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TETRAHEDRON: *ASYMMETRY*

An easy access to (*S*)-pyrrolidinones and -pyrrolidines from chiral benzylic malonates

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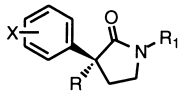
Abstract

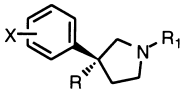
From chiral benzylic malonic acid esters (*R*)-(+)-**4**, available with high enantiomeric excesses by enzymatic hydrolysis (PLE acetonic powder), enantiomerically enriched pyrrolidinones **1** and pyrrolidines **2** were prepared. This rapid and competitive method was developed via enol ether formation, and subsequent one-pot cyclisation, in good overall yield. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

A new series of benzylic quaternary substituted γ-lactams **1** presents a phosphodiesterase type IV (PDE IV) inhibitory activity.[1,2] Their analogues, 3-arylpyrrolidines **2**, exhibit dual histamine H_1/tachykinin NK1 receptor antagonist properties.[3,4] Such molecules have also attracted special attention due to their analgesic effects.[5–7] To our knowledge only a few methods for the synthesis of this class of compounds have been described, moreover rarely in non-racemic form.[5b,8,9]



1



2

In previous papers, we have described the asymmetric construction of quaternary carbons from chiral malonates and their subsequent transformation into sesquiterpenes[10] and alkaloids.[11] Herein, we report that this strategy can be applied to the synthesis of γ-lactams **1** and analogous pyrrolidines **2**, via the enol ether **3**, readily available from chiral malonates **4** (Scheme 1).

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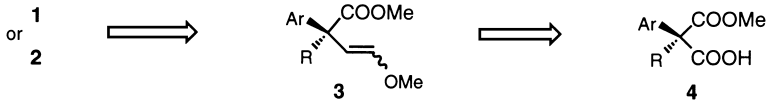
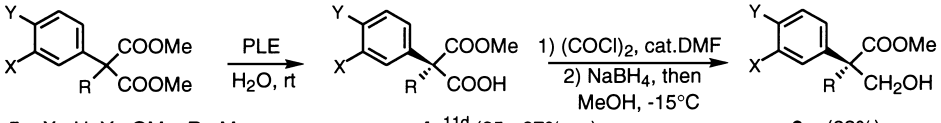


Scheme 1.

2. Results and discussion

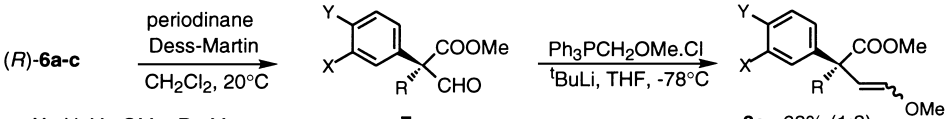
The prochiral dimethyl malonates **5a–c** were prepared in good yields from methyl arylacetate by successive alkylations with methyl iodide (or allyl bromide) and methyl chloroformate. Then these malonates **5a–c** were submitted to enantioselective enzymatic hydrolysis using pig liver esterase (PLE) to provide the acid esters† (*R*)-(+)-**4a–c**[12] in good yields and high enantiomeric excesses.‡ In the case of the acid ester **4a**, the ee was increased to 97% by crystallisation (ether:pentane). Formation of β-hydroxy ester **6a–c** was then achieved using our previously reported procedure (Scheme 2).[10b]



5a: X= H, Y= OMe, R= Me — 92% — **4a**[11d] (85 - 97% ee) — **6a** (83%)
5b: X= Y= OMe, R= allyl — 70% — **4b**[12] (71% ee) — **6b** (94%)
5c: X= OMe, Y=H, R= allyl — 63% — **4c** (86% ee) — **6c** (79%)

Scheme 2.

Thus, reaction of (*R*)-(+)-**4a–c**, with $(COCl)_2$–cat. DMF,[13] followed by reduction of the resulting acyl chlorides ($NaBH_4$, THF then MeOH, 15 equiv.)[14] gave the β-hydroxy esters (*R*)-**6a–c** in excellent yields. These hydroxy esters (*R*)-**6** were then oxidised with the Dess–Martin reagent[15] to lead quantitatively to aldehydes **7a–c**, which under Wittig reaction gave the enol ethers (*S*)-**3a–c**[16] as a mixture of *E–Z* isomers. Good yields were obtained for all these reactions (Scheme 3).



a: X= H, Y= OMe, R= Me — **7a** — **3a** : 68% (1:3)
b: X= Y= OMe, R= allyl — **7b** — **3b** : 70% (1:9)
c: X= OMe, Y=H, R= allyl — **7c** — **3c** : 72% (15:85)

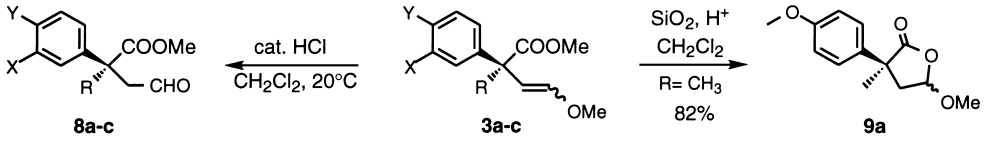
Scheme 3.

The enol ethers **3** were transformed quantitatively, under acidic conditions, into aldehydes **8a–c**. These latter were directly used in the next step without purification. In the case of **3a** we observed that the hydrolysis over silica gel in CH_2Cl_2 in the presence of a catalytic amount of HCl gave the methoxy lactone **9a** (Scheme 4).

The crude aldehydes **8a–c** were transformed by a one-pot procedure (reaction with benzylamine, reduction with $NaBH_3CN$, then heating at 66°C in THF), to a mixture of γ-lactams (*S*)-**1a–c**[17] (50–60% yield) and γ-lactams **10a–c** (10–13% yield) (Scheme 5). These latter were formed by cyclisation of **11a–c** during the heating before reduction with $NaBH_3CN$, since heating of imine **11a**, formed in situ,

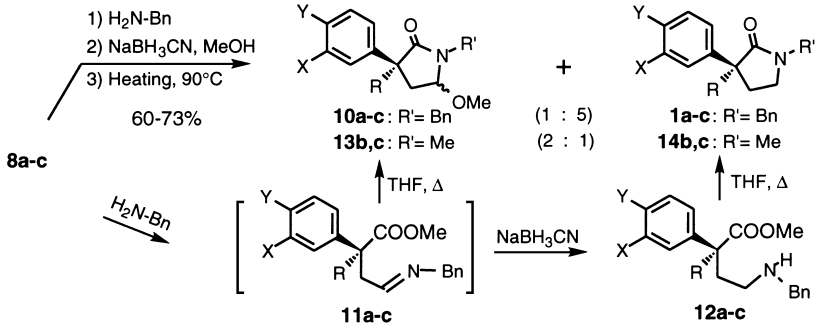
† The absolute configuration of (+)-**4a–c** was assigned to be (*R*) by comparison with aryl malonic acid esters reported previously.[10,11]

‡ The enantiomeric excesses of (*R*)-(+)-**4a–c** were determined from the ^1H NMR spectra of their salts with (*R*)-(+)-1-naphthylethylamine.



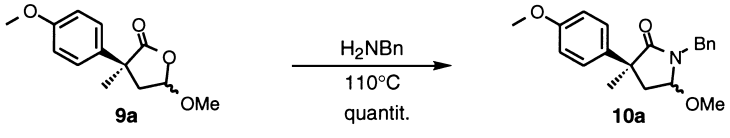
Scheme 4.

with methanol in THF without the reducing reagent gave quantitatively lactam **10a**. Treatment of **10a–c** with an excess of $NaBH_3CN$ (4 equiv.) did not give the expected lactaams (*S*)-**1a–c**. The amines **12a–c** were isolated only as HCl salts. In the case of aldehydes **8b**,**c** we tested this one-pot transformation using methylamine. This led to a 2:1 mixture of the two ɣ-butyrolactams **13b**,**c**:**14b**,**c**, but in lower overall yields (30% for **13b**,**c** and 15% for **14b**,**c**).



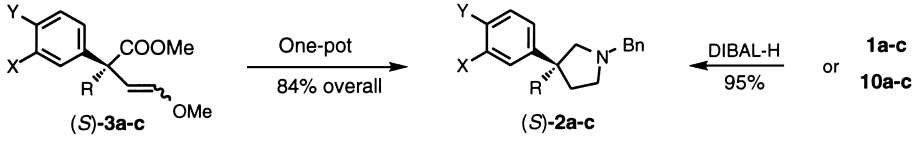
Scheme 5.

On the other hand, the reaction of the lactone **9a** with benzylamine (110°C)[9a] gave quantitatively the lactam **10a** (Scheme 6).



Scheme 6.

The reduction of lactams (*S*)-**1a–c** or **10a–c** by DIBAL-H (−78→20°C) gave the desired pyrrolidines (*S*)-**2a–c**[18] in 95% yields. It is interesting to note that this one-pot procedure starting from enol ethers **3a–c**, by successive hydrolysis (H^+), condensation with amine (H_2NBn), heating (90°C) and then reduction with an excess of DIBAL-H (5 equiv.), gave the expected pyrrolidines (*S*)-**2a–c** in 84% overall yield from **3a–c** (Scheme 7). This procedure thus allows easy and rapid access to a wide variety of pyrrolidines in high yields.



Scheme 7.

In conclusion, from readily available chiral malonates **4** (ee >80%), we have developed, via enol ether formation and subsequent one-pot cyclisation (H^+, H_2NR, Δ, then DIBAL-H), a rapid and competitive method to the pyrrolidines (*S*)-**2** (three steps, 57% overall yield). These compounds constitute potential precursors to a wide variety of analgesic pyrrolidines. Synthetic applications of this method to total synthesis of analgesic pyrrolidines are currently under way.

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12. Selected data: Compound **4b**: $[\alpha]_D^{20}$=+16.5 (*c* 1, $CHCl_3$); (ee=71%); IR (neat): 1750 (C=O), 1730 ($C{=}O_{ester}$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.00–6.79 (m, 3H), 5.90–5.65 (m, 1H), 5.30–5.10 (m, 2H), 3.89 (s, 6H), 3.83 (s, 3H, Me_{ester}), 3.18 [ABX system, $\Delta\nu_{AB}$=47.8 Hz, 3.30 (A part, dd, J_{AB}=13.6 Hz, J_{AX}=8.8 Hz, 1H), 3.06 (B part, dd, J_{AB}=13.6 Hz, J_{BX}=8.1 Hz, 1H)]; ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=173.4 (C_1), 173.3 (C_3) [6 arom C: 148.9, 148.7, 128.5, 119.6, 110.8, 110.7], 132.3 (d), 119.5 (t), 61.5 (C_2), 55.9, 55.8, 53.2, 39.6.
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16. Selected spectroscopic data: Compound **3a** *trans*: $[\alpha]_D^{20}$=−27.5 (*c* 1, $CHCl_3$); (ee=97%); IR (neat): 1720 (C=O), 1640 (C=C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.28–7.18 (m, 2H), 6.92–6.80 (m, 2H), 6.34 (d, *J*=13.5 Hz, 1H), 5.83 (d, *J*=13.5 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.60 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=175.9 (C_1) [6 arom C: 158.2, 136.5, 127.2 (2C), 113.5 (2C)], 148.4 (C_3), 107.4 (C_4), 56.0, 55.0, 52.2, 49.8 (C_2), 24.8; HRMS calcd for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1205. Compound **3b** *trans*: $[\alpha]_D^{20}$=−7 (*c* 1, $CHCl_3$); (ee=71%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=6.95–6.72 (m, 3H), 6.20 (d, *J*=13.5 Hz, 1H), 5.80–5.53 (m, 1H), 5.27 (d, *J*=13.5 Hz, 1H), 5.15–4.98 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.68 (s, 3H), 3.55 (s, 3H), 3.10–2.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=175.0 (C_1), 149.8 (C_3) [6 arom C: 148.4, 147.8, 134.6, 118.1, 110.6, 110.5], 134.0 (d), 119.1 (t), 105.7 (C_4), 56.0, 55.8, 55.7, 53.8 (C_2), 52.2, 42.7. Compound **3c** *trans*: $[\alpha]_D^{20}$=−12.5 (*c* 1, $CHCl_3$); (ee=86%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.35–7.15 (m, 1H), 6.95–6.73 (m, 3H), 6.22 (d, *J*=13.7 Hz, 1H), 5.80–5.50 (m, 1H), 5.26 (d, *J*=13.7 Hz, 1H), 5.20–4.95 (m, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 3.59 (s, 3H), 2.88 [AB system, $\Delta\nu_{AB}$=34.2 Hz, 2.94 (A part, dd, J_{AB}=14.7 Hz, *J*=7.4 Hz, 1H), 2.82 (B part, dd, J_{AB}=14.7 Hz, *J*=7.4 Hz, 1H)]; ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=174.8 (C_1) [6 arom C: 159.3, 143.9, 129.1, 119.4, 113.5, 111.6], 149.8 (d), 133.9 (C_3), 118.1 (t), 105.3 (C_4), 56.0 (C_2), 55.1, 54.1, 52.2, 42.5.
17. Selected spectroscopic data: Compound **1a**: $[\alpha]_D^{20}$=−8 (*c* 1, $CHCl_3$); (ee=97%); IR (neat): 1690 (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.40–7.15 (m, 7H), 6.95–6.80 (m, 2H), 4.53 (s, $2H_{benzyl}$), 3.80 (s, 3H), 3.25–3.15 (dd, J_1=J_2=7.4 Hz, 2H), 2.48–2.30 (m, 1H), 2.20–2.02 (m, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 52.29 MHz): δ=177.5 (C_2) [12 arom C: 158.2, 136.5, 135.8, 128.6 (2C), 128.0 (2C), 127.5, 127.1 (2C), 113.7], 55.2, 48.0 (C_3), 46.9 (t), 43.3 (C_5), 35.2 (C_4), 25.2. Compound **1b**: $[\alpha]_D^{20}$=−8.5 (*c* 1, $CHCl_3$); (ee=71%); IR (neat): 1690 (C=O); ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.40–7.15 (m, 6H), 7.10–6.75 (m, 2H), 5.76–5.55 (m, 1H), 5.16–5.00 (m, 2H), 4.49 (s, 2H), 3.87 (s, 6H), 3.22–3.10 (m, 2H), 2.65 (d, *J*=7.8 Hz, 2H), 2.45–2.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=176.1 (C_2) [12 arom C: 148.8, 147.8, 136.5, 134.3, 129.1, 128.6 (2C), 128.0 (2C), 127.5, 110.7, 110.2], 134.2 (CH=), 118.4 (CH_2=), 55.8 (2C), 51.5 (C_3), 46.9, 43.6 (C_5), 43.5, 30.3 (C_4). Compound **1c**: $[\alpha]_D^{20}$=−21 (*c* 1, $CHCl_3$); (ee=86%); IR (neat): 3080, 1690 (C=O), 1610, 1590; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.38–7.12 (m, 6H), 7.12–7.00 (m, 2H), 6.80 (dd, J_1=7.9 Hz, J_2=2.6 Hz, $1H_b$), 5.79–5.59 (m, 1H), 5.18–5.02 (m, 2H), 4.56 (like AB system, d, *J*=14.7 Hz, $1H_{benzyl}$), 4.47 (d, *J*=14.7 Hz, $1H_{benzyl}$), 3.81 (s, 3H), 3.24–3.08 (m, 2H, CH_2-N), 2.70 (br d, *J*=7.4 Hz, 2H, allyl), 2.45–2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=175.8 (C_2) [12

arom C: 159.6, 143.6, 136.4, 129.3, 128.6 (2C), 128.0 (2C), 127.5, 118.8, 112.6, 112.0], 134.1 (d), 118.5 (t), 55.2, 52.0 (C_3), 46.9, 43.5 (C_5), 43.3, 30.4 (C_4); Anal. calcd for $C_{21}H_{23}N_1O_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.07; H, 7.28; N, 4.31.

18. Selected data: Compound **2**: $[\alpha]_D^{20}=-59.6$ (*c* 1, $CHCl_3$); (ee=97%); ^1H NMR ($CDCl_3$, 200 MHz): δ=7.45–7.15 (m, 7H), 6.90–6.80 (m, 2H), 3.82 (s, 3H), 3.75 (s, $2H_{benzyl}$), 2.84 (s, 2H), 3.05–2.90 (m, 1H), 2.80–2.60 (m, 1H), 2.30–2.15 (m, 1H), 2.10–1.90 (m, 1H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 52.29 MHz): δ=[12 arom C: 157.5, 142.3, 138.7, 128.8 (2C), 128.2 (2C), 127.0, 126.8 (2C), 113.5 (2C)], 67.1, 60.4 (C_2), 55.2, 53.6 (C_5), 45.0 (C_3), 39.7 (C_4), 30.5. Compound **2b**: $[\alpha]_D^{20}=-21$ (*c* 1, $CHCl_3$); (ee=71%); ^1H NMR ($CDCl_3$, 250 MHz): δ=7.45–7.15 (m, 6H), 7.00–6.68 (m, 2H), 5.58–5.38 (m, 1H), 5.07–4.88 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.67 (m, $2H_{benzyl}$), 2.79 [AB system, $\Delta\nu_{AB}$=59.2 Hz, J_{AB}=9.2 Hz, 2H), 2.98–2.36 (m, 2H)], 2.59–2.50 (m, 2H), 2.21–2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.86 MHz): δ=[12 arom C: 148.3, 146.8, 140.7, 139.6, 128.3 (2C), 128.0 (2C), 126.6, 118.5, 110.4, 110.35], 135.4 (CH=), 117.0 (CH_2=), 64.2, 60.2 (C_2), 55.7 (2C), 53.5 (C_5), 48.8 (C_3), 47.2, 37.3 (C_4). Compound **2c**: $[\alpha]_D^{20}=-40$ (*c* 1, $CHCl_3$); (ee=86%); ^1H NMR ($CDCl_3$, 200 MHz): δ=7.42–7.15 (m, 6H), 6.85–6.68 (m, 3H), 5.60–5.35 (m, 1H), 5.05–4.87 (m, 2H), 3.80 (s, 3H), 3.67 [AB system, $\Delta\nu_{AB}$=21.1 Hz, 3.72 (A part, d, J_{AB}=12.6 Hz, $1H_{benzyl}$), 3.62 (B part, d, J_{AB}=12.6 Hz, $1H_{benzyl}$)], 3.04–2.87 (m, 1H), 2.81 [A′B′ system, $\Delta\nu_{A'B'}$=60.2 Hz, 2.96 (d, $J_{A'B'}$=9.0 Hz, 1H), 2.65 (d, $J_{A'B'}$=9.0 Hz, 1H)], 2.63–2.45 (m, 1H), 2.55 (br d, *J*=8.0 Hz, $2H_{allyl}$), 2.24–1.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 52.29 MHz): δ=[12 arom C: 159.3, 149.8, 139.6, 128.8, 128.5 (2C), 128.2 (2C), 126.8, 119.3, 113.2, 110.4], 135.4 (d), 117.1 (t), 64.0, 60.4 (C_2), 55.1, 53.4 (C_5), 49.4 (C_3), 47.3, 36.9 (C_4); HRMS calcd for $C_{21}H_{25}N_1O_1$: 307.1936. Found: 307.1927.