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An asymmetric synthesis of a 4-substituted-1,4-dihydropyridine

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Abstract—A concise, convergent asymmetric synthesis of the 4-substituted-1,4-dihydropyridine **1** [Ohnmacht, C. J., Jr.; Trainor, D. A.; Forst, J. M.; Stein, M. M.; Harris, R. J. Patent No. 5,622, 964] has been achieved via a novel asymmetric Michael addition of an optically pure vinylogous amide to an α,β-unsaturated ketone. The overall process is three steps from readily available starting materials and provides an economical manufacturing route to the title compound, which was required as a candidate drug for the treatment of urinary incontinence.

1. Introduction

Urinary incontinence is a condition in which involuntary loss of urine occurs. Existing pharmacologic therapy consists mainly of antimuscarinic agents, such as oxybutynin, which are limited by their undesirable side effects.

The research project goal was to develop an orally active K_{ATP} potassium channel opener (PCO) that would exhibit in vivo bladder activity, comparable to cromakalim,[1] but with markedly less cardiovascular effects, and none of the side effects associated with the existing antimuscarinic agents. ZD0947, **1**, is a PCO and has been identified for use in the treatment of urinary urge incontinence. This letter is concerned with the development of a concise asymmetric synthesis of **1** suitable for long-term manufacture.

2. Medicinal chemistry synthesis

Initial quantities of **1** prepared in medicinal chemistry at AstraZeneca were synthesised using the route shown below (Scheme 1).[2] Although this synthetic scheme is straightforward and fulfilled its objectives of supplying small quantities of material, it is long and inherently inefficient; in most part due to a classical resolution of free acid **2** to the carboxylate salt **3** which discards the unwanted enantiomer.

Further limitations of this route were observed upon initial scale-up. Simple alkyl ester analogues of the Hantzsch reaction product **4** were discovered to be very resistant to hydrolysis and the conditions necessary to effect this de-esterification led to significant decarboxylation of the resulting free acid **2**, giving rise to racemic ZD0947, **5**.

The isoborneol-derived ester **6** was used on the assumption that it would hydrolyse with sufficient ease to avoid decarboxylation of free acid **2**. However, hydrolysis of **4** on a larger scale turned out to be extremely difficult to control and a dominant pathway of decarboxylation was observed.

3. Asymmetric route to ZD0947

Although several modifications were made to the medicinal chemistry route to **1**, which allowed successful manufacture of an initial 17 kg of optically pure material for pre-clinical use, a more efficient route was obviously required for future material supply that would be amenable to long-term routine manufacture.

Several methods for the synthesis of 4-substituted 1,4-dihydropyridines have been reported, namely classical resolution as described above, diastereoselective addition of aryl lithium to the 4-position of chiral pyridines,[3–5] chiral acetoacetate esters in Hantzsch synthesis,[6] enantioselective Hantzsch synthesis using a chiral auxiliary[7,8] and chemoenzymatic methods.[9]

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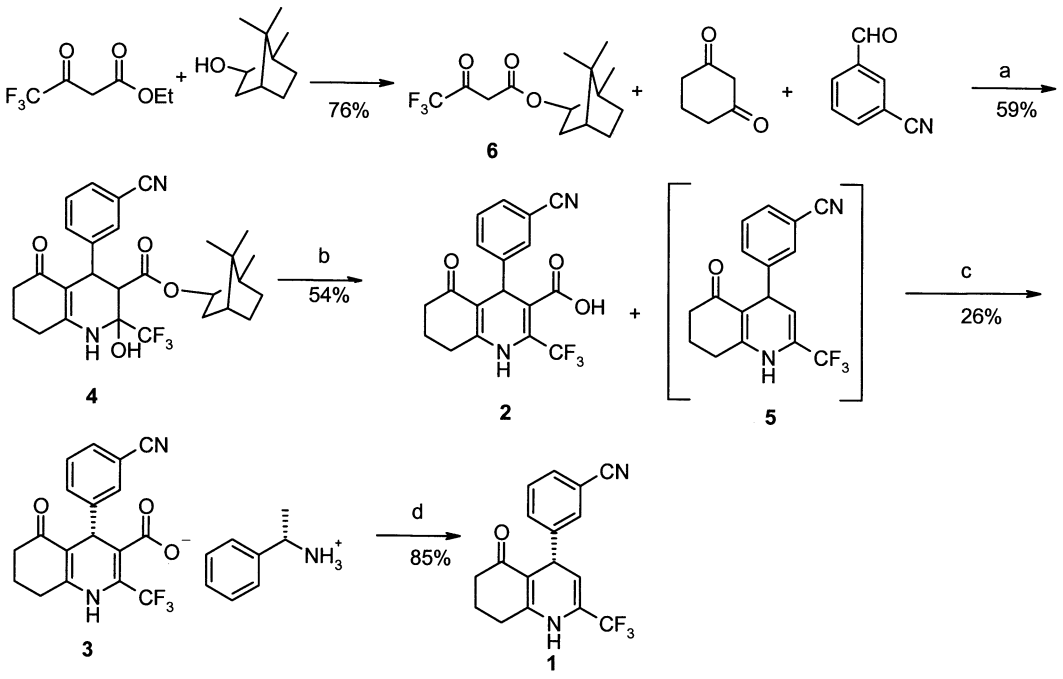


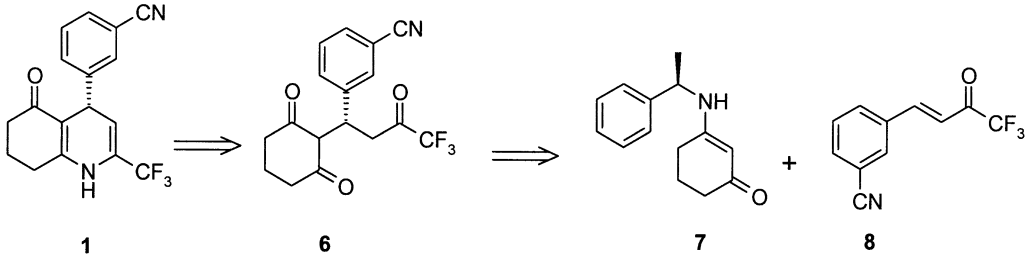
Scheme 1. *Reagents and conditions*: (a) NH_4OAc, EtOH, reflux; (b) *p*TSA, HOAc, 100°C; (c) (*S*)-(α)-methylbenzylamine, toluene/*n*-BuOH; (d) *N*-methylpyrollidin-2-one, Δ.

Retrosynthetic analysis of **1** reveals a primary disconnection to the 1,5-diketone **6**. Strategic bond disconnection employing the method of d'Angelo and co-workers then reveals a Michael addition of vinylogous amide **7** to α,β-unsaturated ketone **8** (Scheme 2).[10,11]

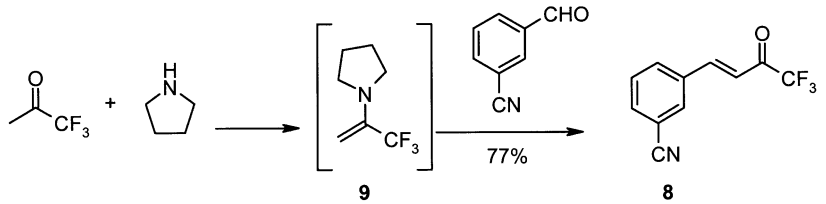
In order to investigate this possible asymmetric process, the vinylogous amide **7** and α,β-unsaturated ketone **8** were required as starting materials and their synthesis is described below.

3.1. Synthesis of 1,1,1-trifluoro-4-(3-cyanophenyl)buten-2-one

Trifluoromethyl ketones can be prepared in various ways but tend to suffer from unattractive reagents such as (trifluoromethyl)trimethylsilane[12] or low yields. We have devised a simple procedure for the preparation of **8** based on the addition of an enamine to a substituted benzaldehyde (Scheme 3). Reaction of 3-cyanobenzaldehyde with the enamine **9**, derived in situ from



Scheme 2.



Scheme 3.

pyrrolidine and trifluoroacetone, in dichloromethane afforded the required compound **8** after aqueous work-up and crystallisation from *t*-amyl methyl ether/isohexane in 77% yield.

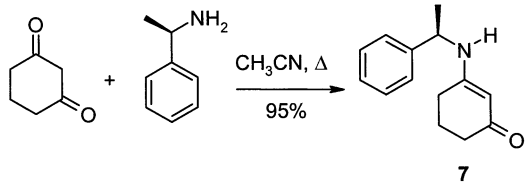
3.2. (*R*)-3-(Phenylethylamino)-2-cyclohexen-1-one

Compound **7** was found to be a low melting solid and was thus prepared in situ by heating (*R*)-α-methylbenzylamine with 1,3-cyclohexanedione in acetonitrile (Scheme 4).

4. Asymmetric Michael reaction

In this work two obstacles were quickly identified. Firstly, **7**, due to conjugation with the carbonyl in the molecule is relatively unreactive. Secondly, α,β-unsaturated ketone **8** decomposes at a steady rate at temperatures exceeding 60°C. A novel process for this elegant, key stereoselective step (Scheme 5) using acetonitrile and a Lewis acid, trimethylsilyl chloride[13] was accordingly developed.

α,β-Unsaturated ketone **8** (1.0 equiv.) is added to a solution of **7** in acetonitrile containing trimethylsilylchloride (1.1 equiv.) and, following stir periods at 5 and 43°C, this provides **10** in a solution of acetonitrile in approximately 70% d.e.[14] This solution is not isolated but then treated with aqueous ammonia in the presence of ammonium chloride under pressure and then finally dehydrated with concentrated HCl. Compound **1** is isolated by aqueous work up and crystallisation from butyl acetate to give the title compound **1**[15] in 29% overall yield from **8** and in 95% e.e.



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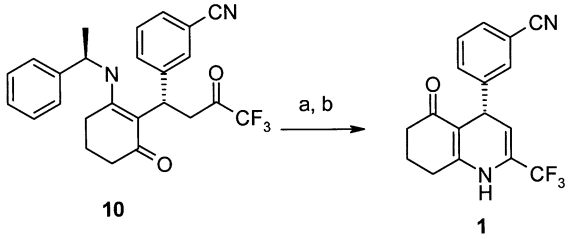
Scheme 4.



10 **1**

Scheme 5. *Reagents and conditions*: (a) aqueous ammonia/NH_4Cl, 80°C; (b) conc. HCl, crystallisation.

In principle, this method can be used for the preparation of other 4-substituted 1,4-dihydropyridines and offers a concise, convergent route viable for large scale manufacture.

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References

1. Nurse, D. A.; Restorick, J. M.; Mundy, A. R. *Br. J. Urol.* **1991**, *68*, 27–31.
2. Internal report: ZD0947 Technology Transfer Document, K. Russell, May 1998.
3. Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989–1996.
4. Meyers, A. I.; Oppenlaender, T. *J. Chem. Soc., Chem. Commun.* **1986**, *108*, 1920–1921.
5. Cheng, Y. C.; Chen, J. Y.; Lee, M. J. *Heterocycles* **1996**, *43*, 2425–2434.
6. Rose, U.; Drager, M. *J. Med. Chem.* **1992**, *35*, 2238–2243.
7. Enders, D.; Miller, S.; Demir, A. S. *Tetrahedron Lett.* **1988**, *29*, 6437.
8. Kosugi, Y.; Hori, M.; Tatsuo, N. *Heterocycles* **1994**, *39*, 591–602.
9. See Ref. 8 and those cited within.
10. d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.
11. Patel, I.; Hopes, P. A.; PCT/ SE01/01 685 and PCT/ SE01/01686.
12. Wiedemann, J.; Heiner, T.; Mloston, G.; Surya Prakash, G. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 820–821.
13. Barta, N. S.; Brode, A.; Stille, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6201–6206.
14. A complex mixture of diastereoisomers is produced and an absolute figure for diastereoselectivity has not been found. However, a correlation of the ratio of the peaks in the HPLC on analysis of **10** when compared to the enantiomeric excess of the crude reaction mixture of **1** can be drawn, and thus the ratio can be reported to be approximately 70% d.e. This is enhanced to greater than 95% e.e. following isolation of **1** as compared to reference materials and analysis by chiral HPLC (Chiralpak AD, 25 cm×4.6 mm).
15. The isolated compound is consistent with reference spectra (NMR and MS).