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Enantioselective total syntheses of ropivacaine and its analogues

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ABSTRACT

An alternative asymmetric synthesis of ropivacaine and analogues employing the 'cation pool' strategy and host/guest supramolecular co-catalysis approach is presented. In this study, chiral auxiliaries, several soft nucleophiles as well as one-pot conditions for anodic oxidation, followed by nucleophilic addition, have been applied.

Bupivacaine is the most widely used drug in childbirth centers as the anesthetic agent given to pregnant women. It has remained the main drug for long-acting local anesthesia for many years. Bupivacaine inhibits calcium channels of central nervous system (CNS), but its systemic neurotoxic effects (e.g., convulsions, seizures) affect infants and mothers in childbirth. Local anesthetics bind to the 'inner vestibule' of the Na^+ channel and an interesting feature of their mechanism of action is that anesthetic drugs affinity to the Na^+ channel varies with the gating state of the channel. Finally, the search for less cardiotoxic but equally long-acting local anesthetic has led to the synthesis and development of levobupivacaine (**1**) and ropivacaine (**2**), which was recently introduced as a new alternative for long-acting local anesthetic drug, being closely related to mepivacaine (**3**) and levobupivacaine (**1**) that were first synthesized by Ekenstam and co-workers in the mid-1950s (Fig. 1).[1] After several experimental and clinical studies, it was confirmed that levobupivacaine (**1**) and ropivacaine (**2**) afforded lower and different toxicity profile at least 70% less compared with bupivacaine that are widely used in Europe and USA as anesthetics in childbirth.[2,3] Recently, Ramachandran and co-workers reported an asymmetric synthesis of levobupivacaine.[4] However, there are few methods available for the enantioselective construction of pipecolic moiety in high yields. Generally, the main process available consists of resolution of racemic mixtures containing the pipecolic ring. Thus, we disclose a novel alternative to reach this important

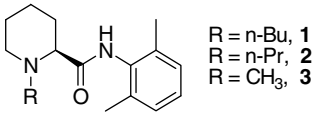

Figure 1. Worldwide used anesthetics levobupivacaine (**1**), ropivacaine (**2**), and mepivacaine (**3**).

class of compounds featuring an efficient and practical synthesis of (*L*)-pipecolic acid derivatives. Our approach is based on the diastereoselective addition of NC^- to *N*-acyliminium ions bearing a chiral auxiliary (α-phenylmenthyl) for the introduction of asymmetry in **1–3**.

Our strategy allowed the use of an interesting new approach to obtain directly a *N*-acyliminium ion through anodic oxidation. The advantages of this technique lie in its utility for selective oxidation of cyclic *N*-carbamates generating highly reactive intermediates under essentially neutral conditions.[5] We also employed the 'cation pool' technique that is useful for *N*-acyliminium ion generation, in which ions are accumulated in solution by low-temperature electrolysis.[6] In the next step, the reactive intermediates are allowed to react in situ with nucleophiles. The idea has been successfully applied to *N*-acyliminium ions.[7,8] Initially, we set up some model experiments to optimize the critical nucleophilic addition step (TMSCN, NaCN, or *n*-Bu_3SnCN) to chiral *N*-acyliminium ion **5a**. According to Table 1, when using 8-phenylmenthyl as chiral auxiliary (entry 1), isolation of the corresponding α-methoxy carbamate, followed by TMSCN addition catalyzed by TMSOTf in CH_2Cl_2 at −78 °C, provided **6a** in 85% yield and 76% ee. The enantiomeric excess was determined after hydrolysis of **6a** to

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Table 1
Addition of cyanide to *N*-acyliminium ions **5**

Entry	5	Conditions	Time (h)	Yield[a] (%)	ee (%)
1	**5a**	(a) Pt anode/W cathode MeOH, 100 mA, −2e⁻, 0 °C, 5 h (b) TMSOTf, TMSCN, CH_2Cl_2, −78 °C, 5 min	5	85	76 (*S*)
2	**5a**	(a) Pt anode/W cathode MeOH, 100 mA, −2e⁻, 0 °C, 5 h (b) β-CD, TMSOTf, TMSCN, CH_2Cl_2, −40 °C, 5 min	5	65	91 (*S*)
3	**5a**	Pt anode/W cathode NaCN, MeOH/H_2O (2:1), 100 mA, −2e⁻, 0 °C, 5 h	5	—	—
4	**5a**	Pt anode/W cathode TMSCN, CH_2Cl_2, 70 mA, −2e⁻, −78 °C	2	18	80 (*S*)
5	**5a**	Pt anode/W cathode Bu_3SnCN, CH_2Cl_2, 70 mA, −2e⁻, −78 °C	3	40	85 (*S*)
6	**5a**	(a) Pt anode/W cathode CH_2Cl_2, 60 mA, −2e⁻, −40 °C, β-CD, 5 h (b) TMSOTf, TMSCN, −40 °C	5	35	90 (*S*)
7	**5b**	(a) Pt anode/W cathode CH_2Cl_2, 60 mA, −2e⁻, −40 °C, β-CD, 5 h (b) TMSOTf, TMSCN, −40 °C	5	65	30 (*S*)

[a] Isolated yields.

(*S*)-(−)-pipecolic acid, and the absolute configuration was determined to be (*S*), $[\alpha]_D$ −26 (*c* 1.0, H_2O), mp 271–272 °C (lit. mp 272 °C).[9] Our first attempt to use the 'cation pool' approach and NC^- as a nucleophile (entry 3) gave a complex mixture and no product was observed in the crude reaction mixture when NaCN was used.[10] When TMSCN was used as nucleophile (entry 4), the 'cation pool' approach afforded (*S*)-**6a** in 18% yield and 80% ee. Using Bu_3SnCN as nucleophile (entry 5), the yield increased to 40% and the ee to 85%, respectively.

Next, we figured out to use β-CD as co-catalyst in the reaction. The use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various transformations is well known.[11,12] Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. CDs catalyze reactions through a supramolecular manner involving reversible formation of host/guest complexes by non-covalent bonding. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. As depicted in Table 1 (entry 6), the production of a 'cation pool' of **5a** (Scheme 1) followed by the addition of TMSCN and TMSOTf at −40 °C afforded (*S*)-**6a** in 35% yield and 90% ee. Then, using the same protocol with *N*-Boc precursor **5b** and β-CD as additive, the yield of **6b** was 65% but low enantiomeric excess was observed (30% ee of *S* isomer).

Finally, as shown in Table 1 and entry 2, using β-CD as additive and the two-step procedure afforded better % ee (90%) with moderate yield (65%) when compared with entry 1 where β-CD was not employed, under otherwise identical experimental conditions. We rationalized the formation of a supramolecular arrangement (β-CD/**5a**, Fig. 2), which might favor *Re*-face attack of the nucleophile. The lower yield observed in entry 2 might be the result of competition for Lewis acid by the hydroxyl groups in β-CD. In fact, increasing the amount of TMSOTf and/or TMSCN to 4 equiv or higher gave only poor selectivities. If nucleophilic solvent is employed, the *N*-acyl iminium ion is trapped and stabilized that is not the case with aprotic solvents such as CH_2Cl_2. In this case, decomposition of electrochemically generated *N*-iminium ion might ensue.

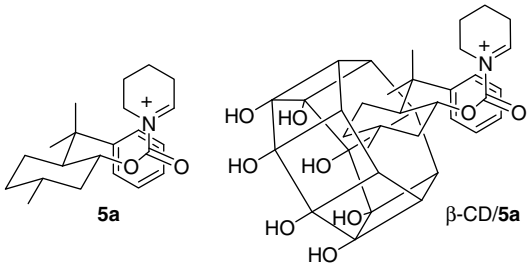
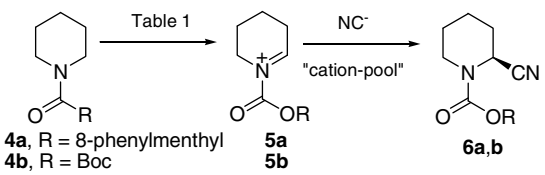


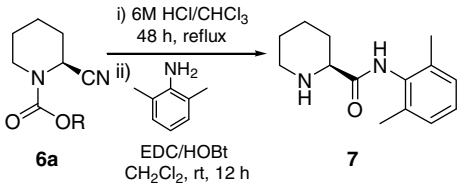
Figure 2.

The absolute configuration at the newly generated stereogenic center of **6a** was established after acidic hydrolysis to give pipecolic acid accompanied by recovery of the chiral auxiliary (95%), as mentioned above. The *Re*-face selectivity displayed by the chiral *N*-acyliminium ion **5a** was rationalized based on our previous results with 8-phenylmenthyl chiral auxiliaries[13] and was assigned to the kinetically preferred attack of the nucleophile to the *s*-cis conformation of *N*-acyliminium ion **5a** (Fig. 2)[14] that might be enforced by π-stacking interactions[15] involving the low-lying LUMO of the carbonyl group and HOMO of the phenyl substituent Scheme 2.

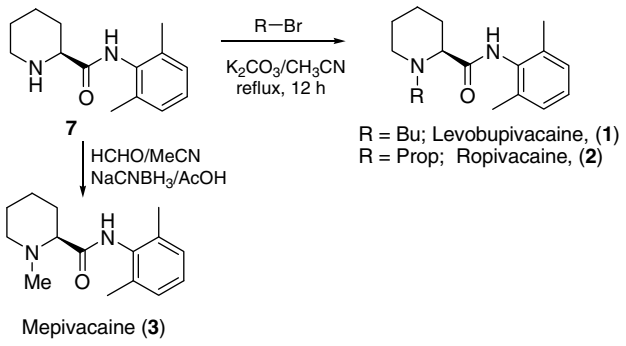
The xylamide **7** was obtained from **6a** in two steps by HCl deprotection of chiral auxiliary (recovered in 95% yield), and concomitant production of pipecolic acid. Next, crude pipecolic acid was treated with EDC/HOBt and 2,6-dimethylaniline affording **7** in 88% yield, $[\alpha]_D$ 35 (*c* 2.0, HCl 1 M), mp 129–130 °C (lit. for *R* isomer $[\alpha]_D$ −46 (*c* 2.3, HCl 2.3 M), mp 130 °C).[16,17] The introduction of alkyl chains (R = *n*-Bu, *n*-Pr, and Me) was carried out using *n*-butyl bromide, *n*-propyl bromide, and K_2CO_3 in MeCN, at reflux for 12 h. Levobupivacaine **1** was obtained in 80% yield and no racemization was observed in the process (Scheme 3), $[\alpha]_D$ −77 (*c* 5.0, MeOH), mp 135–137 °C.[16,17] Analogously, ropivacaine **2** was obtained in 85% yield, $[\alpha]_D$ −78 (*c* 5.0, MeOH), mp 143–145 °C.[17] Finally, mepivacaine **3** was achieved using reductive amination of



Scheme 1.



Scheme 2.



Scheme 3.

7 with formaldehyde (30% v/v) in MeCN and $NaCNBH_3$ reduction affording **3** in 85% yield, $[\alpha]_D$ −43 (*c* 5.0, MeOH), mp 148–150 °C.[16,18]

In conclusion, an alternative asymmetric synthesis of ropivacaine and analogues employing the 'cation pool' strategy and host/guest supramolecular co-catalysis approach is presented. In this protocol, we applied anodic oxidation as well as soft nucleophiles to develop a short and high-yielding synthesis of pipecolic derivatives **1**–**3**.

Acknowledgments

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9. Compared to the available data found in http://www.sigmaaldrich.com.
10. 'Cation pool' procedure: The anodic oxidation was carried out in an undivided glass cell equipped with a platinum plate anode (4.0 cm^2) and a tungsten wire cathode. A solution of **4a**,**b** (0.1 mmol) in 0.2 M Et_4NOTs/CH_2Cl_2 (10.0 mL) was placed in the cell and the substrate was electrolyzed at constant current (70–100 mA). The substrate was electrolyzed at constant current (between 70 and 100 mA) under magnetic stirring and the reaction temperature was maintained between −40 and −78 °C with external bath. After the passage of 3.0 $F.mol^{-1}$ of electricity, the nucleophile (0.3 mmol) was added at −40 °C (or −78 °C, see Table 1) to the 'cation pool' of **5**, and the reaction mixture was stirred for further 0.5 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel.
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18. *Analytical data:* Pipecolic acid: mp 271–272 °C. $[\alpha]_D$ −26 (*c* 1.0, H_2O), 76% ee. ^1H NMR (300 MHz, D_2O), δ 1.40–1.58 (m, 3H), 1.69–1.75 (m, 2H), 2.06 (d, 1H, *J* 12.8 Hz), 2.85 (t, 1H, *J* 12.5 Hz), 3.26 (d, 1H, *J* 12.5 Hz), 3.43 (d, 1H, *J* 7.7 Hz). ^{13}C NMR (75 MHz, D_2O), δ 21.4 (CH_2), 21.7 (CH_2), 26.3 (CH_2), 43.4 (CH_2), 58.8 (CH), 174.1 (C). Levobupivacaine (**1**): mp 135–137 °C. $[\alpha]_D$ −77 (*c* 1.0, MeOH), 76% ee. ^1H NMR (300 MHz, $CDCl_3$), δ 0.94 (t, 3H, *J* 7.3 Hz), 1.29–1.41 (m, 3H), 1.42–1.81 (m, 7H), 2.04–2.19 (m, 2H), 2.26 (s, 6H), 2.80–2.96 (m, 2H), 3.24 (br d, 1H, *J* 9.5 Hz), 7.08 (s, 3H), 8.19 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.2 (CH_3), 18.8 (2× CH_3), 20.7 (CH_2), 23.5 (CH_2), 24.9 (CH_2), 29.7 (CH_2), 30.6 (CH_2), 51.6 (CH_2), 57.4 (CH_2), 68.5 (CH), 126.8 (CH), 129.1 (2× CH), 133.5 (C), 135.1 (2× C), 172.6 (C). HRMS (EI) to $C_{18}H_{28}N_2O$ *m/z* ($M^{+\cdot}$−1): calcd 287.2036, found 287.2123. Ropivacaine (**2**): $[\alpha]_D$ −78 (*c* 5.0, MeOH), mp 143–145 °C (lit. mp 144–146 °C, $[\alpha]_D$ −82 (*c* 2, MeOH)). ^1H NMR (400 MHz, D_2O), δ 0.95 (t, 3H, *J* 12.0 Hz), 1.68–2.10 (m, 7H), 2.19 (s, 6H), 2.40–2.46 (db, 1H), 3.10–3.19 (m, 3H), 3.70–3.75 (br d, 1H), 4.15–4.20 (br d, 1H), 4.78 (s, 3H), 7.17–7.28 (m, 3H). ^{13}C NMR (100 MHz, D_2O), δ 11.3 (CH_3), 17.9 (CH_2), 18.2 (2× CH_3), 21.9 (CH_2), 23.3 (CH_2), 29.9 (CH_2), 53.1 (CH_2), 58.9 (CH_2), 66.8 (CH), 129.3 (2× CH), 129.6 (CH), 132.8 (C), 137.0 (2× C), 170.4 (C). HRMS (EI) to $C_{17}H_{26}N_2O$ *m/z* ($M^{+\cdot}$): calcd 274.2045, found 274.2006. Mepivacaine (**3**): mp 148–150 °C. $[\alpha]_D$ −43 (*c* 1.0, MeOH), 76% ee. ^1H NMR (300 MHz, $CDCl_3$), δ 1.21 (ddt, 1H, *J* 12.8, 8.8, 3.7 Hz), 1.43–1.67 (m, 3H), 1.72 (dt, 1H, *J* 12.8, 2.9 Hz), 2.03 (ddd, 1H, *J* 11.7, 9.2, 2.9 Hz), 1.96–2.10 (m, 1H), 2.17 (s, 6H), 2.34 (s, 3H), 2.57 (dd, 1H, *J* 11.7, 3.7 Hz), 7.00 (s, 3H), 7.96 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9 (2× CH_3), 23.4 (CH_2), 25.5 (CH_2), 31.5 (CH_2), 45.2 (CH_3), 55.6 (CH_2), 70.1 (CH), 126.9 (CH), 128.2 (2× CH), 133.4 (C), 135.1 (2× C), 172.4 (C). HRMS (EI) to $C_{15}H_{22}N_2O$ *m/z* ($M^{+\cdot}$): calcd 246.1732, found 246.1702.