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Notizen/ Notes

Asymmetric Syntheses via Heterocyclic Intermediates, XLV [1]

Asymmetric Synthesis of Diastereomerically and Enantiomerically Pure 3-Substituted (2*R*,3*S*)-Serine Methyl Esters

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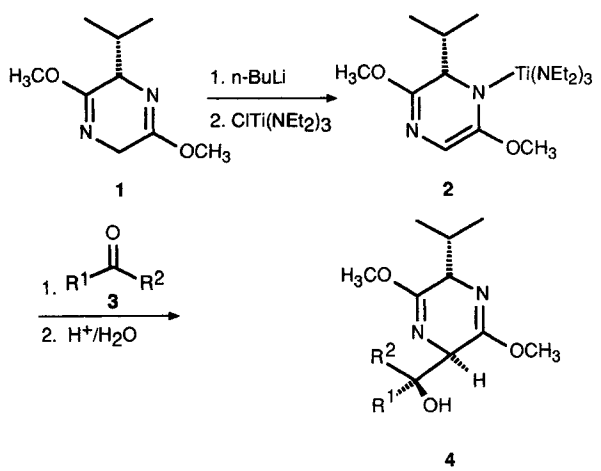
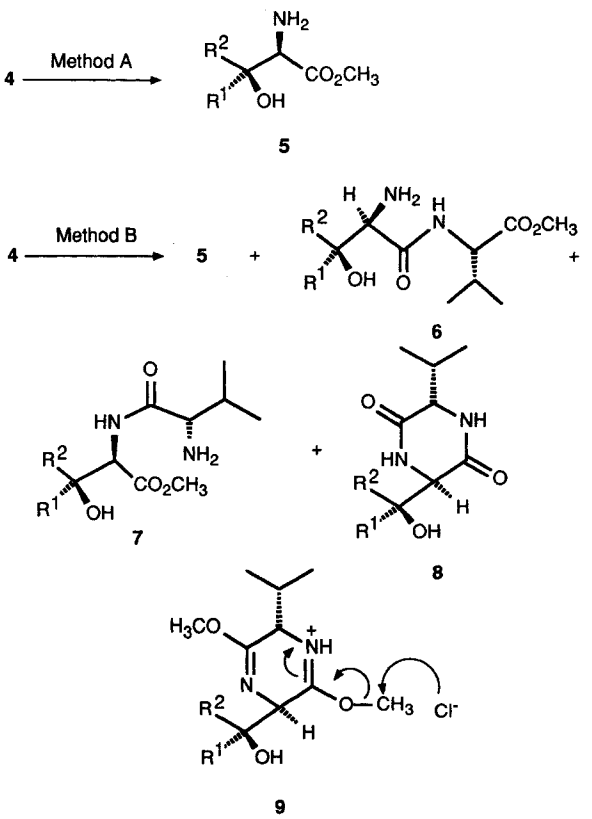
The titanium derivative **2** of the bislactim ether **1** of cyclo(-L-Val-Gly-) reacts with aldehydes and ketones **3** highly diastereoselectively to give the *syn*-addition products **4**. Upon hydrolysis with diluted trifluoroacetic acid the compounds **4** yield besides methyl L-valinate the (2*R*,3*S*)-*threo*-serine methyl esters **5**.

As reported recently, the titanium derivative **2** of the bislactim ether of cyclo(-L-Val-Gly-) reacts with alkyl aldehydes[2], aryl aldehydes[3] and α,β-unsaturated aldehydes[1,4,5] highly diastereoselectively to give almost exclusively the *syn*-addition products **4**. Upon hydrolysis (two equivalents of 0.5 N HCl, room temp.) of the aryl-substituted aldol adducts the corresponding 3-arylserine methyl esters were obtained in reasonable yields (46–66%)[3]. However, aldol adducts such as **4b–e** gave under these hydrolysis conditions the 3-substituted serine esters in only 16–24% yield (Method B). Predominantly the dipeptide esters **6** and **7** and the diketopiperazines **8** were formed by partial cleavage of the bislactim ether ring. In order to achieve a clean hydrolysis of both imino ether groups the hydroxy group of the aldol adducts has to be protected prior to hydrolysis. The acetate[4], the 2-methoxyethoxymethyl (MEM)[4a], and the benzyloxymethyl (BOM) group[5] were suitable for this purpose, but the deprotection of the corresponding protected serine esters turned out to be difficult. Due to the vigorous reaction conditions for the deprotection only small amounts of the serine esters were obtained[6].

This communication describes a widely applicable method for the smooth hydrolysis of unprotected bislactim ether aldol adducts





3-9	R^1	R^2	yield of 4 (%)	yield of 5 (%)	
				method A	method B
a	H	C_6H_5	84	65	56
b	H	CH_3-CH=CH-	91	63	21
c	H	$CH_3(CH_2)_2$-	84	67	24
d	H	CH_3-CH=CH-$(CH_2)_2$-	86	69	--
e		-$(CH_2)_5$-	96	73	16

of type **4**, yielding serine esters with alkyl, aryl, cyclic, and unsaturated substituents at C-3[7]. The formation of the undesired dipeptide esters **6** and **7** can be avoided by using 0.1 N trifluoroacetic acid (TFA) instead of HCl for the hydrolysis (Method A). The serine methyl esters **5** were obtained – besides methyl L-valinate (67–83%) – diastereomerically and enantiomerically pure in 64–73% yield. Even 2′,2′-disubstituted aldol adducts like the cyclohexanone adduct **4e** can be hydrolyzed under these reaction conditions affording the serine methyl ester **5e** in 73% yield.

The remarkable improvement in the hydrolysis of the bislactim ether adducts **4** achieved by using TFA is evidently based on the nonnucleophilic character of the trifluoroacetate ion. Hydrolysis with HCl results in a nucleophilic attack of the chloride ion at the methyl imino ether group of the protonated bislactim ether **9** and probably leads to the formation of the undesired dipeptides **6** and **7** and the diketopiperazines **8**. In contrast to this, the trifluoroacetate ion is not able to cleave the methoxy bond.

According to these and other recent results[8] from our laboratory, the hydrolysis of substituted bislactim ethers by using TFA affords the corresponding amino acid esters in higher yields and with less byproducts in comparison with the hydrolysis using HCl.

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Experimental

The bislactim ether **1** was prepared as described[9] or purchased from Merck-Schuchardt[10]. (*E*)-4-Hexenal (**3d**) was prepared according to ref.[11]. – ^{1}H- and ^{13}C-NMR spectra: Varian XL 200. – IR spectra: Perkin-Elmer 298. – Optical rotations: Perkin-Elmer polarimeter 141. – Low-pressure chromatography: silica gel, Merck, 240–400 mesh.

Aldol Adducts **4**. – *General Procedure:* Butyllithium (5.5 mmol, 3.2 ml of a 1.7 N solution in hexane) was added at −75°C to a solution of **1** (0.92 g, 5 mmol) in anhydrous THF (20 ml). After the resultant solution was stirred for 30 min, chlorotris(diethylamido)-titanium (5.5 mmol, 2.75 g of a 60% solution in hexane) was added and stirring continued for 1 h (formation of **2**). Then the aldehyde **3a**, **b**, **c**, or **d** (6 mmol) was added and stirring continued for 12 h. [For the preparation of **4e** cyclohexanone (6 mmol) was added to the solution of the lithium azaenolate of the bislactim ether and stirring continued for 12 h]. The reaction mixture was allowed to warm up to 0°C and phosphate buffer solution (25 ml, pH = 7) was added. Volatiles were removed in vacuo and the residue was extracted with four portions of diethyl ether (20 ml each). The combined ether layers were dried with magnesium sulfate, the solvent removed in vacuo, and the crude compounds **4** were purified by chromatography (silica gel, 50 g; ether/petroleum ether, 1:1).

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-phenylmethanol (**4a**): 0.64 g (6 mmol) of **3a** was used, yield 1.22 g (84%) of **4a**, R_f = 0.17. – IR (KBr): $\tilde{\nu}$ = 3160–3600 (O–H), 1695 (C=N), 1600 cm^{-1} (C=C). – ^{1}H NMR ($CDCl_3$): δ = 0.66 and 0.96 [2 d, J = 7 Hz, 3 H each, CH(CH_3)$_2$], 2.20 [dsept, J_1 = 7 Hz, J_2 = 3.6 Hz; 1 H, CH(CH$_3$)$_2$], 2.90 (br.; 1 H, OH), 3.69 and 3.74 (2 s; 3 H each, OCH$_3$), 3.77 (dd, $^5J_1$ = J_2 = 3.6 Hz, 1 H, 5′-H), 4.28 (dd, $^5J_1$ = J_2 = 3.6 Hz; 1 H, 2′-H), 5.10 (d, J = 3.6 Hz; 1 H, 1-H), 7.08–7.44 (m; 5 H, phenyl).– ^{13}C NMR ($CDCl_3$): δ = 16.70, 19.04 [CH(*C*H$_3$)$_2$], 31.62 [*C*H(CH$_3$)$_2$], 52.57 (2 OCH$_3$), 60.78, 61.23 (C-2′ and -5′), 74.33 (C-1), 126.57, 127.32, 127.83, 141.62 (phenyl), 161.48, 165.89, (C-3′ and -6′).

$C_{16}H_{22}N_2O_3$ (290.4) Calcd. C 66.19 H 7.64
Found C 66.24 H 7.68

(1S,2E)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-2-buten-1-ol (**4b**): 0.42 g (6 mmol) of **3b** was used; yield 1.16 g (91%) of **4b**; R_f = 0.22. – Spectroscopic data see. ref.[4a].

(1S)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-1-butanol (**4c**): 0.43 g (6 mmol) of **3c** was used; yield 0.85 g (66%) of **4c**; R_f = 0.15. – IR (film): $\tilde{\nu}$ = 3100–3600 (O–H), 1695 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.71 and 1.04 [2 d, J = 7 Hz; 3 H each, CH(CH_3)$_2$], 0.94 (t, J = 6 Hz; 3 H, 3-CH$_3$), 1.54 [m; 4 H, (CH$_2$)$_2$], 1.88 (d, br., J = 10 Hz; 1 H, OH), 2.25 [dsept, J_1 = 7 Hz, J_2 = 3 Hz; 1 H, CH(CH$_3$)$_2$], 3.71 and 3.75 (2 s; 3 H each, OCH$_3$), 3.98 (m; 3 H, 1-H, 2′-H and 5′-H). – ^{13}C-NMR ($CDCl_3$): δ = 14.14 (C-4), 16.78, 19.08 [CH(*C*H$_3$)$_2$], 19.29, 35.95, (C-2 and -3), 31.94 [*C*H(CH$_3$)$_2$], 52.52, 52.56 (2 OCH$_3$), 59.61, 60.93 (C-2′ and -5′), 72.34 (C-1), 162.31, 165.53 (C-3′ and -6′).

$C_{13}H_{24}N_2O_3$ (256.3) Calcd. C 60.91 H 9.44
Found C 60.98 H 9.37

(1S,4E)-1-[(2′R,5′S)-2′,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]-4-hexen-1-ol (**4d**): 0.59 g (6 mmol) of **3d** was used; yield 0.92 g (65%) of **4d**; R_f = 0.21 (ether/petroleum ether, 1:2). – IR (film): $\tilde{\nu}$ = 3200–3650 (O–H), 1600–1700 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): δ = 0.71 and 1.04 [2 d, J = 7.2 Hz; 3 H each, CH(CH_3)$_2$], 1.66 (m, 5 H, CH$_2$ and 5-CH$_3$), 1.94 (d, J = 9 Hz; 1 H, OH), 2.17 (m, 2 H, CH$_2$), 2.24 [dsept, J_1 = 7.2 Hz, J_2 = 3.2 Hz; 1 H, CH(CH$_3$)$_2$], 3.71 and 3.75 (2 s; 3 H each, OCH$_3$), 2.99 (m, 3 H, 2′-H, 5′-H and 1-H), 5.49 (m, 2 H, 4-H and 5-H). – ^{13}C NMR ($CDCl_3$): δ = 16.77, 19.06 [CH(*C*H$_3$)$_2$], 17.95 (5-CH$_3$), 29.10, 33.59 (C-2 and -3), 31.92 [*C*H(CH$_3$)$_2$], 52.53, 52.58 (2 OCH$_3$), 59.57, 60.90 (C-2′ and -5′), 72.11 (C-1), 125.20, 130.94 (C-4 and -5), 162.17, 165.51 (C-3′ and -6′).

$C_{15}H_{26}N_2O_3$ (282.4) Calcd. C 63.80 H 9.29
Found C 63.69 H 9.20

1-[(2′R,5′S)-2,5′-Dihydro-5′-isopropyl-3′,6′-dimethoxy-2′-pyrazinyl]cyclohexanol (**4e**): 0.59 g (6 mmol) of **3e** was used; yield 1.35 g (96%) of **4e**; R_f = 0.44, m.p. = 62°C. – IR (KBR): $\tilde{\nu}$ = 3100–3600 (O–H), 1695 cm^{-1} (C=N). – ^{1}H NMR ($CDCl_3$): δ = 0.68 and 1.07 [2 d, J = 7.2 Hz; 3 H each, CH(CH_3)$_2$], 1.38–1.78 [m, 10 H, (CH$_2$)$_5$], 2.31 [dsept., J_1 = 7.2 Hz, J_2 = 3.2 Hz; 1 H, CH(CH$_3$)$_2$], 3.32 (br.; 1 H, OH), 3.72 and 3.74 (2 s; 3 H each, OCH$_3$), 3.90 (d, ^5J = 3.2 Hz; 1 H, 2′-H), 3.94 (dd, $^5J_1$ = J_2 = 3.2 Hz; 1 H, 5′-H). – ^{13}C NMR ($CDCl_3$): δ = 16.50, 19.17 [CH(*C*H$_3$)$_2$], 21.59, 21.86, 25.93, 33.24, 33.91 [(CH$_2$)$_5$], 31.32 [CH(CH$_3$)$_2$], 52.35, 52.62 (2 OCH$_3$), 60.92, 64.32 (C-2′ and -5′), 74.26 (C-1), 161.91, 164.44 (C-3′ and -6′).

$C_{15}H_{26}N_2O_3$ (282.4) Calcd. C 63.80 H 9.28
Found C 63.95 H 9.32

Serine Methyl Esters **5**. – *General Procedure*: A 0.2 N solution of **4** in acetonitrile was added with stirring to 3 eq. of 0.1 N aqueous TFA and stirring continued for 20 h at ambient temperature. The mixture was evaporated to dryness, the residue was diluted with methylene chloride (20 ml) and conc. aqueous ammonia was added until pH = 10. The solvent was removed in vacuo and the residue chromatographed (silica gel, 10 g; ether/acetonitrile/conc. aqueous ammonia, 10:1:0.1).

Methyl (2R,3S)-2-Amino-3-hydroxy-3-phenylpropanoate (**5a**): 0.32 g (1.1 mmol) of **4a** was used; yield 0.14 g (65%) of **5a**: R_f = 0.21, $[\alpha]_D^{20}$ = −10.97 (*c* = 1.4, methanol). – IR (KBr): $\tilde{\nu}$ = 2980–3640 (O–H, NH$_2$), 1725 (O–C=O), 1580 cm^{-1}

($C-NH_2$). – ^1H NMR ($CDCl_3$): δ = 2.36 (br.; 3H, NH_2 and OH), 3.63 (d, J = 4.5 Hz; 1H, 2-H), 3.67 (s; 3H, OCH_3), 4.91 (d, J = 4.5 Hz; 1H, 3-H), 7.34 (m; 5H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 52.18 (OCH_3), 60.64 (C-2), 74.08 (C-3), 125.95, 127.75, 128.37, 140.93 (phenyl), 173.63 (C-1).

$C_{10}H_{13}NO_3$ (195.2) Calcd. C 61.53 H 6.71
Found C 61.27 H 6.68

Methyl (2R,3S,4E)-2-Amino-3-hydroxy-4-hexenoate (**5b**): 0.40 g (1.6 mmol) of **4b** was used; yield 0.16 g (63%) of **5b**; R_f = 0.16, $[\alpha]_D^{20}$ = −22.08 (c = 1.4, methanol). – IR (film): $\tilde{\nu}$ = 3060–3640 (O–H, NH_2), 1725 (O–C=O), 1585 cm^{-1} ($C-NH_2$). – ^1H NMR ($CDCl_3$): δ = 1.74 (ddd, J_1 = 6.5 Hz, $^4J_2$ = 1.5 Hz, $^5J_3$ = 0.8 Hz; 3H, 5-CH_3), 2.23 (br.; 3H, NH_2 and OH), 3.47 (d, J = 5 Hz; 1H, 2-H), 3.77 (s; 3H, OCH_3), 4.26 (dddq, J_1 = 6.5 Hz, J_2 = 5 Hz, $^4J_3$ = 1 Hz, $^5J_4$ = 0.8 Hz; 1H, 3-H), 5.53 (ddq, J_1 = 15.5 Hz, J_2 = 6.5 Hz, $^4J_3$ = 1.5 Hz; 1H, 4-H), 5.82 (ddq, J_1 = 15.5 Hz, $^4J_2$ = 1 Hz, J_3 = 6.5 Hz; 1H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 17.79 (C-6), 52.16 (OCH_3), 59.08 (C-2), 73.29 (C-3), 128.95, 129.96, (C-4 and -5), 174.02 (C-1).

$C_7H_{13}NO_3$ (159.2) Calcd. C 52.82 H 8.23
Found C 52.66 H 8.27

Methyl (2R,3S)-2-Amino-3-hydroxyhexanoate (**5c**): 0.33 g (1.3 mmol) of **4c** was used; yield 0.14 g (67%) of **5c**; R_f = 0.17, $[\alpha]_D^{20}$ = −20.76 (c = 1.2, methanol). – IR (film): $\tilde{\nu}$ = 3040–3620 (O–H, NH_2), 1720 (O–C=O), 1575 cm^{-1} ($C-NH_2$). – ^1H NMR ($CDCl_3$): δ = 0.95 [m; 3H, CH_2CH_3], 1.22–1.63 [m; 4H $(CH_2)_2$], 2.15 (br.; 3H, NH_2 and OH), 3.38 (d, J = 4.5 Hz: 1H, 2-H), 3.77 (s; 3H, OCH_3), 3.78 (m; 1H, 3-H). – ^{13}C NMR ($CDCl_3$): δ = 14.02 (C-6), 19.01 (C-5), 36.10 (C-4), 52.21 (OCH_3), 58.42 (C-2), 71.83 (C-3), 174.89 (C-1).

$C_7H_{15}NO_3$ (161.2) Calcd. C 52.16 H 9.38
Found C 52.25 H 9.38

Methyl (2R,3S,6E)-2-Amino-3-hydroxy-6-octenoate (**5d**): 0.56 g (2 mmol) of **4d** was used; yield 0.26 g (69%) of **5d**; R_f = 0.46, $[\alpha]_D^{20}$ = −32.77 (c = 1.0, methanol). – IR (film): $\tilde{\nu}$ = 3000–3600 (O–H, NH_2), 1720 (O–C=O), 1580 cm^{-1} ($C-NH_2$). – ^1H NMR ($CDCl_3$): δ = 1.56 (m; 2H, CH_2), 1.64 (ddt, J_1 = 4 Hz, J_2 = 1.2 Hz, J_3 = 0.8 Hz; 3H, 7-CH_3), 2.13 (m; 2H, CH_2), 2.18 (br.; 3H, OH and NH_2), 3.49 (d, J = 4 Hz; 1H, 2-H), 3.77 (s; 3H, OCH_3), 3.80 (dt, J_1 = 4 Hz, J_2 = 8 Hz; 1H, 3-H), 5.46 (m; 2H, 6-H and 7-H). – ^{13}C NMR ($CDCl_3$): δ = 17.93 (C-8), 28.82, 33.81 (C-4 and -5), 52.25 (OCH_3), 58.41 (C-2), 71.58 (C-3), 125.59, 130.50 (C-6 and -7), 174.74 (C-1).

$C_9H_{17}NO_3$ (187.2) Calcd. C 57.73 H 9.15
Found C 57.58 H 8.98

Methyl (2R)-2-Amino-2-(1'-hydroxycyclohexanyl)acetate (**5e**): 0.31 g (1.1 mmol) of **4e** was used; yield 0.15 g (73%) of **5e**; R_f = 0.19, $[\alpha]_D^{20}$ = −42.32 (c = 1.7, methanol). – IR (film): $\tilde{\nu}$ = 3060–3640 (O–H, NH_2), 1725 (O–C=O), 1585 cm^{-1} ($C-NH_2$). – ^1H NMR ($CDCl_3$): δ = 1.11–1.35 and 1.37–1.77 [2m; 10H, $(CH_2)_5$], 2.10 (br.; 3H, NH_2 and OH), 3.31 (s, 1H, 2-H), 3.75 (s; 3H, OCH_3). – ^{13}C NMR ($CDCl_3$): δ = 21.57, 21.78, 25.76, 33.41, 34.30 [$(CH_2)_5$], 51.88 (OCH_3), 62.34 (C-2), 71.80 (C-1'), 174.86 (C-1).

$C_9H_{17}NO_3$ (187.2) Calcd. C 57.73 H 9.15
Found C 57.45 H 9.27

CAS Registry Numbers

1: 78342-42-4 / **2**: 133800-85-8 / **3a**: 100-52-7 / **3b**: 123-73-9 / **3c**: 123-72-8 / **3d**: 25166-87-4 / **3e**: 108-94-1 / **4a**: 87378-25-4 / **4b**: 107384-37-2 / **4c**: 135514-16-8 / **4d**: 135514-17-9 / **4e**: 135514-18-0 / **5a**: 87936-34-3 / **5b**: 135514-19-1 / **5c**: 135514-20-4 / **5d**: 135514-21-5 / **5e**: 135514-22-6 / methyl L-valinate: 4070-48-8 / chlorotris(diethylamino)titanium: 6607-37-0

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