered by suction, the solid residues – the amino acids **1** or **2** – were washed with cold ethanol (2 ml) and dried in vacuo (30°C/0.05 Torr).

(1S,2S)-(+)-1-Amino-2-ethyl-1-cyclopropanecarboxylic Acid [(+)-Coronamic Acid, **2**]: 72 mg (0.5 mmol) of **8** was used and 30 mg (47%) of **2** was obtained. – $[\alpha]_D^{20}$ = +30.8 (*c* = 0.51, H_2O). – Ref.[6b]: $[\alpha]_D^{20}$ = +14.7 (*c* = 1.67, H_2O). – ^1H NMR (100 MHz, D_2O): δ = 0.70 (t, *J* = 7 Hz; 3H, CH_2CH_3), 0.82–1.58 (m; 5H, CH_2CH_3 and cyclopropyl H).

(1R,2S)-(+)-1-Amino-2-ethyl-1-cyclopropanecarboxylic Acid [(+)-*allo*-Coronamic Acid, **1**]: 143 mg (1 mmol) of (+)-**7** was used and 101 mg (78%) of **1** was obtained. – M.p. 183°C (decomp.). – $[\alpha]_D^{20}$ = +55.9 (*c* = 0.56, H_2O). – Ref.[6a]: $[\alpha]_D^{20}$ = +65.0 (*c* = 1.83, H_2O); ref.[6f]: $[\alpha]_D^{20}$ = +73.5 (*c* = 0.4, H_2O); ref.[8]: $[\alpha]_D^{20}$ = –52 (*c* = 1.83, H_2O) for *ent*-**1**. – ^1H NMR (100 MHz, D_2O): δ = 0.62–0.78 (m; 1H, cyclopropyl H), 0.84 (t, *J* = 7 Hz; 3H, CH_2CH_3), 0.94–1.55 (m; 4H, CH_2CH_3 and cyclopropyl H).

CAS Registry Numbers

1: 65878-53-7 / **2**: 63393-56-6 / **3a**: 78342-42-4 / **3b**: 84907-93-7 / (±)-**7**: 138457-96-2 / *ent*-**7**: 138457-95-1 / **8**: 138457-97-3 / (2*S*,5*R*)-**4a**: 138457-98-4 / (2*S*,5*S*)-**4a**: 138512-19-3 / **4b**: 138387-11-8 / (1*R*,3*R*,6*S*)-**5a**: 138512-20-6 / (1*R*,3*S*,6*S*)-**5a**: 138387-13-0 / (1*S*,3*S*,6*S*)-**5a**: 138457-99-5 / (1*S*,3*R*,6*S*)-**5a**: 138458-00-1 / (1*R*,3*R*,6*S*)-**5b**: 138387-12-9 / (1*S*,3*R*,6*S*)-**6a**: 138387-14-1 / (1*S*,3*S*,6*S*)-**6a**: 138458-01-2 / (1*R*,3*S*,6*S*)-**6a**: 138458-02-3 / (1*R*,3*R*,6*S*)-**6a**: 138458-03-4 / (1*S*,3*R*,6*S*)-**6b**: 138387-15-2 / *trans*-1,4-dichloro-2-butene: 110-57-6

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