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# Enantioselective decarboxylation–reprotonation of an α-amino malonate derivative as a route to optically enriched cyclic α-amino acid

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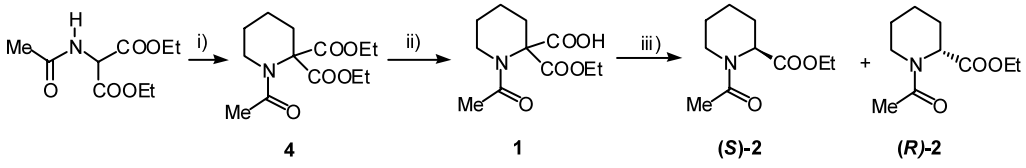
**Abstract**—Chiral tertiary amines have been examined as enantioselective decarboxylation–reprotonation reagents for the synthesis of α-amino acids via α-aminomalonates. *N*-Acetyl pipecolic acid ethyl ester, as a model compound, was obtained in good yield and 52% enantiomeric excess using a quinidine derived base. 

Interest in compounds containing a rigid α-amino acid moiety is still growing since they can be used as conformationally restricted units in peptide mimetics. Moreover, they are often present in natural and biologically active compounds. As an example, the 2-piperidine carboxylate sub-unit is a common structural moiety of peptides[1] and macrolides endowed with immunosuppressant (FK506),[2] antibiotic (rapamicin esters)[3] or anti-inflammatory (ascomycin and derivatives)[4] properties. However, unlike optically active acyclic α-amino acids, catalytic asymmetric synthesis of cyclic α-amino acids has been limited. The best current route to the pure enantiomers is the classical resolution of the racemate.[5] Kinetic resolutions of piperidine 2-carboxylic acid derivatives have been described. They required the search for specific esterases,[6] or bacterial cells.[7] Most of the asymmetric examples developed[8] up to now were carried out under stoichiometric conditions,[9] except the phase transfer catalyst alkylation of a suitable imine,[10] and the hydrogenation of tetrahydropyridines.[11]

As a part of our program on the synthesis of (*R*)- and (*S*)-AF-DX 384,[12] potent and selective muscarinic antagonists, we studied the deracemization of the methyl ester of pipecolic acid. A low enantiomeric excess (36%)[13] was obtained. More successful was the deracemization using asymmetric protonation of pipecolamides.[14] Although efficient both in terms of yields and enantiomeric excesses (ee's >95%), the reaction suffers from the use of *sec*-butyllithium[15] at −78°C. With the aim of avoiding this strong base and the low temperature, we examined the enantioselective decarboxylation–reprotonation of a malonate precursor as an alternative route to α-amino acid derivatives. Whereas this methodology was known in the presence of enzymes or microorganisms,[16] it has received little attention,[17] although being probably the first asymmetric synthesis.[18] Recently,[19] the treatment at rt of 2-aryl-2-cyanopropionic acids with a catalytic amount of cinchona alkaloids led to naproxen derivatives with ee's up to 72%. To our knowledge, the sequence decarboxyl-




4 1 (*S*)-2 (*R*)-2

**Scheme 1.** *Reagents and conditions*: (i) $Cs_2CO_3$, $Br(CH_2)_4Br$, MeCN, reflux, 16 h, 73%; (ii) CsOH, EtOH, rt, 16 h, 82%; (iii) chiral base, THF, 16–24 h, 68–77%.

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ation–reprotonation has been only studied on acyclic malonic derivatives bearing an aryl substituent able to stabilize a carbanionic intermediate. Recent reports on the enantioselective decarboxylation of β-ketobenzyl esters[20] prompt us to describe here our preliminary results on the decarboxylation–reprotonation, in the presence of a chiral base, of the *N*-acyl malonate monoester **1** as a route to nonracemic piperidine-2-carboxylic acid ethyl ester **2**.

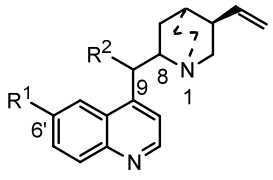
The racemic carboxylic acid–ester **1** was prepared in multigram quantities via a two steps sequence starting from commercially available diethyl acetamidomalonate **3** in 60% overall yield (Scheme 1).

In order to test the feasability of the reaction, the decarboxylation of the acid–ester **1** was first studied in the presence of an achiral base. Yields up to 80% in ester **2** were obtained with triethylamine in THF after 21 h at rt.[21] The enantioselective decarboxylation–reprotonation was then carried out under the following conditions: the chiral base was added to the acid **1** in THF (0.1 M) and allowed to react for 16–24 h at rt. After work-up, the reaction mixture was directly injected onto a chiral HPLC column.[22] Isolated yields of 68–77% were obtained using cinchona alkaloids as the bases. The chromatograms showed only signals corresponding to the chiral base and to the enantiomeric products **2**. No starting material **1** was detected either by HPLC or by $^1$H NMR of the crude mixture. Each enantiomer of the ester **2** were independently synthesized[23] for unambiguous assignement of the HPLC signals. Among a number of chiral amines[24] screened for this reaction, cinchona alkaloids gave the best results. The influence of the substituents on the quinoline ring or on the 9 position, the role of the configurations of carbons 8 and 9 and finally the modifications of the alkaloids by cyclization were studied. (+)-Cinchonine **5**, (−)-cinchonidine **6**, (−)-quinine **7**, (+)-quinidine **8** were purchased from commercial sources. (+)-Cupredine **9**, (+)-cupredine cyclic ether **10**, (+)-cinchonine cyclic ether **11**, (+)-9-mesyloxyquinidine **12**, (+)-9-amino-9-deoxyquinidine **13**, and (+)-2-methoxybenzamide **14** were prepared by literature methods.[19,25]

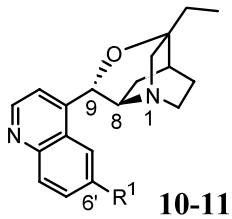
The results presented in Table 1 revealed that the asymmetric induction is dependent on the presence of an hydroxyl or methoxy group on the quinoline ring. Indeed, cinchonine and cinchonidine gave poor ee's compared to quinine and quinidine under stoichiometric (Table 1, entries 1–4) or catalytic conditions (Table 1, entry 5). These results contrast with those reported for the decarboxylation of the monoethyl ester of phenylmalonic acid where cinchonine gave a higher ee than the other cinchona alkaloids.[17e,f] The crucial role of an oxygen group in the 6′ position was confirmed by the ee's obtained with the cyclic ethers **10** ($R^1$ = OH, ee 36.8%) and **11** ($R^1$ = H, ee <5%).

In our experiments with alkaloids **5**–**14**, the configuration of the carbon-8 has a small influence compared to that observed in the decarboxylation–reprotonation of arylcyanopropionic acids.[19] However, a clear pseudo enantiomeric effect was observed with quinine and quinidine whereas with cinchonine and cinchonidine this effect is not so marked due to the low ee's obtained (Table 1, entries 1–5). One question remains concerning the role of the configuration of C-9. The C-9 has an *R* configuration in base **14** and *S* in bases **8**–**11**, but all these compounds generate the same *S* enantiomer of pipecolate **2**. This was also observed previously but not

**Table 1.** Decarboxylation of malonate hemiester **1** in the presence of cinchona alkaloids




**5-9, 12-14**




**10-11**

| Entry | Base | C-8 | C-9 | $R^1$ | $R^2$ | **2** ee[a] | **2** C-2[b] | *n*[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | (+)-Cinchonine **5** | *R* | *S* | H | OH | 5.8±0.7 | *S* | 3 |
| 2 | (−)-Cinchonidine **6** | *S* | *R* | H | OH | 2.2±0.5 | *R* | 3 |
| 3 | (−)-Quinine **7** | *S* | *R* | OMe | OH | 18.0±0.3 | *R* | 2 |
| 4 | (+)-Quinidine **8** | *R* | *S* | OMe | OH | 15.9±3.4 | *S* | 3 |
| 5 | (+)-Quinidine **8**, 10 mol% | *R* | *S* | OMe | OH | 18.5±1.1 | *S* | 3 |
| 6 | (+)-Cupredine **9** | *R* | *S* | OH | OH | 8.8±1.8 | *S* | 2 |
| 8 | (+)-**10** | *R* | *S* | OH | – | 36.8±1.3 | *S* | 3 |
| 9 | (+)-**10**, 10 mol% | *R* | *S* | OH | – | 17.6±2.6 | *S* | 2 |
| 10 | (−)-**11** | *R* | *S* | H | – | 4.1±3.5 | *S* | 2 |
| 11 | (+)-**12** | *R* | *S* | OMe | OMs | 1.0±0.7 | *S* | 3 |
| 12 | (+)-**13** | *R* | *R* | OMe | $NH_2$ | 7.4±1.2 | *S* | 2 |
| 13 | (+)-**14** | *R* | *R* | OMe | NHCO($C_6H_4$-2-OMe) | 52.1±1.8 | *S* | 2 |

[a] Determined by chiral HPLC.
[b] Absolute configuration of the major enantiomer.
[c] Number of experiments.

discussed.[19] To address this question it will be necessary to synthesize the diastereoisomer of **14** with a C-9 of *S* configuration.

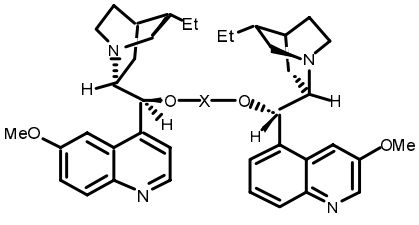
The sterically more hindered dihydroquinidine derivatives **15** and **16** with the C-8*R*, C-9*S* configurations gave higher ee's than their stereoisomers dihydroquinines (C-8*S*, C-9*R*) **18** and **19** (Table 2). A pseudo enantiomeric effect was not observed with these compounds. The PHAL derivatives of quinidine **17** and quinine **18** induced the formation of the same enantiomer *S* of pipecolate **2** (Table 2, entries 5 and 6). With the AQN derivatives of quinidine **15** and quinine **19** the major enantiomers of **2** were respectively *R* (ee 20.3%) and *S* (ee 7.1%), however, with different enantiomeric excesses (Table 2, entries 1 and 7). The discrepancy in the results obtained with these bases leads to a question concerning the role of the spacer between the two quinine/quinidine units. If the spacer is not directly involved in the decarboxylation process, it probably induces a conformational change compared to the monomeric alkaloid. The dimeric cinchona derivatives do not appear to be good candidates for further developments as basic catalysts for the reaction.

Intramolecular hydrogen bonding have been proposed to account for the high enantiomeric excesses obtained in the decarboxylation reaction mediated by amides of 9-amino-9-deoxyepicinchonine.[26,27] Such interactions could also explain the highest enantioselectivity (52%) (Table 1, entry 13) observed in our case with amide **14** and the poor results with the bases **12** and **13** (entries 11 and 12). With the cyclic ether **10**, a relatively high ee (Table 1, entry 8) was obtained. It could result from the stabilization of the intermediate involving ionic interaction between the positive quinuclidinium protonated nitrogen and the anionic side of the substrate (before or after decarboxylation) on the one hand, and on the other hand, hydrogen bonding between the phenolic hydroxy group and the carbonyl of the amide group of the substrate.[28] The lower enantioselectivity excess observed in our case under the best conditions compared to that obtained in enantioselective decarboxylation of naproxene derivatives (52 versus 72%) could result from the lack of an aromatic ring in our substrate. With salt bridging and hydrogen bonding, the π-stacking with the quinoline ring seems essential to achieve a good enantioselectivity.[29]

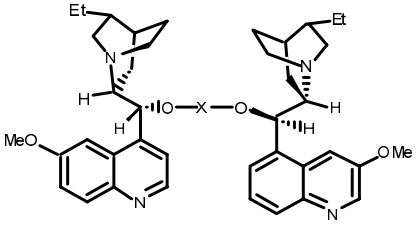
In conclusion, synthesis of optically enriched *N*-protected ethyl pipecolate has been achieved using an enantioselective decarboxylation–reprotonation sequence in the presence of stoichiometric or catalytic amounts of cinchona alkaloids. Although the enantiomeric excess of the *N*-acyl ethylpipecolate seems modest, it is the highest obtained for this substrate. Indeed, kinetic resolutions or reactions of pipecolate esters mediated by lipases have yet been limited by the substituent on the substrate,[6a,b] and the purity of enzymes.[6c]

If the highest ee was obtained with one the most successful chiral base used in the decarboxylation of naproxen derivatives, our preliminary results suggest that much efforts are needed to propose a more selective catalyst. Our current work focus on further improvement of the structure of a base which could stabilize any putative intermediate by hydrogen bonding and π-stacking and thus would probably slow down the reprotonation for a better enantioselectivity. Finally, as both the enantioselectivity of reactions using cinchona alkaloids[30] and the rate constants for decarboxylation of acid[19,31] depend strongly on the solvent, a study of the different parameters of the reaction will be undertaken.

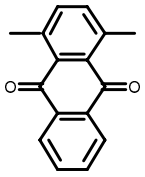
**Table 2.** Decarboxylation of malonate hemiester **1** in the presence of quinidine derivatives



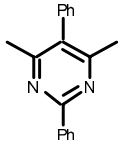
**$(DHQD)_2X$**



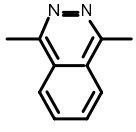
**$(DHQ)_2X$**



**X = AQN**



**PYR**



**PHAL**

| Entry | Base | C-8 | C-9 | **2** ee[a] | **2** C-2[b] | *n*[c] |
|---|---|---|---|---|---|---|
| 1 | (+)-$(DHQD)_2$AQN **15** | *R* | *S* | 20.3±1.2 | *S* | 2 |
| 2 | (+)-$(DHQD)_2$AQN **15**, 10 mol% | *R* | *S* | 13.2±0.1 | *S* | 3 |
| 3 | (+)-$(DHQD)_2$PYR, **16** | *R* | *S* | 23.5±0.6 | *S* | 2 |
| 4 | (+)-$(DHQD)_2$PYR, **16**, 10 mol% | *R* | *S* | 24.6±1.3 | *S* | 3 |
| 5 | (+)-$(DHQD)_2$PHAL, **17** | *R* | *S* | 14.0±0.7 | *S* | 2 |
| 6 | (−)-$(DHQ)_2$PHAL, **18** | *S* | *R* | 7.3±1.2 | *S* | 2 |
| 7 | (−)-$(DHQ)_2$AQN, **19** | *S* | *R* | 7.1±0.9 | *R* | 2 |

[a] Determined by chiral HPLC.
[b] Absolute configuration of the major enantiomer.
[c] Number of experiments.

## Acknowledgements

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21. *N*-Acetyl piperidine-2-carboxylic acid ethyl ester **2**: bp = 75°C, 0.1 mbar; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 1.18 (3H, t, $J$ = 7.0 Hz, $CO_2CH_2CH_3$), 1.15–1.34 (2H, m, H-4), 1.35–1.67 (2H, m, H-5), 2.06 (3H, s, $NCOCH_3$), 2.15–2.2 (2H, br d, 13.4 Hz, H-6), 3.2 (1H, dt, $J$ = 2.3 Hz and 12.1 Hz, H-3b), 3.6–3.7 (1H, app d, $J$ = 12.1 Hz, H-3a), 4.12 (2H, q, 7.0 Hz, $CO_2CH_2CH_3$), 5.27 (1H, app d, $J$ = 5.6 Hz, H-2); $^{13}$C NMR (62 MHz, $CDCl_3$): $\delta$ 171.6 (*C*O), 171.2 (*C*O), 60.1 ($CO_2CH_2CH_3$), 50.7 (C-2), 43.1 (C-3), 25.6 ($NCOCH_3$), 24.3 (C-6), 20.6 (C-5), 19.8 (C-4), 13.2 ($CO_2CH_2CH_3$).
22. Chiral HPLC [AD Column; 1 mL min$^{-1}$, *n*-hexane:*i*-PrOH (97:3), $\lambda_{max}$ = 202.9 nm]. (*R*)-(+)-**2**: $t_R$ = 18 min; $[\alpha]_D^{20}$ = +63.3 (*c* 1, THF); $[\alpha]_D^{20}$ = +67 (*c* 5, $CHCl_3$); (*S*)-(−)-**2**: $t_R$ = 20.5 min; $[\alpha]_D^{20}$ = −60 (*c* 5, $CHCl_3$).
23. In 80% yield from (*S*)-(−)- or (*R*)-(+)-*tert*-butoxycarbonyl piperidine-2-carboxylic acid (Aldrich).
24. Cinchona alkaloids, nicotine, (−)-sparteine, (−)-ephedrine, (−)-cytisine, fully reduced (−)-cytisine, (+)-Troger's base were tested.
25. Compound **9** was prepared by demethylation of quinidine using $BBr_3$ in $CH_2Cl_2$; **10** and **11**,[28] **13** and **14**.[19]
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