Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3179–3181

Alternative esters in the synthesis of ZD0947

Jonathan D. Moseley*

AstraZeneca, Process Research and Development, Avlon Works, Hallen, Bristol, BS10 7ZE, UK

Received 17 February 2005; accepted 10 March 2005

Abstract—Alternatives to the original *iso*-borneol and allyl esters were investigated in the synthesis of ZD0947 (**1**). Homologous allylic esters were prepared in higher yields and were more readily purified than for the existing route, but offered no further benefits later in the synthesis. However, the PNB-substituted ester series provided crystalline intermediates, higher yields and simplified isolations through-out, and utilised a heterogeneous hydrogenation, thus reducing the residual catalyst levels.

ZD0947 (**1**) is a potassium channel opener in clinical development for the treatment of urinary urge incontinence ('overactive bladder').[1] The pharmacological profile of such a compound should have beneficial effects on an overactive bladder but with reduced cardiovascular side effects, and the side effects associated with existing anti-muscarinic agents. The initial medicinal chemistry synthesis, in which the desired (*S*)-enantiomer of **1** was isolated after a lengthy classical resolution has been disclosed.[2] An asymmetric synthesis, which significantly improved on this synthesis has also been reported.[3] At the same time as that work, an investigation into alternative esters was conducted to improve the early stages of the racemic synthesis and avoid the use of a homogenous catalyst. This investigation is the subject of this letter.

The original medicinal chemistry synthesis is shown in Scheme 1. The key step is the unsymmetrical Hantzsch reaction[4] between the benzaldehyde, cyclohexa-1,3-dione, ammonia and acetoacetate **2b** (R = *iso*-borneol) to give the Hantzsch product **3b**. Dehydration of this unusually stable tetrahydropyridine gave dihydropyridine **4b**, and cleavage of the ester gave the desired racemic acid **5**, from which **1** could be isolated after resolution with (*S*)-(α)-methylbenzylamine.

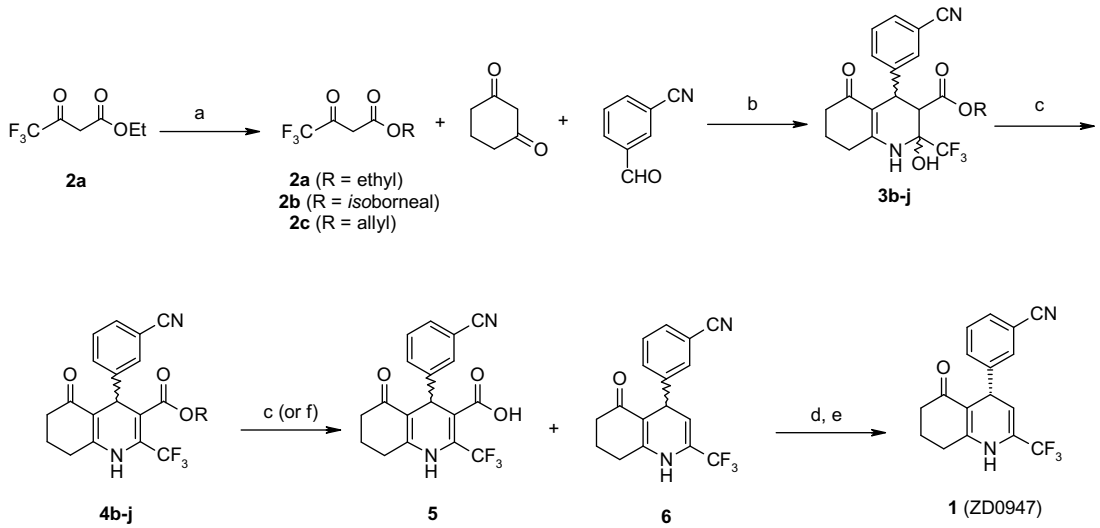
Although this synthetic sequence was straightforward and short, a number of issues were apparent.[5] The acid-labile *iso*-borneol ester had been chosen to avoid decarboxylation under alkaline conditions, but on scale-up, considerable decarboxylation to racemic ZD0947 (**6**) was observed under the forcing acid conditions. A change to the allyl ester **2c** was made; **4c** could then be cleaved with Wilkinson's catalyst to avoid the decarboxylation. This was a major improvement and supplied ZD0947 for pre-clinical trials. However, it proved difficult to remove the Rh catalyst residues to the low levels required for toxicity testing (i.e., <5 ppm).

Preparation of allyl ester **2c** also presented some difficulties. *Trans*-esterification of ethyl TFA acetate (**2a**) with allyl alcohol was achieved by distilling off ethanol, but the yield was moderate (~35%) and the distillation was inefficient due to the similar boiling points of the two alcohols, which required several cycles of distillation and recharging of allyl alcohol.[6] Lastly, the key Hantzsch reaction yielded a moderate 59% after an involved work-up procedure.

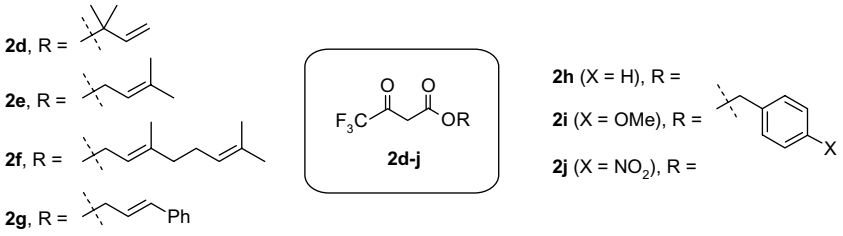
Since the ester was discarded during the synthesis, we felt that these factors could be improved by the use of alternatives to the allyl and *iso*-borneol esters. The alcohol component needed to be commercially available and readily cleaved to avoid decarboxylation. Higher boiling allylic alcohol homologues (**2d**–**g**) offered the prospect of achieving both of these aims, whilst the benzyl esters (**2h**–**j**) offered the additional advantage of cleavage by heterogeneous catalysis (and other methods in the case of **2i** and **2j**)[7] (Scheme 2). Both sets of alternatives conserved methodology with the existing synthesis for the final steps.

Keywords: Hantzsch; ZD0947.
* Tel.: +44 117 938 5601; fax: +44 117 938 5081; e-mail: jonathan.moseley@astrazeneca.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.057

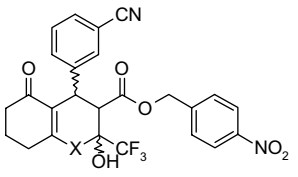


Scheme 1. Reagents and conditions: (a) alcohol, distillation (76%); (b) NH_4OAc, EtOH, reflux (59%); (c) *p*TSA, AcOH, 100 °C (54%); (d) (*S*)-(α)-methylbenzylamine, toluene/*n*-BuOH (26%); (e) NMP, heat (85%); (f) *n*-BuOAc/EtOH/H_2O (4:2:1), AcOH, $(Ph_3P)_3RhCl$, 70 °C (yields a–c given for *iso*-borneol derivatives).



Scheme 2.

Esters **2e**–**j** were readily prepared by distilling off ethanol in toluene.[8] Yields were significantly higher (50–80%) than for **2c** but processes were not optimised. The analogous Hantzsch products **3e**–**j** were prepared in each case, and dehydrated to the analogous dihydropyridines **4e**–**j**.[9] During the dehydration, both the isoprenyl (**3e**, **4e**) and geranyl (**3f**, **4f**) derivatives showed signs of cleavage to **6**. A screen of acids and solvents suggested that *p*TSA or concd H_2SO_4 in toluene or *n*-butanol were the most promising combinations to limit this. The cinnamyl derivative (**3g**, **4g**) proved to be more stable but the Hantzsch reaction yield was poor. Consequently, the Wilkinson's catalyst 'deprotection' was not tested in any of these cases.



It was hoped that the benzyl substituents would confer greater crystallinity on the Hantzsch and dihydropyridine analogues, but the benzyl series (**2/3/4h**) proved to be no better than the existing allyl series in this respect. The acid-labile PMB-substituted series (**2/3/4i**) proved to be too sensitive to the acidic dehydration conditions and **4i** could not be isolated. However, the PNB-substituted series (**2/3/4j**) gave stable crystalline compounds. Initial formation of the Hantzsch product **3j** appeared low (22%), due to large quantities of the intermediate pyran **7** being formed instead (50%). However, addition of NMP as a co-solvent (17% v/v with EtOH) converted **7** in situ to the desired **3j**, and a simple aqueous drown-out gave a 78% overall yield. Conversion to **4j** proceeded as expected and heterogeneous hydrogenation of the PNB group under standard or transfer hydrogenation[10] conditions gave **5** in near quantitative yield.[11]

In conclusion, formation of the esters **2e**–**j** proceeded in higher yields and were more readily purified than for **2c**, but the allyl homologues offered no further advantages compared to the allyl or *iso*-borneol groups. However, the PNB-substituted series (**2/3/4j**) provided crystalline intermediates, higher yields and simplified isolations through-out, and utilised a heterogeneous hydrogenation, thus reducing the residual catalyst levels.

Acknowledgements

The author thanks Claire Ancell for additional laboratory preparations.

References and notes

1. Abdel-Karim, A. M.; Bialecki, R. A.; Elhilali, M. M. *J. Urol.* **2002**, *168*, 837–842.
2. Ohnmacht, C. J.; Trainor, D. A.; Forst, J. M.; Stein, M. M.; Harris, R. J. US Patent 5,622,964.
3. Ashworth, I.; Hopes, P.; Levin, D.; Patel, I.; Salloo, S. *Tetrahedron Lett.* **2002**, *43*, 4931–4933.
4. For a recent review including the Hantzsch reaction, see the following and references cited therein: Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980.
5. The loss of half of the material as the (*R*)-enantiomer was addressed by the asymmetric route (see Ref. 3).
6. This process was later improved by the availability of large scale short-path distillation equipment, and subsequently by an alternative synthesis.
7. Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984.
8. The hindered compound **2d** could not easily be prepared due to the similar b.p. of its alcohol with ethanol.
9. All new compounds gave satisfactory ^{1}H and ^{13}C NMR and mass spec. data, and purities were assayed by HPLC (or GC in the case of the acetoacetates **2b–j**) and by comparison to the ^{1}H NMR spectra (see also Ref. 11).
10. Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1988**, 91.
11. For the PNB-substituted series, dehydration was achieved with *p*TSA in toluene at reflux (82%), standard hydrogenation with 10% Pd/C and H_2 in methanol (95%), or transfer hydrogenation with 10% Pd/C and HCO_2NH_4 in methanol (80%). Full experimental details and analyses of these and other key compounds are described in: Jones, A.; Moseley, J.; Patel, I.; Snape, E.; Young, M. World Patent WO 2003062203, 2003.