A SHORT IMPROVED SYNTHESIS OF N-SUBSTITUTED 5-AZA-2-OXA-3-OXO-BICYCLO [2.2.1]HEPTANES

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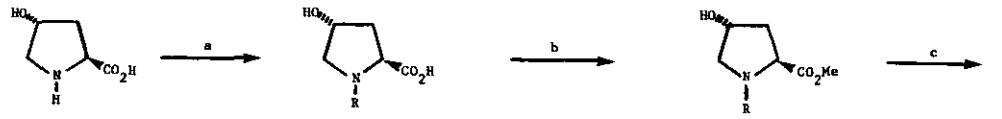
Abstract - N-Substituted 5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptanes are conformationally rigid models that have been used in several ^{1}H-NMR studies. They have previously been obtained by multistep processes. We have devised a one step synthesis for these compounds. The utility of this new route has been demonstrated for five differently N-substituted substrates.

During the last forty-five years, metabolites, analogs, and homologs of proline have received considerable attention.[1-8, 10-19] Among these derivatives one finds trans-4-hydroxy-L-proline which is a component of many proteins, and more specifically an important constituent of collagen, the principal protein of connective tissue.[7] The 4-hydroxyl group of trans-4-hydroxy-L-proline is believed to stabilize the collagen structure by hydrogen bond formation with an adjacent carbonyl group.[11] The Coulombic interactions of dipoles with amide moieties are thought to be important in determining the preferred conformations of peptide bonds in proteins.[15] Therefore, conformationally rigid models were synthesized to examine the effect of a non-contiguous carbonyl group on amide bond rotation.[1,6,12,14-16] The compounds chosen to meet these requirements were N-protected 5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptanes.[1,6,7,11,13-17] A typical method for the synthesis of these systems is shown in Scheme I. The key step of this route involves an SN_2 internal nucleophilic displacement.[11,16] An alternative approach is illustrated in Scheme II. In each case, the total yield of the target compound was less than 65%, after three or four steps.

We have devised an exceptionally facile and general procedure for the synthesis of bridged bicyclic heterocycles. Our approach involves an intramolecular dehydration reaction, under mild, neutral conditions, between an alcohol and a carboxylic acid

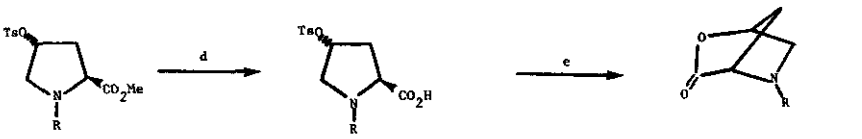
SCHEME I



trans-4-hydroxy-L-proline

1 a R = PhCO (90%[16])
b R = MeCO (83%[5])
c R = $MeC_6H_4SO_2$ (82%[8,12])
d R = $PhCH_2OCO$ (52%[11])

2 a (98%[16])
b (92%[12])



3 a (94%[6])
b (65%[3])
c (ref. 12)
d (62%[11])

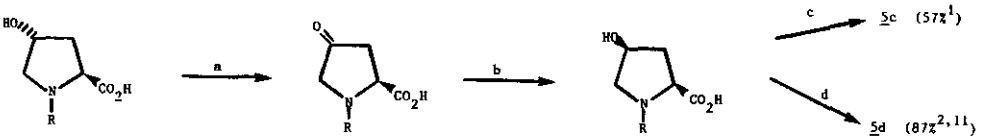
4 a (98%[16])

5 a (70%[16])
b (41%[11])

[a] Schotten-Baumann, [b] CH_2N_2, [c] TsCl, [d] NaOH, [e] K_2CO_3, MEK

on treatment with diethyl azodicarboxylate and triphenylphosphine, the Mitsunobu reaction.[9] Our results are summarized in Scheme III.

SCHEME II



1 c R = $MeC_6H_4SO_2$
d R = $PhCH_2OCO$

6 c (84%[1])
d (68%[11])

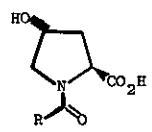
7 c (90%[1])
d (77%[11,19])

5c (57%[1])

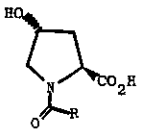
5d (87%[2,11])

[a] CrO_3/H_2SO_4, Me_2CO, [b] $NaBH_4$, [c] DCC/CH_2Cl_2, [d] TsCl/pyr.

Investigations of the mechanism of this reaction have been published recently.[20,21] This approach simplifies the synthesis of the bicyclic bases to one step instead of three or four and the resulting yields are improved as may be seen in Table I. The ^{1}H-NMR data for the N-substituted 4-hydroxyprolines prepared during this investigation are shown in Tables II and III. The existence of rotational isomers in solution, at ambient temperature, was most clearly observed for N-acetyl- and N-Boc-trans-4-hydroxy-L-prolines. Restricted rotation about the N-acyl bond results in the existence of two rotational isomers designated as trans and cis. The identity of the rotational isomers was ascertained by means of the lanthanide



trans



cis

R = Me, $OCMe_3$

shift reagents $PrCl_3 \cdot 6\ H_2O$ and $[Eu(fod)_3]$ which induced a greater downfield shift in the absorptions of the cis isomer. The isomeric ratio was found to be solvent dependent.

Table I. Comparative Yields of N-Substituted 4-Aza-2-oxa-3-oxo-bicyclo[2.2.1]heptanes[a]

R	Yield[b]	Yield[c]	Yield[d]
PhCO	63	--	93
MeCO	27	--	70
$MeC_6H_5SO_2$	--	43	86
$PhCH_2OCO$	--	46	56
Me_3COCO	--	--	72

[a]Total % yields calculated from the corresponding N-substituted 4-hydroxyprolines.

[b]Yields via Scheme I. [c]Yields via Scheme II. [d]Yields via Scheme III; yields are based on isolated pure product and are not optimized.

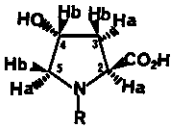
The ^{1}H-NMR data of all N-substituted 5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptanes prepared in this investigation is shown in Tables IV and V. Because of their proximity to the hetero atoms (oxygen and nitrogen) the bridgehead protons of the bicyclic bases are found furthest downfield. These protons may be differentiated by spin decoupling experiments as only H_1 is coupled to the exo proton H_{6b}. In addition, H_4 is more sensitive than H_1 to temperature changes as the former is adjacent to the N-substituent which is subject to rotational isomerism whenever the N-substituent is part of an amide bond.

Previous ^{1}H-NMR studies[14,16] of 2-oxa-5-azabicyclo[2.2.1]heptane systems have shown that the coupling constant between a bridgehead proton and a vicinal endo proton is ~0. The methylene protons H_{6a} and H_{6b} form the AB portion of an ABX spin system in which J_{AX} is ~0 as protons H_{6a} and H_1 form a 90° dihedral angle. Therefore, H_{6a} and H_{6b} appear as a pair of AB doublets. The doublet which is split further can be unequivocally assigned to the exo proton H_{6b}. The remaining bridge

protons H_{7a} and H_{7b} have different chemical shifts and each signal is essentially a doublet broadened by further small couplings. One signal is always broader and more complex than the other. This absorption is assigned to H_{7b} as this proton is expected to display long range coupling with H_{6b}. Protons H_{7b} and H_{6b} are three carbons apart and occupy a planar W configuration, thereby fulfilling the necessary requirements for long range coupling.[14]

The existence of rotational isomers in solution at ambient temperature was best observed in the case of N-acetyl-5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptane (5b). Restricted rotation around the N-acyl bond also results in the existence of two

Table II. ^{1}H NMR Data for N-Substituted 4-Hydroxyprolines



compd		δ (ppm) H_{2a}	H_{3a}	H_{3b}	H_{4b}	H_{5a}	H_{5b}	R
1b[a]	trans	4.48	2.39	2.17	4.58	3.64	3.81	2.12[d]
	cis	4.66	-	-	-	-	3.53	2.02[d]
1b[b]	trans	4.19	2.31	1.81	4.31	3.5-3.2	3.60	1.94[d]
	cis	4 48					3.5-3.2	1.84[d]
1a[a]	trans	4.73	2.49	2.24	4.52	3.51	3.88	-
	cis	-	-	-	-	-	-	-
1a[b]	trans	4.49	2.21	1.95	4.27	3.28	3.72	-
	cis	-	-	-	-	3.56	-	-
1e[a]	trans	4.36	2.43-2.30	2.12	4.54-4.43	3.6	3.3	1.44[e]
	cis	-			- -	-	-	1.49[e]
1e[c]	trans	4.59-4.37	2.35	2.01	4.59-4.37	3 69	3.46	1.49[e]
	cis	- -	-	-	- -	-	-	1.43[e]
1e[b]	trans	4.11	2.2-2.0	2.0-1.8	4.23	3.6	3.2	1.34[e]
	cis	-	- -	- -	-	-	-	1.39[e]
1d[c]		4.35-4.15	2.28	2.06	4.35	3.55	3.30	
			1.06	1.82	4.15			
1c[b]		4.04	1.94		4.21	3.08	3.46	

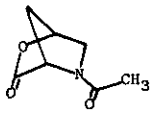
[a] In D_2O. [b] In DMSO-d_6. [c] In $CDCl_3$. [d] R = Me. [e] R = CMe_3.

Table III. J Values for N-Substituted 4-Hydroxyprolines

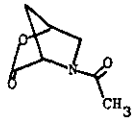
compd	^3J (Hz, vicinal)						^2J (Hz, geminal)	
	$J_{2a,3a}$	$J_{2a,3b}$	$J_{3a,4b}$	$J_{3b,4b}$	$J_{4b,5a}$	$J_{4b,5b}$	$J_{3a,3b}$	$J_{5a,5b}$
1b[a,c] trans	8.3	8.3	2.1	4.6	-	4.0	14.1	11.7
cis	8.0	8.0	-	-	-	4.5	-	12.7
1b[b] trans	7.9	7.9	-	-	-	4.6	-	10.7
cis	7.4	7.4	-	-	-	-	-	-
1a[a] trans	9 6	8.5	4.0	8.1	-	3.7	13.9	12 1
cis	-	-	-	-	-	-	-	-
1a[b] trans	8.6	8.3	4.3	8.0	3.5	-	12.8	11.0
cis	-	-	-	-	-	-	-	-
1e[b]	8.0	8.0	-	-	-	-	-	11.0
1c[b]	7.8	7.8	-	-	2 4	4.3	-	10.6

[a] In D_2O. [b] In DMSO-d_6. [c] ^4J (Hz, long range) for $J_{3a,5a}$ 1.7.

rotational isomers designated as trans and cis.



trans



cis

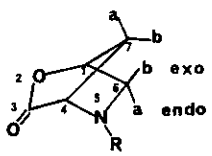
High field ^{1}H-NMR allows resolution of 5b into two separate species. Temperature studies in deuterated dimethyl sulfoxide showed that coalescence of the methyl groups absorptions of the trans and cis forms occurred at 117°C. Additional evidence for this rotational isomerism was provided by the solvent dependence of the isomeric ratio. Resolution of each rotamer was also brought about by the use of a lanthanide shift reagent [Eu(fod)$_3$] which caused the absorptions of one rotational isomer to undergo a greater downfield shift than those of the other isomer.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. Proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WM 250 (250 MHz) and IBM WP 200 SY (200 MHz) Fourier transform spectrometers. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. When deuterium oxide (D_2O) was used

as the solvent, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt hydrate (DSS) was used as the internal standard. Coupling constants (J values) are in hertz (Hz). Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), and multiplet (m). The peaks are integrated in units of protons. Infrared spectra (IR) were run on a Perkin-Elmer Model 281 spectrometer. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center. Either a Hitachi Perkin-Elmer RMH-2 high resolution double focusing electron impact spectrophotometer or a V.G. Micromass 7070-H high resolution mass spectrometer, both interfaced with a Kratos DS-50-S data system were used. Analytical thin layer chromatography (TLC) was performed on Merck silica gel F-254 plates (250 μ). Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in 95% ethanol containing 2% acetic acid and phosphomolybdic acid reagent (7% w/v) in 95% ethanol. Flash chromatography was carried out as described by Still and co-workers.[22] Optical rotations

Table IV. ^{1}H NMR Data for N-Substituted 5-Aza-2-oxa-3-oxobicyclo[2.2.1]heptanes



compd		δ (ppm) H_1	H_4	H_{6a}	H_{6b}	H_{7a}	H_{7b}	R
5b[b]	trans	5.09	4.99	3.48	3.64	2.10	1.95	2.04[c]
	cis		4.39	3.55		2.30	2.25	2.37[c]
5b[a]	trans	4.80	5.33	3.49	3.74	2.33-1.98		1.96[c]
	cis		5.28	3.61-3.26				2.06[c]
5a[b]		5.25	4 62	3.8-3.6	4.0-3.8	2 10	2.30	-
5e[b]		5.01	4.55	3.46	3.54	2.02	2.21	1.48[d]
5d[b]		5.12	4.66	3.54	3.62	2.04	2.25	-
5c[b]		4.49	5.03	3.25	3.65	2.21	2.01	-

[a] In DMSO-d_6. [b] In $CDCl_3$ [c] R = Me. [d] R = CMe_3.

Table V. J. Values for N-Substituted 5-Aza-2-oxa-3-oxo-bicyclo[2.2.1]heptanes

	^2J (Hz, vicinal)		^3J (Hz, geminal)	^4J (Hz, long range)
compd	$J_{6a,6b}$	$J_{7a,7b}$	$J_{6b,1}$	$J_{7b,6b}$
5b[b] trans	10.0	10 8	-	-
cis	-	12.5	-	-
5b[a] trans	10.2	-	-	-
cis	-	-	-	-
5a[b]		11.2		1.7
5e[b]	10.9	11.2	1.1	1.3
5d[b]	10 4	10.4	-	-
5c[b]	10.5	10.9	0.9	1.7

[a] In DMSO-d_6. [b] In $CDCl_3$.

were measured at the sodium D line with a Perkin-Elmer Model 241 polarimeter. All cyclization reactions were carried out under nitrogen in oven-dried glassware (120°C). Tetrahydrofuran was distilled from sodium/benzophenone. trans-4-Hydroxy-L-proline was purchased from Aldrich Chemical Co.

Preparation of N-Benzoyl-trans-4-hydroxy-L-proline (1a). Compound 1a was prepared by a previously described procedure[16] (78% yield), mp 190.5-193°C, lit.[16] 194-196°C, $[\alpha]_D$ -125.18° (c 2.037, EtOH), lit.[16] $[\alpha]_D$ -131.9° (c 1.32, EtOH); IR (KBr) 3600-2400, 3455, 1715, 1620, 1600 cm^{-1}; lit.[16] IR 3540, 1715, 1630 cm^{-1}; HREIMS, m/e (rel. int.) 236, M + 1 (0.2), 235, M^+ (0.3), 217 (0.4), 191 (16.7), 190 (16.1), 105 (100), 86 (2), 77 (56.6), 68 (1.6), exact mass 235.0781 (calcd. for $C_{12}H_{13}NO_4$ 235.0845).

Preparation of N-Acetyl-trans-4-hydroxy-L-proline (1b). Compound 1b was prepared according to a previously described procedure.[5] This product was recrystallized from absolute ethanol (60% yield), mp 132.5-133.5°C, lit.[5,7] 135°C; $[\alpha]_D$ -116.25° (c 1.686, H_2O), lit.[5,7] $[\alpha]_D$ -118° (H_2O); IR (KBr) 2300-3600, 1605, 1730 cm.$^{-1}$ HREIMS; m/e (rel. int.) 174, M 1 (3.1), 173, M^+ (0.4), 129 (33), 128 (34), 86

(100), 85 (23), 68 (55); exact mass 173.0692 (calcd. for $C_7H_{11}NO_4$ 173.0688).

Preparation of N-[p-Toluenesulfonyl]-trans-4-hydroxy-L-proline (1c).[12] A solution of trans-4-hydroxy-L-proline (2.43 g, 18.5 mmol) in 24.5 mL of 2N aqueous sodium hydroxide was treated with a solution of p-toluenesulfonyl chloride (4.13 g, 21.6 mmol) in 30 mL of diethyl ether. The mixture was stirred vigorously at room temperature for 4.75 h. The aqueous layer was separated, acidified with concentrated HCl and refrigerated for 24 h. The crude product was removed by filtration under reduced pressure and recrystallized from ethyl acetate to yield 3.11 g (59% yield) of N-tosylhydroxy-L-proline. Another product was obtained from the ethyl acetate mother liquor by removing the solvent and recrystallizing the residue from 95% ethanol, 1.93 g (36% yield). This product was N,O-ditosylhydroxy-L-proline as confirmed by ^{1}H-NMR (DMSO-d_6, 250 MHz).[23] 1c, mp 152.5 -153.5°C, lit.[7,8,12] 153-155°C; $[\alpha]_D$ -91.99° (c 2.011 EtOH), lit.[12] $[\alpha]_D$ -105.4° (c 2% EtOH); IR (KBr) 3600-2200, 1755, 1725, 1700, 1600 cm^{-1}. HRCIMS m/e (rel. int.) 286, M^+ 1 (24.3), 240 (62.1), 226 (13.2), 225 (100), 129 (26), 116 (65.5), 91 (23.1), 89 (68.9), 86 (17.8), exact mass 286.0768 (calcd. for $C_{12}H_{15}NO_5S$, 286.0749).

Preparation of N-Carbobenzoxy-trans-4-hydroxy-L-proline (1d). Compound 1d was prepared by a previously described procedure[11] (73% yield) as an oil.[24] IR ($CHCl_3$) 3740-2340, 1705, 1440 cm^{-1}; HRCIMS, m/e (rel. int.), 266, M + 1 (1.0), 265, M^+ (0.4), 222 (4.3), 180 (94.3), 155 (1.5), 154 (13.3), 115 (1.4), 114 (22.3), 107 (3.0), 91 (29.8), 89 (100), exact mass 265.0957 (calcd. for $C_{13}H_{15}NO_5$ 265.0950).

Preparation of N-tert-Butoxycarbonyl-trans-4-hydroxy-L-proline (1e). A mixture of trans-4-hydroxy-L-proline (1.31 g, 10.0 mmol) in 20 mL of a 2:1 mixture of THF/H_2O was treated first with 4 mL of 10% aqueous NaOH, and then with di-tert-butyldicarbonate (2.97 g, 13.6 mmol) also in 15 mL of 2:1 THF/H_2O. The reaction mixture (pH9) was stirred at room temperature for several hours, and then flash evaporated to remove the THF. The aqueous solution was acidified to pH 2-3 with 12.5 mL of 10% aqueous $KHSO_4$ and extracted several times with ethyl acetate. The ethyl acetate layers were combined, washed first with water, then with saturated aqueous NaCl, and finally dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent concentrated under reduced pressure to afford 2.30 g (99% yield) of 1e as a clear, colorless syrup. HRCIMS; m/e (rel. int.) 232, M + 1 (1.0), 186 (12.1), 176 (61.1), 132 (58.1), 131 (22.3), 130 (100), 86 (98.8), exact mass 232.1184 (calcd. for $C_{10}H_{17}NO_5$ 232.1184); ^{1}H-NMR (D_2O) δ = 4.54-4.43 (1H, trans, H_{4b}, broad m), 4.36 (1H, trans, H_{2a}, dd, ^3J = 7.6 Hz), 3.6-3.3 (2H, H_{5a},

H_{5b}, m), 2.43-2.30 (1H, H_{3a}, m), 2.12 (1H, H_{3b}, seven line m), 1.49 (2.6 H, cis, $-C(CH_3)_3$, s), 1.44 (6.4 H, trans, $-C(CH_3)_3$, s); ^{1}H-NMR ($CDCl_3$) δ = 5.17 (1H, OH, broad m), 4.59-4.37 (2H, H_{4a}, H_{2a}, broad m), 3.69-3.46 (2H, H_{5a}, H_{5b}, broad m), 2.53-2.01 (2H, H_{3a}, H_{3b}, broad m), 1.49 (5.01 H, trans, $-C(CH_3)_3$, s), 1.43 (3.99 H, cis, $-C(CH_3)_3$, s); ^{1}H-NMR (DMSO-d_6) δ = 12.58 (1H, COOH, broad m), 5.07 (1H, OH, broad m), 4.23 (1H, H_{4b}, broad m), 4.11 (1H, H_{2a}, dd, $^3J_{2a,3a} = {}^3J_{2a,3b}$ = 8.0 Hz), 3.6-3.2 (2H, H_{5a}, H_{5b}, m, ^2J = 11.0 Hz), 2.2-2.0 (1H, H_{3a}, m), 2.0-1.8 (1H, H_{3b}, m), 1.39 (3.31 H, cis, $-C(CH_3)_3$, s), 1.34 (5.69 H, trans, $-C(CH_3)_3$, s).

The preparation of all N-substituted 5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptanes will be illustrated with the preparation of 5b.

Preparation of 5-Acetyl-5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptane (5b). A stirred solution of previously prepared 1b (0.8004 g, 4.62 mmole) and triphenylphosphine (1.2706 g, 4.84 mmole) in 70 mL of tetrahydrofuran was cooled to 0°C, then treated with diethyl azodicarboxylate (0.846 g, 0.765 mL, 4.86 mmole) as the reaction mixture warmed to room temperature. Stirring was continued for several hours. The reaction mixture was flash evaporated and the residue flash chromatographed on a 35mm x 6" Merck silica gel 60, 230-400 mesh column and eluted in 20 mL fractions with acetonitrile, to yield 0.50 g (70% yield) of 5-acetyl-5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptane. The product was recrystallized from methyl ethyl ketone/hexane, mp 95.5 -98.0°C, lit.[7,11] 99-101°C; $[\alpha]_D$ + 67.30° (c 1.902, $CHCl_3$) lit.[7,11] $[\alpha]_D$ + 61.1° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1798, 1655 cm^{-1}, lit.[11] 1799, 1664 cm^{-1}; HREIMS, m/e (rel. int.) 156, M + 1 (1.0), 155, M^+ (6.1), 111 (42.8), 85 (16.0), 69 (65.1), 68 (84.1), 56 (100), exact mass 155.0591 (calcd. for $C_7H_9NO_3$ 155.0583); ^{13}C NMR ($CDCl_3$) δ = 170.58 (C_3), 169.43 (N-C=O), 78.63, 78.39 (C_1, cis, trans), 59.22, 55.84 (C_4, cis, trans), 50.78, 49.69 (C_6, cis, trans), 39.70, 38.40 (C_7, cis, trans), 21.97 (CH_3); ^{1}H-NMR ($CDCl_3$) δ = 5.09 (1H, H_1, s), 4.99 (0.38H, trans, H_4, s), 4.39 (0.62 H, cis, H_4, s), 3.64 (0.38 H, trans, H_{6b}, d, ^2J = 10.0 Hz), 3.55 (1.24 H, cis, H_{6a}, H_{6b}, s), 3.48 (0.38 H, trans, d, ^2J = 10.0 Hz), 2.37 (1.86 H, cis, CH_3, s), 2.30 (0.62H, cis, H_{7a}, dd, ^2J = 12.5 Hz), 2.25 (0.62H, cis, H_{7b}, dd, ^2J = 12.5 Hz), 2.10 (0.38H, trans, H_{7a}, dd, ^2J = 10.8 Hz), 2.04 (1.14H, trans, CH_3, s), 1.95 (0.38H, trans, dd, ^2J = 10.8 Hz); ^{1}H-NMR (DMSO-d_6) δ = 5.33 (0.58H, trans, H_4, s), 5.28 (0.42H, cis, H_4, s), 4.80 (1H, H_1, s), 3.74 (0.58H, trans, H_{6b}, d, ^2J = 10.2 Hz), 3.61-3.26 (0.84H, cis, H_{6a}, H_{6b}, m), 3.49 (0.58H, trans, H_{6a}, d, ^2J = 10.2 Hz), 2.33-1.98 (2H, H_{7a}, H_{7b}, m), 2.06 (1.26H, cis, CH_3, s), 1.96 (1.74H, trans, CH_3, s).

Preparation of 5-Aza-5-benzoyl-2-oxa-3-oxo-bicyclo[2.2.1]heptane (5a). Compound 5a was prepared as described for 5b. The residue was flash chromatographed as for 5b but eluted with acetone/hexane (6:4, v/v). Early fractions were combined and rechromatographed on a 35mm x 6 inch silica gel column, as described above, and eluted in 20 mL fractions with diethyl ether/acetone (3:1, v/v, R_f = 0.34) to yield 1.23 g (78% yield) of homogeneous product. The later fractions containing 5a and triphenylphosphine oxide were pooled and rechromatographed on a 35mm x 6 in. silica gel column as described above and eluted with acetonitrile to yield an additional 249 mg of homogeneous product (R_f = 0.69) (93% total yield), mp 132-133.5°C, lit.[16] 131.5-133.5°C; $[\alpha]_D$ + 80.29 (c 1.943, EtOH), lit.[16] $[\alpha]_D$ + 91.2° (c 1.25, EtOH); IR ($CHCl_3$) 1789, 1630 cm^{-1}, lit.[16] 1792, 1625 cm^{-1}; HREIMS, m/e (rel. int.) 217 (0.8), 173 (16.8), 106 (7.9), 105 (100), 77 (44), 57 (19.5), exact mass 217.0751 (calcd. for $C_{12}H_{11}NO_3$ 217.0763).

Preparation of 5-tert-Butoxycarbonyl-5-aza-2-oxa-3-oxo-bicyclo[2.2.1]heptane (5e). Compound 5e was prepared as described for 5b. The residue was triturated with Et_2O/PE (9:1), the precipitate collected by filtration and the filtrate concentrated. The residue was flash chromatographed on a 50mm x 6 in. Merck silica gel 60, 230-400 mesh column and eluted in 30 mL fractions with CH_2Cl_2/acetone (20:1, v/v) to afford 1.52 g (74% yield) of crude product. Recrystallization from EtOAc/PE yielded, in two crops, 1.49 g (72% yield) of homogeneous product, mp 109.0-111.0°C; $[\alpha]_D$ + 45.95° (c 1.480, $CHCl_3$) IR ($CHCl_3$) 1800, 1700 cm^{-1}; HREIMS, m/e (rel. int.) 213 (0.4), 140 (16.6), 113 (10.1), 69 (16.1), 57 (100), 56 (18.7), exact mass 213.1004 (calcd. for $C_{10}H_{15}NO_4$ 213.1001); ^{1}H-NMR ($CDCl_3$) δ = 5.09 (1H, H_1, s), 4.55 (1H, H_4, m), 3.54 (1H, H_{6b}, dd, ^2J = 10.9 Hz, $^3J_{6b,1}$ = 1.1 Hz), 3.46 (1H, H_{6a}, ^2J = 10.9 Hz), 2.21 (1H, H_{7b}, dt, ^2J = 11.2 Hz, ^3J = 1.3 Hz), 2.02 (1H, H_{7a}, d, ^2J = 11.2 Hz), 1.48 (9H, $-C(CH_3)_3$, s), Anal. Calcd. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.20; H, 7.34; N, 6.61.

Preparation of 5-Aza-5-carbobenzoxy-2-oxa-3-oxo-bicyclo[2.2.1]heptane (5d). Compound 5d was prepared as described for 5b. The final product was chromatographed on silica gel as previously described and eluted with 20 mL fractions of CH_2Cl_2/acetone (30:1, v/v) to yield 0.91 g (56% yield) of homogeneous product, mp 98.5-100°C, lit.[7,11] 102-103°C; $[\alpha]_D$ + 33.32° (c 2.191, $CHCl_3$), lit.[11] $[\alpha]_D$ + 33.6° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 1800, 1710 cm^{-1}, lit.[11] 1799, 1706 cm^{-1}; HREIMS, m/e (rel. int.), 248, M + 1 (0.5), 247, M^+ (1.9), 203 (7.4), 92 (10.8), 91 (100), 68 (4.3), 66 (2.5), exact mass 247.0849 (calcd. for $C_{13}H_{13}NO_4$ 247.0845).

Preparation of 5-Aza-5-(p-Toluenesulfonyl)-2-oxa-3-oxo-bicyclo[2.2.1]heptane (5c). Compound 5c was prepared as described for 5b. The residue was flash chromatographed as previously described and eluted with 30 mL fractions of CH_2Cl_2/acetone (60:1, v/v) to afford 1.61 g (86% yield), mp 108.5-110.5°C, lit.[1,7,14] 106-107°C; $[\alpha]_D$ + 30.48 (c 3.839, $CHCl_3$), lit.[1] $[\alpha]_D$ + 27.7° (3% $CHCl_3$); IR ($CHCl_3$) 1815, 1800, 1350 cm^{-1}, lit.[1] ($CHCl_3$) 1800 cm^{-1}. IR (KBr) 1820, 1795, 1600, 1350 cm^{-1}, lit.[14] (KBr) 1789 cm^{-1}; HREIMS, m/e (rel. int.), 268, M + 1 (0.3), 267, M^+ (1.3), 223 (67.2), 156 (7.9), 91 (100), 68 (68.7), 67 (5.7), 65 (44.9), exact mass 267.0565 (calcd. for $C_{12}H_{13}NO_4S$ 267.0565).

SCHEME III

1 a R = PhCO
b R = MeCO
c R = $MeC_6H_4SO_2$
d R = $PhCH_2OCO$
e[b] R = Me_3COCO

5 a (93%)
b (70%)
c (86%)
d (56%)
e (72%)

[a] Ph_3P, diethyl azodicarboxylate (DEAD), THF, [b] Prepared from 4-hydroxy-L-proline, di-tert-butyldicarbonate $(BOC)_2O$, aq. NaOH, THF (99%)

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23. ^{1}H-NMR (DMSO-d_6) δ = 7.64 (2H, -O-Tosyl-H, d, ^{3}J = 8.3 Hz), 7.59 (2H, -N-Tosyl-H, d, ^{3}J = 8.2 Hz), 7.47 (2H, -O-Tosyl-H, d, ^{3}J = 8.3 Hz), 7.38 (2H, -N-Tosyl-H, d, ^{3}J = 8.2 Hz), 5.01 (1H, H_{4b}, broad m), 4.02 (1H, H_{2a}, dd, $^{3}J_{2a3a}$ = 9.3 Hz, $^{3}J_{2a3b}$ = 7.5 Hz), 3.59 (1H, H_{5b}, dd, $^{2}J_{5a5b}$ = 12.9 Hz, $^{3}J_{5b4b}$ = 3.6 Hz), 3.48-3.27 (1H, H_{5a}, m), 2.44 (3H, O-Tosyl-CH_3, s), 2.38 (3H, N-Tosyl-CH_3, s).
24. Addition of a large excess of benzyl chloroformate resulted in (in addition to the desired CBZ derivative) the formation of an appreciable amount of the N,O-dicarbobenzoxy-L-proline as confirmed by ^{1}H-NMR and mass spectrum. ^{1}H-NMR ($CDCl_3$) δ = 7.4-7.1 (10H, Ar-H, m), 5.31-4.94 (4H, -OCOOCH_2Ph, NCOOCH_2Ph, m), 4.64-4.43 (2H, H_{2a}, H_{4b}, m), 3.74-3.50 (2H, H_{5a}, H_{5b}, m), 2.40-2.00 (2H, H_{3a}, H_{3b}, m).

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