Tetrahedron Letters 50 (2009) 2750–2753

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient three-step sequence for the deamination of α-aminoesters. Application to the synthesis of CysLT1 antagonists

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ARTICLE INFO

Article history:
Received 29 January 2009
Revised 13 March 2009
Accepted 17 March 2009
Available online 21 March 2009

Keywords:
Deamination
α-Aminoesters
α-Diazoesters
α-Hydrazonoesters
Reduction
CysLT1 antagonists

ABSTRACT

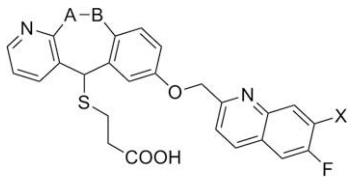
A practical and efficient three-step sequence for the deamination of α-aminoesters is reported. This method is based on the $NaBH_4$-mediated selective reduction of α-diazoesters to α-hydrazonoesters and has been successfully applied to the deamination of several representative α-aminoesters including some L-cysteine ethyl ester derivatives, key intermediates in the synthesis of a series of CysLT1 antagonists.

Asthma is a complex, chronic inflammatory disease of the airways which affects around 300 million people worldwide, and is the most common chronic disease in children.[1] Cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) are products of the 5-lipoxygenase pathway of arachidonic acid metabolism which play a crucial role in asthma pathophysiology by causing bronchoconstriction, mucus production and increased vascular permeability.[2] They exert their biological actions by activating two G-protein-coupled receptors called CysLT1 and CysLT2.[3] CysLT1 receptor antagonists have been shown to be effective in the treatment of asthma[4] and several compounds with this mechanism of action have reached the market in recent years.[5]

As part of an Almirall research programme for the design, synthesis and pharmacological evaluation of novel CysLT1 antagonists, the preparation of a series of tricyclic carboxylic acids (Fig. 1) has been carried out.[6] In order to prepare multigram quantities of these new anti-asthmatic compounds for further testing, an efficient synthesis of both enantiomers of compounds **1a–c** was developed.

The first step in our synthetic approach towards acids **1a–c** in an enantiomerically pure form was the reaction of L-cysteine ethyl ester hydrochloride with racemic alcohols **2a–c**[6] to give the diastereoisomeric aminoesters **3a–c** and **4a–c** in a 1:1 ratio (Scheme 1). Although all attempts to separate diastereoisomers by crystallization failed, we were successful in separating them by crystallizating the corresponding mixtures of formamides **5a–c** and **6a–c** (easily prepared from aminoesters by reaction with HCOOEt). Deprotection of the formyl group by using EtOH/HCl/H_2O gave the desired isolated aminoesters **3a–c** and **4a–c** with de values >97% in all cases (measured by ^1H NMR analysis).

With the separation of diastereoisomers successfully accomplished in all three examples, our attention was then focused on the removal of the α-amino group. Deamination of aminoesters **3a–c** and **4a–c**, the key step in our synthetic approach towards enantiomerically pure acids **1a–c**, proved to be more difficult than anticipated. At this point, aminoesters **3a–c** and **4a–c** were transformed to the corresponding α-acetamidoesters, α-aminoacids and α-isonitriloesters[7] and several methods for the reductive



1a : A-B = CH_2-CH_2, X = Cl
1b : A-B = N(Me)CH_2, X = F
1c : A-B = CH_2O, X = F

Figure 1. Tricyclic carboxylic acids as CysLT1 receptor antagonists.

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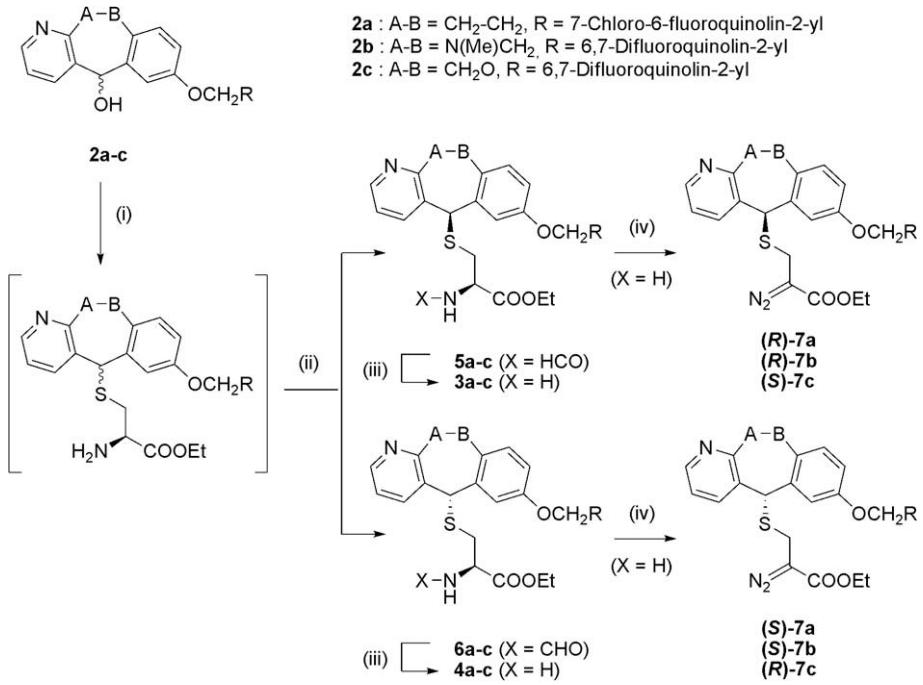
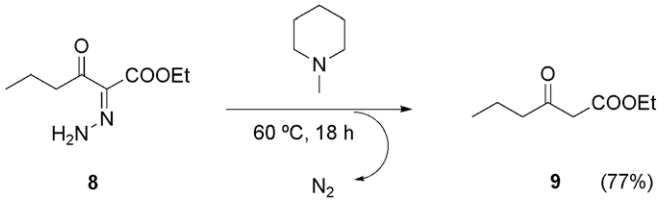
doi:10.1016/j.tetlet.2009.03.118



Scheme 1. Reagents and conditions: (i) L-Cysteine ethyl ester hydrochloride, TFA, 60 °C (80–91%); (ii) ethyl formate, reflux; separation of diastereoisomers by crystallization (42–74%); (iii) EtOH, HCl, H_2O, reflux, 30 min (80–98%); (iv) isoamyl nitrite, AcOH (cat.), $CHCl_3$, reflux (60–98%).

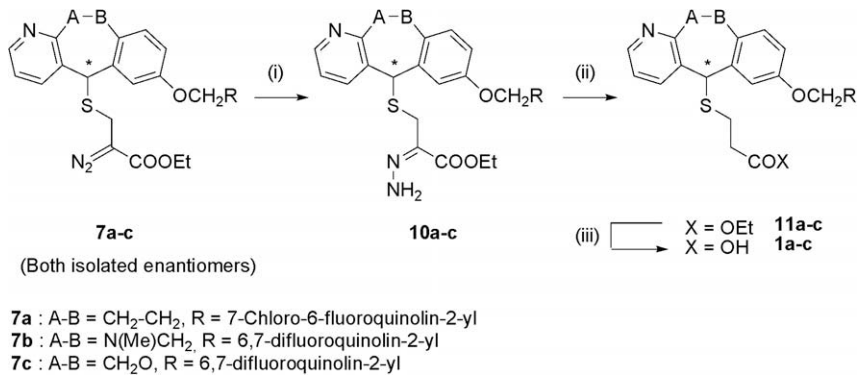
cleavage of such intermediates were explored without reward.[8] Methods involving the reduction of both enantiomers of α-diazoesters **7a–c** (easily prepared by treatment of aminoesters **3a–c** and **4a–c** with isoamyl nitrite)[9] were also studied with little success.[10] Of these, only HI-mediated reduction of α-diazoesters[10c,6] gave moderate yields of the desired deaminated products in just one of the examples (**7c**) so a different approach for the cleavage of the amino group was needed.

The key to the solution of our problems was found in a reaction reported by Bestmann and Kolm who observed that elimination of N_2 from α-hydrazonoester **8** was achieved under very mild conditions by treating this compound with a tertiary amine through a Wolff–Kishner type process (Scheme 2).[11] With this result in mind, an alternative strategy for the deamination of aminoesters **3a–c** and **4a–c** was then investigated. This new approach was based on the conversion of our α-aminoesters into the corresponding α-hydrazonoesters **10a–c** in order to perform N_2 elimination by treatment of such intermediates with a suitable base as described by Bestmann and Kolm. α-Hydrazonoesters could be prepared by selective reduction of α-diazoesters **7a–c**, intermediates already prepared in an enantiomerically pure form from aminoesters **3a–c** and **4a–c**.



Scheme 2. N_2 elimination of α-hydrazonoester **8** described by Bestmann and Kolm.

Although several examples of selective reduction of α-diazoesters to α-hydrazonoesters have been described in the literature, reports on practical and general examples of such a process are scarce.[12] In this context, there was a need to devise a mild and general method for the selective reduction of α-diazoesters to α-hydrazonoesters. To our delight and after examining a host of reducing agents and conditions, we observed that $NaBH_4$ in THF was able to effect this reduction in excellent yields in all examples under very mild reaction conditions (Scheme 3). At this juncture and with both enantiomers of α-hydrazonoesters **10a–c** in hand, we were prepared to test the base-promoted elimination of N_2. Of all the bases investigated, the best results were obtained with



Scheme 3. Reagents and conditions: (i) $NaBH_4$, THF, rt (77–98%); (ii) DBU, $CHCl_3$, rt (77–81%); (iii) LiOH, THF, H_2O, rt (80–93%).