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Stereospecific Synthesis of the Anaesthetic Levobupivacaine

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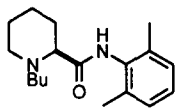
Abstract: Enantiomerically pure (S)-Bupivacaine is synthesised from the chiral pool using cheap and readily available (S)-lysine. The key steps in this efficient synthesis include an oxidative de-amination and stereospecific ring closure to form the pipecolamide core structure. Copyright © 1996 Elsevier Science Ltd

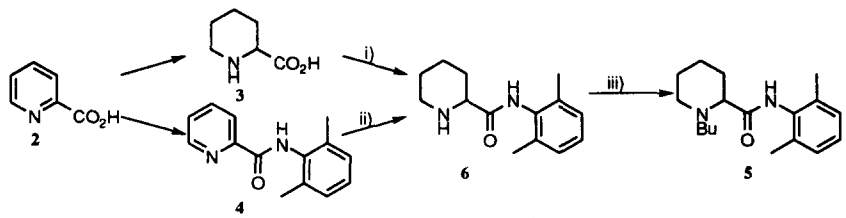
We are currently investigating the synthesis of single isomer versions of drugs currently marketed as racemates for use as local anaesthetics and treatment of cancer and inflammation. These drugs have been identified where the single enantiomer should have considerable patient benefit through lower toxicity and/or through increased potency and efficacy.

One of these drugs, (S)-bupivacaine **1** (levobupivacaine), is a prime candidate. This drug is currently used in racemic form as an epidural anaesthetic during labour and for ulna nerve block for local anaesthesia in minor operations. At high doses, however, the racemate is potentially hazardous due to cardiotoxicity problems. We have demonstrated that the (S) isomer of bupivacaine **1** is considerably less cardiotoxic and, therefore, safer than the racemate.[1] This decrease in cardiotoxicity has even allowed additional clinical endpoints, such as analgesia, to be evaluated.



1

Currently, racemic bupivacaine **5** (Marcaine) can be prepared from pyridine-2-carboxylic acid **2** either by reduction to the non-proteinogenic amino acid pipecolic acid (±)**3** and then coupling 2,6-dimethyl aniline to the acid chloride hydrochloride salt of **3** or by reducing the pyridyl amide **4** over platinum oxide giving the amide **6**.[2-4] The amide intermediate **6** can also be used to prepare the anaesthetics ropivacaine[2] and mepivacaine in which the alkyl group attached to nitrogen is propyl and methyl respectively. Alkylation of the amino acid nitrogen is accomplished either by direct alkylation using butyl bromide and a suitable base such as potassium carbonate[3] or by reductive amination using butyraldehyde.[4,5]



i) $SOCl_2$, 2,6-dimethyl aniline ii) H_2, PtO_2 iii)BuBr, K_2CO_3 or PrCHO, [H]

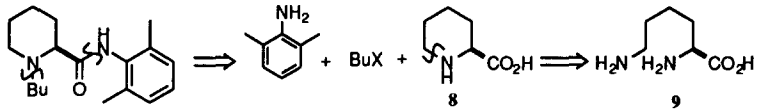
Single enantiomer bupivacaine **1** (R=Butyl) can be prepared via diastereomeric salt resolution with tartaric acid or by resolution of the amide **6** (R=H) with O,O-dibenzoyl tartaric acid followed by butylation as described previously.[5-7]

5 R=Bu
6 R=H

1 R=Bu
7 R=H

5→1 i) (+) tartaric acid ii) base
6→7 i) O, O' dibenzoyl tartaric acid ii) base

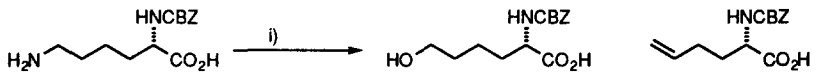
Retrosynthetic analysis of (S)-bupivacaine indicates that the single enantiomer of the non-proteinogenic amino acid (S)-pipecolic acid **8** is an obvious synthon. Further disconnection reveals (S)-lysine **9** as having the correct carbon count and the required stereochemistry and indeed (S)-pipecolic **8** acid has been prepared from lysine previously. This starting material is particularly attractive due to the ready availability and low cost (~£3/kg) of (S)-lysine.



8 **9**

The published routes to (S)-pipecolic acid or its derivatives from (S)-lysine are, unfortunately, unreliable in our hands or impractical industrially because extensive and difficult protecting group chemistry is used.[8-13] We have devised a chiral pool synthesis of (S)-bupivacaine starting from (S)-lysine which utilises a minimum amount of protecting group chemistry. This synthetic methodology can also be used to prepare analogous anaesthetics ropivacaine and mepivacaine in single enantiomer form and optically pure (S)-pipecolic acid **8**.

Baldwin discovered that the ε-amino group of N^{α}-CBZ (S)-lysine **10** can be oxidatively de-aminated with potassium ferricyanide to yield (S)-N-CBZ 6-hydroxynorleucine **11**.[14] We found that use of this reagent indeed produces the alcohol **11** but the yield is poor and the alkene **12** is produced as a contaminant.



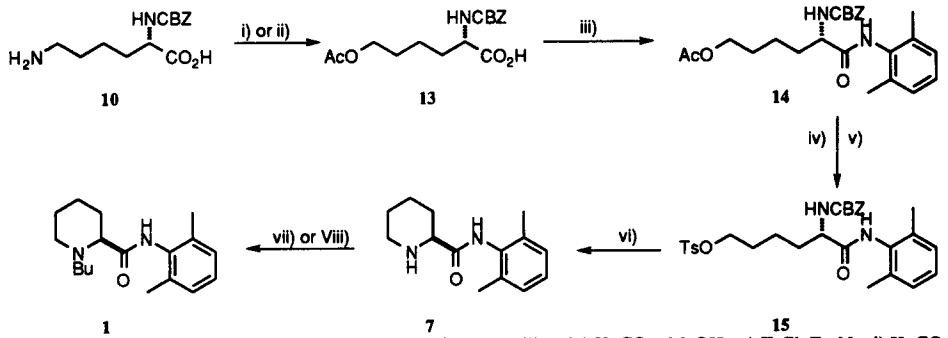
10

11
42%

12
28%

i) $Na_2[Fe(CN)_5NO]$, K_2CO_3

We examined the synthesis (S)-bupivacaine from (S)-lysine using this type of transformation and tried to increase the efficiency of the deamination. It has been reported that treatment of primary alkyl amines with amyl nitrite in acetic acid can effect the transformation of the amino group to an acetate group.[15] When we perform this reaction on **10** the acetate **13** is obtained in 60% yield together with ~20% alkene **12**. Other simple alkyl nitrites can also be used in this transformation and we found that the yields are comparable.

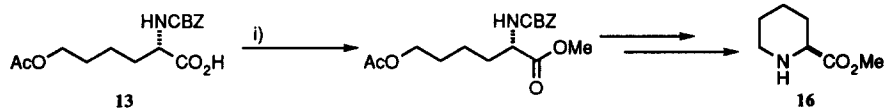


10 13 14 15 7 1

i) RONO, AcOH ii) $NaNO_2$, NaOAc, AcOH iii) DCC, 2,6-dimethylaniline iv) K_2CO_3, MeOH v) TsCl, Et_3N vi) K_2CO_3, EtOH, 10%Pd/C, H_2 vii) BuBr, K_2CO_3, viii) PrCHO, [H]

However, an alternative method gives the acetate **13** in better yield. Treatment of N$^{\alpha}$-CBZ (S)-lysine **10** with sodium nitrite in acetic acid[16] yields the de-aminated acetate **13** in 80% yield. Addition of sodium acetate to this reaction increases the yield of **13** due to an effective increase in the concentration of acetate ion as the nucleophile which suppresses elimination and rearrangement. The acetate **13** is then coupled with dimethyl aniline using DCC to give the amide **14** in good yield (>70%). The acetate group is then converted into the tosylate **15** (75%) which is deprotected and cyclised stereospecifically in an efficient one pot reaction to give the amide **7** in 90% yield. Chiral HPLC[17] of **7** showed it to be >98%e.e. Alkylation is most easily achieved using an alkyl bromide and an appropriate base such as K_2CO_3. There is no observable racemisation at this stage. Butylation can also be achieved using butyraldehyde/formic acid although we have found that the former is a much simpler process and is less anti-social.

This synthesis can also be used to prepare optically pure (S)-pipecolic acid by diverting the synthetic scheme before the diimide coupling stage. Preparation of the methyl ester of the acetate **13** followed by identical chemistry as above yields (S)-pipecolic acid methyl ester **16**.



13 16

i) $(CH_3)_3SiCHN_2$

In summary, we have identified an efficient 5 step (38% overall from N$^{\alpha}$-CBZ lysine) route to the anaesthetic levobupivacaine and the analogous anaesthetics mepivacaine and ropivacaine from cheap and readily available starting materials.

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