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Asymmetric Syntheses via Heterocyclic Intermediates, XLIV[1]

Asymmetric Synthesis of Methyl (2*R*,3*S*)-2-Amino-3-cyclopropyl-3-hydroxyalkanoates via Diastereoselective Simmons-Smith Reactions

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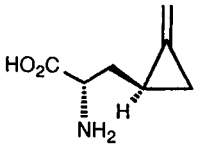
The cyclopropanation of the bislactim ethers **3** with diiodomethanes and diethylzinc proceeds in good yields and with high diastereoselectivities, affording the cyclopropyl bislactim ethers **6**. Protection of the hydroxy group and subsequent hydrolysis furnish virtually enantiomerically and diastereomerically pure methyl (2*R*,3*S*)-2-amino-3-cyclopropyl-3-hydroxyalkanoates **8**. The bislactim ethers of type **3** are obtained by a known method diastereomerically pure, starting from the bislactim ether of cyclo(-L-Val-Gly-).

The asymmetric synthesis of cyclopropyl amino acids deserves special attention because of the interesting biological activity of amino acids of this kind. The outstanding reactivity of the cyclopropyl group seems to be responsible for the selective inhibition of enzymes by many cyclopropyl compounds[2]. In any case, cyclopropanes are very widespread among various classes of natural compounds, such as fatty acids, terpenes, steroids, and amino acids. The best known cyclopropyl amino acid is the achiral 1-amino-1-cyclopropanecarboxylic acid, the biosynthetic precursor of ethylene, which is responsible for the ripening of fruits[3]. But even more interesting are chiral 2-amino-3-cyclopropyl amino acids such as hypoglycine A (**1**) effecting hypoglycemia[4] and cyclopropyl-L-alanine (**2**), an inhibiting analogon of L-leucine[5].



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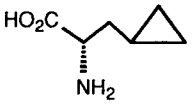

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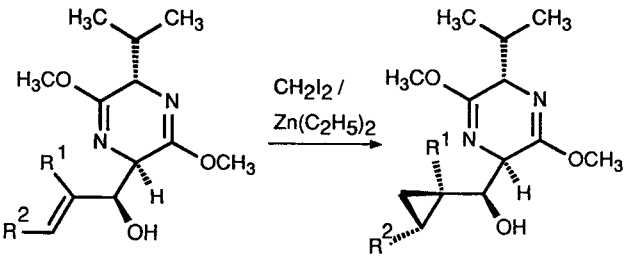
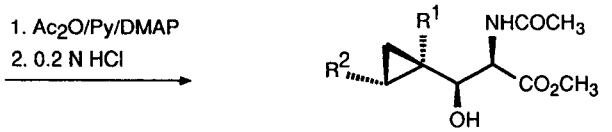
So far, only a few syntheses of cyclopropyl amino acids have been reported, most of which are concerned with the preparation of 1-aminocyclopropanecarboxylic acids[6]. The asymmetric synthesis of 2-amino-3-cyclopropylcarboxylic acids has remained a challenging problem.

The Simmons-Smith reaction is a powerful method for the conversion of olefins into cyclopropanes. It has been extensively studied under mechanistic aspects, but only a few applications of the Simmons-Smith reaction to diastereoselective cyclopropanations are known[7]. Indeed, the Simmons-Smith reaction with a highly reactive intermediate seems to be not very suitable for an asymmetric synthesis.

In 1966, Furukawa, Kawabata, and Nishimura[8] reported on a variation of the Simmons-Smith reaction with diiodomethane and diethylzinc, which proceeded much faster with allylic alcohols or allylic ethers than with simple olefins[9]. This remarkable chemoselectivity is probably due to a coordination of the zinc atom in the reactive intermediate to the oxygen atom of the alcohol or ether. The coordination of the zinc to the oxygen function may also ex-



3 **4**



5

3-5	R^1	R^2	yield of **4** (%)	d.e. (%)	yield of **5** (%)
a	H	CH_3	61	> 98	86
b	H	C_6H_5	76	> 98	82
c	CH_3	H	68	----*	71

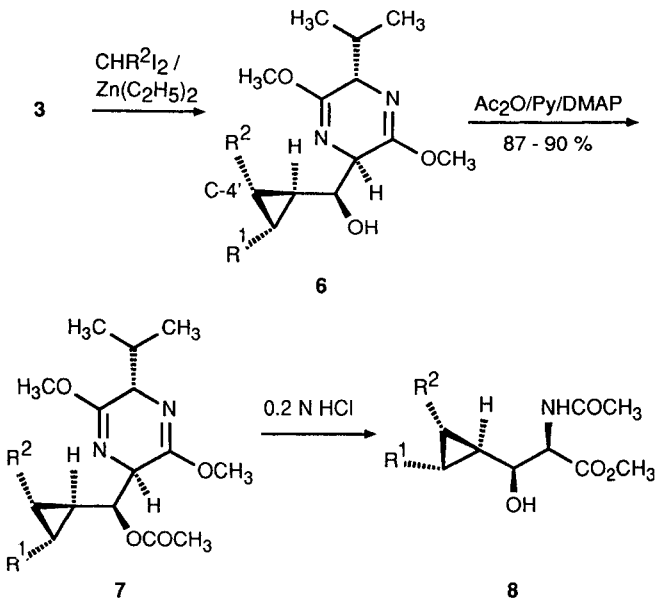
* No chiral center in the cyclopropyl ring.

plain the remarkable diastereoselectivity of this cyclopropanation reaction, which has been observed in the cyclopropanation of cyclic allylic alcohols and ethers[7b].

In 1986, Yamamoto et al. described a highly interesting asymmetric Simmons-Smith cyclopropanation of α,β-unsaturated acetals derived from dialkyl tartrates yielding protected cyclopropyl aldehydes with very high diastereoselectivities[7d].

Recently, we have found[10a] that treatment of the bislactim ethers **3** with diiodomethane and diethyl zinc delivers only one diastereomer **4**. The protection of the hydroxy function with acetic anhydride/pyridine and subsequent hydrolysis with dilute hydrochloric acid afford enantiomerically and diastereomerically pure methyl (2*R*,3*S*)-2-amino-3-cyclopropyl-3-hydroxyalkanoates **5**. The configuration of the cyclopropyl compounds **4** and **5** has been established by an X-ray analysis of the amino acid ester **5a**.

We now present a cyclopropanation reaction of the allylic alcohols **3** with alkyl- or aryl-substituted carbenoids of type CHR or CHAr. In this reaction up to three stereogenic centers are built up with high diastereoselectivities. The bislactim ethers **3** are treated with alkyl- or aryl-substituted diiodomethanes and diethylzinc to furnish the bislactim ethers **6** in 52–80% yield with diastereoselectivities of 68–86% d.e. Compounds **6** are protected with acetic anhydride as the *O*-acetyl bislactim ethers **7**, which are hydrolyzed to the methyl (2*R*,3*S*)-2-amino-3-cyclopropyl-3-hydroxyalkanoates **8**. Upon aqueous work-up, the acetyl group migrates from the oxygen to the nitrogen. After crystallization the enantiomerically and diastereomerically pure esters **8** are obtained. The cyclopropanation of **3** with cyclohexyldiiodomethane has not been achieved under the described conditions.



6 **7** **8**

3	6-8	R^1	R^2	yield of **6** (%)	d.e. (%)	yield of **8** (%)
a	**a**	CH_3	CH_3	80	68	67
a	**b**	CH_3	C_6H_5	52	68	72
b	**c**	C_6H_5	CH_3	74	86	
b	**d**	C_6H_5	C_6H_5	62	85	78
d	**e**	H	CH_3	76	79	

The analysis of the ^{1}H-NMR data confirms that the substituent R^2, which is introduced by the carbenoid, always occupies the position *trans* to the carbinol substituent at the cyclopropyl ring. Consistently, it has been proven that the substituents R^1 and R^2 derived from the (*E*) olefin and the carbenoid are *cis* to each other.

A comparison of the analytical data of the bislactim ethers **4a** and **6e** proves that both compounds display *trans* configuration at the cyclopropyl ring but different absolute configurations at C-1″ and C-2″. For **4a** the (1″*R*, 2″*R*) configuration has been established by an X-ray analysis. Therefore, the bislactim ether **6e** adopts the (1″*S*,2″S) configuration. The attack of the carbenoid must have taken place from the same diastereotopic side of the C=C bond. The directing effect of the carbinol center is obviously not much affected by a substituent of the diiodomethane. Analogously, based on this information, we assume that the cyclopropyl compounds **6**–**8** have the stereochemistry shown in the formulas above.

Financial support by the *Stiftung Volkswagenwerk* and the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged. T. T. thanks the *Stiftung Stipendien-Fonds der Chemischen Industrie* for a fellowship. We thank the *Degussa AG* for providing valuable starting materials.

Experimental

The bislactim ether of cyclo(-L-Val-Gly-) was prepared as described[11] or purchased from Merck-Schuchardt[12]. The 1N solution of diethylzinc in hexane was purchased from Aldrich Chemical Co. – IR spectra: Perkin-Elmer 298. – ^{1}H- and ^{13}C-NMR spectra: Varian XL 200 and VXR 200. – Low-pressure chromatography (1–1.5 bar): silica gel, 240–400 mesh, Merck, Darmstadt.

Cyclopropanation of the Bislactim Ethers **3**. – *Compounds* **6**. – *General Procedure:* For the preparation of the bislactim ethers **3** see ref.[10]. Phenyl- and cyclohexyldiiodomethane were prepared according to ref.[13]. 1,1-Diiodoethane was prepared as described in ref.[14]. A solution of diethylzinc in hexane (1.0 N, 5.0 ml, 5.0 mmol) was added to a solution of **3** (2.0 mmol) in dry hexane at 0°C. Then the diiodomethane (5.0 mmol) was added dropwise at the same temperature. The reaction mixture was stirred at room temp. for 1 to 3 d. The mixture was poured into a saturated aqueous solution of NH_4Cl (30 ml) and the aqueous layer extracted with ether (4 portions of 40 ml). The conbined etheral extracts were dried with magnesium sulfate and the solvent was evaporated in vacuo. The crude compounds **6** were purified by low-pressure chromatography (silica gel, 50 g, ether/petroleum ether, 1:1 or 1:2).

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(2″R,3″S)-2″,3″-dimethylcyclopropyl]methanol (**6a**): 0.51 g of **3a** and 1.41 g of 1,1-diiodoethane were used, and the mixture was stirred for 3 d; yield 0.45 g (1.60 mmol, 80%) of **6a**; diastereomeric excess: 68%. – R_f (ether/petroleum ether, 1:2) = 0.09. – IR (film): $\tilde{\nu}$ = 3200–3600 (O–H), 1690 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.44 (ddd, J_1 = 8.5 Hz, J_2 = J_3 = 4.5 Hz; 1H, 1″-H), 0.6–0.9 (m; 2H, 2″- and 3″-H), 0.73 and 1.06 [2d, *J* =

7 Hz; 3H each, $CH(CH_3)_2$], 1.01 and 1.04 (2d, J = 6 Hz; 3H each, 2″- and 3″-CH_3), 2.20 (d, J = 9 Hz; 1H, OH), 2.29 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 3.34 (ddd, J_1 = 9 Hz, J_2 = 8.5 Hz, J_3 = 3 Hz; 1H, 1-H), 3.72 und 3.74 (2s; 3H each, OCH_3), 3.99 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.11 (dd, $^5J_1$ = 3.5 Hz, J_2 = 3.0 Hz; 1H, 2′-H). – ^{13}C NMR ($CDCl_3$): δ = 12.14, 12.52 (C-2″ and -3″), 14.97, 15.11 (2″- and 3″-CH_3), 16.66, 19.12 [$CH(CH_3)_2$], 30.11, 31.70 [C-1″ and $CH(CH_3)_2$], 52.48 (2 OCH_3), 60.34 60.76 (C-2′ and -5′), 76.76 (C-1), 162.08, 165.00 (C-3′ and -6′).

$C_{15}H_{26}N_2O_3$ (282.4) Calcd. C 63.80 H 9.28
Found C 63.84 H 9.19

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(1″S,2″R,3″S)-2″-methyl-3″-phenylcyclopropyl]methanol (**6b**): 0.51 g of **3a** and 1.61 g of diiodophenylmethane were used, and the mixture was stirred for 1 d; yield 0.36 g (1.02 mmol, 52%) of **6b**; diastereomeric excess: 68%. – R_f (ether/petroleum ether, 1:2) = 0.07. – IR (film): ṽ = 3600–3100 (O–H), 3080, 3060, 3020 (C–H/phenyl), 1695 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.74 and 1.06 [2d, J = 7 Hz; 3H each, $CH(CH_3)_2$], 0.84 (d, J = 6 Hz; 3H, 2″-CH_3), 1.19 (ddq, J_1 = 9 Hz, J_2 = 6 Hz, J_3 = 5 Hz; 1H, 2″-H), 1.40 (ddd, J_1 = 7.5 Hz, J_2 = 5.5 Hz, J_3 = 5 Hz; 1H, 1″-H), 2.20 (dd, J_1 = 9 Hz; J_2 = 5.5 Hz; 1H, 3″-H), 2.29 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 2.3–2.4 (br; 1H, OH), 3.56–3.67 (m; 1H, 1-H), 3.73 and 3.74 (2s; 3H each, OCH_3), 4.02 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.18 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 2′-H), 7.12–7.37 (m; 5H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 12.87 (C-2″), 18.04 (2″-CH_3), 16.59, 19.11 [$CH(CH_3)_2$], 26.37, 28.13 (C-1″ and -3″), 31.73 [$CH(CH_3)_2$], 52.52 (2 OCH_3), 60.17, 60.78 (C-2′ and -5′), 75.64 (C-1), 125.66 (phenyl), 127.85, 129.20 (2C each, phenyl), 138.86 (C-1, phenyl), 161.89, 165.19 (C-3′ and -6′).

$C_{20}H_{28}N_2O_3$ (344.5) Calcd. C 69.74 H 8.19
Found C 69.63 H 8.25

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(1″R,2″S,3″R)-2″-methyl-3″-phenylcyclopropyl]methanol (**6c**): 0.63 g of **3b** and 1.41 g of 1,1-diiodoethane were used, and the mixture was stirred for 1 d; yield 0.51 g (1.48 mmol, 74%) of **6c**; diastereomeric excess: 86%. – R_f (ether/petroleum ether, 1:2) = 0.07. – IR (film): ṽ = 3600–3100 (O–H), 3070, 3050 (C–H/phenyl), 1690 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.71 and 1.04 (2d, J = 7 Hz; 3H each, $CH(CH_3)_2$), 0.85 (d, J = 6 Hz; 3H, 2″-CH_3), 1.18–1.38 (m; 1H, 2″-H), 1.46 (ddd, J_1 = 8 Hz, J_2 = 5.5 Hz, J_3 = 5 Hz; 1H, 1″-H), 2.09 (dd, J_1 = 9 Hz; J_2 = 5.5 Hz; 1H, 3″-H), 2.20 (d, J = 9 Hz; 1H, OH), 2.26 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 3.55–3.66 (m; 1H, 1-H), 3.73 and 3.75 (2s; 3H each, OCH_3), 3.99 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.18 (dd, $^5J_1$ = 3.5 Hz, J_2 = 3.0 Hz; 1H, 2′-H), 7.15–7.35 (m; 5H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 13.42 (C-2″), 16.72, 18.63, 19.12 [2″-CH_3 and $CH(CH_3)_2$], 26.16, 28.04 (C-1″ and -3″), 31.75 [$CH(CH_3)_2$], 52.46 (2 OCH_3), 60.23, 60.78 (C-2′ and -5′), 76.27 (C-1), 125.79 (phenyl), 127.94, 129.33 (2 C each, phenyl), 138.59 (C-1, phenyl), 161.95, 165.22 (C-3′ and -6′).

$C_{20}H_{28}N_2O_3$ (344.5) Calcd. C 69.74 H 8.19
Found C 69.74 H 8.25

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(2″R,3″S)-2″,3″-diphenylcyclopropyl]methanol (**6d**): 0.63 g of **3b** and 1.61 g of diiodophenylmethane were used, and the mixture was stirred for 1 d; yield 0.50 g (1.24 mmol, 62%) of **6d**; diastereomeric excess: 85%. – R_f (ether/petroleum ether, 1:1) = 0.09. – IR (film): ṽ = 3600–3100 (O–H), 3080, 3060, 3020 (C–H/phenyl), 1690 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.73 and 1.04 [2d, J = 7 Hz; 3H each, $CH(CH_3)_2$], 2.22 (ddd, C part of an ABCM system, J_{CM} = 7.5 Hz, J_{CB} = 6 Hz, J_{CA} = 5.5 Hz; 1H, 1″-H), 2.27 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 2.37 (br. d, J = 9 Hz; 1H, OH), 2.52 (dd, B part of an ABC system, J_{AB} = 9.5 Hz, J_{BC} = 6 Hz; 1H, 2″-H), 2.60 (dd, A part of an ABC system, J_{AB} = 9.5 Hz, J_{AC} = 5.5 Hz; 1H, 3″-H), 3.74 and 3.75 (2s; 3H each, OCH_3), 3.8–3.9 (m; 1H, 1-H), 4.00 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.26 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 2′-H), 6.88–7.15 (m; 10 H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 16.80, 19.07 [$CH(CH_3)_2$], 28.73, 29.17, 29.57 (C-1″ to -3″), 31.91 [$CH(CH_3)_2$], 52.63 (2 OCH_3), 59.93, 60.91 (C-2′ and -5′), 75.44 (C-1), 125.66, 125.76 (phenyl), 127.63, 127.74, 128.80, 129.13 (2C each, phenyl), 137.55, 137.98 (C-1, phenyl), 161.73, 165.57 (C-3′ and -6′).

$C_{25}H_{30}N_2O_3$ (406.5) Calcd. C 73.86 H 7.44
Found C 73.77 H 7.42

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(1″S,2″S)-2″,3″-methylcyclopropyl]methanol (**6e**): 0.48 g of **3d** and 1.41 g of 1,1-diiodoethane were used, and the mixture was stirred for 1 d; yield 0.41 g (1.52 mmol, 76%) of **6e**; diastereomeric excess: 79%. – R_f (ether/petroleum ether, 1:2) = 0.21. – IR (film): ṽ = 3600–3200 (O–H), 1690 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.27 (ddd, J_{1cis} = 8.5 Hz, $^2J_2$ = J_{3trans} = 5 Hz; 1H, 3″-H), 0.46 (ddd, J_{1cis} = 8.5 Hz, $^2J_2$ = 5 Hz, J_{3trans} = 4.5 Hz; 1H, 3″-H), 0.72 and 1.05 [2d, J = 7 Hz; 3H each, $CH(CH_3)_2$], 0.75–1.02 (m; 2H, 1″- and 2″-H), 1.07 (d, J = 6 Hz; 3H, 2″-CH_3), 2.0 (br.; 1H, OH), 2.28 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 3.33 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz; 1H, 1-H), 3.73 and 3.74 (2s; 3H each, OCH_3), 4.00 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.09 (dd, $^5J_1$ = 3.5 Hz, J_2 = 2.5 Hz; 1H, 2′-H). – ^{13}C NMR ($CDCl_3$): δ = 10.94 (C-3″), 11.39 (2″-CH_3), 16.71, 18.76, 19.12, 22.85 [$CH(CH_3)_2$, C-1″ and -2″], 31.73 [$CH(CH_3)_2$], 52.48 (2 OCH_3), 60.10, 60.79 (C-2′ and -5′), 76.67 (C-1), 162.03, 165.47 (C-3′ and -6′).

$C_{14}H_{24}N_2O_3$ (268.3) Calcd. C 62.66 H 9.01
Found C 62.62 H 9.06

With cyclohexyldiiodomethane and **3a** and **3b** no cyclopropanation product was observed under the described conditions. Higher temperatures or longer reaction times only led to decomposition of the starting compounds.

Acetylation of Bislactim Ethers **6**. – *Compounds* **7**. – *General Procedure:* Acetic anhydride (0.26 g, 2.5 mmol) was added to a solution of **6** (2.0 mmol), DMAP (50 mg, 0.4 mmol) and pyridine (0.24 ml, 3.0 mmol) in CH_2Cl_2 (10 ml). Stirring at room temp. was continued for 15 h. The mixture was poured into water (15 ml)/CH_2Cl_2 (30 ml) and vigorously shaken. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 (30 ml each). The combined organic layers were dried with $MgSO_4$, the solvent and the pyridine evaporated in vacuo and the crude compounds **7** purified by low-pressure chromatography (silica gel, 30 g, ether/petroleum ether, 1:1 or 1:2).

O-Acetyl-(1S)-1-[(2′R,5′S)-2′,5′-dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(2″R,3″S)-2″,3″-dimethylcyclopropyl]methanol (**7a**): 0.56 g of **6a** was used; yield 0.56 g (1.74 mmol, 87%) of **7a**. – R_f (ether/petroleum ether, 1:1) = 0.41. – IR (film): ṽ = 1740 (C=O), 1690 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.67 and 1.07 [2d, J = 7 Hz; 3H each, $CH(CH_3)_2$], 0.7–1.0 (m; 3H, cyclopropyl H), 1.00 and 1.04 (2d, J = 6 Hz; 3H each, 2″- and 3″-CH_3), 1.98 (s; 3H, O_2CCH_3), 2.32 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 3.66 and 3.75 (2s; 3H each, OCH_3), 3.92 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.20 (dd, $^5J_1$ = 3.5 Hz, J_2 = 3.0 Hz; 1H, 2′-H), 4.64 (dd, J_1 = 9 Hz, J_2 = 3 Hz; 1H, 1-H). – MS (70 eV): m/z (%) = 324 (10) [M^+], 296 (5) [$M^+ - C_2H_4$], 281 (10) [$M^+ - C_3H_7$], 141 (100) [Gly-Gly].

O-Acetyl-(1S)-1-[(2′R,5′S)-2′,5′-dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(1″S,2″R,3″S)-2″-methyl-3″-phenylcyclopro-

pyl]methanol (**7b**): 0.69 g of **6b** was used; yield 0.69 g (1.80 mmol, 90%) of **7b**. – R_f (ether/petroleum ether, 1:2) = 0.37. – IR (film): $\tilde{\nu}$ = 1730 (C=O), 1695 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 0.67 and 1.06 [2d, J = 7 Hz; 3H each, $CH(CH_3)_2$], 0.70 (d, J = 6 Hz; 3H, 2″-CH_3), 1.42 (ddq, J_1 = 9.5 Hz, J_2 = 6 Hz, J_3 = 5 Hz; 1H, 2″-H), 1.73 (ddd, J_1 = 9.5 Hz, J_2 = J_3 = 5 Hz; 1H, 1″-H), 2.01 (s; 3H, O_2CCH_3), 2.16 (dd, J_1 = 9.5 Hz, J_2 = 5 Hz; 1H, 3″-H), 2.31 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 3.65 and 3.82 (2s; 3H each, OCH_3), 3.97 (dd, $^5J_1$ = J_2 = 3.5 Hz, 1H, 5′-H), 4.27 (dd, $^5J_1$ = 3.5 Hz, J_2 = 3.0 Hz; 1H, 2′-H), 4.89 (dd, J_1 = 9.5 Hz, J_2 = 3Hz; 1H, 1-H), 7.10–7.35 (m; 5H, phenyl).

$C_{22}H_{30}N_2O_4$ Calcd. 386.2206 Found 386.2206 [HRMS (70 eV)]

O-Acetyl-(1S)-1-[(2′R,5′S)-2′,5′-dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-[(2″R,3″S)-2″,3″-diphenylcyclopropyl]methanol (**7d**): 0.81 g of **6d** was used; yield 0.81 g (1.80 mmol, 90%) of **7d**. – R_f (ether/petroleum ether, 1:1) = 0.26. – IR (film): $\tilde{\nu}$ = 3080, 3050, 3020 (C–H/phenyl), 1740 (C=O), 1690 cm^{-1} (C=N). – ^1H NMR ($CDCl_3$): δ = 0.68 and 1.06 [2d, J = 7 Hz; 3H each, $CH(CH_3)_2$], 1.98 (s; 3H, O_2CCH_3), 2.34 [dsept, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $CH(CH_3)_2$], 2.54 (ddd, A part of an ABCX system, J_{AX} = 8.5 Hz, J_{AB} = 6 Hz, J_{AC} = 5.5 Hz; 1H, 1″-H), 2.59 (dd, B part of an ABC system, J_{BC} = 10 Hz, J_{AB} = 6 Hz; 1H, 2″-H), 2.72 (dd, C part of an ABC system, J_{BC} = 10 Hz; J_{AC} = 5.5 Hz; 1H, 3″-H), 3.68 and 3.84 (2s; 3H each, OCH_3), 4.00 (dd, $^5J_1$ = J_2 = 3.5 Hz; 1H, 5′-H), 4.38 (dd, $^5J_1$ = 3.5 Hz, J_2 = 3 Hz; 1H, 2′-H), 5.12 (dd, J_{AX} = 8.5 Hz, J = 3Hz; 1H, 1-H), 6.84-7.44 (m; 10H, phenyl).

$C_{27}H_{32}N_2O_4$ Calcd. 448.2362 Found 448.2362 [HRMS (70 eV)]

Hydrolysis of the Bislactim Ethers **7**. – *3-Cyclopropylserine Esters* **8**. – *General Procedure:* A solution of **7** (1.5 mmol) in THF (15 ml) was added to hydrochloric acid (0.2 N, 15 ml, 3.0 mmol) and stirring continued at room temp. for 24 h. The solution was brought to pH 8–10 with conc. ammonia and extracted four times with ether (30 ml each). The combined ethereal layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. Methyl L-valinate was removed with the kugelrohr apparatus (30°C/0.01 Torr), and the residues – the crude compounds **8** – were purified by chromatography (silica gel, 30 g, ether).

Methyl (2R,3S)-2-Acetamido-3-[(2′R,3′S)-2′,3′-dimethylcyclopropyl]-3-hydroxypropanoate (**8a**): 0.49 g of **7a** was used; yield 0.23 g (1.01 mmol, 67%) of **8a**. – R_f = 0.09. – $[\alpha]_D^{20}$ = –57.1 (c = 0.2, methanol). – IR (film): $\tilde{\nu}$ = 3100–3600 (N–H, O–H), 1740 (C=O, ester), 1650 cm^{-1} (C=O, amide). – ^1H NMR ($CDCl_3$): δ = 0.34 (ddd, J_1 = 9 Hz, J_2 = J_3 = 4.5 Hz; 1H, 1′-H), 0.64–1.00 (m; 2H, 2′- and 3′-H), 1.01 and 1.06 (2d, J = 6 Hz; 3H each, 2′- and 3′-CH_3), 2.10 (s; 3H, $NHCOCH_3$), 2.16–2.38 (br., 1H, OH), 3.45 (dd, J_1 = 9 Hz, J_2 = 3 Hz; 1H, 3-H), 3.78 (s; 3H, CO_2CH_3), 4.77 (dd, J_1 = 8.5 Hz, J_2 = 3 Hz; 1H, 2-H), 6.47 (br. d, J = 8.5 Hz; 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 11.77, 12.33 (2′- and 3′-CH_3), 16.11, 17.88 (C-2′ and -3′), 22.93 (C-1′), 30.36 ($NHCOCH_3$), 52.37 (CO_2CH_3), 57.03 (C-2), 75.87 (C-3), 170.94, 171.56 (CO_2CH_3, $NHCOCH_3$).

$C_{11}H_{19}NO_4$ (229.2) Calcd. C 57.63 H 8.35
Found C 57.50 H 8.17

Methyl (2R,3S)-2-Acetamido-3-hydroxy-3-[(1′S,2′R,3′S)-2′-methyl-3′-phenylcyclopropyl]propanoate (**8b**): 0.58 g of **7b** was used; yield 0.31 g (1.08 mmol, 72%) of **8b**. – R_f = 0.06. – M.p. 149°C. – $[\alpha]_D^{22}$ = –76.4 (c = 0.7, methanol). – IR (film): $\tilde{\nu}$ = 3100–3600 (N–H, O–H), 3080, 3050, 3010 (C–H/phenyl), 1740 (C=O, ester), 1650 cm^{-1} (C=O, amide). – ^1H NMR ($CDCl_3$): δ = 0.84 (d, J = 6 Hz; 3H, 2′-CH_3), 1.17–1.32 (m; 2H, 1′- and 2′-H), 2.04–2.12 (m; 1H, 3′-H), 2.11 (s; 3H, $NHCOCH_3$), 2.26 (br., 1H, OH), 3.67 (s; 3H, CO_2CH_3), 3.69 (dd, J_1 = 7.5 Hz, J_2 = 3.5 Hz; 1H, 3-H), 4.86 (dd, J_1 = 9 Hz, J_2 = 3.5 Hz; 1H, 2-H), 6.44 (br. d, J = 9 Hz; 1H, NH), 7.11–7.32 (m; 5H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 13.11 (2′-CH_3), 18.15 (C-2′), 23.01 (C-1′), 26.11 (C-3′), 27.89 ($NHCOCH_3$), 52.45 (CO_2CH_3), 57.26 (C-2), 75.11 (C-3), 126.01 (phenyl), 128.04, 129.14 (2C each, phenyl), 137.44 (C-1, phenyl), 171.03, 171.47 (CO_2CH_3, $NHCOCH_3$).

$C_{16}H_{21}NO_4$ (291.3) Calcd. C 65.96 H 7.26
Found C 65.95 H 7.21

Methyl (2R,3S)-2-Acetamido-3-[(2′R,3′S)-2′,3′-diphenylcyclopropyl]-3-hydroxypropanoate (**8d**): 0.67 g of **7d** was used; yield 0.41 g (1.17 mmol, 78%) of **8d**. – R_f = 0.11. – $[\alpha]_D^{20}$ = –27.8 (c = 0.1, methanol). – IR (film): $\tilde{\nu}$ = 3600–3100 (N–H, O–H), 3080, 3060, 3020 (C–H/phenyl), 1740 (C=O, ester), 1650 cm^{-1} (C=O, amide). – ^1H NMR ($CDCl_3$): δ = 1.98 (ddd, M part of an ABM system, J = 7.5 Hz, J_{AM} = 6 Hz, J_{BM} = 5.5 Hz; 1H, 1′-H), 2.03 (s; 3H, $NHCOCH_3$), 2.2 (br., 1H, OH), 2.48 (dd, A part of an ABM system, J_{AB} = 10 Hz, J_{AM} = 6 Hz; 1H, CH, phenyl), 2.58 (dd, B part of an ABM system, J_{AB} = 10 Hz, J_{BM} = 5.5 Hz; 1H, CH, phenyl), 3.68 (s; 3H, CO_2CH_3), 3.99 (dd, J_1 = 7.5 Hz, J_2 = 3.5 Hz; 1H, 3-H), 4.98 (dd, J_1 = 8.5 Hz, J_2 = 3.5 Hz; 1H, 2-H), 6.55 (br. d, J = 8.5 Hz; 1H, NH), 6.86–7.44 (m; 10H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 22.66 ($NHCOCH_3$), 28.20, 28.56, 29.08 (C-1′ to -3′), 52.28 (CO_2CH_3), 57.54 (C-2), 73.58 (C-3), 125.71, 125.84 (phenyl), 127.64, 127.73, 128.72, 128.97 (2C each, phenyl), 136.71, 137.33 (C-1, phenyl), 171.35, 171.50 (CO_2CH_3, $NHCOCH_3$).

$C_{21}H_{23}NO_4$ (353.4) Calcd. C 71.37 H 6.56
Found C 71.43 H 6.53

CAS Registry Numbers

3a: 107384-37-2 / **3b**: 134929-84-3 / **3d**: 134929-85-4 / **6a**: 134815-83-1 / **6b**: 134815-84-2 / **6c**: 134929-86-5 / **6d**: 134815-85-3 / **6e**: 120190-49-0 / **7a**: 134847-11-3 / **7b**: 134815-86-4 / **7d**: 134815-87-5 / **8a**: 134815-88-6 / **8b**: 134815-89-7 / **8d**: 134815-90-0 / 1,1-diiodoethane: 594-02-5 / phenyldiiodomethane: 28000-59-1 / cyclohexyldiiodomethane: 65826-85-9 / diethylzinc: 557-20-0

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