SYNTHESIS OF A SIMPLE KAINIC ACID ANALOGUE BY MEANS OF CARBAMOYLMETHYL RADICAL CYCLIZATION†

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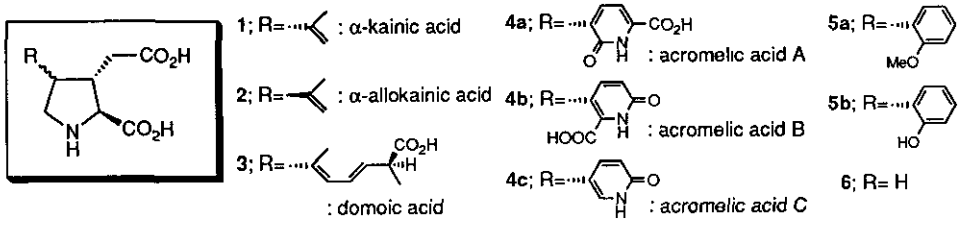
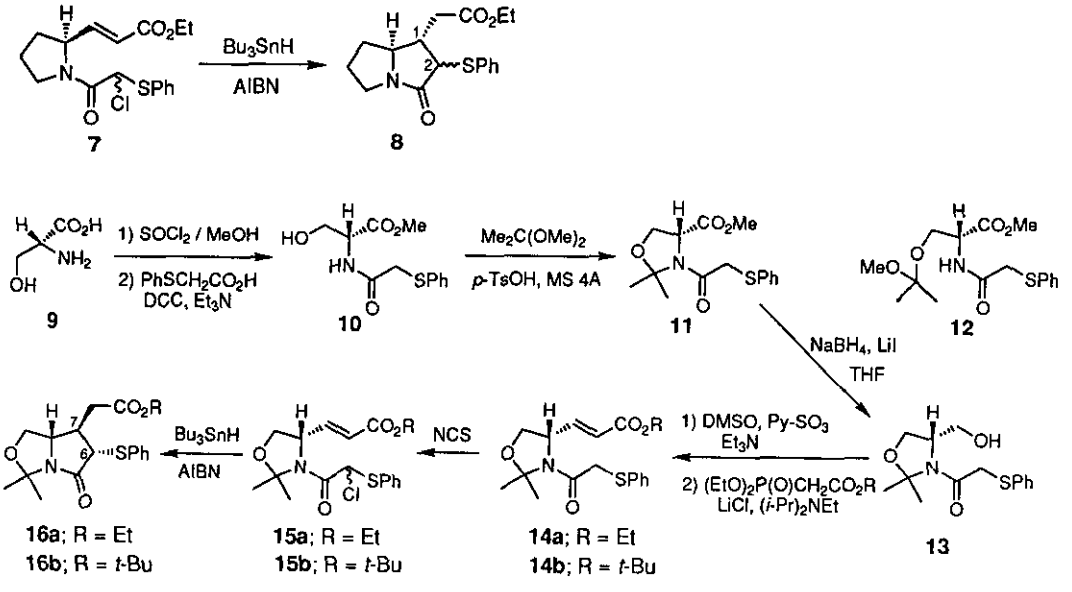
Abstract—A new approach to (-)-(2*S*, 3*R*)-2-carboxy-3-pyrrolidineacetic acid (**6**) starting from D-serine is described. The key step is a radical cyclization of *tert*-butyl (*S*)-3-[2,2-dimethyl-*N*-[chloro(phenylthio)acetyl]oxazolidin-4-yl]-(*E*)-propenoate (**15b**), which gave *tert*-butyl (6*S*, 7*R*, 7a*S*)-5,6,7,7a-tetrahydro-3,3-dimethyl-5-oxo-6-phenylthio-1*H*, 3*H*-pyrrolo[1,2-*c*]oxazol-7-ylacetate (**16b**) in a highly regio- and diastereo-selective manner. The compound (**16b**) was then converted into *tert*-butyl (4*R*, 5*S*)-5-(*tert*-butyldimethylsilyloxymethyl)-1-methoxycarbonyl-2-oxopyrrolidin-4-ylacetate (**19**) by standard chemical manipulations, which has already been transformed to **6**.

Kainic acids (**1** and **2**), domoic acid (**3**), acromelic acids (**4a-c**), and the related compounds are called kainoids and possess potent neuronal excitatory activity.[1] In addition to these naturally occurring compounds, some



†This paper is dedicated to Professor Rolf Huisgen, University of Münich, on the occasion of his 75th birthday.

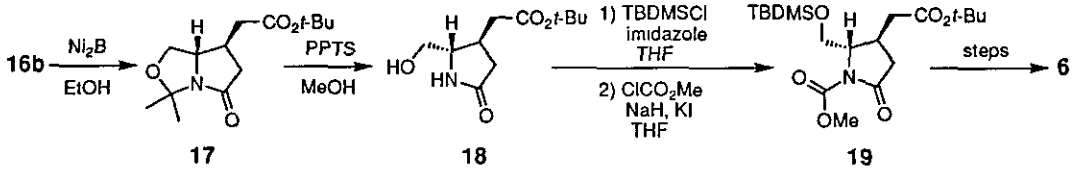
synthetic analogues such as **5a,b** have also been shown to have the strong biological activity.[2] Recently we have reported that a tributyltin hydride-mediated radical cyclization of the α-chlorosulfide (**7**) gives ethyl (1*S*,7a*S*)-hexahydro-3-oxo-2-phenylthio-3*H*-pyrrolizin-1-ylacetate (**8**) in a highly stereoselective manner.[3,4] We have now applied this method to the synthesis of an optically active kainic acid analogue (**6**).[5] The key step of our approach is the radical cyclization of the α-chlorosulfide (**15b**), which can be envisaged to be derived from the readily accessible precursor (**11**), which will in turn be prepared from D-serine (**9**). D-Serine (**9**) provides the correct configuration at C-2 of α-kainic acid (**1**).



Methyl ester of D-serine (**9**) was *N*-acylated with phenylthioacetic acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to give the phenylthioacetamide (**10**) in 86% yield. Conversion of **10** to the oxazolidine (**11**) was initially carried out by heating with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid in refluxing benzene to give **11** (49%) and the uncyclized compound (**12**) (15%), along with the unchanged starting material (22%). However, when the same reaction was performed in the presence of molecular sieves 4A, only the desired oxazolidine (**11**) was obtained in 76% yield. Reduction of **11** with lithium borohydride (prepared *in situ* from sodium borohydride and lithium iodide)[6] gave the alcohol (**13**) in 92% yield. Oxidation of **13** with sulfur trioxide-pyridine complex in dimethyl sulfoxide followed by Horner-Emmons reaction of the resulting aldehyde with triethyl phosphonoacetate or *tert*-butyl diethylphosphonoacetate in the presence of *N*, *N*-diisopropylethylamine (DIPEA) and lithium chloride in

acetonitrile[7] gave the α,β-unsaturated esters (**14a**) (82%) and (**14b**) (84%), respectively. Chlorination of **14a,b** with *N*-chlorosuccinimide (NCS) gave the corresponding α-chlorosulfides (**15a,b**) in quantitative yield, which were subjected to the radical cyclizations.

When a boiling solution of the α-chlorosulfide (**15a**) in toluene was treated with 1.1 mol equiv. of Bu_3SnH in the presence of a catalytic amount of azoisobutyronitrile (AIBN), the cyclized product (**16a**) was obtained in 57 % yield as an essentially single stereoisomer. Similar treatment of **15b** gave **16b** in 51 % yield. The observed coupling constants ($J_{6,7}$) of 11.9 Hz for **16a** and 11.7 Hz for **16b**, are in good agreement with the value for the trans vicinal coupling ($J_{1,2}$=11.2 Hz) (7.0 Hz for the *cis*-isomer) in the closely related pyrrolizidinone (**8**).[3] The stereochemistry of the alkoxycarbonylmethyl group was confirmed by chemical transformation of **16b** to the known compound (**19**).[8] Thus, desulfurization of **16b** with nickel boride in ethanol[9] gave the desulfurized compound (**17**) (70%). Treatment of **17** with pyridinium *p*-toluenesulfonate in methanol followed by *O*-silylation of the resulting alcohol (**18**) and *N*-acylation gave **19** in 46 % overall yield from **17**, whose ir and ^{1}H-nmr spectra were identical with those of an authentic sample given by Professor Langlois. Compound (**19**) has already been transformed to (-)-(2*S*, 3*R*)-2-carboxy-3-pyrrolidineacetic acid (**6**).[8,10]



17 **18** **19**

In conclusion, the radical cyclization of ethyl and *tert*-butyl (*S*)-3-[2,2-dimethyl-*N*-[chloro(phenylthio)-acetyl]oxazolidin-4-yl]-(*E*)-propenoates (**15a,b**) was found to proceed in a highly regio- and diastereo-selective manner to give ethyl and *tert*-butyl (6*S*,7*R*,7a*S*)-5,6,7,7a-tetrahydro-3,3-dimethyl-5-oxo-6-phenylthio-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-7-ylacetates (**16a,b**), respectively, which would be potential precursors for the synthesis of kainic acid and its analogues.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded with a JASCO IR A-100 spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were determined with a JNM-EX270 or a Varian XL-300 spectrometer, using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a Hitachi M-80 instrument at 20 eV. Optical rotations were recorded with a JASCO DIP-360 digital polarimeter. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

***N*-(Phenylthioacetyl)-D-serine Methyl Ester (10)** Thionyl chloride (3.82 ml, 52.3 mmol) was added dropwise to a solution of D-serine (5.0 g, 47.6 mmol) in methanol (60 ml) at 0°C, and the mixture was heated under reflux for 1 h. The solvent was evaporated off to give D-serine methyl ester hydrochloride as colorless crystals. The salt was dissolved in dichloromethane (50 ml) containing triethylamine (8.0 ml, 57.1 mmol) under cooling. Phenylthioacetic acid (8.8 g, 52.3 mmol), DMAP (581 mg, 4.8 mmol), and a solution of DCC (10.8 g, 52.3 mmol) in dichloromethane (10 ml) was added to this solution, and the whole was stirred at room temperature overnight. Precipitated *N,N*-dicyclohexylurea was filtered off, and the filtrate was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 1:2) to give **10** (11.0 g, 86%) as an oil; $[\alpha]_D^{21}$ -7.9° (*c* 0.34, $CHCl_3$); ir ν_{max} (CCl_4) cm^{-1}: 3375, 1740, 1670; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 3.63 (2H, s, CH_2S), 3.66 (3H, s, OMe), 3.70-3.79 (2H, m, one of CH_2OH and OH), 3.86-3.96 (1H, m, one of CH_2OH), 4.57 (1H, dt, *J*=7.9, 3.3 Hz, $CHCO_2Me$), 7.19-7.38 (5H, m, ArH), 7.74 (1H, br d, *J*=7.9 Hz, NH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 37.83, 52.60, 54.75, 62.68, 126.95, 129.13, 134.38, 168.55, 170.40. *Anal.* Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.68; H, 5.62; N, 5.31.

Methyl (*R*)-2,2-Dimethyl-3-(phenylthioacetyl)oxazolidine-4-carboxylate (11) and Methyl (*R*)-3-(1-Methoxy-1-methylethoxy)-2-(phenylthioacetamido)propanoate (12) A solution of *p*-toluenesulfonic acid monohydrate (70 mg, 0.37 mmol) in benzene (50 ml) was heated under reflux with azeotropic removal of water for 1 h, then cooled under a nitrogen atmosphere. A solution of **10** (6.61 g, 24.6 mmol) in benzene (10 ml) and 2,2-dimethoxypropane (7.56 ml, 61.5 mmol) was added to the solution containing anhydrous *p*-toluenesulfonic acid, and the whole mixture was heated again under reflux with azeotropic removal of water overnight. The reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 5:1). The first eluate gave **11** (3.72 g, 49%) as an oil; $[\alpha]_D^{22}$ +92.9° (*c* 0.63, $CHCl_3$); ir ν_{max} (CCl_4) cm^{-1}: 1750, 1660; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 1.47 (3H, s, 2-Me), 1.66 (3H, s, 2-Me), 3.52 and 3.62 (1H each, ABq, *J*=14.2 Hz, CH_2S), 3.78 (3H, s, OMe), 4.07 (1H, dd, *J*=9.2, 5.9 Hz, 5-H), 4.26 (1H, dd, *J*=9.2, 1.0 Hz, 5-H), 4.63 (1H, br d, *J*=5.9 Hz, 4-H), 7.24-7.33 (3H, m, ArH), 7.42-7.46 (2H, m, ArH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 22.93, 25.02, 39.07, 52.92, 59.10, 66.79, 96.78, 127.28, 128.95, 130.85, 134.02, 165.23, 170.60. *Anal.* Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.41; H, 6.07; N, 4.33.

The second eluate gave the unchanged starting material (1.44 g, 22%) and the third eluate gave **12** (1.36g, 15%) as an oil; ir ν_{max} ($CHCl_3$) cm^{-1}: 1740, 1665; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 1.20, 1.23 (3H each, both s, 2xMe), 3.03 (3H, s, OMe), 3.52 (1H, dd, *J*=9.6, 3.0 Hz), 3.68 (2H, s, CH_2S), 3.70 (3H, s, OMe), 3.82 (1H, dd, *J*=9.6, 3.0 Hz), 4.73 (1H, dt, *J*=8.3, 3.0 Hz), 7.17-7.36 (5H, m, ArH), 7.63 (1H, br d, *J*=8.3 Hz, NH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 23.78, 23.85, 37.23, 48.16, 52.08, 52.29, 60.68, 99.93, 126.45, 128.34, 128.90, 134.45, 167.55, 170.13. Exact MS m/z: Calcd for $C_{16}H_{23}NO_5S$: 341.1295. Found: 341.1277.

When the same reaction was carried out in the presence of molecular sieves 4A, only **11** (76%) was obtained.

(*S*)-2,2-Dimethyl-3-(phenylthioacetyl)oxazolidine-4-methanol (13) Sodium borohydride (388 mg, 10.3 mmol) and lithium iodide (1.37 g, 10.3 mmol) were added to a solution of **11** (2.11 g, 6.83 mmol) in dry tetrahydrofuran (THF, 25 ml) at 0°C, and the mixture was stirred at room temperature overnight. Water (50 ml) was added and the whole was extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **13** (1.77 g, 92%), mp 70-71.5°C (from hexane-AcOEt); $[\alpha]_D^{21}$ +38.7° (*c* 0.30, $CHCl_3$); ir ν_{max} (CCl_4) cm^{-1}: 3425, 1625; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 1.43 (3H, s, Me), 1.58 (3H, s, Me), 3.56 (2H, d, *J*=6.9 Hz, CH_2OH), 3.65 and 3.91 (1H each, ABq, *J*=13.9 Hz, CH_2S), 3.79 (1H, dd, *J*=9.2, 5.0 Hz, 5-H), 3.88-3.99 (2H, m), 4.00-4.30 (1H, br, OH), 7.20-7.30 (3H, m, ArH), 7.40-7.45 (2H, m, ArH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 22.52, 26.63, 38.91, 58.76, 62.98, 65.30, 95.53, 127.24, 128.88, 131.07, 134.23, 166.25. *Anal.* Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.47; H, 6.72; N, 4.79.

Ethyl (*S*)-3-[2,2-Dimethyl-3-(phenylthioacetyl)oxazolidin-4-yl]-(*E*)-propenoate (14a) SO_3-pyridine complex (2.83 g, 17.8 mmol) was added portionwise to a solution of **13** (1.25 g, 4.4 mmol) and triethylamine (4.4 ml, 31.6 mmol) in DMSO (4.4 ml) and dichloromethane (30 ml) at 0°C, and the mixture was stirred at the same temperature for 1 h and diluted with ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give the crude aldehyde, which was used for the next reaction without purification. Thus obtained aldehyde (1.23 g) and DIPEA (0.78 ml, 4.5 mmol) were added to a suspension of LiCl (226 mg, 5.3 mmol) and triethyl phosphonoacetate (1.06 ml, 5.3 mmol) in dry acetonitrile (20 ml) at 0°C, and the mixture was stirred at the same temperature for 3 h, diluted with water and concentrated. The residue was extracted with ether and the extract was washed with 1N hydrochloric acid and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 3:1) to give **14a**

(1.26 g, 82%) as an oil; ir ν_{max} ($CHCl_3$) cm^{-1}: 1710, 1640; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 1.30 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.49 (3H, s, 2-Me), 1.69 (3H, s, 2-Me), 3.56 (2H, s, CH_2S), 3.87 (1H, d, *J*=9.2 Hz, 5-H), 4.10 (1H, dd, *J*=9.2, 6.3 Hz, 5-H), 4.21 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 4.62 (1H, t, *J*=6.3 Hz, 4-H), 5.93 (1H, d, *J*=15.7 Hz, olefinic proton), 6.88 (1H, dd, *J*=15.7, 6.3 Hz, olefinic proton), 7.24-7.32 (3H, m, ArH), 7.40-7.45 (2H, m, ArH). Exact ms *m/z*: Calcd for $C_{18}H_{23}NO_4S$: 349.1346. Found: 349.1365.

***tert*-Butyl (*S*)-3-[2,2-Dimethyl-3-(phenylthioacetyl)oxazolidin-4-yl]-(*E*)-propenoate (14b)** Following a procedure similar to that described above except for the use of *tert*-butyl diethylphosphonoacetate instead of triethyl phosphonoacetate, **14b** (955 mg, 84% overall yield) was obtained from **13** (843 mg, 3.0 mmol) as fine needles, mp 72-72.5°C (from hexane); ir ν_{max} (CCl_4) cm^{-1}: 1715, 1650; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 1.49 (12H, s, CMe_3 and 2-Me), 1.69 (3H, s, 2-Me), 3.57 (2H, s, CH_2S), 3.85 (1H, d, *J*=9.2 Hz, 5-H), 4.08 (1H, dd, *J*=9.2, 6.3 Hz, 5-H), 4.59 (1H, br t, *J*=6.3 Hz, 4-H), 5.84 (1H, d, *J*=15.5 Hz, olefinic proton), 6.77 (1H, dd, *J*=15.5, 6.3 Hz, olefinic proton), 7.23-7.33 (3H, m, ArH), 7.40-7.45 (2H, m, ArH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 22.68, 25.79, 27.87, 38.87, 57.90, 67.87, 81.04, 96.26, 124.85, 127.24, 128.90, 130.89, 134.09, 143.72, 164.47, 165.28. *Anal.* Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71. Found: C, 63.65; H, 7.09; N, 3.75.

Preparation and Cyclization of Ethyl (*S*)-3-[3-[Chloro(phenylthio)acetyl]-2,2-dimethyloxazolidin-4-yl]-(*E*)-propenoate (15a) NCS (354 mg, 2.65 mmol) was added portionwise to a solution of **14a** (842 mg, 2.41 mmol) in carbon tetrachloride (20 ml) at 0°C and the mixture was stirred at room temperature for 12 h. The precipitate was filtered off and the filtrate was concentrated to give the crude α-chlorosulfide (**15a**), which was used for the cyclization reaction without purification. To a solution of **15a** (1.02 g) in toluene (150 ml) under reflux was added dropwise a solution of Bu_3SnH (771 mg, 2.65 mmol) and AIBN (41 mg, 0.25 mmol) in toluene (50 ml) over 1 h, and the mixture was further refluxed for 4 h. After evaporation of the solvent, ether (10 ml) and an 8% aqueous solution of KF (10 ml) were added and the whole mixture was vigorously stirred for 1 h. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 5:1) to give ethyl (6*S*,7*R*,7a*S*)-5,6,7,7a-tetrahydro-3,3-dimethyl-5-oxo-6-phenylthio-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-7-ylacetate (**16a**) (478 mg, 57%) as an oil; ir ν_{max} (CCl_4) cm^{-1}: 1730, 1705; ^{1}H-nmr (270 MHz, $CDCl_3$) δ: 1.27 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.46 (3H, s, 3-Me), 1.54 (3H, s, 3-Me), 2.24 (1H, tdd, *J*=11.9, 8.0, 3.3 Hz, 7-H), 2.47 (1H, dd, *J*=16.6, 11.9 Hz, one of CH_2CO),

2.95 (1H, dd, *J*=16.6, 3.3 Hz, one of CH_2CO), 3.36 (1H, t, *J*=9.0 Hz, 1-H), 3.72 (1H, d, *J*=11.9 Hz, 6-H), 3.84 (1H, ddd, *J*=9.0, 8.0, 5.9 Hz, 7a-H), 4.11 (1H, dd, *J*=9.0, 5.9 Hz, 1-H), 4.14 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 7.27-7.31 (3H, m, ArH), 7.57-7.65 (2H, m, ArH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 14.16, 23.59, 26.58, 35.78, 41.33, 59.51, 60.97, 63.81, 69.95, 91.86, 128.44, 129.00, 132.16, 134.05, 167.04, 171.50. Exact *MS m/z*: Calcd for $C_{18}H_{23}NO_4S$: 349.1346. Found: 349.1323.

Preparation and Cyclization of *tert*-Butyl (*S*)-3-[3-[Chloro(phenylthio)acetyl]-2,2-dimethyloxazolidin-4-yl]-(*E*)-propenoate (15b) Following a procedure similar to that described for the preparation of **16a, 14b** (675 mg, 1.74 mmol) was chlorinated with NCS (256 mg, 1.92 mmol) to give the crude α-chlorosulfide (**15b**) (717 mg), which was cyclized with Bu_3SnH (559 mg, 1.92 mmol) and AIBN (28 mg, 0.17 mmol) to give *tert*-butyl (6*S*,7*R*,7a*S*)-5,6,7,7a-tetrahydro-3,3-dimethyl-5-oxo-6-phenylthio-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-7-ylacetate (**16b**) (335 mg, 51%) as fine needles, mp 141-142°C (from hexane-AcOEt); $[\alpha]_D^{24}$ +0.8° (*c* 0.13, $CHCl_3$); ir ν_{max} (CCl_4) cm^{-1}: 1725, 1705; ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 1.44 (9H, s, CMe_3), 1.46 (3H, s, 3-Me), 1.54 (3H, s, 3-Me), 2.21 (1H, tdd, *J*=11.7, 8.0, 3.1 Hz, 7-H), 2.38 (1H, dd, *J*=16.3, 11.7 Hz, one of CH_2CO), 2.88 (1H, dd, *J*=16.3, 3.1 Hz, one of CH_2CO), 3.35 (1H, t, *J*=9.0 Hz, 1-H), 3.70 (1H, d, *J*=11.7 Hz, 6-H), 3.82 (1H, ddd, *J*=9.0, 8.0, 5.6 Hz, 7a-H), 4.10 (1H, dd, *J*=9.0, 5.6 Hz, 1-H), 7.27-7.35 (3H, m, ArH), 7.56-7.64 (2H, m, ArH); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 23.47, 26.47, 27.94, 36.88, 41.33, 59.35, 63.69, 69.88, 81.28, 91.65, 128.28, 128.84, 132.17, 133.93, 167.06, 170.69. *Anal.* Calcd for $C_{20}H_{27}NO_4S$: C, 63.63; H, 7.21; N, 3.71. Found: C, 63.72; H, 7.20; N, 3.68.

***tert*-Butyl (7*R*,7a*S*)-5,6,7,7a-Tetrahydro-3,3-dimethyl-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-7-ylacetate (17)** To a solution of **16b** (320 mg, 0.85 mmol) containing $NiCl_2 \cdot 6H_2O$ (2.02g, 8.5 mmol) in ethanol (15ml) was added dropwise a solution of $NaBH_4$ (965 mg, 26 mmol) in ethanol (10 ml) at 0°C and the mixture was heated under reflux for 2 h. The insoluble material was filtered off, the filtrate was concentrated, and the residue was chromatographed on silica gel (hexane-AcOEt, 3:1) to give **17** (161 mg, 70%) as needles, mp 110-111 °C (from hexane); $[\alpha]_D^{22}$ +3.7° (*c* 0.30, $CHCl_3$); ir ν_{max} (CCl_4) cm^{-1}: 1725, 1700; ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 1.45 (9H, s, CMe_3), 1.46 (3H, s, 3-Me), 1.66 (3H, s, 3-Me), 2.30-2.74 (5H, m), 3.60 (1H, t, *J*=8.7 Hz, 1-H), 3.88-3.97 (1H, m, 7a-H), 4.15 (1H, dd, *J*=8.7, 5.7 Hz, 1-H); ^{13}C-nmr (67.8 MHz, $CDCl_3$) δ: 23.69, 26.69, 28.03, 35.82, 38.67, 43.15, 66.96, 69.71, 81.24, 91.23, 169.97, 170.80. *Anal.* Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.06; H, 8.48; N, 5.15.

***tert*-Butyl (4*R*, 5*S*)-5-Hydroxymethyl-2-oxopyrrolidin-4-ylacetate (18)** A solution of **17** (290 mg, 1.08 mmol) and pyridinium *p*-toluenesulfonate (81 mg, 0.32 mmol) in methanol (10 ml) was heated under

reflux for 16 h. After evaporation of the solvent, the residue was dissolved in dichloromethane (20 ml) and washed successively with saturated sodium bicarbonate solution, 1N hydrochloric acid, and brine, then dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **18** (178 mg, 72%) as fine needles, mp 82.5-84°C (from hexane-AcOEt); $[\alpha]_D^{21}$ +2.7° (*c* 0.11, $CHCl_3$); ir $\nu_{max}(CCl_4)$ cm^{-1}: 3300, 1720, 1690; ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 1.45 (9H, s, CMe_3), 2.08 (1H, dd, *J*=16.6, 5.1 Hz, 3-H), 2.32-2.70 (4H, m), 3.43-3.57 (2H, m), 3.73 (1H, ddd, *J*=10.9, 5.1, 3.1 Hz, 5-H), 3.97 (1H, br t, *J*=5.7 Hz, OH), 7.12-7.18 (1H, br, NH); ^{13}C-nmr (75.4 MHz, $CDCl_3$) δ: 28.05, 32.67, 36.60, 40.10, 61.69, 64.84, 81.24, 171.04, 177.81. *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.46; H, 8.50; N, 6.00.

***tert*-Butyl (4*R*, 5*S*)-5-(*tert*-Butyldimethylsilyloxymethyl)-1-methoxycarbonyl-2-oxopyrrolidin-4-ylacetate (19)** To a solution of **18** (178 mg, 0.78 mmol) in *N,N*-dimethylformamide (8 ml) were added imidazole (133 mg, 1.95 mmol) and *tert*-butyldimethylchlorosilane (142 mg, 0.94 mmol), and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with dichloromethane (20 ml) and water (5 ml). The organic layer was separated, washed twice with saturated ammonium chloride solution, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane-AcOEt, 1:1) to give *tert*-butyl (4*R*, 5*S*)-5-(*tert*-butyldimethylsilyloxymethyl)-2-oxopyrrolidin-4-ylacetate (251 mg, 94%) as a colorless oil; $[\alpha]_D^{24}$ +21.1° (*c* 0.38, $CHCl_3$); ir $\nu_{max}(CCl_4)$ cm^{-1}: 3450, 1725, 1695; ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 0.056 (3H, s, Me), 0.060 (3H, s, Me), 0.89 (9H, s, CMe_3), 1.45 (9H, s, CMe_3), 2.06 (1H, dd, *J*=17.1, 4.9 Hz, 3-H), 2.36 (1H, dd, *J*=17.1, 9.8 Hz, one of CH_2CO_2), 2.43-2.55 (2H, m, 3-H and 4-H), 2.63 (1H, dd, *J*=17.1, 8.7 Hz, one of CH_2CO_2), 3.41 (1H, dt, *J*=6.8, 3.9 Hz, 5-H), 3.53 (1H, dd, *J*=10.0, 6.8 Hz, one of CH_2O), 3.69 (1H, dd, *J*=10.0, 3.9 Hz, one of CH_2O), 6.30-6.35 (1H, br, NH); ^{13}C-nmr (75.4 MHz, $CDCl_3$) δ: 18.15, 25.78, 28.03, 32.98, 36.44, 40.40, 61.10, 66.10, 81.02, 170.89, 176.84.

To a suspension of sodium hydride [60% oil dispersion, 45 mg, 1.12 mmol; washed twice with hexane (5 ml)] in anhydrous THF (5 ml) was added dropwise a solution of the pyrrolidone (191 mg, 0.56 mmol) obtained above in THF (5 ml) at 0°C, and the mixture was stirred at room temperature for 30 min. To this solution were added sequentially potassium iodide (139 mg, 0.84 mmol) and methyl chloroformate (106 mg, 1.12 mmol), and the mixture was kept stirring at the same temperature for 16 h. After evaporation of the solvent, the residue was dissolved in dichloromethane (20 ml) and the organic layer was washed successively with 1N hydrochloric acid, saturated sodium bicarbonate solution, and brine, dried ($MgSO_4$), and concentrated. The residue was

chromatographed on silica gel (hexane-AcOEt, 3:1). The first eluate gave **19**[8] (152 mg, 68%) as a colorless oil; $[\alpha]_D^{22}$ -28.0° (*c* 0.70, $CHCl_3$); ir ν_{max} (CCl_4) cm^{-1}: 1795, 1755, 1725; ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 0.01 (3H, s, Me), 0.03 (3H, s, Me), 0.87 (9H, s, CMe_3), 1.45 (9H, s, CMe_3), 2.15 (1H, dd, *J*=17.9, 1.7 Hz, 3-H), 2.34 (1H, dd, *J*=16.1, 7.1 Hz, one of CH_2CO_2), 2.42 (1H, dd, *J*=16.1, 8.2 Hz, one of CH_2CO_2), 2.63-2.74 (1H, m, 4-H), 2.99 (1H, dd, *J*=17.9, 9.1 Hz, 3-H), 3.76 (1H, dd, *J*=10.5, 1.8 Hz, one of CH_2O), 3.87 (3H, s, OMe), 3.94-3.97 (1H, m, 5-H), 4.00 (1H, dd, *J*=10.5, 3.1 Hz, one of CH_2O); ^{13}C-nmr (75.4 MHz, $CDCl_3$) δ: 18.10, 25.76, 28.04, 30.57, 38.59, 40.74, 53.50, 63.84, 64.28, 81.24, 152.31, 170.67, 173.46. The ir and ^{1}H-nmr spectra were identical with those of an authentic sample provided by Prof. Langlois.

From the second eluate the pyrrolidone (the NH congener of **19**) (53 mg, 28%) was recovered.

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