(s, 3 H, OCH_3), 4.30 (q, J = 7.2 Hz, 2 H), 4.44 (h, J = 6 Hz, 1 H); ^{13}C NMR δ 13.87, 22.32, 52.98, 54.88, 62.27, 78.27, 111.81, 118.56, 120.57 (q, $^1J_{CF}$ = 273.75 Hz), 143.09 (q, $^2J_{CF}$ = 35.2 Hz), 161.62, 161.93, 164.09, 164.65; ^{19}F NMR δ −67.36. Anal. Calcd for $C_{15}H_{18}F_3N_1O_6$: C, 49.32; H, 4.97; N, 3.83. Found: C, 49.37; H, 5.03; N, 3.79.

Ethyl 4-Methoxy-6-(1-methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate (8a). A solution of 5 g (0.017 mol) of **4a** and 4.26 g (0.03 mol) of methyl iodide in 100 mL of acetone was added to 4.14 g (0.03 mol) of anhydrous K_2CO_3. The resulting suspension was vigorously stirred and heated at reflux for 24 h. After being cooled to room temperature, the mixture was filtered to remove insoluble salts and the filtrate was evaporated. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography (preparative HPLC, SiO_2, 10% ethyl acetate/hexane) afforded 3.6 g (69%) of **8a** as a colorless oil: ^1H NMR δ 1.25 (d, J = 6.2 Hz, 6 H, $(CH_3)_2$), 1.31 (t, J = 7.16 Hz, 3 H), 4.33 (q, J = 7.16 Hz, 2 H), 5.25 (h, J = 6.2 Hz, 1 H), 6.25 (s, 1 H, ArH), 11.15 (br s, 1 H, OH); ^{13}C NMR δ 13.85, 21.75, 56.23, 62.08, 69.7, 95.44, 114.16, 121.0 (q, $^1J_{CF}$ = 273.2 Hz), 142.35 (q, $^2J_{CF}$ = 35.05 Hz), 164.58, 164.69, 165.48; ^{19}F NMR δ −67.33. Anal. Calcd for $C_{13}H_{16}F_3N_1O_4$: C, 50.82; H, 5.25; N, 4.56. Found: C, 50.98; H, 5.31; N, 4.50.

5-Ethyl 3-Methyl 4-Methoxy-2-(1-methylethoxy)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8b). Treatment of 1.2 g (0.0034 mol) of **4b** and 1.42 g (0.01 mol) of methyl iodide in 100 mL of acetone with 1.38 g (0.01 mol) of anhydrous K_2CO_3 as above and purification of the crude product by radial chromatography (SiO_2, 10% ethyl acetate/hexane) gave 0.8 g (64%) of **8b** as a colorless oil: ^1H NMR δ 1.19 (t, J = 7.2 Hz, 3 H), 1.24 (d, J = 6.1 Hz, 6 H, $(CH_3)_2$), 3.83 (s, 3 H, CO_2CH_3), 4.26 (q, J = 7.15 Hz, 2 H), 5.32 (h, J = 6.1 Hz, 1 H), 12.65 (br s, 1 H, OH); ^{13}C NMR δ 13.79, 21.58, 52.87, 60.68, 62.29, 71.18, 110.17, 116.53, 120.57 (q, $^1J_{CF}$ = 273.52 Hz), 142.86 (q, $^2J_{CF}$ = 34.95 Hz), 161.31, 162.88, 163.98, 164.8; ^{19}F NMR δ −67.55. Anal. Calcd for $C_{15}H_{18}F_3N_1O_6$: C, 49.32; H, 4.97; N, 3.83. Found: C, 49.40; H, 4.99; N, 3.82.

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Supplementary Material Available: ORTEP diagram (Figures 1 and 2) and tables of crystallographic data, fractional coordinates, bond distances and angles, isotropic and anisotropic thermal parameters, and hydrogen atom coordinates for 6 (19 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of 3-Alkylated Glutamic Acids: Application to the Synthesis of Secokainic Acid

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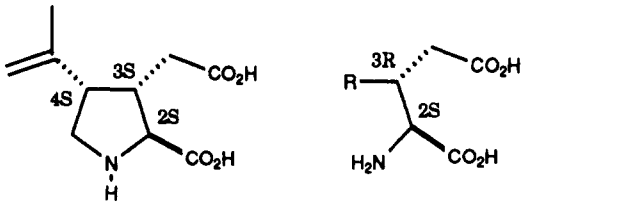
Recently great effort has been devoted to elucidating the physiological role of glutamic acid. Several glutamic receptor subtypes have been identified as a result of biochemical experimentation with natural and synthetic glutamic acids. A physiological function has been tentatively attributed to each subtype.[1] Kainic acid (1) exerts a powerful neuroexcitatory effect on glutamate receptors, but its neurotoxicity has prohibited pharmacological application.[2] After noting that kainic acid and glutamic acid are structurally similar, we addressed the following question: do acyclic analogues of kainic acid like the methallyl- or benzyl-substituted glutamic acids 2 and 3 display the desirable biochemical activity of kainic acid but not the toxic side effects?

Scheme I



1 Kainic acid 2 R = methallyl (seco-kainic acid) 3 R = benzyl

As a first step toward answering this question, we decided to prepare homochiral β-substituted glutamic acids in a stereoselective manner, one that would generate in 2 and 3 the same absolute configuration about C(2) and C(3) that exists in kainic acid, i.e., S and R, respectively (Scheme I).[3] The Michael type addition of the synthetic equivalent of an N-protected glycine anion to enoates can, in theory, provide access to β-substituted glutamates. However, such additions are apparently possible with only a few enoates, and the regeneration of the amino acid functionality in the final products is rather tedious.[4,5] This knowledge prompted us to study the 1,4-addition of lithium dialkylcuprates to oxazolidine 5. The amino-substituted allylic carbon atom of 5 is incorporated into an oxazolidine derived from (R)-serine.[6] Although the stereochemical outcome of conjugate additions to enoates that bear γ-alkyl or γ-alkoxy substituents has been intensively investigated,[7] only a few examples of such additions of

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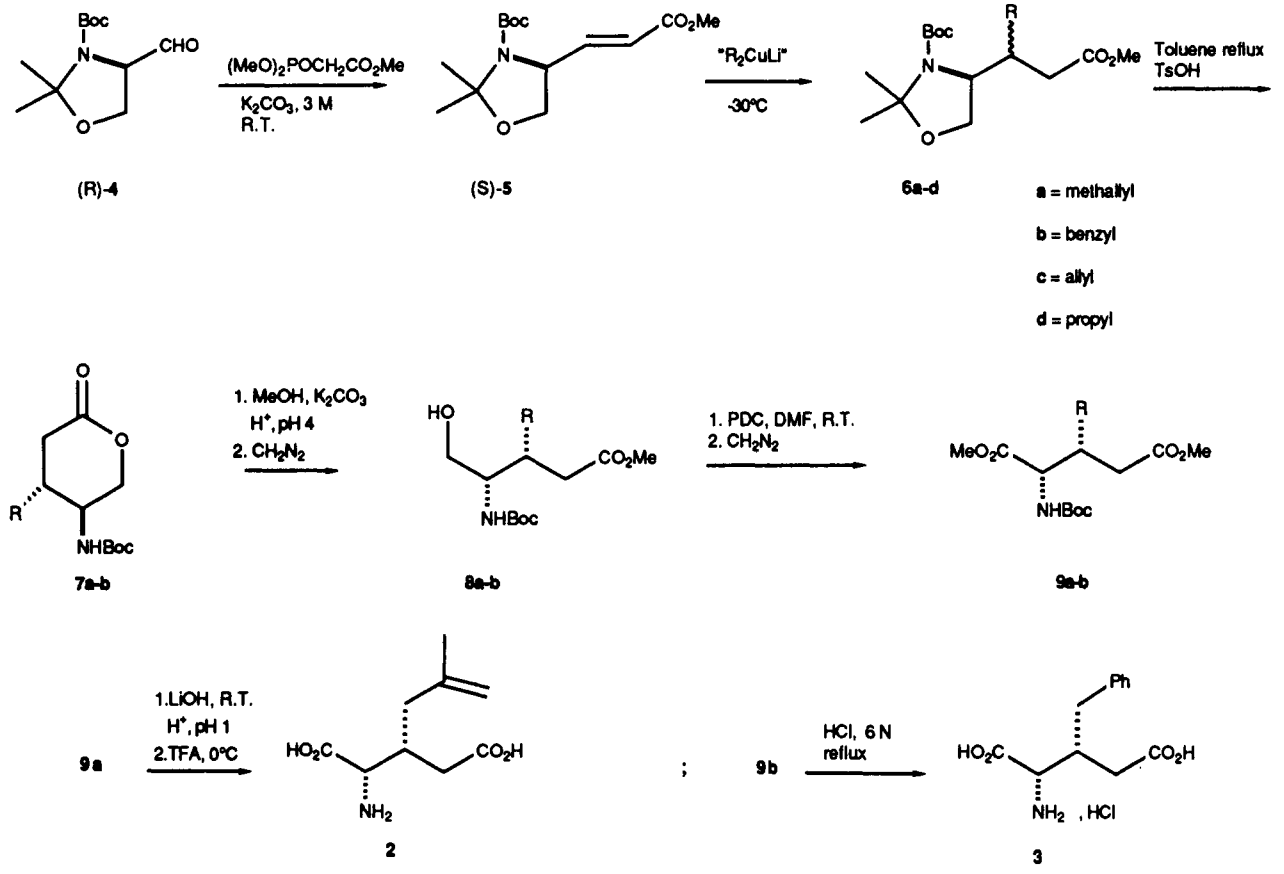
Scheme II



γ-amino-substituted enoates have been described.[8] However, success in controlling the stereoselectivity of 1,2-additions to the N,O-diprotected serinal 4[9] has been extended to include success in controlling the stereoselectivity of 1,4-additions to enoate 5.[10] While the work described here was in progress, Shirahama[11] reported the preparation of the four isomers of 3, via the conjugate addition of the synthetic equivalent of a benzyl anion to an enoate.

Our synthesis began with the known aldehyde 4, which was obtained from (*R*)-serine (Scheme II).[12] The Wittig–Horner reaction of 4 and trimethyl phosphonoacetate under protic conditions gave a 95:5 mixture of the *E* and *Z* isomers of ester 5 in 85% yield (the mixture has been used for the addition of the cuprates).[10,13] After some experimentation, it was found that, in the presence of TMSCl,[14] the addition of lithium dialkylcuprates to the acrylate 5 occurred smoothly. Unfortunately, it was not possible to separate the syn and anti isomers by column chromatography on silica gel. However, syn:anti ratios of 9:1, 8:2, 9:1, and 95:5, respectively, were established for **6a–d** by high-field ^{1}H NMR analysis (400 MHz, C_6D_6 at 60 °C).[15] It was hoped that treatment of the products with a mild acid would deprotect the acetonide and promote lactonization. Indeed, when the diastereomeric pairs **6a–d** were refluxed in toluene in the presence of *p*-TsOH, the respective ^{1}H and ^{13}C NMR spectra of the isolated products were consistent with single diastereomers of lactones **7a–d**. Thus, lactonization proved to be a practical way of purifying the diastereomeric mixtures **6a–d**. From the

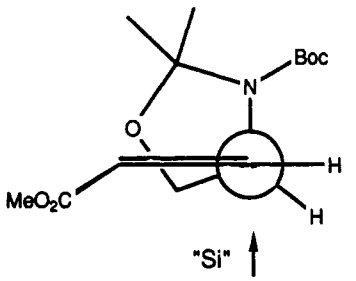


Figure 1. Felkin–Anh model for the 1,4 nucleophilic addition of lithium dialkylcuprates to enoate 5.

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(15) The dynamic equilibrium existing at room temperature for **6a–d** was suppressed in this way. We thank a referee for suggesting this experiment.

magnitudes of the coupling constants of the two methinyl proton signals (J = 7.5, 7.4, 6.2, and 7.5 Hz for **7a–d**, respectively) obtained by spin-decoupling experiments, it was inferred that the two protons were trans to each other. Because 1,4-additions of *allyl*cuprates to enoates have been reported[16] to occur with a diastereoselectivity opposite to that of the 1,4-addition of *alkyl*cuprates, we compared the ^1H and ^{13}C NMR spectra of lactone **7d** (prepared by addition of lithium dipropylcuprate to compound **5** and subsequent lactonization of the product) to those of the product obtained by the hydrogenation of lactone **7c**. The spectra were identical, which supported the tentative conclusion that, under the conditions employed in this work, alkyl- and allylcuprates reacted with the same diastereoselectivity. Also, X-ray structural analysis of compound **7b** confirmed the expected trans relationship between the two methinyl protons. From a mechanistic point of view, the stereochemical outcome of the addition of cuprates to enoate **5** can be explained in terms of the Felkin–Anh model, which shows that the axis of the carbon–nitrogen bond of the enoate is perpendicular to that of the carbon–carbon double bond (a favored conformation for the electrophile) (Figure 1).[17] Therefore, in the work described here, the conjugate addition of the cuprate occurred from the *si* diastereotopic face of the substrate and, as expected, the nonchelating conditions favored the formation of the syn rather than the anti adduct.[8] Similar behavior has been observed with other oxazolidines that have been used as chiral auxiliaries.[18] Finally, the configurations about the chiral centers C(4) and C(5) of the lactones **7a,b** (*R* and *S*, respectively) correspond to the stereochemistry desired for the acyclic kainoids **1** and **2**. To complete the synthesis, lactones **7a** and **7b** were cleaved by treatment with methanolic potassium carbonate. Then, esterification of the γ acid functionality (CH_2N_2/Et_2O) provided the hydroxy esters **8a** and **8b**. Oxidation of the primary alcohol functionality (PDC/DMF) and subsequent esterification (CH_2N_2/Et_2O) gave the diesters **9a** and **9b**. Removal of the N- and O-protecting groups, under successive basic and acidic conditions in the case of **9a** and under acidic conditions in the case of **9b**, gave the amino acids **2** and **3**, respectively.

In summary, the synthesis of 3-substituted glutamic acids described here has some merit when compared to existing syntheses.[4,5,11] First, it allows the stereoselective introduction of a variety of substituents. Second, when D-serine is the starting material, the absolute configuration about C(3) of the products is the same as that of kainic acid. Finally, the ready availability of the optically pure valerolactones **7a–d** simplifies the chemical processing. The biochemical aspects of this work, as well as further extensions of the synthetic aspects, will be reported elsewhere.

Experimental Section

IR spectra were of $CHCl_3$ solutions. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 25 °C, unless otherwise noted. Melting points were determined with a capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Service de Microanalyse du CNRS de Strasbourg, France. TLC visualization was achieved by spraying with 2% ethanolic phosphomolybdic acid and charring, or with ninhydrin (0.5% solution in *n*-BuOH/AcOH, 97:3). All reactions were performed under argon. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium benzophenone ketyl under argon.

(4*S*)-1,1-Dimethylethyl 4-[(*E*)-3′-Methoxy-3′-oxo-1′-propenyl]-2,2-dimethyl-3-oxazolidinecarboxylate (5). A mixture of aldehyde **4**[12] (3.8 g, 16.6 mmol), trimethyl phosphonoacetate (6.6 mL, 33.2 mmol), n-$Bu_4N^+I^-$ (613 mg, 1.66 mmol), and 3 M aqueous K_2CO_3 (8 mL, 23 mmol) was stirred at room temperature for 16 h. The mixture was then diluted with water (40 mL) and extracted with hexane (3 × 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give **5** (4.87 g, 88%), an oil that crystallized on standing. Pure **5** could be obtained as a white solid by flash chromatography on silica gel (hexane/Et_2O, 4:1). **5**: mp 50 °C; $[\alpha]_D$ +66° (c 0.3, $CHCl_3$); R_f (hexane/Et_2O, 1:1) 0.59; IR 1720, 1690 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.42 (s, 9 H), 1.50 (s, 3 H), 1.56 (s, 3 H), 3.76 (s, 3 H), 3.80 (dd, J = 2, 9 Hz, 1 H), 4.10 (dd, J = 6, 9.1 Hz, 1 H), 4.36–4.49 (m, $^1/_2$ H), 4.49–4.63 (m, $^1/_2$ H), 5.95 (br t, J = 15 Hz, 1 H), 6.88 (dd, J = 7, 15 Hz, 1 H). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.88; H, 8.06; N, 4.90. Found: C, 58.69; H, 8.38; N, 4.79.

General Method for the Preparation of Lithium Dialkylcuprates. Lithium diallyl-, dibenzyl- and dipropylcuprate were generated from the corresponding alkylmagnesium bromides (2 equiv), CuBr (1 equiv), Me_2S (1 equiv), and LiBr (2 equiv). Lithium dimethallylcuprate was generated from methallyltriphenyltin (1 equiv), PhLi (1 equiv), CuI (0.5 equiv), and n-Bu_2S (0.5 equiv).[19]

(4*S*,1′*R* and 1′*S*)-1,1-Dimethylethyl 4-(3′-Methoxy-3′-oxo-1′-benzylpropyl)-2,2-dimethyl-3-oxazolidinecarboxylate (6b). The preparation of compound **6b** is typical. Compounds **6a** and **6c,d** were prepared in a similar manner. To a magnetically stirred mixture of CuBr, Me_2S (205 mg, 1 mmol, 3 equiv), LiBr (173 mg, 2 mmol, 6 equiv), and THF (6 mL) under Ar was added BnMgBr (2 mmol, 1 mL of a 2 M solution in Et_2O, 6 equiv) drop by drop at −40 °C. The mixture rapidly became darkly colored. After 30 min, a solution of TMSCl (0.14 mL, 1 mmol, 3 equiv) in THF (2 mL) was added, followed by a solution of **5** (94 mg, 0.33 mmol, 1 equiv) in THF (3 mL). The dark-colored mixture was stirred for 1 h at −40 °C and then was allowed to warm to room temperature over 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL). Et_2O was then added (10 mL), and the two liquid layers were separated. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The oily residue was purified by column chromatography on silica gel (hexane/Et_2O, 4:1) to yield **6b** (105 mg, 86%) of sufficient purity to be used in the next step. An analytical sample was obtained by a second purification by column chromatography. **6b**: R_f (hexane/Et_2O, 1:1) 0.77; IR 1720, 1685 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 1.49 (s, 9 H), 1.62 (s, 6 H), 1.75 (m, 1 H), 2.28 (dd, J = 6, 13 Hz, 1 H), 2.35 (dd, J = 3, 13 Hz, 1 H), 2.78 (dd, J = 6, 15 Hz, 1 H), 2.95 (dd, J = 6, 15 Hz, 1 H), 3.59 (s, 3 H), 3.78 (d, J = 7 Hz, 1 H), 3.90 (dd, J = 3, 7 Hz, 1 H), 3.98–4.10 (m, 1 H), 7.10–7.35 (m, 5 H). Minor isomer: ^1H NMR (400 MHz, C_6H_6, 60 °C) δ 3.51 (s). Isomeric ratio: 8:2.

Anal. Calcd for $C_{21}H_{31}O_5N$: C, 66.82; H, 8.27; N, 3.71. Found: C, 66.65; H, 8.39; N, 3.49.

(4*S*,1′*R* and 1′*S*)-1,1-Dimethylethyl 4-[3′-methoxy-3′-oxo-1′-(2″-methyl-2″-propenyl)propyl]-2,2-dimethyl-3-oxazolidinecarboxylate (6a): yield, 78%; an oil; R_f (hexane/ether, 1:1) 0.70; IR 1720, 1690 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 1.50 (s, 9 H), 1.60 (s, 6 H), 1.77 (s, 3 H), 1.75–1.80 (m, 1 H), 1.90–2.25 (m, 2 H), 2.75–2.93 (m, 2 H), 3.66 (s, 3 H), 3.85 (d, J = 6 Hz, 1 H), 3.95 (dd, J = 3, 6 Hz, 1 H), 4.05–4.15 (m, 1 H), 4.71 (br s, 1 H), 4.82 (br s, 1 H). Minor isomer: ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 3.63 (s). Isomeric ratio: 9:1.

Anal. Calcd for $C_{18}H_{31}O_5N$: C, 63.32; H, 9.15; N, 4.10. Found: C, 63.05; H, 9.27; N, 4.25.

(4*S*,1′*R* and 1′*S*)-1,1-Dimethylethyl 4-[3′-methoxy-3′-oxo-1′-(2″-propenyl)propyl]-2,2-dimethyl-3-oxazolidinecarboxylate (6c): yield, 74%; an oil; R_f (hexane/Et_2O, 1:1) 0.65; IR 1720, 1685 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 1.52 (s, 9 H), 1.63 (s, 6 H), 1.70–1.80 (m, 1 H), 2.25 (dd, J = 4, 11 Hz, 1 H), 2.35 (dd, J = 5, 11 Hz, 1 H), 2.75–2.93 (m, 2 H), 3.62 (s, 3 H), 3.80 (d, J = 7 Hz, 1 H), 3.88 (dd, J = 3, 7 Hz, 1 H), 3.95–4.05 (m,

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1 H), 4.98 (br s, 1 H), 5.14 (br s, 1 H); 5.65–6.10 (m, 1 H). Minor isomer: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 3.64 (s). Isomeric ratio: 9:1.

Anal. Calcd for $C_{17}H_{29}O_5N$: C, 62.36; H, 8.92; N, 4.28; Found C, 62.65; H, 8.72; N, 4.46.

(4*S*,1′*R* and 1′*S*)-1,1-Dimethylethyl 4-(3′-methoxy-3′-oxo-1′-propylpropyl)-2,2-dimethyl-3-oxazolidinecarboxylate (6d): yield, 71%; an oil; R_f (hexane/Et_2O, 1:1) 0.80; IR 1720, 1685 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.91 (t, J = 7.5 Hz, 3 H), 1.18–1.34 (m, 4 H), 1.49 (s, 9 H), 1.60 (s, 6 H), 2.05–2.22 (m, 1 H), 2.41–2.61 (m, 2 H), 3.63 (s, 3 H), 3.80 (d, J = 7 Hz, 1 H), 3.95 (dd, J = 2, 7 Hz, 1 H), 4.01–4.08 (m, 1 H). Minor isomer: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 3.60 (s). Isomeric ratio: 95:5.

Anal. Calcd for $C_{17}H_{31}O_5N$: C, 61.96; H, 9.48; N, 4.27. Found: C, 62.25; H, 9.66; N, 4.52.

(4*R*,5*S*)-5-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-benzyltetrahydro-2*H*-pyran-2-one (7b). The preparation of **7b** is typical. Compounds **7a** and **7c,d** were prepared in a similar manner. A solution of oxazolidine **6b** (2.64 g, 7 mmol), toluene (100 mL), and *p*-TsOH (250 mg) was refluxed for 4 h. Evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to yield lactone **7b** as a solid (1.55 g, 73%): mp 86 °C; $[\alpha]_D$ −16° (*c* 2, $CHCl_3$) [lit.[11] mp 92 °C, $[\alpha]_D$ −16° (*c* 1, $CHCl_3$)]; IR 3410, 1720, 1695, 1480 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.46 (s, 9 H), 2.10–2.36 (m, 2 H), 2.48–2.62 (m, 2 H), 3.01 (dd, J = 4.7, 13.7 Hz, 1 H), 3.77–3.84 (m, 1 H), 4.11 (br dd, J = 5.9, 11.5 Hz, 1 H), 4.34 (dd, J = 4.5, 11.5 Hz, 1 H), 4.85 (br d, J = 7.5 Hz, 1 H), 7.13–7.37 (m, 5 H); ^{13}C NMR δ 28.2, 33.5, 39.0, 39.7, 49.4, 70.0, 126.7, 128.8, 129.0, 137.5, 155.1, 171.1; MS *m/e* 306.1709 (M + 1, 306.1709 calcd for $C_{17}H_{24}O_4N$), 249, 206, 232, 190, 117, 91.

Anal. Calcd for $C_{17}H_{23}O_4N$: C, 66.86; H, 7.56; N, 4.59. Found: C, 66.54; H, 7.78; N, 4.40.

(4*R*,5*S*)-5-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-(2′-methyl-2′-propenyl)tetrahydro-2*H*-pyran-2-one (7a): yield, 86%; R_f (hexane/Et_2O, 1:1) 0.25; mp 90 °C; $[\alpha]_D$ −24° (*c* 1, $CHCl_3$); IR 3415, 1730, 1700, 1480, 1150 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.38 (s, 9 H), 1.65 (s, 3 H), 1.93–2.35 (m, 4 H), 2.63 (dd, J = 5.1, 16.1 Hz, 1 H), 3.55–3.75 (m, 1 H), 4.07 (dd, J = 5.8, 11.6 Hz, 1 H), 4.30 (dd, J = 4.2, 11.6 Hz, 1 H), 4.68 (s, 1 H), 4.74 (br s, 1 H), 4.84 (br s, 1 H); ^{13}C NMR δ 21.8, 28.2, 33.5, 35.0, 42.4, 49.4, 69.7, 80.1, 113.4, 141.1, 155.1, 177.1.

Anal. Calcd for $C_{14}H_{23}O_4N$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.64; H, 8.67; N, 5.07.

(4*R*,5*S*)-5-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-(2′-propenyl)tetrahydro-2*H*-pyran-2-one (7c): yield, 59%; an oil; R_f (hexane/Et_2O, 1:1) 0.25; $[\alpha]_D$ −11° (*c* 1, $CHCl_3$); IR 3410, 1730, 1700, 1490 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.45 (s, 9 H), 1.92–2.44 (m, 4 H), 2.70 (dd, J = 6.1, 16.8 Hz, 1 H), 3.68–3.88 (m, 1 H), 4.13 (dd, J = 5.7, 11.6 Hz, 1 H), 4.35 (dd, J = 4.2, 11.6 Hz, 1 H), 4.72 (br d, J = 7.2 Hz, 1 H), 5.03–5.17 (m, 2 H), 5.63–5.86 (m, 1 H); ^{13}C NMR δ 28.3, 33.4, 37.1, 37.7, 48.9, 69.9, 118.7, 133.6, 155.0, 181.8.

Anal. Calcd for $C_{13}H_{21}O_4N$: C, 61.14; H, 8.29; N, 5.51. Found: C, 61.05; H, 8.20; N, 5.40.

(4*R*,5*S*)-5-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-propyltetrahydro-2*H*-pyran-2-one (7d): yield, 52%; R_f (hexane/Et_2O, 1:1) 0.13; mp 48 °C; $[\alpha]_D$ −6° (*c* 1, $CHCl_3$); IR 3410, 1740, 1700, 1490, 1160 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.87 (t, J = 6.8 Hz, 3 H), 1.07–1.58 (m, 13 H), 1.77–1.88 (m, 1 H), 2.19 (dd, J = 9.4, 16.6 Hz, 1 H), 2.65 (dd, J = 6.1, 16.6 Hz, 1 H), 3.44–3.75 (m, 1 H), 4.08 (br dd, J = 5.4, 11.6 Hz, 1 H), 4.26 (dd, J = 4.2, 11.6 Hz, 1 H), 5.07 (d, J = 7.9 Hz, 1 H); ^{13}C NMR δ 13.9, 19.4, 28.3, 34.0, 36.2, 37.5, 49.7, 69.9, 155.1, 171.0.

Anal. Calcd for $C_{13}H_{23}O_4N$: C, 60.68; H, 9.01; N, 5.44. Found: C, 61.03; H, 9.06; N, 5.18.

Lactone **7d** was also obtained by the catalytic hydrogenation (10% Pd/C, THF, 1 h, 50 psi of H_2) of **7c**.

Methyl (3*R*,4*S*)-3-(2′-Methyl-2′-propenyl)-4-[[(1,1-dimethylethoxy)carbonyl]amino]-5-hydroxypentanoate (8a). Compound **8b** was prepared in a similar manner. A mixture of **7a** (2.05 g, 7.6 mmol), MeOH (80 mL), and K_2CO_3 (1.6 g, 12 mmol) was stirred at room temperature. After 4 h, the mixture became homogeneous. The solvent was then evaporated in vacuo and the residue taken up in water (80 mL). The solution was cooled to 0 °C, and a saturated solution of $KHSO_4$ was carefully added until the pH reached 4. The solution was saturated with solid NaCl and was extracted with Et_2O (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in MeOH (20 mL), and the solution was treated with CH_2N_2/Et_2O until TLC (hexane/Et_2O, 1:1) showed complete transformation of the acid to a less polar compound (R_f = 0.45). Excess CH_2N_2 was destroyed by drop-by-drop addition of HOAc. Evaporation of the solvent and flash chromatography on silica (hexane/Et_2O, 1:1) gave pure **8a** as an oil (1.95 g, 80%).

8a: $[\alpha]_D$ +13.1° (*c* 0.5, $CHCl_3$); IR 3420, 1700, 1490, 1150 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.45 (s, 9 H), 1.73 (s, 3 H), 1.83–1.90 (m, 1 H), 2.10–2.40 (m, 4 H), 2.85 (br s, 1 H, exchangeable with D_2O), 3.52 (br s, 2 H), 3.62 (br s, 3 H +1 H), 4.61 (br s, 1 H), 4.66 (br s, 1 H), 5.05 (br s, 1 H, exchangeable with D_2O).

Anal. Calcd for $C_{15}H_{27}O_5N$: C, 59.77; H, 9.05; N, 4.64. Found: C, 59.86; H, 9.36; N, 4.42.

Methyl (3*R*,4*S*)-3-benzyl-4-[[(1,1-dimethylethoxy)carbonyl]amino]-5-hydroxypentanoate (8b): yield, 79%; an oil; $[\alpha]_D$ +27.3° (*c* 1, $CHCl_3$); IR 3420, 1700, 1490, 1150 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.48 (s, 9 H), 1.80–1.90 (m, 1 H), 2.15–2.55 (m, 4 H), 3.05 (br s, 1 H, exchangeable with D_2O), 3.45 (m, 2 H), 3.63 (s, 3 H), 3.75 (m, 1 H), 5.15 (br s, 1 H, exchangeable with D_2O), 7.15–7.45 (m, 5 H).

Anal. Calcd for $C_{18}H_{27}O_5N$: C, 64.41; H, 8.06; N, 4.15. Found: C, 64.12; H, 7.90; N, 4.25.

Dimethyl (2*S*,3*R*)-2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-(2′-methyl-2′-propenyl)-1,5-pentanedioate (9a). Compound **9b** was prepared in a similar manner. A mixture of alcohol **8a** (965 mg, 3.2 mmol), DMF (50 mL), and pyridinium dichromate (PDC, 8.48 g, 22.5 mmol, 7 equiv) was stirred vigorously for 12 h at room temperature. The mixture was then diluted with water (250 mL), acidified to pH 2 with 10% aqueous HCl, and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with brine and concentrated in vacuo. The oily residue was dissolved in MeOH, and then CH_2N_2/Et_2O was added until the color of the solution remained yellow. After 4 h of stirring, excess HOAc was added and the solvent was evaporated in vacuo. The residual oil was purified by column chromatography on silica gel (hexane/Et_2O, 4:1) to give **9a** as an oil (470 mg, 47%): $[\alpha]_D$ +18.2° (*c* 1.5, $CHCl_3$); IR 3420, 1730, 1490, 1150 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.45 (s, 9 H), 1.70 (s, 3 H), 1.85–2.06 (m, 2 H), 2.32 (dd, J = 3.0, 7.5 Hz, 1 H), 2.59–2.80 (m, 2 H), 3.68 (s, 3 H), 3.76 (s, 3 H), 4.57 (dd, J = 3.4, 9.0 Hz, 1 H), 4.68 (br s, 1 H), 4.75 (br d, J = 6 Hz, 1 H), 5.17 (d, J = 9.0 Hz, 1 H, exchangeable with D_2O).

Anal. Calcd for $C_{16}H_{27}O_6N$: C, 58.34; H, 8.25; N, 4.25. Found: C, 58.62; H, 8.35; N, 4.10.

Dimethyl (2*S*,3*R*)-3-benzyl-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1,5-pentanedioate (9b): yield, 42%; an oil; $[\alpha]_D$ +25.4° (*c* 2, $CHCl_3$); IR 3410, 1720 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.45 (s, 9 H), 2.17–2.85 (m, 5 H), 3.61 (s, 3 H), 3.67 (s, 3 H), 4.59 (dd, J = 3.2, 8.7 Hz, 1 H), 5.22 (d, J = 8.7 Hz, 1 H), 7.14–7.39 (m, 5 H).

Anal. Calcd for $C_{19}H_{27}O_6N$: C, 62.45; H, 7.25; N, 3.83. Found: C, 62.70; H, 7.65; N, 4.10.

(2*S*,3*R*)-2-Amino-3-(2′-methyl-2′-propenyl)-1,5-pentanedioic Acid (2). A solution of LiOH (200 mg, 4.76 mmol) in water (10 mL) was added to a solution of diester **9a** (450 mg, 1.4 mmol) in 1,2-dimethoxyethane (10 mL). The mixture was stirred at room temperature for 5 h. The pH of the mixture was adjusted to 1 with 10% aqueous HCl, and then the mixture was extracted with Et_2O (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to yield an oily residue. Trifluoroacetic acid (15 mL) was added, and the mixture was stirred for 1 h at 0 °C. Water (10 mL) was added, and the mixture was concentrated in vacuo to yield an oil. Water (15 mL) was again added. The mixture was washed with Et_2O (3 × 5 mL) and was again concentrated in vacuo. The semisolid residue was triturated with Et_2O. The crystals that formed were collected and dried to yield **2** (160 mg, 54%): mp 137 °C; $[\alpha]_D$ +7° (*c* 0.2, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 1.76 (s, 3 H), 2.10–2.37 (m, 2 H), 2.47 (dd, J = 7.3, 10.9 Hz, 1 H), 2.60–2.70 (m, 2 H), 4.04 (d, J = 2.5 Hz, 1 H), 4.83 (s, 1 H), 4.91 (s, 1 H); ^{13}C NMR (CD_3OD) δ 21.9, 35.1, 35.8, 40.2, 57.4, 114.6, 143.6, 180.1.

Anal. Calcd for $C_9H_{15}O_4N \cdot {}^1/_2H_2O$: C, 51.42; H, 7.67; N, 6.66. Found: C, 51.18; H, 7.36; N, 6.70.

(2S,3R)-2-Amino-3-benzyl-1,5-pentanedioic acid, Hydrochloride (3). A suspension of diester **9b** (335 mg, 0.92 mmol) in 6 N aqueous HCl (10 mL) was refluxed. After ca. 2 h, the mixture became homogeneous. The solvent was then evaporated. The solid residue was suspended in Et_2O. The suspension was filtered, and the solid that was collected was dried to yield **3** (75%) as white crystals: mp 117 °C; $[\alpha]_D$ +13.5° (*c* 1.2, H_2O);[20] ^1H NMR (400 MHz, D_2O) δ 2.52 (dd, *J* = 5, 13.5 Hz, 1 H), 2.86 (dd, *J* = 4, 13.5 Hz, 1 H), 2.70 (dd, *J* = 6, 17.5 Hz, 1 H), 2.85 (m, 1 H), 3.05 (dd, *J* = 3, 17.5 Hz, 1 H), 3.95 (m, 1 H), 7.24-7.45 (m, 5 H); ^{13}C NMR (TFA) δ 35.3, 38.1, 39.9, 58.6, 128.3, 130.1, 130.6, 139.9, 175.9.

Anal. Calcd for $C_{12}H_{15}O_4N\cdot HCl\cdot H_2O$: C, 49.40; H, 6.22; N, 4.80. Found: C, 49.50; H, 6.12; N, 4.88.

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Supplementary Material Available: Tables of coordinates, anisotropic temperature factors, distances, and angles and ORTEP drawings for **7b** (8 pages). Ordering information is given on any current masthead page.

(20) The corresponding TFA salt[11] has the following physical properties: mp 155 °C; $[\alpha]_D$ +15.7° (*c* 0.2, H_2O).

Carboxyl-Mediated Pictet-Spengler Reaction. Improved Synthesis of 2,3,5,6,11,11b-Hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indoles from Tryptamine-2-carboxylic Acids

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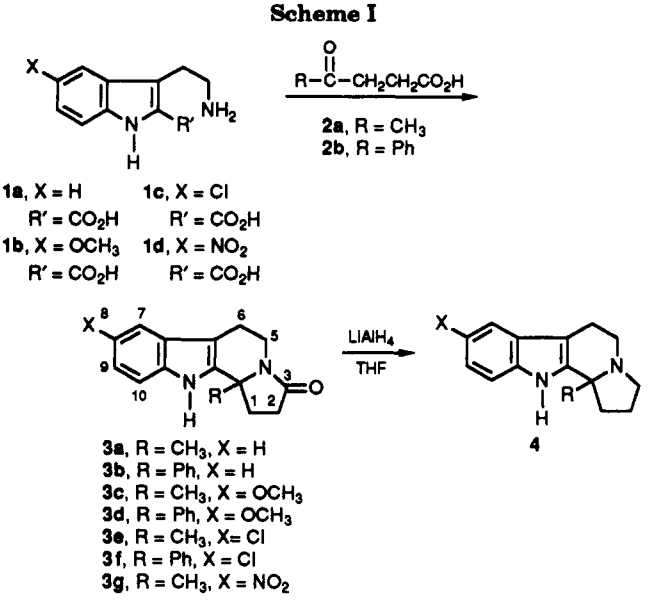
Indolizino[8,7-*b*]indoles are important intermediates in the pharmaceutical industry.[1-3] A number of these indoles have been shown to exhibit analgesic and antiinflammatory activity;[2,3] moreover, some of these compounds have been converted into indoloazonine or indolazecine derivatives, which exhibit diuretic activity.[3,4] A wide variety of indoles of the general formula **3** have been prepared by the Pictet-Spengler reaction of ring A substituted tryptamines **1** (R′ = H) with keto esters **2**, as illustrated in Scheme I. Reduction of the amide function, according to the published procedure,[2-4] provides the parent indolizino[8,7-*b*]indoles **4**. The sequence, however, depicted in Scheme I suffers from the limited availability of the required tryptamines when R′ = H.

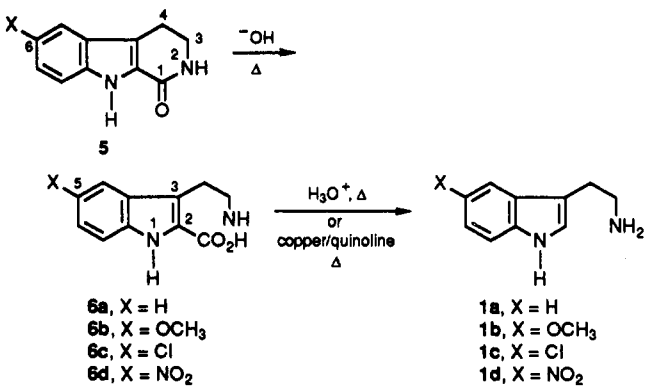
Recently, a modification of the Pictet-Spengler reaction has been developed[8] that permits direct use of tryptamine-2-carboxylic acids **1** (R′ = CO_2H) in this condensation. This improved synthesis of 11_b-substituted indolizino[8,7-*b*]indoles forms the subject of this paper.

One of the most versatile routes to ring A substituted tryptamines is the Abramovitch-Shapiro process[5] wherein

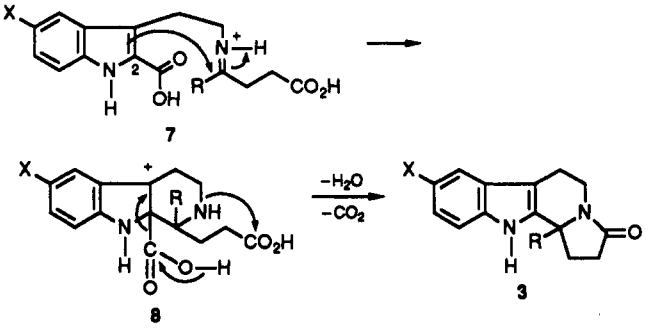
Scheme I



Scheme II



Scheme III



the Japp-Klingemann and Fischer indole[6] reactions are combined to furnish ring A substituted 1-oxo-1,2,3,4-tetrahydro-β-carbolines **5**. Although the hydrolysis of **5** to provide the tryptamine-2-carboxylic acid **6** proceeds in high yield,[6] the decarboxylation step to generate the desired tryptamine **1** often fails[5,7,8] under acidic conditions or even under the conditions of copper/quinoline (Δ).[9] For example, 5-chlorotryptamine-2-carboxylic acid (**6c**)

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