Pergamon

Tetrahedron Letters, Vol. 35, No. 24, pp. 4205-4208, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0746-K

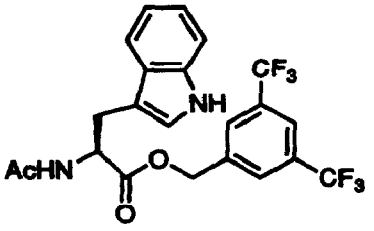
Synthesis of Homochiral Ketones Derived from L-Tryptophan: Potent Substance P Receptor Antagonists.

Kevin J. Merchant*, Richard T. Lewis and Angus M. MacLeod.

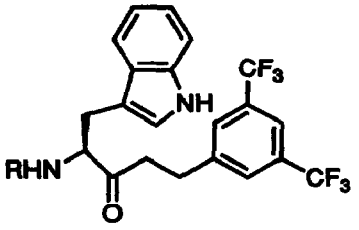
Merck, Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.

Abstract: The synthesis in 36% overall yield of (S)-2-amino-5-(3,5-bis(trifluoromethyl)phenyl)-1-(3-indolyl-3-pentanone, the precursor to a novel class of substance P antagonists, is described.

Substance P, an undecapeptide neurotransmitter, is the endogenous ligand for the tachykinin NK_1 receptor that is widespread throughout the body.[1] It has been implicated in the transmission of pain signals and the initiation of inflammatory responses. Because of these effects substance P antagonists may have potential use in analgesia[2] and as novel anti-inflammatory agents for use in the treatment of migraine[3] and rheumatoid arthritis.[4] Until recently[5], the only available substance P antagonists were peptides with poor bioavailability and stability which limited their potential for investigating clinical applications.



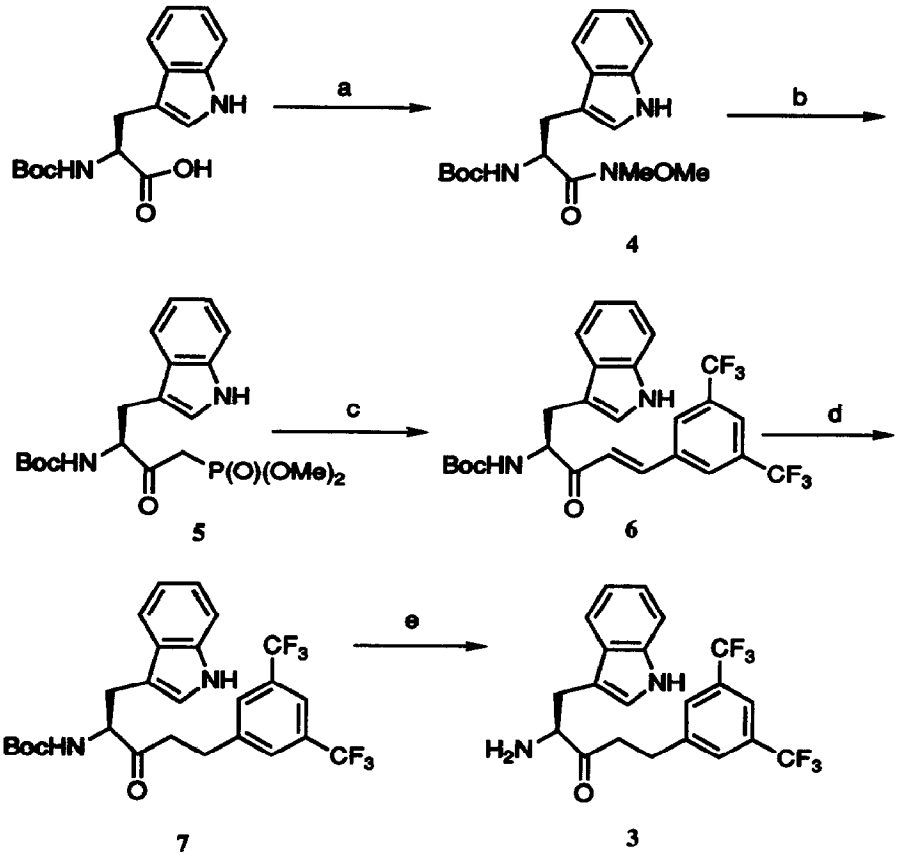
1



2 R = Ac 3 R = H

The tryptophan ester 1 derived from a screening lead in our laboratories has been shown *in vitro* to be a potent NK_1 antagonist.[6] While 1 was active *in vivo* after dosing by intra-peritoneal administration in animal models of inflammation, its potency was markedly reduced by the oral route, conceivably as a result of enzymatic hydrolysis of the ester moiety. This paper discloses the synthesis of the non-hydrolysable ketone analogue 2 which retains the same high affinity[7,8] for the NK_1 receptor as 1. Previous work in the ester series demonstrated that NK_1 activity resided predominantly with the S enantiomer. To provide material for extensive structure activity studies a reliable route to multigram quantities of the active S enantiomer of the parent amino ketone 3 has been developed.

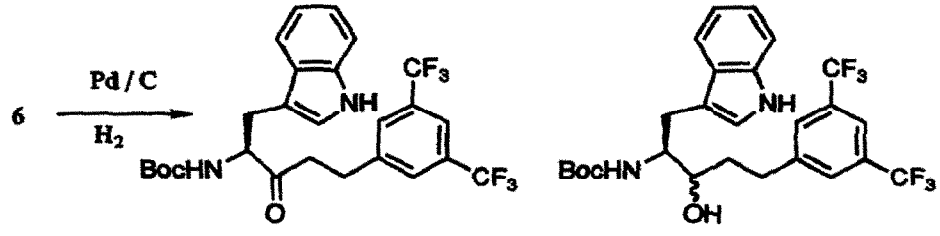
Scheme 1



Reagents and conditions: (a) Isobutyl chloroformate,triethylamine, DMF, HNMeOMe, - 15°C; (b) $LiCH_2PO(OMe)_2$, THF, -78°C; (c) 3,5-Bis(trifluoromethyl)benzaldehyde, K_2CO_3, CH_3CN; (d) Wilkinson's catalyst, EtOAc, H_2, 40 p.s.i.; (e) Et_2O/ HCl.

Literature precedent[9] exists for the reaction of α-amino esters with phosphonate anions to give keto-phosphonates in high yield and with retention of absolute configuration. We have found that this procedure is reliable in a number of instances, however attempts to obtain 5 *via* N-α-Boc L-tryptophan methyl ester gave very low yields with racemisation. A superior substrate[10,11] in this case was found in the Weinreb amide 4, prepared from N-α-Boc-L-tryptophan (Scheme 1). In order to maintain high enantiomeric purity it was found to be essential to pre-cool lithio dimethylmethylphosphonate to -78°C in THF before adding the anion slowly *via* cannula to 4 in THF, also at -78°C. The resulting phosphonate 5 could be purified by chromatography on silica but it was more convenient to use this material crude in subsequent steps. Reaction of 5 with 3,5-bis(trifluoromethyl)benzaldehyde by stirring in acetonitrile with potassium carbonate yielded the yellow, crystalline α,β-unsaturated ketone 6 which was recrystallised to constant optical rotation from ethyl acetate / petroleum ether in an overall yield of 47% from 4.

Hydrogenation of 6 using palladium on charcoal as catalyst was accompanied by up to 20% overreduction to the corresponding saturated alcohol 8 as well as the desired amino ketone 7 (Scheme 2), necessitating chromatography to separate these two products.



Scheme 2

When 6 was heated with one equivalent of tributyl tin hydride in toluene at reflux for 16 hours 7 was obtained in 76% yield but again chromatography was required to remove tin residues. However, hydrogenation of 6 using freshly prepared Wilkinson's catalyst gave clean reduction to the saturated amino ketone, obtained in 96% yield after crystallisation.

Deprotection of the amino ketone using dry gaseous hydrogen chloride in ether gave crystalline 3 in an overall yield of 36% from N-α-Boc L-tryptophan.[12] Attempts to assess the enantiomeric excess of intermediates in the synthesis were unsuccessful but derivatisation of 3 as the camphanamide using (-)-camphanic acid chloride allowed analysis by ^{1}H NMR. The amino ketone obtained had an enantiomeric excess of 92% by NMR analysis. Recrystallisation of the hydrochloride salt from methanol / water gave material which was homochiral within the limits of detection. While the free base of 3 is unstable, no racemisation or decomposition of 3 was observed after prolonged storage as the hydrochloride salt. The acetamide 2 was prepared by adding the salt to acetic acid activated with benzotriazolyloxytris(dimethylamino)phosphonium chloride (BOP chloride). Data describing the biological activity of this compound and other derivatives will be reported in due course.

Acknowledgements

We are grateful to Sarah Hardwicke for technical assistance and to Margaret Cascieri and Sharon Sadowski for providing biological data.

References and notes

1. von Euler, U.S.; Gaddum, J. H. *J.Physiol.* **1931**, 72, 74-87.
2. Otsuka, M.; Yanigasawa, M. *J.Physiol..(London)* **1988**, 395, 255-270.
3. Moskowitz, M.A. *Trends Pharmacol. Sci.* **1992**, 13, 307-311.
4. Lotz, M.; Vaughn, J.H.; Carson, D.A.; *Science* **1987**, 235, 893-895.
5. Snider, R.M.; Constantine, J.W.; Lowe, J.A., III; Longo, K.P.; Lebel, W.S.; Woody, H.A.; Drozda, S.E.; Desai, M.C.; Vinick, F.J.; Spencer, R.W.; Hess, H.-J.; *Science* **1991**, 251, 435-437.
6. MacLeod, A.M.; Merchant, K.J.; Cascieri, M.A.; Sadowski, S.; Ber, E.; Swain, C.J.; Baker, R. *J. Med . Chem.* **1993**, 36, 2044-2045.
7. Binding affinities for these compounds were measured in radioligand binding experiments determined by displacement of [^{125}I]Tyr^{8} substance P from the cloned human NK_1 receptor, stably expressed in CHO cells. In this assay 1 and 2 had IC_{50} = 1.6nM and 3nM respectively.
8. Cascieri, M.A.; Ber, E.; Fong, T.M.; Sadowski, S.; Bansal, A.; Swain, C.; Seward, E.; Frances, B.; Burns, D.; Strader, C.D.; *Mol. Pharmacol.* **1992**, 42, 458 - 465.
9. Chakravarty, P.K.; Combs P.; Roth, A. ; Greenlee, W.J.; *Tetrahedron Lett.* **1987**, 28, 611-612.
10. Dufour, M.N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro B.; *JCS Perkin Trans. I* **1986**, 11, 1895-1899.
11. Namh, S.; Weinreb, S.M.; *Tetrahedron Lett.* **1981**, 22, 3815-3818
12. All new compounds gave satisfactory elemental analyses.
    3: mp 194-196 °C; ^{1}H NMR (d_6 DMSO) δ 11.13 (1H,s); 8.42 (2H,bs); 7.89 (1H,s); 7.82 (2H,s); 7.61 (1H,d,J = 7Hz); 7.38 (1H,d,J = 7Hz); 7.26 (1H,d,J = 1Hz); 7.10 (1H,t,J = 7Hz); 7.01 (1H,t,J = 7Hz); 4.36 (1H,t,J = 7Hz); 3.34 - 2.77 (6H,m); $[\alpha]_D^{20}$ = +46.0° (c = 1, methanol). 4: mp 129-130°C; ^{1}H NMR (d_6 DMSO) δ 10.80 (1H,s); 7.51 (1H,d,J =7Hz); 7.16 (1H,s); 7.08 - 6.97 (3H,m); 4.62 - 4.58 (1H,m); 3.72 (3H,s); 3.34 (3H,s); 3.02-2.81 (2H,m); 1.31 (9H,s); $[\alpha]_D^{20}$ = - 11.2° (c = 1, methanol). 5: viscous oil; ^{1}H NMR ($CDCl_3$) δ 10.84 (1H,s); 7.56 (1H,d,J = 7Hz); 7.33 (1H,d,J = 7Hz); 6.98 (1H,t,J = 7Hz); 4.34 - 4.31 (1H,m); 3.63 (6H,d,J = 11Hz); 3.39 (2H,d,J = 22Hz); 3.19 - 3.11 (1H,m); 2.91 - 2.84 (1H,m); $[\alpha]_D^{20}$ = - 22.2° (c = 1, methanol). 6: mp 137-138°C; ^{1}H NMR ($CDCl_3$) δ 8.00 (1H,s); 7.81 (1H,s); 7.72 (1H,d,J = 7Hz); 7.53 (2H,s); 7.43 (1H,d,J = 18Hz); 7.39 (1H,d,J = 7Hz); 7.30 - 7.14 (2H,m); 6.98 (1H,d,J = 2Hz; 6.54 (1H,d,J =18Hz); 5.43 - 5.41 (1H,m); 5.08 - 5.04 (1H,m); 3.41 - 3.36 (1H,m); 3.18 - 3.13 (1H,m); 3.36 (1H,m); 1.46 (9H.s); $[\alpha]_D^{20}$ = + 53.4° (c = 1, methanol). 7: mp 138-140°C; ^{1}H NMR ($CDCl_3$) δ 8.03 (1H,s); 7.88 (1H,s); 7.57 (1H,d,J = 7Hz); 7.36 (1H,d,J = 7Hz); 7.35 (2H,s); 7.22 (1H,t,J = 7Hz; 7.14 (1H,t, J = 7Hz); 6.89 (1H,s); 5.18 (1H,m); 4.58 (1H,m); 3.25 - 3.19 (1H,m); 3.11 - 3.05 (1H,m); 2.88 - 2.38 (4H,m); 1.42 (9H,s); $[\alpha]_D^{20}$=+5.6 ° (c = 1, methanol).

(*Received in UK* 7 *February* 1994; *revised* 6 *April* 1994; *accepted* 15 *April* 1994)