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

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ABSTRACT

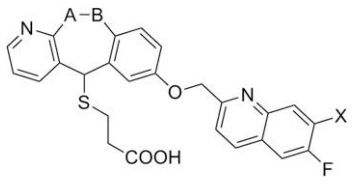
A practical and efficient three-step sequence for the deamination of α-aminoesters is reported. This method is based on the $NaBH_4$-mediated selective reduction of α-diazoesters to α-hydrazonoesters and has been successfully applied to the deamination of several representative α-aminoesters including 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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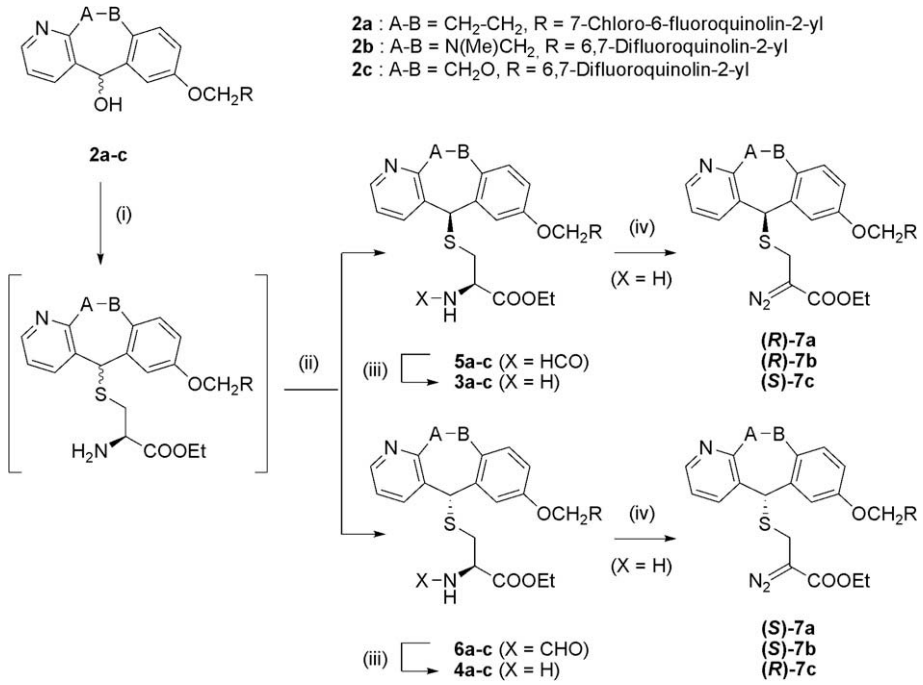
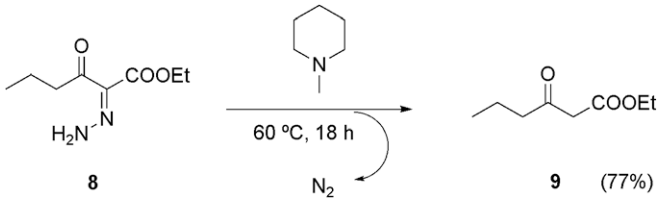


Scheme 1. Reagents and conditions: (i) L-Cysteine ethyl ester hydrochloride, TFA, 60 °C (80–91%); (ii) ethyl formate, reflux; separation of diastereoisomers by crystallization (42–74%); (iii) EtOH, HCl, H_2O, reflux, 30 min (80–98%); (iv) isoamyl nitrite, AcOH (cat.), $CHCl_3$, reflux (60–98%).

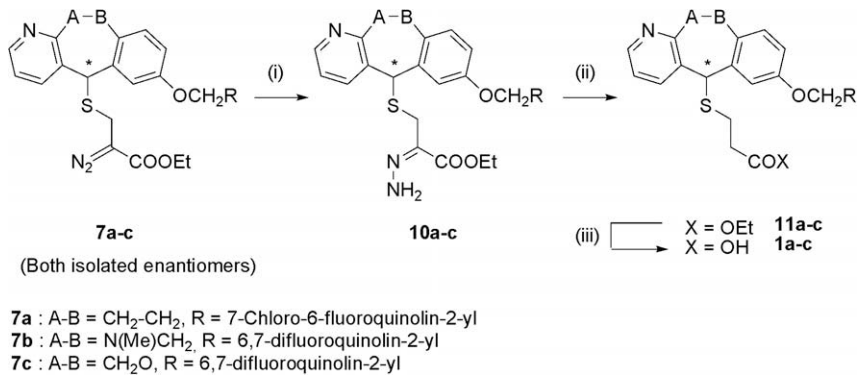
cleavage of such intermediates were explored without reward.[8] Methods involving the reduction of both enantiomers of α-diazoesters **7a–c** (easily prepared by treatment of aminoesters **3a–c** and **4a–c** with isoamyl nitrite)[9] were also studied with little success.[10] Of these, only HI-mediated 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.

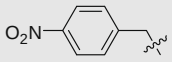
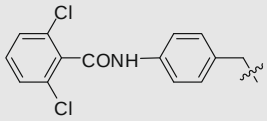
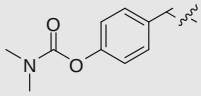
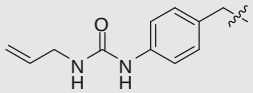
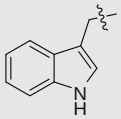
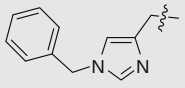
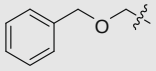
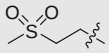
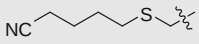
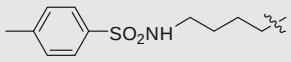
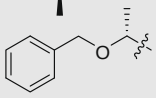
Although several examples of selective reduction of α-diazoesters to α-hydrazonoesters have been described in the literature, reports on practical and general examples of such a process are scarce.[12] In this context, there was a need to devise a mild and general method for the selective reduction of 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%).

Table 1
Three-step deamination sequence of several representative α-aminoesters[a]

12a-n **13a-n** **14a-n** **15a-n**

Entry	R^1	R^2	α-Aminoester	Step 1 yield (%)	Step 2 yield (%)	Step 3 yield (%)
1		Me	**12a**	81	92	79
2		Me	**12b**	71	72	80[e]
3		Me	**12c**	81	65[e]	95
4		Me	**12d**	50	46[e]	56
5		Me	**12e**	62	35[e]	52
6		Me	**12f**	41	49	75
7		Me	**12g**	75	83[e]	94
8		Me	**12h**	75	71	95[e]
9		Et	**12i**	76	97	97[e]
10		Et	**12j**	83	70[e]	61
11		Me	**12k**	77	59[e]	83
12		Bn	**12l**	94	11[f]	80
13		Bn	**12m**	94	28[f]	53
14		Bn	**12n**	95	19[f]	70

[a] All isolated products were characterized by ^{1}H NMR, MS and HPLC or GC.
[b] General procedure: A solution of α-aminoester (1 mmol), isoamyl nitrite (1.2 mmol) and AcOH (6 μL) in $CHCl_3$ (14 mL) was heated at reflux for 2.5 h.
[c] General procedure: $NaBH_4$ (1 mmol) was added to a solution of α-diazoester (1 mmol) in THF (20 mL) and the resulting mixture was stirred for 2 h at rt.
[d] General procedure: A solution of DBU (2 mmol) and α-hydrazonoester (1 mmol) in $CHCl_3$ (14 mL) was heated at reflux overnight.
[e] Reaction was carried out at rt for 24 h.
[f] Reaction was carried out with 4 mmol of $NaBH_4$ at rt for 3 days.

DBU. When 2 equiv of DBU was added to an α-hydrazonoester solution in $CHCl_3$, elimination of N_2 proceeded efficiently at rt to give esters **11a–c** in excellent yields. Finally, hydrolysis of the ester group with LiOH in THF/H_2O furnished both enantiomers of the desired acids **1a–c**, whose optical purity was analyzed by capillary electrophoresis giving ee values >97% in all cases.[13]

Encouraged by these remarkable results and having established the preferred reaction conditions for each step, deamination of several representative α-aminoesters bearing a variety of functional groups was performed to demonstrate the versatility of this three-step deamination sequence. As shown in Table 1, many functional groups tolerated the mild reaction conditions of all three steps, including amides (entry 2), carbamates (entry 3), ureas (entry 4), nitriles (entry 9) and sulfonamides (entry 10). Phenylalanine derivatives (entries 1–4) proved to be excellent substrates for the deamination process with good yields in almost all the steps and examples. Successful deamination of aminoester **12d** is also a good example of the potential of the method: Although yields in all three synthetic steps are only moderate, the allylic urea functionality of aminoester **12d** probably would be affected by the reaction conditions of many of the deamination methods described in the literature. On the other hand, yields obtained in diazo formation and reduction steps in other aromatic α-aminoesters (entries 5–6) were only moderate.

For the reduction step, steric factors seemed to play an important role and contributed to the decreased reactivity of β-substituted-α-diazoesters (entries 12–14) compared with the non-substituted ones. In these examples, not only a large excess of $NaBH_4$ and longer reaction times (up to three days) were needed in order to obtain significant amounts of the desired β-substituted-α-hydrazonoesters but also higher reaction temperatures did not have a beneficial effect on the reaction.

Finally, treatment of α-hydrazonoesters with DBU led to the desired deaminated esters with satisfactory results in all the examples studied. In order to force the reaction to completion, N_2 elimination was carried out under reflux in $CHCl_3$ in many examples.

In summary, we have developed an efficient and practical three-step sequence for the reductive elimination of the amino group in α-aminoesters based on the $NaBH_4$-mediated selective reduction of α-diazoesters to α-hydrazonoesters. The scope and limitations of this method have been examined with several representative α-aminoesters bearing different functionalities with excellent results in most of the examples. This methodology has also been successfully applied to the synthesis of a series of CysLT1 antagonists.

Supplementary data

Supplementary data (experimental procedures and characterization data are provided for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.118.

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13. Separated enantiomers of carboxylic acids **1a–c** are identified based on the sign of their optical rotation values. Studies to assign the absolute configuration of these isolated enantiomers are underway.