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Chemoenzymatic synthesis of a non-peptide tachykinin NK-2 antagonist

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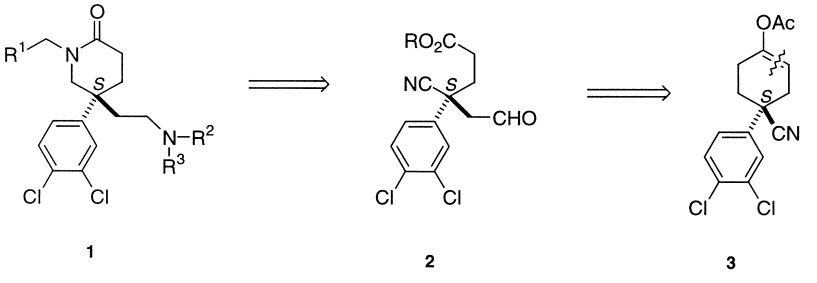
Abstract

The synthesis of a tachykinin NK-2 antagonist (*S*)-**11** has been carried out in four steps starting from the the (*S*)-(+)-enol acetate **3**, which was obtained in 100% e.e. by resolution of the racemic ester with *Pseudomonas fluorescens* lipase. The absolute configuration of the enol acetate (+)-**3** was confirmed by X-ray analysis of the camphanyl derivative **13**.

The sensoneuropeptide tachykinins, which include substance P and neurokinins A and B, are distributed in the peripheral and central nervous systems and are known to be involved in neurological inflammation, pain transmission and bronchoconstriction.[1] The effects of these tachykinins are mediated through the activation of NK-1, NK-2 and NK-3 receptors, and new antagonists are being sought as a means of controlling pain and inflammation. Pfizer have developed a class of non-peptidic neurokinin NK-2 antagonists generally consisting of (*S*)- 5-(3,4-dichlorophenyl)-5-dialkylaminoethyl-*N*-alkyl δ-lactams as shown in structure **1** (Scheme 1).[2]



1 **2** **3**

Scheme 1.

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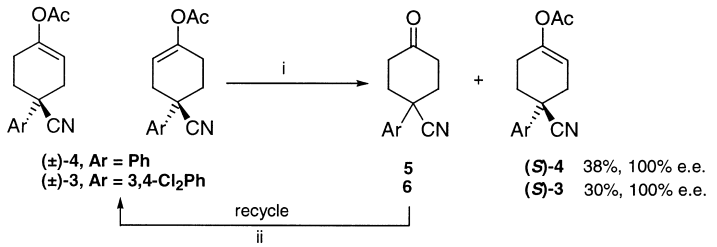
We envisaged an asymmetric synthesis of this important class of drugs in which the quaternary chiral centre in the lactam **1** could be accessed from the chiral enol acetate **3**. Oxidative cleavage of the enol double bond in the enol ester would give an intermediate aldehyde ester **2**, possessing the correct (*S*) absolute configuration, which upon reductive cyclisation[3] of the cyano group onto the ester would give the required lactam. The aldehyde group could then be reductively aminated with any secondary amine followed by alkylation of the lactam nitrogen.

We have recently developed the lipase resolution of racemic enol acetates derived from prochiral ketones where the product ketone can be recycled, leading to greater than 50% yields of the enol acetate after several cycles (Scheme 2).[4,5] For example, the racemic enol acetate **4**, derived from ketone **5**, was resolved using Amano *Pseudomonas fluorescens* lipase (PFL) to give unreacted enantiomerically pure (100% e.e.) (*S*)-enol acetate **4** and recovered ketone **5**.[5] We were pleased to find that biotransformation of the 3,4-dichlorophenyl substrate **3**[6] with the same enzyme gave a 30% yield of the (+)-enol ester **3** in 100% e.e. after 68% conversion to ketone. Although the selectivity was not optimal, the resolution could be carried out in batches of up to 10 g under the same conditions as used previously for substrate **4**, and both the enzyme and ketone could easily be recycled.[7] In related work, we have found that the active site of PFL can accommodate changes in the nature of the substitution on the phenyl ring of the substrate without affecting the selectivity significantly.[8]

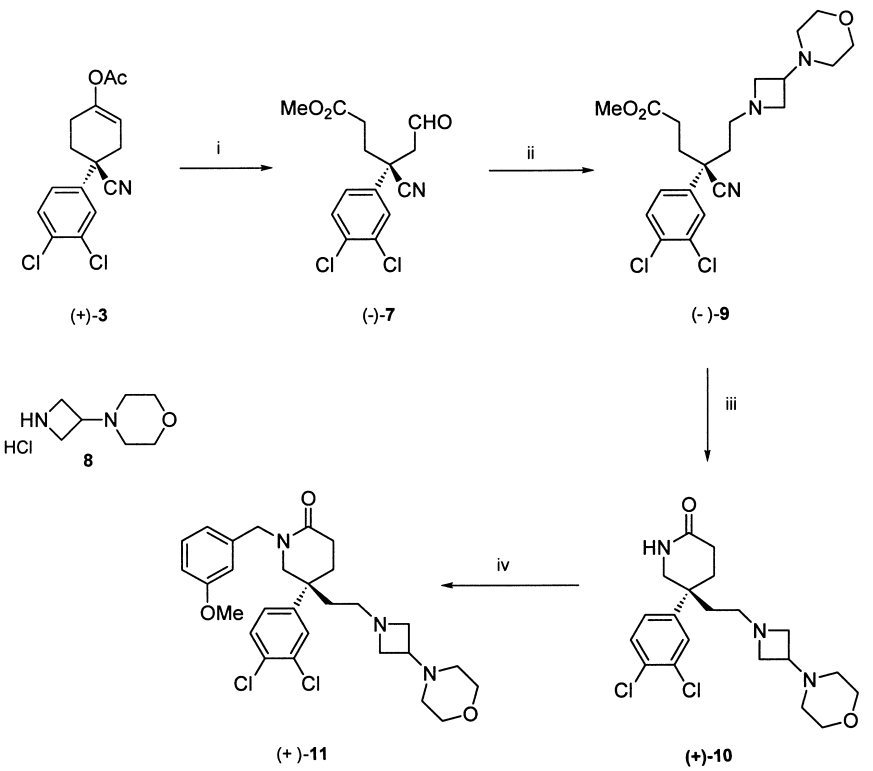


Scheme 2. Reagents and conditions: (i) *Pseudomonas fluorescens* lipase, THF, *n*-BuOH; (ii) isopropenyl acetate, *p*-TsOH

As a comparison with the well-established chiral lithium amide methodology, we treated the ketones **5** and **6** with lithium (*R,R*)-(–)-bis(α-methylbenzyl)amide at –78°C, and trapped the enolate with acetic anhydride to give the enol acetates (*R*)-**4** (54% e.e., 50%) and (*R*)-**3** (57% e.e., 54%), respectively. Treatment of 4-cyano-4-phenylcyclohexanone with the same base at –100°C and trapping with TMSCl gave 64% yield and 64% e.e.

Hence, with these particular substrates, the enzymatic resolution provides the best method for obtaining enantiomerically pure material.

With a method for the production of the chiral enol ester **3** in hand, we embarked on our proposed synthesis of a representative member of the NK-2 antagonists, (*S*)-lactam **11** (Scheme 3). At this stage, we assumed the (*S*)-configuration for (+)-**3** by analogy to that previously established for the enol acetate **4**.[5] Oxidative cleavage with ozone in methanol:dichloromethane (1:4) gave the aldehyde-ester (–)-**7** in 60% yield. Reductive amination with morpholinoazetidine[9] hydrochloride **8** under hydrogenation conditions (Pd–C/H_2) was not successful. The presence of the triethylamine used to release the free azetidine amine from its hydrochloride salt or the resultant triethylamine hydrochloride may have poisoned the palladium catalyst. However, prior formation of the imine between **8** and (–)-**7** in THF in the presence of triethylamine followed by

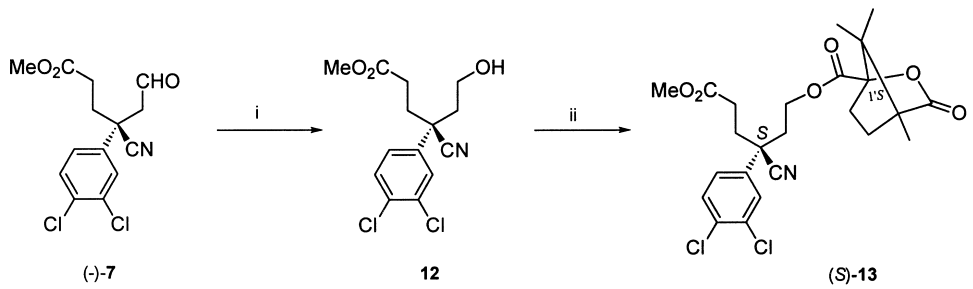


Scheme 3. Reagents and conditions: (i) O_3, MeOH:CH_2Cl_2 (1:4), –78°C then PPh_3, rt (60%); (ii) (a) **8**, THF, Et_3N, rt, (b) $NaB(OAc)_3H$, AcOH (91%); (iii) H_2, raney-Ni, MeOH, 45°C (86%); (iv) NaH, 3-methoxybenzylbromide, DMF, 18-crown-6, 0°C (27%)

reduction with sodium triacetoxyborohydride afforded the intermediate (–)-**9** in 91% overall yield. The reductive cyclization of (–)-**9** to give lactam (+)-**10** was achieved in 86% yield using hydrogenation over raney-nickel. Fortunately, no dechlorination of the phenyl ring was observed under these conditions. Lactam **10** underwent *N*-benzylation with 3-methoxybenzyl bromide to furnish the target NK-2 antagonist (+)-**11** in 27% yield. In attempts to improve this step, we used valerolactam as a model substrate. This underwent *N*-benzylation cleanly with 3-methoxybenzyl bromide or chloride under a variety of conditions, including sodium hydride and 18-crown-6 in DMF and potassium hydroxide in DMSO/water, giving yields of around 75%. However, when these conditions were applied to the lactam **10**, low yields resulted. The morpholinoazetidine group may undergo *N*-benzylation and the resulting alkylammonium species may not be efficient alkyl donors or may undergo ring cleavage leading to more polar products.

In order to confirm the suspected (*S*)-configuration of the enol acetate (+)-**3**, we converted the aldehyde (–)-**7** into the crystalline camphanic ester derivative **13** via alcohol **12**, as shown in Scheme 4. Crystallisation of the ester **13** from 2-propanol gave crystals suitable for X-ray analysis (Fig. 1).[10] By reference to the 1′(*S*) camphanyl moiety, the absolute configuration of the cyano-substituted centre was determined to be (*S*), thus confirming the configuration of the enol acetate (+)-**3** and the NK-2 antagonist (+)-**11** as (*S*).

In summary, the enantiomerically pure enol acetate (*S*)-**3** was obtained by biotransformation and used to synthesise the tachykinin NK-2 antagonist (*S*)-**11** in four steps. As previously stated,



Scheme 4. Reagents and conditions: (i) $NaB(OAc)_3H$, AcOH, $<20^{\circ}C$ (72%); (ii) (–)-1(*S*)-camphanic acid chloride, DMAP, Et_3N, DCM (83%)

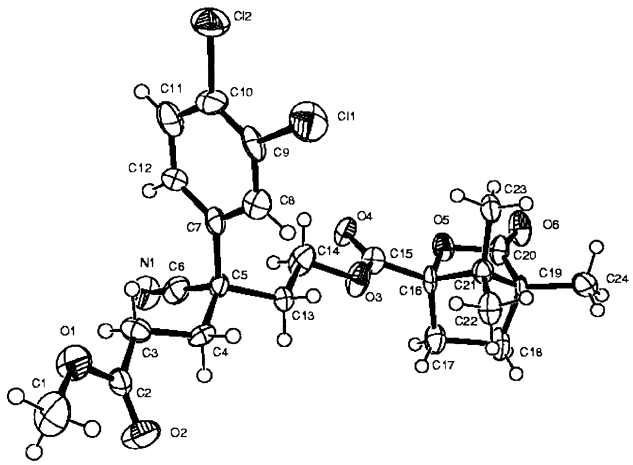


Figure 1. X-Ray crystal structure of camphanyl derivative **13** showing the crystallographic numbering

the ketone product of the biotransformation is prochiral and can easily be separated and chemically recycled, thus providing greater than 50% yield of the chiral enol ester over several cycles. We are currently developing an in situ method for this recycling, which will be reported elsewhere.

Acknowledgements

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7. Preparative scale biotransformation: the enol acetate **3** (10 g, 32.4 mmol), *P. fluorescens* lipase (8 g) and *n*-BuOH (5.21 ml, 64.7 mmol) were stirred in tetrahydrofuran at room temperature for 9.5 h, whereupon HPLC (Chiracel AD) indicated 100% e.e. for the enol acetate. R_t: (*R*)-**3** 15.5 min; (*S*)-**3** 20.9 min; eluent 100% EtOH, 0.5 ml/min. The solution was filtered through a glass sinter funnel, the residual enzyme washed with tetrahydrofuran and the solvent removed by evaporation under reduced pressure. The crude residue was purified by flash column chromatography (eluent, diethyl ether:petroleum ether, 1:2) to give the ketone **6** (7 g) and the (*S*)-enol acetate **3** (2.8 g, 28%) as a white solid (HRMS: found M^+ 309.03227. $C_{15}H_{13}ClO_2N$ requires 309.03235); mp 153.5°C; ν_{max} (neat) 2233 (CN), 1755 (C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.23 (3H, s, $COCH_3$), 2.23–2.67 (6H, m, 2×H-3, 2×H-5 and 2×H-6), 5.46 (1H, s, H-2), 7.22–7.56 (3H, Ar); δ_C (75 MHz, $CDCl_3$) 20.9 (CH_3), 24.6, 32.7, 35.4 (C-3, C-5 and C-6), 40.0 (C-4), 110.5 (C-2), 121.5 (CN), 125.3, 128.1, 131.1 (C-2′, C-5′, C-6′), 132.8, 133.5, 139.6 (C-1′, C-3′ and C-4′), 148.1 (C-1), 169.3 (C=O); *m*/*z* (EI) 309 (3%, M^+), 267 (11), 70 (69), 43 (100).
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9. Morpholinoazetidine **8** was kindly donated by Pfizer Ltd.
10. Sheldrick, G. M. SHELX97, Universität Göttingen, 1997. *Crystal data* for $C_{24}H_{27}Cl_2O_6$ (**13**): $M = 496.42$, orthorhombic, $a = 7.3163(8)$, $b = 10.194(2)$, $c = 32.052(4)$ Å, $U = 2390.6$ $Å^3$, $T = 213$ K, space group $P2_12_12_1$, $Z = 4$, μ(Mo-K) = 0.263 mm^{-1}, Stoe IPDS diffractometer, 15326 reflections measured, 3770 unique ($R_{int} = 0.1987$), which were used in all calculations. $R1$ ($F > 4F$) = 0.0468 $wR(F^2)$, 0.1103 (all data). Single crystals of compound **13** were obtained by recrystallisation from 2-propanol, mounted in inert oil and transferred to a cold gas stream in the diffractometer. The structure was solved using direct methods and refined by full least-squares on F^2.