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Dipeptides Containing D-Serine or D-Isoserine From the Same (R)-Aziridine-2-imide by a Simple Reversal of the Synthetic Procedure

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Abstract. The ring expansion of 3-unsubstituted (R)-aziridine-2-imide-containing dipeptide under acidic conditions gives rise to oxazoline-5-imide regio and stereosclectively, which can be hydrolysed to the dipeptide containing D-isoserine. On the other hand, the ring opening of 3-unsubstituted (R)-aziridine-2-ester dipeptide, easily obtained from the same (R)-aziridine, gives the regioisomeric dipeptide containing D-serine. © 1999 Elsevier Science Ltd. All rights reserved.

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Introduction

Several natural oligopeptides containing β -hydroxy α -amino acid¹ or α -hydroxy β -amino acid² residues possess interesting biological properties and are gaining much interest as potential pharmacological compounds. The introduction of unusual or unnatural amino acid residues in the amino acid sequence could induce massive structural modifications that strongly influence the biological activity. In this paper we describe the synthesis of D-serine and D-isoserine-containing dipeptides through ring opening of aziridine-dipeptides,³ prepared from the same (*R*)-aziridine, by changing the steps of the same synthetic plan. The asymmetric synthesis of optically pure D-serine⁴ or D-isoserine⁵ is very lengthy; moreover, hydroxy group protection-deprotection extra steps⁶ are often necessary to introduce these residues in a peptidic sequence.

N-Activated aziridines are well known versatile amino acid precursors,⁷ as they allow the synthesis of α or β -substituted amino acids by way of regio and stereoselective nucleophilic ring opening reactions in the presence of Lewis acids. Recently we reported that *N*-acyl 3-alkyl aziridine-2-imides are good β -hydroxy α -amino acid precursors⁸ and that *N*-(α -amino acyl) 3-methyl aziridines are suitable precursors of threonine-containing dipeptides.⁹ These preparations are based on a regioselective ring expansion of the three membered ring to an oxazoline.¹⁰ The reaction spontaneously occurs in the presence of a catalytic amount of Lewis acid, affording the oxazoline with retention of configuration. Concerning the regiochemistry, 3-substituted aziridines afforded in our experiments exclusive attack at C3'.

Following the same strategy, the preparation of serine or isoserine-containing dipeptides starts from the synthesis of 3-unsubstituted aziridine-2-acid derivatives in enantiomerically pure form. Unfortunately, the synthetic procedures reported in the literature¹¹ often require many steps or, starting from natural serine, they give rise to (2*S*)-aziridines.

Results and Discussion

Recently we reported the preparation of optically pure 3-unsubstituted (2R)-aziridine-2-imide 3^{11f} by way of conjugate addition of N-BOC O-benzyl hydroxylamine to chiral acryloyl imide 2. After BOC removal, cyclization gave 3 in good overall yield and 86/14 diastereoselectivity. Including hydroxylamine protection and deprotection, this procedure involved four steps. On the other hand, the straightforward diastereoselective Gabriel-Cromwell¹² reaction from 2 resulted in the synthesis of 3 in a very simple way with 80/20 diastereoselectivity (Scheme 1).

Scheme 1



The stereochemistry of the reaction is controlled by the (-)-(4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2one 1¹³ chiral auxiliary, which is also available in the opposite configuration. The acryloyl imide 2^{11f} was treated with bromine and the dibromo derivative so obtained was converted into an aziridine by bubbling ammonia in DMSO. The reaction gave a mixture of diastereoisomers in 80/20 ratio and the major R isomer 3^{11f} was isolated by flash cromatography.

The aziridine 3 was coupled with N-Ac leucine using EDCI/HOBt at 0°C in dichloromethane and DMF, giving in quantitative yield the aziridine-dipeptide 4 (Scheme 2). This compound fastly rearranged to oxazoline 5 upon treatment with boron trifluoride-Et₂O complex giving a single regio and stereoisomer. The final hydrolysis of 5 under acidic conditions afforded the leucine-isoserine dipeptide 6.



The regiochemistry of the ring expansion was determined by ¹H NMR decoupling experiments performed on 6; indeed, it was observed that the HN peptidic proton couples with the two H3' protons. To remove and recover the chiral auxiliary, 6 was treated with lithium hydroxide or lithium hydroperoxide under the conditions described by Evans for oxazolidin-2-ones,¹⁴ but yields of free dipeptide were less than 20%. In an attempt to obtain the corresponding dipeptide methyl ester 7, compound 6 was treated with methanol in the presence of boron trifluoride-Et₂O complex, giving 7 in poor yield. On the contrary, on refluxing 6 for 3h in methanol in the presence of an excess of triethylamine,¹⁵ ester 7 was obtained in 75% yield, as revealed by ¹H NMR of the crude mixture. Extended reaction times gave an increasing amount of undetermined by-products arising from decomposition of 7. The crude mixture containing 7, unreacted 6 and 1 was treated with benzoyl chloride and triethylamine and the resulting 8 was purified by flash chromatography.

To definitively confirm the regiochemistry of 5, 6, 7, and 8, commercially available *rac*-isoserine methyl ester was coupled with *N*-Ac leucine under the above reported conditions, and the diastereomeric mixture so obtained showed a ¹H NMR which contained the ¹H NMR spectra of 7.

The determination of the absolute stereochemistry of the isoserine moiety was obtained by refluxing 6 in 3N HCl/MeOH for 2h. These drastic conditions caused the complete cleavage of the chiral auxiliary and the formation of a mixture of dipeptide acid Ac-Leu-Isoser-OH, free isoserine and N-Ac leucine. After derivatization of the mixture by treatment with benzoyl chloride and diazomethane (Scheme 3), N, O-dibenzoyl isoserine methyl ester 9 was isolated and its absolute stereochemistry assumed (R) by comparison with a sample obtained by derivatization of optically pure (S)-isoserine.¹⁶



In order to also prepare a dipeptide containing a D-serine residue, we decided to remove the chiral auxiliary in an earlier stage of the procedure, and to transform the aziridine-2-imide 3 into an aziridine-2-ester. Indeed, in our experience N-acyl aziridine-2-esters or amides undergo a slow ring expansion to oxazolines compared to N-acyl aziridine-2-imides.⁸ For this reason, we anticipated that by treatment of an aziridine-2-ester dipeptide with 1 equivalent of water in the presence of a Lewis acid, a fast ring opening of aziridine in the less hindered C3 position could likely occur.⁷

Aziridine 3 was transformed into benzyl ester 10^{11f} with lithium benzyloxide in THF, according to a procedure reported in the literature by us (Scheme 4). On the other hand, treatment of 3 with triethylamine in refluxing methanol¹⁵ gave the corresponding methyl aziridine-2-carboxylic acid in 40% yield only.



We performed the coupling of 10 and N-Ac leucine with EDCI/HOBt, and this reaction gave (R)-aziridine-2-ester dipeptide 11 in essentially quantitative yield. We unsuccessfully attempted to react 11 with traces of water in the presence of boron trifluoride- Et_2O complex. Finally, treatment of 11 with MgBr₂ Et_2O and 1.1 equivalents of water in THF gave D-serine-containing dipeptide 12. The presence of a larger amount of water should be avoided, for we observed that under these conditions the Lewis acid promoted dehydration to benzyl 2-leucylamino acrylic acid 13.

The regiochemistry was determined again with ¹H NMR decoupling experiments, which demonstrated that in this case the H2 proton couples with the HN proton. Concerning the stereochemistry of the serine residue, it is sufficient to mention that the ring opening of 11 occurs by cleavage of the C3-N bond, and that no epimerization is possible at this position.

Conclusion

Starting from the same optically pure 3'-unsubstituted aziridine imide 3 it is possible to obtain both a serine and an isoserine dipeptide with retention of the (R) configuration by varying the synthetic sequence. Indeed, the ring expansion and hydrolysis of (R)-aziridine-containing dipeptide 4 carrying the chiral auxiliary 1 gives a Disoserine-containing dipeptide which can be transformed into the dipeptide Ac-Leu-D-Isoser-OMe by final removal of 1. On the other hand, the removal of 1 at the beginning gives access to (R)-aziridine-2-estercontaining dipeptide 11 which is hydrolysed to the dipeptide Ac-Leu-D-Ser-OBzl

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Experimental Section

General methods. ¹H and ¹³C NMR spectra were recorded at 300 MHz and 75 MHz respectively in CDCl₃ with a Varian Gemini apparatus, and chemical shift are reported in ppm relative to the solvent peak. IR spectra were recorded with a FT-IR 210 Nicolet spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature. EI MS was obtained with a VG 7070 at 70 eV. TLC were performed on Merck fluoresent silica gel plates. Flash cromatography was performed at medium pressure with Merck silica gel 60 (230-400 mesh). THF was distilled from sodium benzophenone ketyl. CH₂Cl₂ was distilled from P₂O₅. DMSO and DMF were distilled from activated molecular sieves. Solvents for flash-chromatography were simply distilled. Reagents were purchased from Aldrich and used without purification.

(4R,5S,2'R)-1,5-Dimethyl-3-[(2'-aziridinyl)carbonyl]-4-phenylimidazolidin-2-one (3). Gabriel-Cromwell method. Bromine (0.32 mL, 6.2 mmol) is added to a solution of 2 (1.0 g, 4.1 mmol) in CH₂Cl₂ (20 mL) at 0°C with exclusion of light. After 6 h the reaction is quenched with 1M Na₂SO₃ (10 mL) and extracted three times with CH₂Cl₂. The collected organic layers are dried over Na₂SO₄ and the solvent is evaporated at reduced pressure, giving an oily residue. This dibromo derivative is used without further purification. It is dissolved in DMSO (5 mL) and ammonia is bubbled at 0°C until solvent saturation. After 1 h the solution is diluted with

EtOAc (50 mL), the organic layer is washed three times with small portions of water, and it is dried over Na₂SO₄. After evaporation of the solvent at reduced pressure, the residue is purified by flash chromatography (EtOAc:Cyclohexane 80:20) giving pure (2'R)-3^{11f} (0.72 g, 68%) and its (2'S) diastereoisomer (0.18 g, 17%).

(4R,5S,2'R,2''S)-1,5-Dimethyl-3-{[1'-(2''-acetamido-4''-methylpentanoyl)-2'-aziridinyl]carbonyl}-4-

phenylimidazolidin-2-one (4). A mixture of aziridine-2-imide 3 (0.36 g, 1.4 mmol), *N*-acetyl leucine (0.29 g, 1.7 mmol), EDCI (0.32 g, 1.7 mmol), triethylamine (0.39 mL, 2.8 mmol), and HOBt (0.23 g, 1.7 mmol) in CH₂Cl₂ (20 mL) and DMF (2 mL) is stirred under nitrogen at 0°C. After 6 h the reaction is diluted with Et₂O (40 mL) and washed with: sat. NaHCO₃ (5 mL); 1M HCl (5 mL); brine (5 mL). The organic layer is dried over Na₂SO₄, then solvent is removed at reduced pressure. The residue is purified by flash chromatography (EtOAc:Cyclohexane 50:50) giving 4 (0.55 g, 95%) as a waxy solid. IR (neat) v 3200, 1743, 1680 cm⁻¹; ¹H NMR 8 0.76 (d, J = 6.2 Hz, 6H, CH₃), 0.82 (d, J = 6.6 Hz, 3H, CH₃), 1.38-1.70 (m, 2H, CH₂CH), 1.93 (s, 3H, COCH₃), 2.50 (dd, J = 1.6, 3.1 Hz, 1H, CH₂N), 2.63 (dd, J = 1.6, 6.0 Hz, 1H, CH₂N), 2.87 (s, 3H, NCH₃), 3.94 (dq, 1H, J = 6.6, 8.6 Hz, CH₃CHCHPh), 4.54 (dt, J = 4.8, 7.9 Hz, 1H, CHNAc), 4.94 (dd, J = 3.1, 6.0 Hz, 1H, COCHCH₂), 5.29 (d, J = 8.6 Hz, 1H, CH₃CHCHPh), 6.06 (d, J = 7.9 Hz, 1H, NH), 7.05-7.39 (m, 5H, Ph); ¹³C NMR 8 14.8, 21.8, 22.7, 24.6, 28.1, 30.9, 35.0, 41.4, 52.6, 52.8, 54.3, 59.5, 127.0, 128.1, 128.3, 128.4, 135.8, 155.2, 166.5, 169.8, 184.0; [α]²⁰D = -27 (*c* 2.4 MeOH). Anal. Calcd for C₂₁H₃₀N₄O₄: H 7.51, C 62.67, N 13.9; found: H 7.50, C 62.69, N 13.8.

(5R,4'R,5'S,1''S)-4,5-dihydro-2-(1''-acetamido-3''-methyl-1''-butyl)-5-{(1',5'-dimethyl-4'-phenyl

imidazolidin-2'-on-3'-yl)carbonyl]oxazole (5). A solution of 4 (0.55 g, 1.3 mmol) and boron trifluoride-Et₂O complex (0.17 mL, 1.3 mmol) is stirred in CH₂Cl₂ (10 mL) at r.t. under nitrogen for 2 h. Then sat. NaHCO₃ (5 mL) is added and the reaction is extracted three times with CH₂Cl₂. The organic layer is dried over Na₂SO₄ and solvent is removed at reduced pressure. After flash chromatography (EtOAc:Cyclohexane 30:70), **5** (0.49 g, 90%) is obtained as an oil. IR (neat) v 3287, 3050, 1733, 1690, 1394, 1260 cm⁻¹, ¹H NMR & 0.82 (d, J = 6.7 Hz, 3H, CH₃), 0.92 (d, J = 6.0 Hz, 6H, CH₃), 1.44-1.76 (m, 3H, CH₂CH), 1.98 (s, 3H, COCH₃), 2.84 (s, 3H, NCH₃), 3.84 (dd, J – 6.2, 14.6 Hz, 1H, CH₂N), 3.98 (dq, J = 6.7 Hz, 8.6 Hz, 1H, CH₃C//CHPh), 4.32 (dd, J = 10.8, 14.6 Hz, 1H, CH₂N), 4.81 (dt, J = 4.6, 9.0 Hz, 1H, CHNAc), 5.24 (d, J = 8.6 Hz, 1H, CH₃CHCHPh), 6.02 (dd, J = 6.2, 10.8 Hz, 1H, CHCH₂N), 6.19 (d, J = 9.0 Hz, 1H, NH), 7.10-7.41 (m, 5H, Ph); ¹³C NMR & 14.8, 22.3, 22.6, 23.0, 24.7, 28.1, 41.8, 51.5, 54.5, 59.2, 59.8, 77.2, 127.1, 128.0, 128.3, 135.5, 154.5, 155.3, 165.4, 177.1; MS *m/z* 224 (19), 190 (80), 181 (3), 143 (25), 99 (30), 56 (100); [α]²⁰_D = -60 (*c* 1 MeOH). Anal. Calcd for C₂₁H₃₀N₄O₄: H 7.51, C 62.67, N 13.9; found: H 7.51, C 62.64, N 13.8.

(4R,5S,2'R,2''S)-1,5-Dimethyl-3-[3'-(2''-acetamido-4''-methylpentanoy])amino-2'-hydroxypropionyl]-4-

phenylimidazolidin-2-one (6). To a stirred solution of 5 (0.49 g, 1.2 mmol) in THF (10 mL), 0.5 M HCl (3 mL) is added at 0°C. After 1 h THF is evaporated at reduced pressure and NaHCO₃ is added until neutrality. The mixture is extracted three times with CH₂Cl₂, and the collected organic layers are dried over Na₂SO₄. Solvent is removed at reduced pressure affording 6 (0.47 g, 95%), without further purification. IR (neat) v 3300, 3050, 1720, 1650, 1550, 1490 cm⁻¹; ¹H NMR δ 0.82 (d, J = 6.6 Hz, 3H, CH₃), 0.92 (d, J = 5.2 Hz, 6H, CH₃), 1.40-1.62 (m, 3H, CH₂CH), 1.96 (s, 3H, COCH₃), 2.86 (s, 3H, NCH₃), 3.47 (dt, J = 4.8, 9.5 Hz, 1H, NCH₂CH),

3.75-3.85 (m, 1H, NCH₂CH), 4.05 (dq, J = 6.6, 8.5 Hz, 1H, CH₃CHCHPh), 4.40 (dt, J = 5.7, 6.1 Hz, 1H, CHNAc), 5.17 (d, J = 8.5 Hz, 1H, CH₃CHCHPh), 5.16-5.23 (m, 1H, CHOH), 6.10 (d, J = 6.1 Hz, 1H, NHAc), 6.51-6.62 (m, 1H, NHCH₂), 7.10-7.41 (m, 5H, Ph); ¹³C NMR δ 14.2, 22.0, 22.1, 22.4, 24.0, 28.3, 41.0, 51.3, 52.1, 54.0, 59.5, 59.9, 127.1, 128.4, 128.6, 136.0, 155.3, 167.0, 170.1, 170.2; [α]²⁰_D = -1.7 (c 1.6 CHCl₃). Anal. Calcd for C₂₁H₃₂N₄O₅: H 7.67, C 59.98, N 13.32; found: H 7.67, C 60.00, N 13.31.

Methyl (2*R*,2'*S*)-3-(2'-acetamido-4'-methylpentanoyl)amino-2-benzoyloxypropanoate (8). A mixture of 6 (0.24 g, 0.57 mmol), and triethylamine (0.31 mL, 2.3 mmol) in methanol (5 mL) is refluxed under nitrogen. After 3 h solvent is removed at reduced pressure. The residue, which contains 1, 7 and unreacted 6, is diluted with CH₂Cl₂ (5 mL), and stirred with ClCOPh (0.10 mL, 0.11 mmol) and cat. DMAP at 0°C for 2 h. The reaction is quenched with water (5 mL) and extracted three times with CH₂Cl₂. The organic layers are collected and dried over Na₂SO₄. Solvent is evaporated at reduced pressure and the residue is purified by flash chromatography (EtOAc:Cyclohexane 50:50, to EtOAc) giving sequentially 8 (0.12 g, 74%), reagent 6 (0.048 g, 20%) and 1 (0.088 g, 80%), $[\alpha]^{20}_{D} = -43.5$ (*c* 1.5, MeOH); lit.¹³ $[\alpha]^{20}_{D} = -44.5$ (*c* 2, MeOH). 8: IR (neat) v 3310, 3064, 1742, 1719, 1645, 1550 cm⁻¹, ¹H NMR δ 0.81 (d, J = 6.0 Hz, 3H, CH₃), 0.85 (d, J = 6.0 Hz, 3H, CH₃), 1.40-1.63 (m, 3H, CH₂CH), 1.89 (s, 3H, COCH₃), 3.66 (dt, J = 4.5, 14.2 Hz, 1H, CHCH₂N), 3.74 (s, 3H, COOCH₃), 3.98 (dt, J = 6.9, 14.2 Hz, 1H, CHCH₂N), 4.50 (dt, J = 6.3, 8.4 Hz, 1H, CHNAc), 5.36 (dd, J = 4.5, 6.6 Hz, 1H, CHOCOPh), 6.63 (d, J = 8.4 Hz, 1H, AcNH), 7.38-7.44 (m, 3H, Ph); 7.57 (t, J = 7.3 Hz, 1H, NH), 8.06 (d, J = 7.0 Hz, 2H, Ph); ¹³C NMR δ 22.3, 22.6, 22.9, 24.7, 39.9, 41.0, 51.6, 52.6, 71.2, 128.3, 128.8, 128.9, 133.4, 165.5, 168.5, 170.3, 172.7; $[\alpha]^{20}_{D} = -41.9$ (*c* 1.1, CHCl₃). Anal. Calcd for C₁₉H₂₆N₂O₆: H 6.93, C 60.30, N 7.40; found: H 6.91, C 60.27, N 7.39.

(2*R*)-Methyl 3-benzoylamino-2-benzoyloxypropanoate (9). A mixture of 6 (0.24 g, 0.57 mmol) and 3N HCl (2 mL) in MeOH (5 mL) is refluxed for 2h. After evaporation of THF at reduced pressure, the mixture is extracted twice with EtOAc. The aqueous layer is neutralized with 2N NaOH. Acetone (5 mL) is added and the mixture is cooled at 0°C. Then K₂CO₃ (0.23 g, 1.7 mmol) and ClCOPh (0.20 mL, 1.7 mmol) are added and the reaction is stirred for 2 h. The organic solvent is evaporated at reduced pressure, pH is adjusted to 4 with 0.5 M HCl, and the mixture is extracted twice with EtOAc. The collected organic layers are dried over Na₂SO₄, solvent is evaporated at reduced pressure and the residue is treated with an excess of diazomethane solution in Et₂O. Solvent is evaporated at reduced pressure and the residue is purified by flash chromatography (EtOAc:Cyclohexane 30:70) affording isolated 9 (0.065 g, 35%) as an oil. IR (neat) v 3330, 3064, 1757, 1719, 1645, 1539, 1272, 1117 cm⁻¹, ¹H NMR δ 3.81 (s, 3H, COOCH₃), 4.05-4.15 (m, 2H, CH₂N), 5.48 (t, J = 5.4 Hz, 1H, CHOCOPh), 6.65 (t, J = 5.7 Hz, 1H, NH), 7.30-7.60 (m, 6H, Ph), 7.75 (d, J = 8.0 Hz, 2H, Ph), 8.10 (d, J = 8.0 Hz, 2H, Ph); ¹³C NMR δ 40.5, 52.7, 71.5, 127.0, 128.4, 128.5, 128.6, 128.9, 129.9, 131.7, 133.6, 165.7, 167.7, 169.0; α]²⁰_D = -10.9 (c 0.5, CHCl₃); authentic sample of (S)-N, O-dibenzoyl isoserine methyl ester, from (S)-isoserine:¹⁶ [α]²⁰_D = +9.4 (c 0.2, CHCl₃). Anal. Calcd for C₁₈H₁₇NO₅: H 5.28, C 66.05, N 4.28; found: H 5.27, C 66.02, N 4.28.

Benzyl (2R,2'S)-1-(2'-acetamido-4'-methylpentanoyl)aziridine-2-carboxylate (11). Under the same conditions reported for the synthesis of 4, a mixture of 10 (0.18 g, 1.0 mmol), N-acetyl leucine (0.21 g, 1.2

mmol), EDCI (0.23 g, 1.2 mmol), triethylamine (0.28 mL, 2.0 mmol), and HOBt (0.16 g, 1.2 mmol) in CH₂Cl₂ (10 mL) and DMF (1 mL) is stirred for 6 h. After the above reported work up, the mixture is purified by flash chromatography (Et₂O:Cyclohexane 50:50) giving 11 (0.32 g, 95%) as an oil. IR (neat) 3190, 1743, 1690, 1670 cm⁻¹; ¹H NMR δ 0.90 (d, J = 6.0 Hz, 3H, CH₃), 0.91 (d, J = 6.0 Hz, 3H, CH₃), 1.60-1.80 (m, 3H, CH₂CH), 1.97 (s, 3H, COCH₃), 2.58 (d, J = 2.7 Hz, 1H, CH₂N), 2.63 (d, J = 5.7 Hz, 1H, CH₂N), 3.51 (dd, J = 2.7, 5.7 Hz, 1H, CHCH₂N), 4.51 (m, 1H, CHNAc), 5.22 (s, 2H, CH₂Ph), 5.89 (bs, 1H, NH), 7.33-7.41 (m, 5H, Ph); ¹³C NMR δ 22.0, 22.7, 22.9, 24.8, 30.5, 34.6, 41.7, 52.8, 67.5, 128.4, 128.5, 128.6, 135.0, 167.8, 170.0, 183.6; MS *m/z* 241 (3), 177 (22), 156 (19), 128 (49), 91 (75), 86 (100); [α]²⁰_D = +35.0 (*c* 1.6, CHCl₃). Anal. Calcd for C₁₈H₂₄N₂O₄: H 7.28, C 65.04, N 8.43; found: H 7.29, C 65.02, N 8.41.

Benzyl (2R,2'S)-2-(2'-acetamido-4'-methylpentanoyl)amino-3-hydroxypropionate (12). A mixture of 11 (0.32 g, 0.95 mmol), MgBr₂-Et₂O complex (0.049 g, 0.19 mmol), and water (0.018 mL, 0.95 mmol) in THF (10 mL) was stirred for 4 h at 0°C. Solvent was evaporated at reduced pressure, the residue was diluted in CCl₄ (5 mL), and the suspension was filtered on celite. Compound 12 (0.26 g, 80%) was precipitated from the filtrate by adding cold pentane. The mother liquor was evaporated at reduced pressure and the residue was analyzed by ¹H NMR, revealing a 1:1 mixture of 12 and 13. An alternative purification by flash chromatography (Et₂O:Cyclohexane 40:60) was also attempted, but 13 (0.30 g, 94%) was obtained as the unique product.

12: IR (neat) 3320 br, 3050, 1735, 1680, 1660 cm⁻¹; ¹H NMR δ 0.95 (d, J = 6.0 Hz, 6H, CH₃), 1.55-1.80 (m, 3H, CH₂CH), 1.98 (s, 3H, COCH₃), 3.74 (dd, J = 3.6, 10.8 Hz, 1H, CH₂OH), 3.81 (dd, J = 3.6, 10.8 Hz, 1H, CH₂OH), 4.50-4.60 (m, 1H, CHNAc), 4.99 (dt, J = 3.6, 7.5 Hz, 1H, CHN), 5.17 (d, J = 12.3 Hz, 1H, CH₂Ph), 5.24 (d, J = 12.3 Hz, 1H, CH₂Ph), 6.00 (bs, 1H, NHAc), 7.20 (d, J = 7.5 Hz, 1H, NH), 7.35-7.50 (m, 5H, Ph); ¹³C NMR δ 21.8, 22.0, 22.8, 24.2, 32.3, 40.4, 51.2, 52.5, 67.7, 127.8, 128.0, 128.1, 134.0, 168.0, 171.1, 174.1; MS *m*/*z* 332 (4), 177 (20), 128 (38) 91 (90), 86 (100); $[\alpha]^{20}_{D} = -47.3$ (*c* 0.4, CHCl₃). Anal. Calcd for C₁₈H₂₆N₂O₅: H 7.48, C 61.70, N 7.99; found: H 7.47, C 61.73, N 8.00.

13: IR (neat) 3050, 1730, 1695, 1660 cm⁻¹; ¹H NMR δ 0.96 (d, J = 6.0 Hz, 3H, CH₃), 0.98 (d, J = 6.0 Hz, 3H, CH₃), 1.42-1.61 (m, 3H, CH₂CH), 2.02 (s, 3H, COCH₃), 4.54 (dt, J = 5.4, 8.1 Hz, 1H, CHNAc), 5.28 (s, 2H, CH₂Ph), 5.91 (d, J = 8.1 Hz, 1H, NHAc), 5.92 (s, 1H, =CH), 6.59 (s, 1H, =CH), 7.25-7.45 (m, 5H, Ph), 8.35 (bs, 1H, NH); ¹³C NMR δ 21.7, 22.5, 22.6, 24.5, 40.5, 52.2, 67.4, 109.4, 127.8, 128.1, 130.5, 134.6, 163.1, 170.0, 170.2; MS *m*/*z* 332 (M⁺, 1), 276 (4), 241 (5), 177 (16), 156 (13), 128 (46) 91 (79), 86 (100); $[\alpha]^{20}_{D} = -43.9$ (*c* 0.5, CHCl₃). Anal. Calcd for C₁₈H₂₄N₂O₄: H 7.28, C 65.04, N 8.43; found: H 7.28, C 65.01, N 8.42.

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