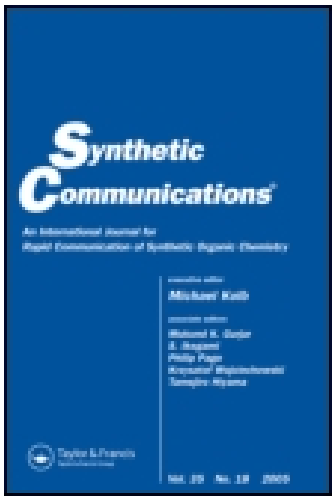

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A Versatile Method for the Preparation of Enantiomeric Benzene-1,2-*bis*(alanine) Derivatives

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ABSTRACT

A versatile method for the preparation of dicarba analogues of cystine as substituted benzene-, dihydrobenzene-, and tetrahydrobenzene-1,2-*bis*(alanine) derivatives is described. The partially saturated products resulted from Diels-Alder adduct formation with stereoselectively prepared (2*R*,7*R*)-2,7-diacetamido-4,5-*bis* (methylene)octane-1,8-dioic acid dimethyl ester. Aromatization of the dihydro adducts by manganese dioxide provided the parent benzene-1,2-*bis*(alanine) derivatives.

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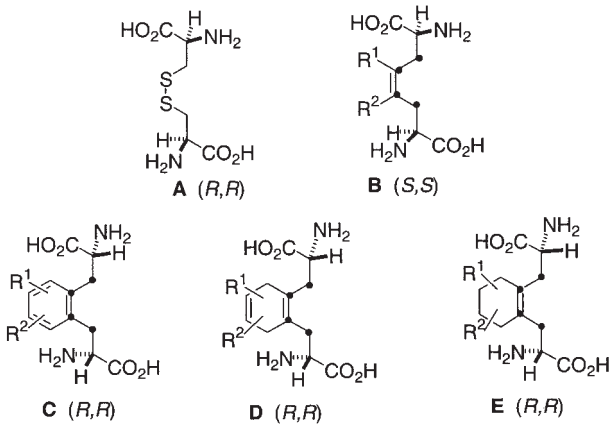
Key Words: Dicarba cystines; Rigid *bis*(α-amino acids); Benzene-1,2-*bis*(alanines).

INTRODUCTION

Incorporation of conformationally constrained noncoded amino acids into peptides will affect secondary and tertiary peptide structures and thereby provide useful information about structural requirements for bioactivity.[1] We have reported on synthetic routes for the preparation of conformationally restricted or stiffened amino acid analogues (*vide infra*) and in particular for the preparation of dicarba analogues of cystine which is a main structural element in peptide and protein architecture. When cystine exerts mainly a skeletal, structural function, isosteric structures may be envisaged to take its place. In some cases it may also be desirable to replace cystine with a nonreducible isosteric analogue. In the structurally simplest case, when the -CH_2-*S*-*S*-CH_2- bridge between the two glycine α-carbons in (*R*)-cystine is replaced by an all-carbon -$(CH_2)_4$-bridge, the new C_4-bridge amino acid (*S*,*S*)-2,7-diaminosuberic acid [(*S*,*S*)-2,7-diaminooctanedioic acid] is a nonreducible isosteric dicarba analogue of cystine. Early studies of the replacement of cystine by (*S*,*S*)-2,7-diaminosuberic acid in essential peptides include work with peptides such as oxytocin, calcitonin, and somatostatin.[2]

In Sch. 1 cystine has been drawn in a *cisoid* form **A**. The dicarba analogues **B–E** can be regarded as derived from the *cisoid* form, the alkene **B** from (*R*)-cystine, the ring structures **C–E** from (*S*)-cystine. Replacement of the disulfide linkage with an ethylene unit will increase the conformational freedom of the bridged amino acid as compared to cystine. Substitution in the C_4-bridge, however, will increase conformational constraints and may be explored for subtle-tuning of conformational constraints in the amino acid and its derived peptides. For the purpose of generating molecules with strongly favored conformers, two vicinal hydroxy substituents have been introduced and fixed as a five-membered acetal in the bridge.[3] Additional substitution at the glycine α-carbon provides conformationally constrained quaternary bridged cystine analogues.[4]

We and others have introduced conformational constraints by insertion of a C–C double bond in the chain with *trans*-stereochemistry[3,5–7] and with *cis*-stereochemistry as in structure **B** in Sch. 1.[3,5] Additional carbosubstitution in the unsaturated bridge has



Scheme 1.

been effected.[5] C_4-Bridged structures with triple bond insertion have been described.[8,9] Additional α-substitution in the glycine with propargyl units, and with allyl and propenyl units, provide novel and highly unsaturated and conformationally constrained bridge amino acids.[9] Such structures have been employed as intermediates in the preparation of strongly rigidified cystine substitutes in which the α-carbons of the amino acid were embedded in annulated cyclic bridge structures.[10,11] Benzene-1,4-*bis*(glycine) constitutes another C_4-bridge structure with high conformational restrictions related to *cis*-conformational species of cystine.[12] α,α′-Substitution in *o*-xylene will provide a C_4-bridge with an inserted benzene ring between two glycine units as drawn in structure **C** in Sch. 1. Groups of corresponding dihydrobenzene **D** and tetrahydrobenzene **E** derivatives become accessible by the work herein described.

The aromatic structure **C** can also be regarded as benzene-1,2-*bis* (alanine).[13] The latter was first prepared by α,α′-dibromo-1,2-xylene alkylation of lithiated Seebach chiron (*S*)-2-*t*-butyl-1-*t*-butyloxycarbonyl-3-methyl-4-imidazolidinone. High yield and diastereoselectivity were obtained.[14] The methodology suffers from the vigorous acidic conditions required for hydrolytic cleavage of the imidazolidinone intermediate, and is thus limited to the preparation of acid stable products as in the present case.[14] Hydrolysis of the alkylation product from the Schöllkopf chiron (*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine is normally effected under mild acid conditions to furnish the new amino acid. Good stereoselectivity in the alkylation reactions

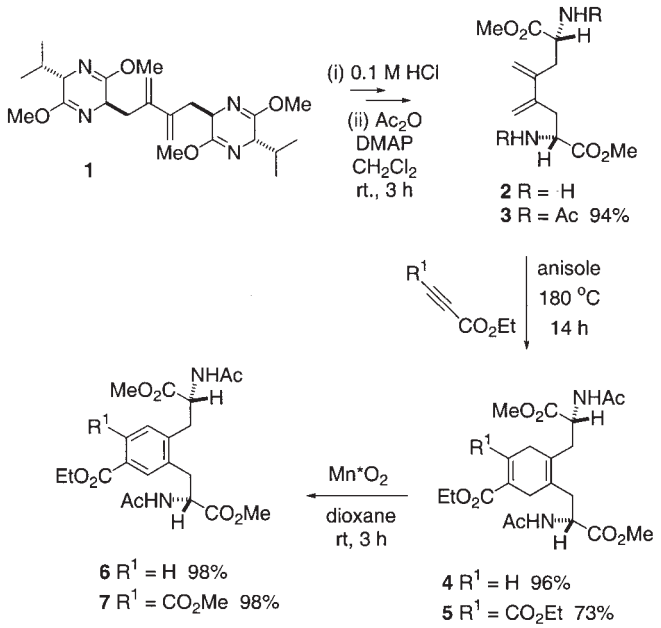
is often observed. However, the stereoselectivity was moderate with the lithiated Schöllkopf chiron and α,α′-dichloro-1,2-xylene.[13] Moderate stereoselectivity has also been observed with related vicinal dialkylating agents. It is our experience, however, that the diastereomeric products are readily separated by flash chromatography.[13] In an alternative approach for the preparation of benzene-1,2-*bis*(alanine), a benzophenone-derived glycine imine was used as substrate for enantioselective alkylation under phase transfer conditions with chiral quaternary ammonium salts derived from cinchona alkaloids. The bridged *bis*-imine product was formed in a moderate yield, but with high enantiomeric excess using α,α′-dibromo-1,2-xylene. Subsequent hydrolysis under mild acidic conditions furnished the amino acid.[7] In a second procedure, the chiron (*S,S*)-1,4-*bis*(2-phenethyl)diketopiperazine was alkylated with α,α′-dibromo-1,2-xylene resulting in high diastereoselectivity. Strongly acidic conditions, 57% HI, were used for the hydrolysis to furnish the amino acid product.[15]

RESULTS AND DISCUSSION

In a search for a versatile method which would allow access to both aromatic, dihydro, and tetrahydro benzene rings inserted into the C_4-bridge, the 1,3-diene (2*R*,7*R*)-2,7-diacetamido-4,5-*bis*(methylene) octane-1,8-dioic acid dimethyl ester (**3**) in Sch. 2 was the substrate.

The substrate **1** was prepared in a two-step process, initially by alkylation of lithiated (*S*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine with 2,3-dibromopropene which proceeded with high diastereoselectivity (92%, de. 94%).[16] A subsequent homocoupling gave the substrate **1** under Pd(0)-catalysis. Mild conditions for acid hydrolysis provided the stereochemically pure diamine **2** (Sch. 2). For the Diels-Alder reaction the amino groups were protected by acylation. For simplicity acetylation was used to provide the substrate **3**. In the literature the diethyl ester analogue of the acetylated compound **3** has been described as a stereoisomeric mixture after a preparation from ethyl α-acetamido-4-tributylstannyl-4-pentenoate by a copper(II) nitrate mediated homocoupling process.[17] In a different approach, the lithium enolate from the benzophenone imine of glycine ethyl ester and 1,4-dibromo-2,3-dimethylenebutane were reacted under the influence of Pd(0)-catalysis to form the corresponding *bis*(imino) ester. Acid hydrolysis of the product yielded a stereoisomeric mixture.[6]

An initial attempt to effect a Diels-Alder reaction with the bulky diene **1** as substrate was unsatisfactory. The homocoupled diene **1** was



Scheme 2.

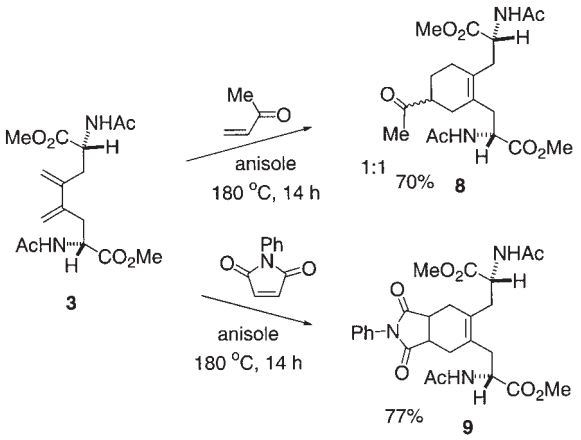
therefore hydrolyzed to the corresponding amino acid and the amino groups protected by acetylation. Anisole was found to be a good solvent for the Diels-Alder reaction at 180°C. The principle is illustrated with ethyl propiolate and diethyl acetylenedicarboxylate as dienophiles. High yields of the dihydrobenzene adducts **4** and **5** resulted. The products belong to the group **D** classification in Sch. 1.

Aromatization reactions with activated manganese dioxide gave the benzene *bis*(amino acid) derivatives **6** and **7** in almost quantitative yields.

For the preparation of tetrahydrobenzene-bridged dicarba analogues **E** of cystine (Sch. 1), olefinic dienophiles were used. From the reaction with methyl vinyl ketone the tetrahydro derivative **8** was isolated as a stereoisomeric 1:1 mixture. The apparent lack of stereoselectivity may result from epimerization of the acetyl group under the conditions of the reaction, or simply for lack of stereocontrol in the adduct formation.

With *N*-phenylmaleinimide as dienophile, the tetrahydrobenzene adduct **9** was isolated in high yield.

In conclusion, we describe a versatile method for the preparation of substituted benzene-, dihydrobenzene-, and tetrahydrobenzene-1,2-*bis* (alanine) derivatives as sterically constrained dicarba analogues of



Scheme 3.

cystine. The partially saturated products resulted from Diels-Alder adduct formation with stereoselectively prepared (2*R*,7*R*)-2,7-diacetamido-4,5-*bis*(methylene)octane-1,8-dioic acid dimethyl ester. Aromatization of the dihydro Diels-Alder adducts by manganese dioxide provided the parent benzene-1,2-*bis*(alanine) derivatives.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 200 MHz or 300 MHz and the ^{13}C NMR spectra at 50 MHz or 75 MHz. The mass spectra under electron impact conditions were recorded at 70 eV (EI). Methane was used for chemical ionization (CI). The spectra are presented as *m*/*z* (% rel. int). Infrared spectra were recorded on a Nicolet Magna FT-IR 550 spectrometer using ATR (attenuated total reflectance).

(2*R*,7*R*)-2,7-Diacetamido-4,5-*bis*(methylene)octane-1,8-dioic acid dimethyl ester (3). Acetic anhydride (0.44 g, 4.32 mmol) in dry dichlorometane (5 mL) was added dropwise to a solution of (2*R*,7*R*)-2,7-diamino-4,5-*bis* (methylene)octane-1,8-dioic acid dimethyl ester (**2**) (0.46 g, 1.79 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.53 g, 4.32 mmol) in dry dichloromethane (20 mL) under argon at 0°C. The mixture was stirred at 0°C for 2 h, at ambient temperature for 3 h, diluted with dichloromethane, and washed with 10% aqueous ammonium chloride. The dried ($MgSO_4$) solution was evaporated, and the product was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 0.58 g (94%) of a yellow solid.

M.p.: 207–210°C. Found: C, 56.04; H, 7.13. Calcd. for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11%. $[\alpha]_D$ −48.6 ($c = 0.0078$ in $CHCl_3$). IR (ATR plate): ν_{max} cm^{-1} 3292 (m), 3078 (w), 2999 (w), 2955 (m), 1740 (s), 1743 (s), 1652 (s), 1655 (s), 1541 (m), 1436 (m), 1374 (m), 1270 (w), 1208 (m), 1013 (w), 909 (w), 752 (w). ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 6H, 2 × C-CH_3), 2.71 (dd, J 6.2 and 14.3 Hz, 2H, 2 × CH_2C=), 2.86 (dd, J 5.1 and 14.3 Hz, 2H, 2 × CH_2C=), 3.71 (s, 6H, 2 × OCH_3), 4.69 (ddd, J 5.1, 6.2 and 8.3 Hz, 2H, 2 × C*H*CH_2), 4.97 (s, 2H, 2 × =CH_2), 5.19 (s, 2H, 2 × =CH_2), 6.69 (d, J 8.3 Hz, 2H, 2 × NH). ^{13}C NMR ($CDCl_3$): δ 23.5 (2 × C-*C*H_3), 36.7 (2 × *C*H_2C=), 51.3 (2 × N*C*HCH_2), 52.6 (2 × OCH_3), 116.5 (2 × =CH_2), 140.3 (2 × *C*=CH_2), 168.9 (2 × NC=O), 171.7 (2 × OC=O). MS(EI): 340 (2, M^+), 309 (2), 297 (5), 281 (7), 222 (19), 210 (100), 190 (18), 180 (40), 168 (67), 150 (39), 108 (70), 88 (82), 43 (74).

Dimethyl (2′*R*,2″*R*)-3,6-dihydro-4-ethoxycarbonylbenzene-1,2-*bis*(2′-acetamido-3′-propionate) (4). (2*R*,7*R*)-2,7-Diacetamido-4,5-*bis*(methylene) octane-1,8-dioic acid dimethyl ester (**3**) (63 mg, 0.186 mmol) and ethyl propiolate (24 mg, 0.242 mmol) were heated together in dry anisole (2.5 mL) in a sealed tube at 180°C for 14 h. The anisole was removed by distillation at reduced pressure and the residual product was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 78 mg (96%) of a yellow-white solid. M.p.: 146–149°C. $[\alpha]_D$ −34.6 ($c = 0.073$ in $CHCl_3$). IR (ATR plate): ν_{max} cm^{-1} 3287 (m), 3069 (w), 2984 (w), 2955 (m), 2852 (w), 1744 (s), 1718 (s), 1655 (s), 1541 (m), 1437 (m), 1373 (m), 1274 (s), 1216 (s), 1179 (m), 1134 (m), 1022 (m), 758 (m). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J 7.1 Hz, 3H, CH_2CH_3), 1.96 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 2.38 (dd, J 9.5 and 14 Hz, 1H, CH_2CH_2C), 2.46 (dd, J 9.4 and 14 Hz, 1H, CH_2CH_2CH), 2.55 (dd, J 6.5 and 14 Hz, 1H, CH_2CH_2CH), 2.60 (dd, J 6.0 and 14.0 Hz, 1H, CH_2CH_2C), 2.82 (s, 4H, =CHCH_2 and =CCH_2C=), 3.69 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.14 (q, J 7.1 Hz, 2H, C$H_2$$CH_3$), 4.5–4.8 (m, 2H, 2 × C*H*-NH), 6.58 (d, J 7.7 Hz, 1H, NH), 6.72 (d, J 7.4 Hz, 1H, NH), 6.84 (s, 1H, =C*H*-CH_2). ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_2*C*H_3), 22.7, 22.8 (2 × NCO*C*H_3), 30.2, 31.5 (=CH*C*H_2 and =C*C*H_2C=), 34.4 (NCH*C*H_2), 35.0 (NCH*C*H_2), 50.6, 51.0 (2 × N*C*HCH_2), 52.5 (2 × OCH_3), 60.5 (*C*$H_2$$CH_3$), 125.4 (N*C*HC$H_2$), 127.2, 127.3 (3 × =*C*-CH_2), 135.2 (=*C*HCH_2), 166.3 (C=C*C*O_2), 170.4, 170.5 (2 × NHC=O), 172.7, 172.8 (2 × CH-*C*O_2). MS(EI): 438 (2, M^+), 437 (5), 409 (14), 395 (1), 393 (4), 364 (6), 349 (2), 332 (13), 294 (11), 262 (27), 248 (32), 204 (23), 88 (48), 43 (100).

Dimethyl (2′*R*,2″*R*)-3,6-dihydro-4,5-*bis*(ethoxycarbonyl)benzene-1,2-*bis*(2′-acetamido-3′-propionate) (5). (2*R*,7*R*)-2,7-Diacetamido-4,5-*bis* (methylene)octane-1,8-dioic acid dimethyl ester (**3**) (64 mg, 0.188 mmol)

and diethyl acetylenedicarboxylate (42 mg, 0.245 mmol) were heated together in dry anisole (2.5 mL) in a sealed tube at 180°C for 14 h. The anisole was distilled off at reduced pressure and the product was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 70 mg (73%) of a white solid. M.p.: 150–153°C. HRMS: Calcd. for $C_{24}H_{34}N_2O_{10}$: 510.2213. Found: 510.2203. $[\alpha]_D$ −36.8 ($c = 0.0176$ in $CHCl_3$). IR (ATR plate): ν_{max} cm^{-1} 3280 (m), 3065 (w), 2985 (m), 2956 (w), 1732 (s), 1728 (s), 1659 (s), 1542 (m), 1438 (m), 1371 (m), 1297 (s), 1219 (s), 1176 (m), 1140 (m), 1037 (m), 1022 (m), 755 (m). ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J 7.1 Hz, 6H, 2 × CH_2CH_3), 1.98 (s, 6H, 2 × CCH_3), 2.42 (dd, J 9.3 and 14.2 Hz, 2H, 2 × $CHCH_2$), 2.59 dd, J 6.3 and 14.2 Hz, 2H, 2 × $CHCH_2$), 2.93 (s, 4H, 2 × =CCH_2C=), 3.70 (s, 6H, 2 × OCH_3), 4.18 (q, J 7.1 Hz, 4H, 2 × CH_2CH_3), 4.64 (ddd, J 6.3, 7.4 and 9.3 Hz, 2H, 2 × $CHCH_2$), 6.64 (d, J 7.4 Hz, 2H, 2 × NH). ^{13}C NMR ($CDCl_3$): δ 14.0 (2 × CH_2CH_3), 22.7 (2 × CCH_3), 32.3 (2 × =CCH_2C=), 34.5 (2 × $CHCH_2$), 50.7 (2 × $NCHCH_2$), 52.5 (2 × OCH_3), 61.3 (2 × CH_2CH_3), 125.7 (2 × $CHCH_2$-C=), 131.7 (2 × =CC=O), 167.2 (2 × C=C-CO_2), 170.4 (2 × NC=O), 172.5 (2 × $CHCO_2$). MS(EI): 510 (2, M^+), 481 (6), 479 (4), 451 (2), 435 (20), 393 (20), 380 (3), 366 (17), 334 (17), 320 (100), 276 (21), 264 (12), 250 (13), 245 (12), 204 (19), 88 (22), 43 (31).

Dimethyl (2′*R*,2″*R*)-4-ethoxycarbonylbenzene-1,2-*bis*(2′-acetamido-3-propionate) (6). Dimethyl (2′*R*,2″*R*)-3,6-dihydro-4-ethoxycarbonylbenzene-1,2-*bis*(2′-acetamido-3′-propionate) (**4**) (68 mg, 0.155 mmol) was stirred together with activated manganese dioxide (310 mg) in dioxane (5 mL) at ambient temperature for 3 h. The reaction mixture was filtered, the filtrate evaporated and the product further purified by flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 66 mg (98%) of a yellow-white solid. M.p.: 152–156°C. HRMS: Calcd. for $C_{21}H_{28}N_2O_8$: 436.1845. Found: 436.1835. $[\alpha]_D$ −38.1 ($c = 0.032$ in $CHCl_3$). IR (ATR plate): ν_{max} cm^{-1} 3287 (m), 3061 (w), 2985 (w), 2955 (m), 1745 (s), 1720 (s), 1657 (s), 1547 (m), 1537 (m), 1437 (m), 1372 (m), 1275 (s), 1215 (s), 1179 (m), 1135 (m), 1023 (m), 756 (m). ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J 7.1 Hz, 3H, CH_2CH_3), 1.85 (s, 3H, $NCOCH_3$), 1.87 (s, 3H, $NCOCH_3$), 2.96 (dd, J 9.0 and 14.3 Hz, 1H, $CHCH_2$), 3.04 (dd, J 9.2 and 14.6 Hz, 1H, $CHCH_2$), 3.22 (dd, J 6.0 and 14.6 Hz, 1H, $CHCH_2$), 3.24 (dd, J 5.8 and 14.3 Hz, 1H, $CHCH$), 3.68 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.30 (q, J 7.1 Hz, 2H, CH_2CH_3), 4.7–5.0 (m, 2H, 2 × $CHNH$), 6.59 (d, J 7.8 Hz, 1H, NH), 6.72 (d, J 7.4 Hz, 1H, NH), 7.16 (d, J 8.0 Hz, 1H, H-5), 7.73 (d, J 1.8 Hz, 1H, H-2), 7.79 (dd, J 1.8 and 8.0 Hz, 1H, H-6). ^{13}C NMR (CDC_3): δ 14.2 (CH_2CH_3), 22.5, 22.6 (2 × $NCOCH_3$), 34.4, 34.9 (2 × $NCHCH_2$), 52.1, 52.2 (2 × $NCHCH_2$), 52.4, 52.5 (2 × OCH_3), 60.9 (CH_2CH_3), 128.2 (C-6), 129.1 (C-1), 129.7

(C-5), 131.3 (C-2), 135.1 (C-3), 140.2 (C-4), 166.1 (Ar-CO_2), 170.0, 170.3 ($2\times$NHC=O), 172.1, 172.2 ($2\times$CH-CO_2). MS(EI): 436 (37, M^+), 405 (10), 404 (34), 393 (16), 391 (14), 377 (15), 362 (11), 347 (7), 331 (18), 318 (25), 307 (15), 286 (20), 276 (44), 258 (72), 216 (85), 204 (62), 88 (64), 43 (100).

Dimethyl (2*R*′,2″*R*)-4,5-*bis*(ethoxycarbonyl)benzene-1,2-*bis*(2′-acetamido-3′-propionate (7). Dimethyl (2′*R*,2″*R*)-3,6-dihydro-4,5-*bis*(ethoxycarbonyl)benzene-1,2-*bis*(2′-acetamido-3′-propionate) (**5**) (54 mg, 0.106 mmol) was stirred together with activated manganese dioxide (250 mg) in dioxane (5 mL) at ambient temperature for 3 h, the reaction mixture filtered, the filtrate evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 52 mg (98%) of a white solid. M.p.: 139–142°C. HRMS: Calcd. for $C_{24}H_{32}N_2O_{10}$: 508.2057. Found: 508.2059. $[\alpha]_D$ −35.5 ($c=0.049$ in $CHCl_3$). IR (ATR plate): ν_{max} cm^{-1} 3281 (m), 3062 (w), 2984 (m), 2956 (m), 1728 (s), 1656 (s), 1546 (m), 1537 (m), 1438 (m), 1371 (m), 1297 (s), 1219 (s), 1139 (m), 1037 (m), 1022 (m), 755 (m). ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J 7.1 Hz, 6H, $2\times CH_2CH_3$), 1.90 (s, 6H, $2\times NCOCH_3$), 3.05 (dd, J 8.3 and 14.4 Hz, 2H, $2\times CHCH_2$), 3.21 (dd, J 6.3 and 14.4 Hz, 2H, $2\times CHCH_2$), 3.70 (s, 6H, $2\times OCH_3$), 4.30 (q, J 7.1 Hz, 4H, $2\times CH_2CH_3$), 4.83 (ddd, J 6.3, 7.4 and J 8.3 Hz, 2H, $2\times NCHCH_2$), 6.55 (d, J 7.4 Hz, 2H, $2\times$NH), 7.41 (s, H-3, H-6). ^{13}C NMR ($CDCl_3$): δ 14.1 ($2\times CH_2CH_3$), 22.8 ($2\times NCOCH_3$), 34.6 ($2\times NCHCH_2$), 52.2 ($2\times NCHCH_2$), 52.6 ($2\times OCH_3$), 61.7 ($2\times CH_2CH_3$), 130.6 (C-1, C-2), 130.8 (C-3, C-6), 138.4 (C-4, C-5), 167.0 ($2\times$Ar-CO_2), 170.2 ($2\times$NHC=O), 171.9 ($2\times$CH-CO_2). MS(EI): 508 (15, M^+), 477 (3), 463 (35), 449 (6), 433 (49), 419 (6), 403 (37), 391 (18), 379 (16), 362 (41), 344 (17), 333 (56), 304 (32), 288 (21), 274 (89), 44 (100).

Dimethyl (2′*R*,2″*R*)-4-acetyl-3,4,5,6-tetrahydrobenzene-1,2-*bis*(2′-acetamido-3′-propionate) (8). (2*R*,7*R*)-2,7-Diacetamido-4,5-*bis*(methylene) octane-1,8-dioic acid dimethyl ester (**3**) (72 mg, 0.212 mmol) and methyl vinyl ketone (19 mg, 0.275 mmol) were heated together in dry anisole (2.5 mL) in a sealed tube at 180°C for 14 h. The anisole was distilled off at reduced pressure and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 61 mg (70%) of a yellow oil. HRMS: Calcd. for $C_{20}H_{30}N_2O_7$: 410.2053. Found: 410.2049. ^{1}H NMR ($CDCl_3$): δ 1.4–2.0 (m, 2H, CH_2CH_2CH), 1.98 (s, 3H, $NCOCH_3$), 2.00 (s, 3H, $NCOCH_3$), 1.9–2.2 (m, 4H, $CH_2CHCH_2C=$ and $=CCH_2CH_2$), 2.14 (s, 3H, $CHCOCH_3$), 2.3–2.7 (m, 5H, $2\times NCHCH_2$ and $CHCOCH_3$), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.5–4.8 (m, 2H, $2\times NCHCH_2$), 6.39 (d, J 7.6 Hz, 1H, NH), 6.5–6.7 (m, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 22.8, 22.9

($2 \times NCOCH_3$), 24.7 (CH_2CH_2CH), 27.8, 27.9 ($CHCOCH_3$), 28.3, 28.8, 30.6, 31.1 ($CH_2CHCH_2C=$ and CH_2CH_2CH), 35.0, 35.3, 35.4 ($2 \times NCHCH_2$), 46.9, 47.3 (CH_2CHCH_2), 50.7, 50.8, 50.9, 51.2 ($2 \times NCHCH_2$), 52.5 ($2 \times OCH_3$), 128.1, 128.9, 129.0 ($2 \times CH_2C=$), 170.2, 170.3, 170.4 ($2 \times NC=O$), 172.7, 172.8, 172.9 ($2 \times CHCO_2$), 210.7, 210.8 ($CHCOCH_3$). MS(EI): 410 (3, M^+), 379 (2), 267 (2), 351 (2), 319 (19), 280 (75), 260 (6), 250 (10), 238 (31), 179 (52), 88 (62), 43 (100).

Dimethyl (*R*,*R*)-α,α′-acetamido-1,2,3,6-tetrahydro-*N*-phenylphthalimide-4,5-dipropionate (9). (*R*,*R*)-2,7-Diacetamido-4,5-*bis*(methylene) octane-1,8-dioic acid dimethyl ester (71 mg, 0.206 mmol) and *N*-phenylmaleimide (47 mg, 0.269 mmol) were heated together in anisole (2.5 mL) at 180°C for 14 h. The solution was evaporated to dryness at reduced pressure and the product was isolated from the residue by flash chromatography on silica gel using CH_2Cl_2:MeOH 20:1. Yield: 82 mg (77%) of a yellow–white solid. M.p.: 88–90°C. HRMS: Calcd. for $C_{26}H_{31}N_3O_8$: 513.2111. Found: 513.2109. $[\alpha]_D$ −35.5 ($c = 0.0049$ in $CHCl_3$). IR (ATR plate): ν_{max} cm^{-1} 3357 (m), 3288 (m), 3064 (w), 3008 (w), 2955 (m), 2851 (w), 1741 (s), 1707 (s), 1654 (s) 1540 (m), 1500 (m), 1437 (m), 1379 (m), 1206 (m), 753 (m). ^1H NMR ($CDCl_3$): δ 1.92 (s, 3H, C-CH_3), 1.94 (s, 3H, C-CH_3), 2.2–2.8 (m, 8H, $4 \times CHCH_2$), 3.1–3.4 (m, 2H, $2 \times NCO$-C*H*), 3.67, 3.68 (s, 3H, $2 \times OCH_3$), 4.5–4.8 (m, 2H, $2 \times CHNH$), 6.53 (d, *J* 8.0 Hz, 1H, NH), 6.67 (d, *J* 7.7 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 22.6 ($NCOCH_3$), 22.7 ($NCOCH_3$), 28.6 ($NCOCHCH_2$), 29.3 ($NCOCHCH_2$), 34.9 ($NCHCH_2$), 35.2 ($NCHCH_2$), 39.3 ($NCOCH$), 39.6, ($NCOCH$), 50.8 ($NCHCH_2$), 51.6 ($NCHCH_2$), 52.4 and 52.5 ($2 \times OCH_3$), 126.1 (C-2, C-6), 128.5 (C-4), 128.9 (C-3, C-5), 131.3 ($CH_2C=$), 131.4 ($CH_2C=$), 131.7 (C-1), 170.2 ($NHC=O$), 170.3 ($NHC=O$), 172.1 (CH-CO_2), 172.5 (CH-CO_2), 178.7, 179.0 ($2 \times NCOCH$). MS(EI): 513 (10, M^+), 482 (7), 454 (8), 422 (29), 395 (5), 383 (100), 363 (32), 353 (21), 341 (80), 335 (20), 324 (20), 293 (60), 281 (50).

REFERENCES

1. (a) Cativiela, C.; Díaz-de-Villegas, M.D. Stereoselective synthesis of quaternary α-amino acids. Part 2: cyclic compounds. Tetrahedron: Asymmetry **2000**, *11*, 645; (b) Goodman, M.; Shao, H. Peptidomimetic building blocks for drug discovery: An overview. Pure Appl. Chem. **1996**, *68*, 1303; (c) Rovero, P.; Pellegrini, M.; Di Fenza, A.; Meini, S.; Quartara, L.; Maggi, C.A.; Formaggio, F.; Toniolo, C.; Mierke, D.F. Agonist activity at the kinin B1 recep-

tor: structural requirements of the central tetrapeptide. J. Med. Chem. **2001**, *44*, 274.
2. Nutt, R.F.; Strachan, R.G.; Veber, D.F.; Holly, F.W. Useful intermediates for synthesis of dicarba analogs of cystine peptides: selectively protected α-aminosuberic acid and α,α′-diaminosuberic acid of defined stereochemistry. J. Org. Chem. **1980**, *45*, 3078.
3. Kremminger, P.; Undheim, K. Asymmetric synthesis of unsaturated and bis-hydroxylated (*S*,*S*)-2,7-diaminosuberic acid derivatives. Tetrahedron **1997**, *53*, 6925.
4. Lange, M.; Undheim, K. Stereoselective synthesis of α,α′-bridged bis(α-alanine) derivatives. Tetrahedron **1998**, *54*, 5337.
5. Efskind, J.; Benneche, T.; Undheim, K. Stereoselective synthesis of alkenyl α,α′-bridged bis(glycines) using palladium promoted substitution in the bridge. Acta Chem. Scand. **1997**, *51*, 942.
6. Mazón, A.; Nájera, C.; Ezquerra, J.; Pedregal, C. Synthesis of bis(α-amino acids) by palladium-catalyzed allylic double substitution. Tetrahedron Lett. **1995**, *36*, 7697.
7. Lygo, B.; Crosby, J.; Peterson, J.A. An enantioselective approach to bis-α-amino acids. Tetrahedron **2001**, *57*, 6447.
8. Undheim, K.; Kreminger, P. Preparation of double chain peptide compounds having hemoregulatory activity. PCT Int. Appl. WO 9,324,523; Chem. Abstr. **1995**, *122*, 10682a.
9. Hoven, G.B.; Efskind, J.; Rømming, C.; Undheim, K. Ru(II)-catalyzed cascade reactions in stereocontrolled construction of rigid *as*-indacene-bridged bis(α-amino acid) derivatives. J. Org. Chem. **2002**, *67*, 2459.
10. Undheim, K.; Efskind, J. Ru(II)-catalyzed ring closing metathesis in stereoselective spiroannulations and cascade reactions of cyclic dipeptide substrates. Tetrahedron **2000**, *56*, 4847.
11. Efskind, J.; Rømming, C.; Undheim, K. Stereocontrolled construction of rigid tricyclic bis(α-amino acid) derivatives by Ru(II)-catalyzed cascade and Diels-Alder reactions. J. Chem. Soc., Perkin Trans. 1 **2001**, 2697.
12. Falck-Pedersen, M.L.; Undheim, K. Asymmetric syntheis of phenylbis(glycines). Tetrahedron **1996**, *52*, 7761.
13. Hammer, K.; Benneche, T.; Hope, H.; Undheim, K. Stereoselective synthesis of thiophenedimethyl- and benzenedimethyl-α,α′-bridged bis(glycines). Acta Chem. Scand. **1997**, *51*, 392.
14. Fitzi, R.; Seebach, D. Resolution and use in α-amino acid synthesis of imidazolidinone glycine derivatives. Tetrahedron **1988**, *44*, 5277.

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15. Paradisi, F.; Porzi, G.; Rinaldi, S.; Sandri, S. Stereoselective synthesis of α,α′-diamino-dicarboxylic acids. Part 2. Tetrahedron: Asymmetry **2000**, *11*, 4617.
16. Møller, B.S.; Benneche, T.; Undheim, K. Palladium catalysis in bridge-forming reactions between stereoselectively substituted glycine auxiliaries. Tetrahedron **1996**, *52*, 8807.
17. Crisp, G.T.; Glink, P.T. Synthesis and transformations of trialkylstannyl-substituted allylglycine derivatives. Tetrahedron Lett. **1992**, *33*, 4649.

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