# An Asymmetric Synthesis of Novel Aminocyclopropyl Carboxylic Acids (ACC)

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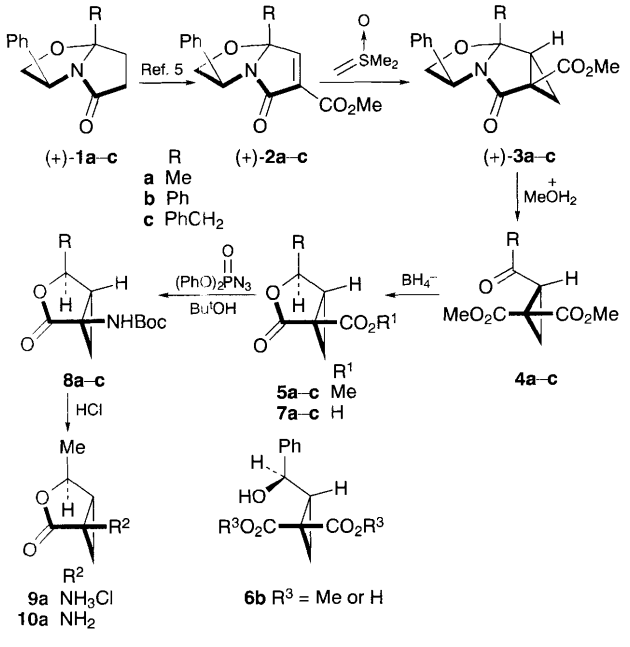
Cyclopropanation of chiral bicyclic lactams **2** followed by removal of the chiral auxiliary and a Curtius rearrangement leads to the title compounds in >99% e.e.

The research activity associated with reaching chiral, non-racemic cyclopropanes, particularly as isosteric substitutes of peptides, is becoming a major focus for many laboratories.[1,2] As part of a general programme to demonstrate the versatility of chiral bicyclic lactams **1** to reach a wide variety of enantiomerically pure substances[1a,3] we felt that a route to chiral, non-racemic ACC's would be feasible. Herein we describe a relatively efficient route to trisubstituted cyclopropane α-amino acids **8,9** which also contain another stereocentre to impart further topographical properties to the molecule.

By utilizing as starting materials the (*R*)-phenylglycinol-derived lactams **1a–c**[4] readily prepared in optically pure form and in high yield, three members of the cyclopropane amino lactones **8** were efficiently produced by the sequence shown in Scheme 1. Transformation of (+)-**1** to the unsaturated esters (+)-**2** was accomplished by a procedure using methyl chloroformate in place of benzyl chloroformate as previously described.[5]† These unsaturated chiral lactams now served as starting materials for the ACC syntheses which follows. Addition of trimethyl sulfoxonium ylide[6] to the three unsaturated lactams **2** gave the cyclopropyl derivatives **3** in excellent diastereoselectivity and in 68–83% yields.‡ Again, as seen in previous examples involving cyclopropanations, the angular alkyl or aryl groups in **2** cause addition of the sulfoxonium ylide to enter from the *endo* face.[1]§ Hydrolysis of the cyclopropane adducts **3** with methanolic sulfuric acid (5 : 1, v/v) for 3–5 days at reflux gave the cyclopropane keto esters **4** in 64–73% yields. Reduction of the latter using sodium borohydride (methanol, −20 °C) proceeded with high stereoselectivity (>30 : 1) affording the cyclopropyl lactones **5a–c** in 77–85% yields. In the case of the phenyl ketone, **4b** (R = Ph), reduction gave a *ca.* 1 : 1 mixture of lactone **5b** and hydroxyester **6b**. However, saponification of the esters **5,6** (2 mol $dm^{-3}$ NaOH) followed by acidification with hydrochloric acid, concentration *in vacuo*, and extraction with $CHCl_3$, gave the pure cyclized lactone carboxylic acids **7a–c**.¶ The carboxy group was transformed to amino group, using the modified Curtius reaction,[7] which employs diphenylphosphoryl azide-*tert*-butanol. This proceeded smoothly in all three cases, affording the *tert*-Boc derivatives **8a–c** in 62–82% yields.‖ The NMR spectra of the *tert*-Boc derivatives were, at first, rather complicated due to hindered rotation about the C–N bond; however, raising the temperature to 50 °C while recording the spectra gave sharp signals which were consistent with the structures shown. Removal of the *tert*-Boc in **8a**, **8b** took place without complication, using 1 mol $dm^{-3}$ HCl in ethyl acetate (1 : 1, 24 h) to produce the amino lactone hydrochloride **9a** along with some hydroxyamino acid. For **9a** treatment with 2 mol $dm^{-3}$ NaOH, acidification with 2 mol $dm^{-3}$ HCl, then passing it through a Dowex-50 resin gave 79% of the free amino lactone, **10a**, mp 95–96 °C ($^1$H NMR, 250 MHz, $D_2O$), δ 0.67 (br t, 1), 0.75 (br d, 4), 3.41 (br t, 1).**




Scheme 1

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## Footnotes

† *Physical data for* **2a–c**: **2a**; mp 88–91 °C; $[\alpha]_D$ +117 (*c* 1.2, $CHCl_3$); IR (film) 1756, 1732, 1633 $cm^{-1}$; NMR ($CDCl_3$) δ 1.54 (s, 3), 3.87 (s, 3), 4.34 (m, 1), 4.66 (t, 1), 5.16 (t, 1), 7.3 (m, 5). **2b**; foam; IR (film) 1756, 1731 $cm^{-1}$; NMR ($CDCl_3$) δ 3.78 (s, 3), 4.08 (t, 1), 4.80 (m, 1) 5.10 (t, 1), 7.12–7.52 (m, 2), 7.71 (s, 1). **2c**; foam; $[\alpha]_D$ +161 (*c* 2 $CH_2Cl_2$); IR (film) 1757, 1732 $cm^{-1}$; NMR ($CDCl_3$) δ 2.90 (d, 1), 3.25 (d, 1), 3.84 (s, 3), 4.57 (m, 1), 4.75 (m, 1), 5.25 (t, 1) 7.1–7.4 (m, 10), 7.68 (s, 1).

‡ *Physical data for* **3a–c**: **3a**; mp 125 °C; $[\alpha]_D$ +889 (*c* 1, $CHCl_3$). **3b**; mp 118 °C; $[\alpha]_D$ +672 (*c* 1.4, $CHCl_3$). **3c**; mp 124 °C; $[\alpha]_D$ +128 (*c* 2, $CH_2Cl_2$).

§ At one time we invoked the Cieplek effect to account for the *endo* addition to **2** (A. I. Meyers, J. Romine and S. A. Fleming, *J. Am. Chem. Soc.*, 1988, **110**, 7245). However, this rationale is currently in doubt.

¶ *Physical data for* **7a–c**: **7a**; mp 117 °C; $[\alpha]_D$ −662 (*c* 1.0, $CHCl_3$); IR (film) 2979, 2800–2500, 1769 $cm^{-1}$; NMR ($CDCl_3$) 1.47 (d, 3), 1.55 (t, 1), 2.09 (dd, 1), 2.75 (dd, 1), 4.55 (q, 1), 10.60 (br s, 1). **7b**; mp 129 °C; $[\alpha]_D$ −920° (*c* 1, $CHCl_3$); IR (KBr) 3528, 3220–2420, 1774, 1724 $cm^{-1}$; NMR ($CDCl_3$) δ 1.73 (s, 1), 2.22 (s, 1), 3.00 (s, 1), 5.39 (s, 1), 7.26–7.43 (m, 5). **7c**; mp 96–97 °C; $[\alpha]_D$ −107.3 (*c* 2, MeOH); IR (film) 3062, 1774, 1732 $cm^{-1}$; NMR ($CDCl_3$) 1.48 (dd, 1), 2.00 (dd, 1), 2.77 (dd, 1), 3.06 (d, 2) 4.69 (t, 1), 7.38 (m, 5). All of the above gave satisfactory combustion analysis.

‖ *Physical data for* **8a–c**: **8a**; mp 102–103 °C; $[\alpha]_D$ −259 (*c* 3, $CHCl_3$); IR (film) 3359, 1777, 1716 $cm^{-1}$; NMR ($CDCl_3$) 1.18 (t, 1), 1.46 (s, 9), 1.50 (t, 1), 1.51 (d, 3), 2.22 (br t, 1), 4.37 (br q, 1), 5.35 (br s, 1). **8b**; mp 149 °C; $[\alpha]_D$ −247 (*c* 2.5, $CHCl_3$); IR (KBr) 3376, 1766, 1716 $cm^{-1}$; NMR ($CDCl_3$) δ 1.38 (t, 1), 1.43 (br s, 9), 1.64 (dd, 1), 2.54 (dd, 1), 5.16 (s, 1) 5.38 (s, 1), 7.36–7.45 (m, 3), 7.63 (br s, 2). **8c**; mp 131–133 °C; $[\alpha]_D$ −237 (*c* 2.1, $CH_2Cl_2$); IR (film) 3032, 1776, 1714 $cm^{-1}$; NMR

($CDCl_3$) δ 1.13 (t, 1) 1.43 (m, 1), 1.45 (s, 9) 2.27 (dd, 1), 3.23 (m, 2), 4.39 (t, 1), 5.24 (br s, 1), 7.29 (m, 5).
** All of the above gave satisfactory combustion analysis.

## References


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