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A CONCISE ASYMMETRIC SYNTHESIS OF THE POTENT ENKEPHALINASE INHIBITOR KELATORPHAN.

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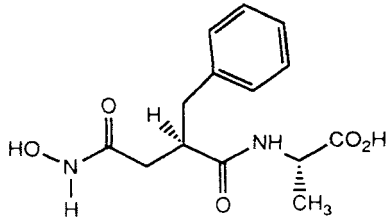
Abstract. A concise asymmetric synthesis of the enkephalinase inhibitor Kelatorphan has been completed in seven steps from commercially available hydrocinnamyl chloride. The synthesis features as a key step an asymmetric C-C bond formation which utilizes Oppolzer bornane-sultam alkylation methodology.

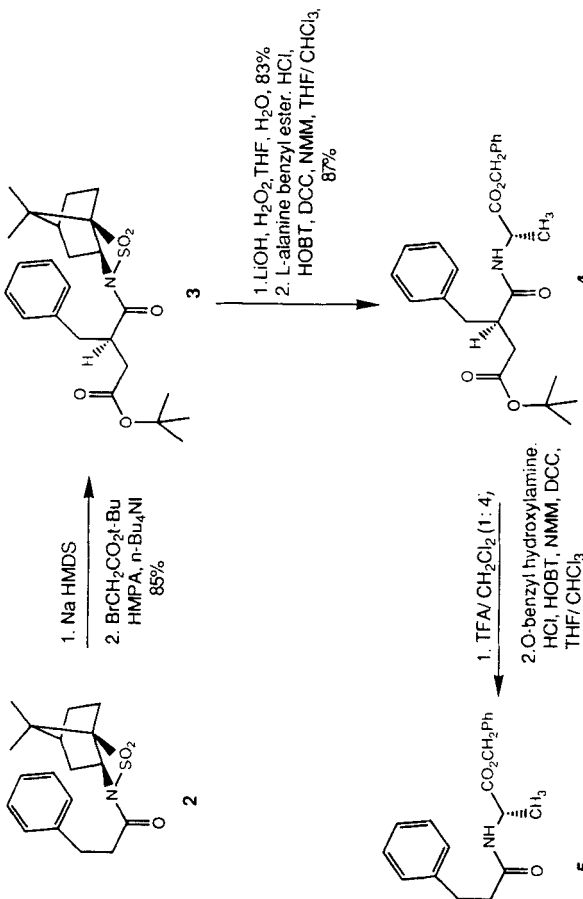
Neutral endopeptidase 24.11 (enkephalinase, NEP) is a zinc metalloprotease which degrades a variety of neuropeptides. This enzyme has been implicated as major degradative enzyme for the enkephalins in vivo.[1] Kelatorphan **I**, a peptide derived hydroxamate, is a potent inhibitor of all enkephalin degrading peptides including NEP, enkephalin degrading aminopeptidases and dipeptidyl aminopeptidase. In order to obtain a supply of **I** for use as a standard in biological

assays we undertook a novel synthesis of this material. Kelatorphan had previously been obtained, in racemic form, by the original workers in this area Roques and Fournie-Zaluski.[2] We felt that utilization of the Oppolzer innovation for the asymmetric alkylation of bornane-sultam derived enolates[3] would provide a rapid and convenient access to the target molecule. This perception proved to be true and the successful route is detailed in Scheme 1.



Kelatorphan, 1

Commercially available hydrocinnamyl chloride was converted to its bornane sultam derivative **2** utilizing conditions previously described by Oppolzer and co-wo.kers. Alkylation of the sodium enolate derived from **2** with bromo t-butylacetate in the presence of tetrabutylammonium iodide in THF/HMPA at -70°C for ten hours provided the ester-sultam **3**



Scheme 1

in 85% yield and greater than 98% de after recrystallization from ether/hexane. Non-destructive removal of the chiral auxiliary with lithium hydroperoxide in aqueous tetrahydrofuran proceeded uneventfully to furnish the corresponding optically pure carboxylic acid which was immediately coupled with (L)-alanine benzyl ester under standard coupling conditions to provide diester **4** in 72% yield for the two steps. Exposure of **4** to trifluoroacetic acid in dichloromethane followed by coupling of the crude acid with O-benzylhydroxylamine hydrochloride under the conditions elaborated for compound **4** accessed the dibenzyl derivate **5** in 70% yield. **5** underwent smooth catalytic reductive debenzylation using 10% palladium on carbon under a hydrogen atmosphere at STP to provide Kelatorphan in 95% yield after recrystallization and 35% overall yield.

Summarily, we have described a concise, practical synthesis of the enkephalinase inhibitor Kelatorphan in seven steps starting from commercially available hydrocinnamyl chloride and L(-) bornane-10,2-sultam in 35% overall yield which is of considerable utility for the production of gram quantities of this pharmacologically significant material.

EXPERIMENTAL SECTION

General

NMR spectra were obtained on either a GE-QE300 or a Varian VXR-400 spectrometer in the solvent indicated. ^{1}HNMR spectra are reported in ppm from internal tetramethylsilane on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 685 spectrophotometer in $CHCl_3$. Optical rotations are reported as follows: $[\alpha]_D$, concentration, c(g/100mL) and solvent. Mass spectral data was obtained on a Finnegan-MAT 8430 spectrometer using EI or CI techniques. Melting points are uncorrected. Flash chromatography was performed according to the general procedure of Still,[4] employing Merck 60 silica gel with the solvent system indicated.

1,1-Dimethylethyl tetrahydro-8,8-dimethyl-γ-oxo-ßR-(phenylmethyl)-7aß-3H-3aR,3aα, 6α -methano-2,1- benzisothiazole-1(4H)-butanoate, 3.

Bornane sultam **2**, (3.47g, 10mMol) was dissolved in dry THF (50 cm^3) and the solution cooled to -70°C. A solution of $NaN(TMS)_2$ (1.0M in THF, 10cm^3) was added dropwise via syringe and the mixture stirred magnetically under argon at

–70°C for 1 hour. At this juncture, a solution of t-butylbromoacetate (5.85g, 30 mMol) in HMPA (5.4g) was added dropwise via syringe followed by a suspension/solution of n-Bu_4NI (0.4g, 1mMol) in THF (5cm^3) and the mixture stirred at –70°C for 10 hours. A dense white precipitate formed during this time. The mixture was quenched with water (100 cm^3) and extracted with ether (3x 100 cm^3). The combined organic extracts were washed with brine and dried (Na_2SO_4). Evaporation of the volatiles in vacuo afforded 6.2g of a crude white solid which was crystallized from ether to provide 3.7 g of pure alkylation product **3**.

3 mp=148-151°C (softens 125°C), IR ($CHCl_3$) 2960, 1725, 1685, 1410, 1390, 1365, 1330, 1150, 1130 cm^{-1}, NMR ($CDCl_3$, 400MHz) 0.98 (3H, s), 1.26 (3H, s), 1.35 (1 H, m), 1.38 (9H, s), 1.43 (1H, m), 1.84 - 1.97 (3H, complex band), 2.03 (1H, dd, J=13.8, 7.7 Hz), 2.16 (1 H, dddd, J=13.8, 5.0, 3.5, 3.0 Hz), 2.34 (1H, dd, J=16.2, 4.8 Hz), 2.55 (H, dd, J=13.5, 9.9), 2.67 (1H, dd, J=16.2, 9.3 Hz), 3.33 (1H, dd, J=13.5, 4.5), 3.46 (1H, d, J=13.7 Hz), 3.53 (1H, d, J=13.7 Hz), 3.61 (1H, dddd, J=9.9, 9.3, 4.8, 4.5 Hz), 3.92 (1H, dd, J=7.7, 5.0 Hz), 7.18 - 7.32 (5H, complex band),

mass spectrum (EI), M/Z 461 (M+), 406, 405, 388, 348, 346, 282, 217, 216. $[\alpha]_D$ + 72.4° (c, 0.12, $CHCl_3$). Anal. Calcd. for $C_{24}H_{35}NO_5S$: C, 65.05, H, 7.64, N, 3.03. Found C, 65.26, H, 7.75, N, 2.98.

1,1-Dimethylethyl R-[[[15-methyl-2-oxo-2-(phenyl-methoxy)ethyl]amino]carbonyl] benzenebutanoate 4.

3 (4.6g, 10mMol) was dissolved in the THF/H_2O (20 cm^3, 16.4 mMol) at 0°C under an argon atmosphere and stirred magnetically whilst lithium hydroxide powder (0.96 g, 40 mMol) was added along with a 30% wt in water solution of hydrogen peroxide (9.0 cm^3). The mixture was stirred at 0°C for 1 hour and then slowly allowed to warm to room temperature and stirred for a further four hours. The mixture was partitioned between CH_2Cl_2 (200 cm^3) and 1N HCl (80 cm^3) and the organic layer separated and dried (Na_2SO_4). Evaporation of the volatiles in vacuo afforded a colorless oil which was purified by chromatography using ethyl acetate/hexane/acetic acid 6:4:0.1 as eluant to afford 2.2 gms of product, R-(Phenylmethyl) butanedioic acid, -4-(1,1-dimethylethyl)ester as a viscous syrup (85%) which

crystallized on standing plus recovered auxiliary (83%). mp=56-8°C, IR ($CHCl_3$) 3500, 2600 (br), 1720, 1710, 1450, 1365, 1225, 1150 cm^{-1}, NMR ($CDCl_3$, 400 MHz) 1.42, (9H, s), 2.35 (1H, dd, J=16.8, 4.6 Hz), 2.56 (1H, dd, =16.8, 8.9 Hz). 2.77 (1H, dd, J=15.4, 10.4 Hz), 3.05 - 3.14 (2H, complex band), 7.16-7.33 (5H, complex band), mass spectrum (EI), M/Z 209 ($M^+-C_4H_9$-2H), 208, 191, 190, 173, 163, 162, 149, 148, 162, $[\alpha]_D$ + 6.4° (c, 0.11, $CHCl_3$), Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16, H, 7.63. Found C, 67.96, H, 7.69.

This acid, (0.96g 3.63 mMol) was dissolved in dry THF (15 cm^3) and the solution cooled to 0°C under argon with magnetic stirring. L-Alanine benzyl ester.HCl (0.78g, 3.63 mMol) was added in one portion followed by N-methylmorpholine (0.41 cm^3 in 5 cm^3 $CHCl_3$). The mixture was stirred at 0°C for 5 minutes and then a solution of 1-hydroxybenzotriazole. H_2O (HOBT.H_2O, 0.49g 3.63 mMol) in THF (10 cm^3) was added followed by a solution of dicyclohexylcarbodiimide (0.82 g) in $CHCl_3$ (10 cm^3). The mixture was stirred at 0°C for 1 hour and then allowed to warm to RT. The mixture was filtered through sintered glass, diluted with $CHCl_3$ (50 cm^3) and washed

sequentially with water (25 cm^3), 10% citric acid (25 cm^3), water (25 cm^3), 10% $NaHCO_3$ (25 cm^3), water (25 cm^3) and brine (25 cm^3). Evaporation of the dried (Na_2SO_4) solvent afforded 1.5 g of crude material which was purified by chromatography using ethyl acetate/hexane (3:7) as eluant to afford 1.3 g of pure product **4** as a viscous syrup (87%).

4. IR ($CHCl_3$) 3410, 1725 (br), 1670, 1510, 1450, 1365 cm^{-1}, NMR ($CDCl_3$, 400MHz) 1.35 (3H, d, J=7.2 Hz), 1.40 (9H, s), 2.32 (1H, dd, J=16.9, 4.3 Hz), 2.63 (1H, dd, J=16.9, 9.7 Hz), 2.69 (1H, dd, J=13.2, 7.7 Hz), 2.83 (1H, dddd, J=9.7, 7.7, 7.2, 4.3 Hz), 2.95 (1H, dd, J=13.2, 7.2 Hz), 4.56, (1H, p, J=7.2 Hz), 5.13 (2H, s), 6.12 (1H, d, J=7.2 Hz), 7.14 - 7.40 (10H, complex band), Mass spectrum (EI), M/Z 425 (M^+), 369, 352, 310, 278, 234, 189, 173, 163, 145 117.

N-[1,4-dioxo-4-[(phenylmethoxy)amino]-2R-(phenylmethyl)butyl]-L-alanine, phenylmethyl ester, 5.

4, (1.3g, 3.16 mMol) was dissolved in TFA/CH_2Cl_2 (25 cm^3, 1:4) and refrigerated at 0°C for 24 hours. The solvent was evaporated in vacuo and the crude residue passed through a short silica pad using ethyl acetate/ hexane/acetic acid,

(3.5:6.5:0.1) as eluant to afford acid, R-[[[1S-methyl-2-oxo-2-(phenylmethoxy)ethyl]amino]carbonyl] benzenebutanoic acid as a viscous gum which crystallized slowly on standing.

mp=89-91°C, IR ($CHCl_3$) 3690, 3420 (br), 1735, 1720, 1670, 1510, 1450 cm^{-1}, NMR ($CDCl_3$, 400 MHz) 1.34, (3H, d, J=7.2 Hz), 2.48 (1H, distorted dd, J=15.5, 2.4 Hz), 2.74 (1H, distorted dd, J=12.8, 7.5 Hz), 2.74 - 2.87 (2H, complex band), 2.95 (1H, distorted dd, J-12.8, 6.8 Hz), 4.53 (1H, p, J=7.2 Hz), 5.13 (2H, s), 6.12 (1H, d, J=7.2 Hz), 7.12 - 7.41 (10H, complex band).

This acid (0.75g, 2mMol) was dissolved in dry THF (20 cm^3) and the solution cooled to 0°C under argon. O-Benzyl-hydroxylamine. HCl (0.32g, 2mMol) was added followed by a solution of N-methylmorpholine in $CHCl_3$ (0.23 cm^3 NMM in 10 cm^3 $CHCl_3$) and the mixture stirred for 10 minutes. At this point, HOBT.H_2O (0.27g, 2 mMol) in THF (10 cm^3) was added followed by a solution of DCC (0.45g, 2.2 mMol) in $CHCl_3$ (10cm^3). The mixture was stirred at 0°C for 40 minutes and then at 25°C for 8 hours. The solution was filtered through sintered glass and the solvent evaporated in vacuo to afford a

crude product which was dissolved in ethyl acetate (200 cm^3). The organic layer was washed sequentially with water (75 cm^3), 10% citric acid (75 cm^3) water (50 cm^3), 10% sodium bicarbonate (75 cm^3), water (50 cm^3) and brine (75 cm^3). Evaporation of the dried solvent in vacuo afforded a crude amorphous white powder which was purified by chromatography on silica gel using ethyl acetate/hexane, 1:1, as eluant to provide 0.55g pure product **5**.

5 mp=149-15°C, IR ($CHCl_3$) 3400, 3250 (br.sh), 1740, 1670 (br), 1510, 1495, 1450 cm^{-1}, NMR ($CDCl_3$, 400 MHz) 1.34 (3H, d, J=7.2 Hz), 2.19 (1H, dd), 2.36 (1H, dd), 2.7 (1H, dd), 2.9 - 3.05 (2H, complex band), 4.48 (1H, p), 4.84 (2H, s), 5.13 (2H, s), 6.16 (1H, d), 7.10 - 7.41 (10H, complex band), $[\alpha]_D$ + 16.9° (c, 0.14, $CHCl_3$). Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 70.80, H, 6.33, N, 5.91. Found C, 70.80, H, 6.50, N, 5.92.

N-[4-(hydroxyamino)-1,4-dioxo-2R-(phenylmethyl)-butyl]-L-alanine, Kelatorphan, I.

5 (0.53g, 1.1 mMol) was dissolved in methanol (25 cm^3) and hydrogenated at 5psi and RT using 10% Pd/C as catalyst. Hydrogen uptake was quantitated and stopped after 12 minutes

when the theoretical amount had been absorbed. The catalyst was removed by filtration and the solvent removed in vacuo to afford a colorless oil. Trituration with dry ether containing 2% ethyl acetate afforded Kelatorphan as a white crystalline solid, 0.29g, 91%, identical to authentic material[2].

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