# Rapid diastereocontrolled synthesis of 2,2,5-trisubstituted pyrrolidines†

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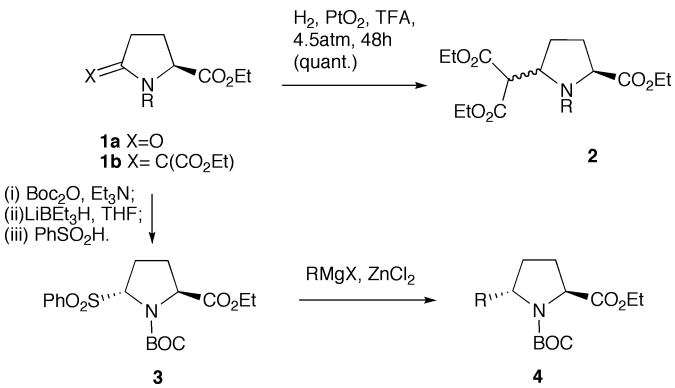
*Received 9th July 2008, Accepted 31st July 2008*
*First published as an Advance Article on the web 5th September 2008*
**DOI: 10.1039/b811642c**

**2,2,5-Trisubstituted pyrrolidines are available from allylic pyroglutamates by Ireland–Claisen ester rearrangement followed by Eschenmoser sulfide contraction and reduction in a highly diastereoselective and efficient sequence. Some of the products from this sequence exhibit activity against *S. aureus*, but are much less active against *E. coli*.**

We recently reported that 2,5-disubstituted pyrrolidines were available from pyroglutamic acid **1a**, by application of an Eschenmoser sulfide contraction[1] to give an enamine intermediate **1b** followed by reduction (Scheme 1); depending on the nature of the R group, either *cis*- or *trans*-2,5-disubstituted pyrrolidines **2** could be accessed.[2,3] We have also shown that *trans*-2,5-disubstituted pyrrolidines **4** are readily available by Grignard displacement of the sulfone **3**,[4] but interestingly using both of these methods, further manipulation of either the C-2 or C-6 positions *via* enolate formation proved to be problematic, probably on steric grounds. The development of stereoselective approaches to functionalised pyrrolidines is a topic of considerable interest in the context of natural product and small molecule synthesis, and medicinal chemistry.[5–7] Of interest to us were the recent reports of the application of Ireland–Claisen ester rearrangements on furyl[8,9] and pyrrolidinyl[10,11] substrates, and we wondered if this approach might provide rapid access to 2,2,5-trisubstituted pyrrolidine derivatives from pyroglutamic acid. Such a substitution pattern occurs in a range of natural products, including brevianamide C,[12] fusarin,[6] azaspirene,[13,14] lepadiformine,[15] and kaitocephalin.[16] We report here the successful application of this strategy for the preparation of 2,2,5-trisubstituted pyrrolidines using a short and high yielding sequence, which is highly diastereoselective.

Esterification of pyroglutamic acid **5** under acidic or DCC conditions conveniently gave the allylic esters **6a–c** in excellent yield (Scheme 2), and rearrangement using Kazmaier's conditions[11] efficiently gave the rearranged products **7a–c** again in high yield; this reaction was highly diastereoselective, giving **7a**, **7b** and **7c** as single diastereomers. Interestingly, the Claisen rearrangement only occurred in the presence of the quinine ligand, but in its absence, unreacted starting material was recovered from the reaction.[17] The relative stereochemistry of the new stereocentres of **7b** and **7c** was established by single crystal X-ray analysis (Fig. 1, ESI†)[18] and found to be *syn*- in both cases, consistent with a chair transition state in which the phenyl and methyl substituents respectively occupy an equatorial position,[19] an outcome which has been reported in a related system.[20] Esterification of the acid with acidic




**Scheme 1**

methanol gave the methyl esters **8a–c** in high yield, and conversion of these lactams **8a–c** to thiolactams **9a–c** with Lawesson's reagent and reaction with diethyl bromomalonate–sodium bicarbonate to effect an Eschenmoser sulfide contraction[1] gave enamines **10a–c** in excellent yield, which could be reduced to the 2,2,5-trisubstituted pyrrolidine system using sodium cyanoborohydride or sodium borohydride–ruthenium trichloride giving vinyl lactams **11a–c** or propyl lactam **12** respectively in good yield. Pyrrolidines **11b** and **11c** were obtained as single diastereomers, but **11a** as a 4 : 1 ratio of *cis*-/*trans*- diastereomers. Noteworthy is the reduction of the vinyl double bond in the latter case;[21] this borohydride-type reduction of enamines compares very favourably with the diastereoselectivity of our earlier approaches[2,3,22] but is significantly superior in terms

**Table 1** Bioactivity of lactams against *S. aureus* and *E. coli* (hole plate bioassay) at 4 mg ml$^{-1}$

| | Activity/mm[a] (relative potency%[b]) | |
|---|---|---|
| Substrate | *S. aureus* | *E. coli* |
| **7a** | Inactive | 15 (0.024) |
| **7b** | Inactive | 16 (0.031) |
| **7c** | Inactive | 16 (0.042) |
| **8a** | Inactive | Inactive |
| **8b** | Inactive | 14 (0.024) |
| **8c** | Inactive | 15 (0.037) |
| **9a** | 14 (3.8) | Inactive |
| **9b** | Inactive | 14 (0.026) |
| **9c** | 15 (5.9) | 16 (0.047) |
| **10a** | 16 (7.9) | 13 (0.033) |
| **10b** | 16 (8.2) | 15 (0.049) |
| **10c** | 15 (8.7) | 14 (0.051) |
| **11a** | 14 (6.3) | 12 (0.029) |
| **11b** | 14 (6.6) | 12 (0.030) |
| **11c** | 12 (5.9) | 14 (0.050) |

[a] Zone size (mm) measured from hole plate bioassay at 4 mg ml$^{-1}$ (7 : 3 DMSO–$H_2O$).[29] [b] Expressed as zone size per mg ml$^{-1}$, relative to cephalosporin C standard.

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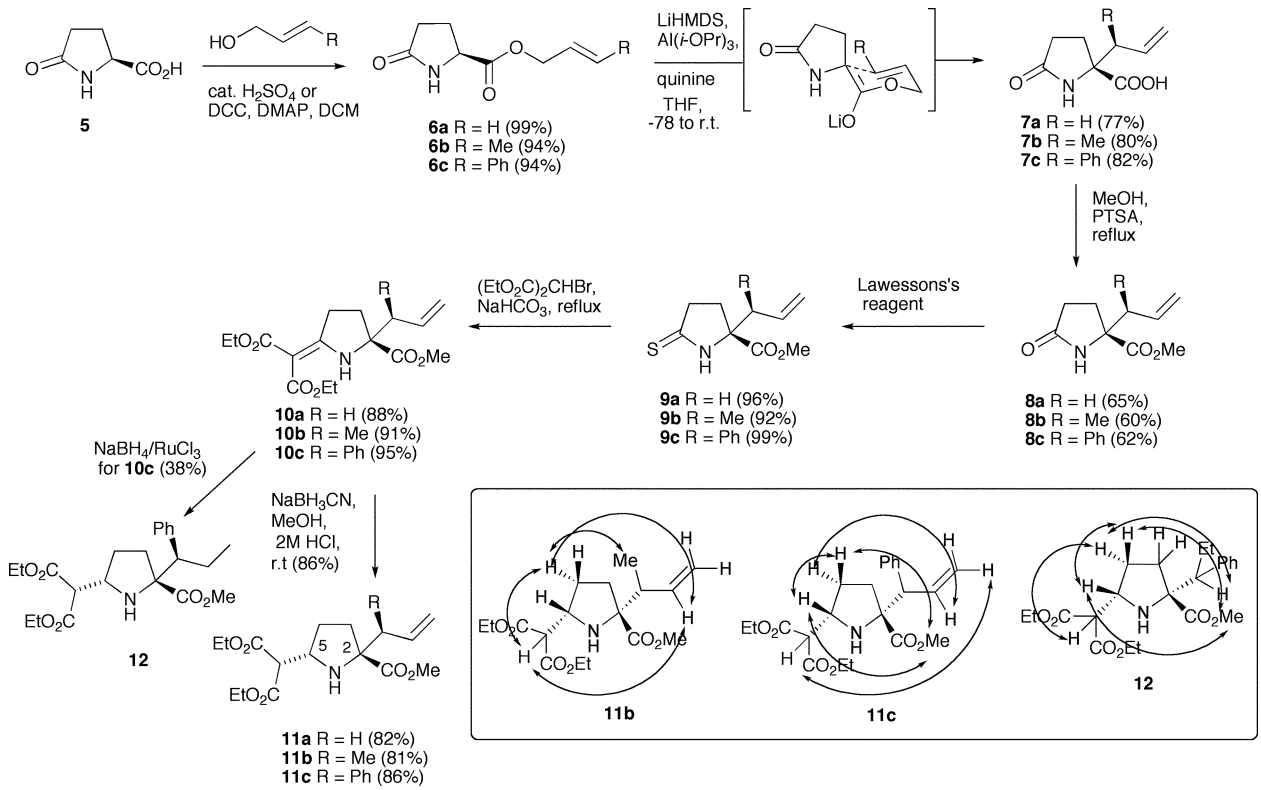
† Electronic supplementary information (ESI) available: Thermal ellipsoid plots for compounds **7a–c**. CCDC reference numbers 689197–689199. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b811642c




**Scheme 2**

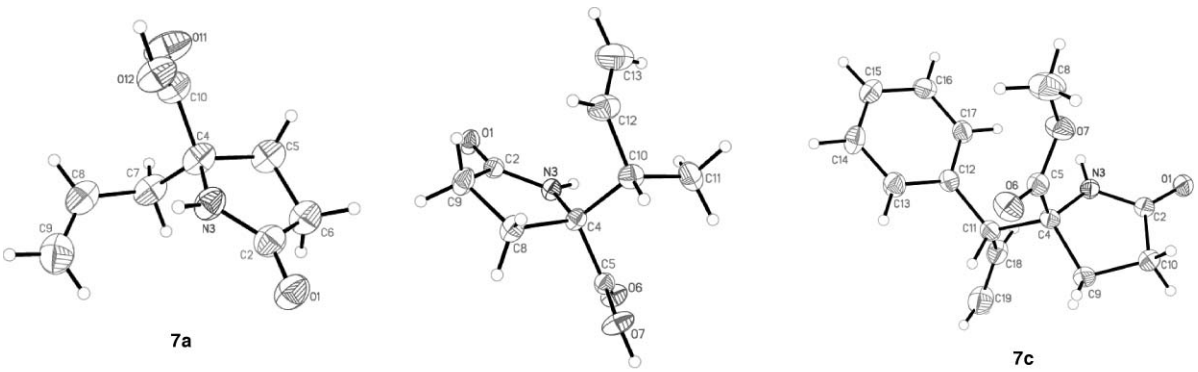



**Fig. 1** Thermal ellipsoid plots (ORTEP-3[4]) at 40% probability level for compounds **7a–c**.

of experimental execution, avoiding forcing reductive conditions.[23] The establishment of 2,5-relative stereochemistry as that arising by entry of hydride *syn*- to the C-2 ester, probably as a result of steric control, was confirmed by careful nOe analysis (Scheme 2), which showed that H-5 (multiplet at $\delta$3.83) gave a small but observable nOe to the C-2 methyl ester as did the facially co-located H-4. H-6 (doublet at $\delta$3.35) also gave a weak nOe to the terminal vinylic hydrogens, as did pro*R* H-4 to the remaining vinylic hydrogen. Enhancements over this distance were suggestive of a well-defined conformation in which the bulky C-2 and C-5 substituents adopted a pseudodiequatorial conformation and the smaller ethoxycarbonyl group a pseudoaxial position, with the long chain allyl group folded over the molecule; conformations in simpler α-substituted prolines have recently been determined.[24]

In view of the known antibacterial activity of pyrrolidine- and piperidine-containing natural products (such as monomorine, anisomycin and solenopsine)[25–27] and their importance in synthetic antibiotics,[28] bioassays of compounds against *S. aureus* and *E. coli* (hole plate method) at 4 mg ml$^{-1}$ were made (Table 1); this showed that compounds **9**, **10** and **11** were active against both organisms. Although only giving weak antibacterial activity against *E. coli*, these compounds are much more active against *S. aureus*, and this structurally novel template offers a platform suitable for further optimisation of this starting activity.

We have shown that rapid diastereoselective elaboration of pyroglutamic acid to 2,2,5-trisubstituted pyrrolidines is possible in a short, reliable sequence and in good overall yield, and that these products exhibit antibacterial activity against *S. aureus* and *E. coli.*

## Acknowledgements

NC gratefully acknowledges receipt of a National Overseas Scholarship from the Indian Ministry of Social Justice and Empowerment (GF6-352746), and MGM receipt of EPSRC grant GR/T20380/01. We gratefully acknowledge the assistance of Dr A. Knight with the X-ray analyses and the use of the EPSRC Chemical Database Service at Daresbury.[30]

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18 Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 689197, 689198 and 689199. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.
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23 *Reduction of enamines by sodium cyanoborohydride:* typical method. To a solution of enamine (100 mg, 0.25 mmol) in methanol, sodium cyanoborohydride (61.8 mg, 1.0 mmol) and acetic acid were added. After the reaction mixture was stirred for 36 h, methylene chloride (20 ml) was added and the solution was washed with 10% $NaHCO_3$, the aqueous layer was extracted with methylene chloride and the combined organic phase dried with $MgSO_4$, evaporated under reduced pressure, and the crude material purified by flashed chromatography, (ethyl acetate–petroleum ether 1 : 7). **11a**: $R_f = 0.61$ (30% EtOAc : 70% petrol); $[\alpha]_D^{20.7} = -7.82$ ($c = 1.15$, $CHCl_3$), $\nu_{max}/cm^{-1}$ (neat) 3215(bs), 2979(s), 1731(s), 1200(s); $\delta_H$($CDCl_3$, 400 MHz), 1.25–1.26 (6H, t, $J = 7.1$, $2 \times OCH_2CH_3$), 1.64 (1H, m, C4*H*), 1.82 (1H, m, C4*H′*), 2.13 (1H, m, C3*H*), 2.30 (1H, m, C3*H′*), 2.45 (2H, m, $CH_2CH{=}CH_2$), 3.30 (1H, d, $J = 9.0$, $CH(COOEt)_2$), 3.69 (3H, s, $OCH_3$), 3.79 (1H, m, C5*H*), 4.16–4.20 (4H, q, $J = 7.1$, $2 \times OCH_2CH_3$), 5.04 (2H, m, $CH_2$=CH), 5.70 (1H, m, $CH{=}CH_2$); $\delta_C$(400, $CDCl_3$), 13.6($2 \times OCH_2CH_3$), 27.9 ($C4H_2$), 32.9 ($C3H_2$), 43.9 ($CH_2CH{=}CH_2$), 51.7 ($OCH_3$), 56.1 (*C*5H), 58.5 ($CH(CO_2Et)_2$), 60.8 ($2 \times OCH_2CH_3$), 68.7 (C2), 117.4 ($CH_2$=CH), 133.2 ($CH{=}CH_2$), 167.6–167.9 ($2 \times CO_2Et$), 176.5 ($CO_2Me$); *m/z* ($ES^+$) 328 (M + $H^+$, 100%), 350 (M + $Na^+$, 90%); HRMS (M + $H^+$) accurate mass 328.1751, $C_{16}H_{26}NO_6$ requires 328.1755. **11b**: $R_f = 0.67$ (30% EtOAc : 70% petrol); $[\alpha]_D^{20.7} = -8.8$ ($c = 1.25$, $CHCl_3$); $\nu_{max}/cm^{-1}$(neat) 3215(bs), 2979(s), 1731(s), 1447(s), 1369(bs), 1251(s), 1200(s), 1036(s), 917(s), 862(s); $\delta_H$($CDCl_3$, 400 MHz), 0.84 (3H, d, $CHCH_3$), 1.25 (6H, t, $J = 7.1$, $2 \times OCH_2CH_3$), 1.54 (1H, m, C4*H*), 1.76 (1H, m, C4*H′*), 1.86 (1H, m, C3*H*), 1.99 (1H, m, C3*H′*), 2.45 (1H, m, $CHCH_3$), 2.89 (1H, bs, NH), 3.25 (1H, d, $J = 8.9$, $CH(COOEt)_2$), 3.70 (3H, s, $OCH_3$), 3.76 (1H, m, C5*H*), 4.17 (4H, q, $J = 7.1$, $2 \times OCH_2CH_3$), 5.02 (2H, m, $CH_2$=CH), 5.72 (1H, m, $CH{=}CH_2$); $\delta_C$ (400, $CDCl_3$), 14.3 ($2 \times OCH_2CH_3$), 16.4 ($CH_3CH$), 28.7 ($C4H_2$), 32.4 ($C3H_2$), 45.8 ($CH_3CH$), 52.4 ($OCH_3$), 56.8 (*C*5H), 59 ($CH(CO_2Et)_2$), 61.5 ($2 \times OCH_2CH_3$), 72.1 (C2), 115.9 ($CH_2$=CH), 140.2 ($CH{=}CH_2$), 168.4–168.7 ($2 \times CO_2Et$), 177.7 ($CO_2Me$); *m/z* ($ES^+$) 342 (M + $H^+$, 100%), 340 (M – $H^+$, 85%), 364 (M + $Na^+$, 97%); HRMS (M + $H^+$) accurate mass 342.1898, $C_{17}H_{28}NO_6$ requires 342.1911. **11c**: $R_f = 0.42$ (20% EtOAc : 80% petrol), $[\alpha]_D^{20.7} = -13.36$ ($c = 2.2$, $CHCl_3$); $\nu_{max}/cm^{-1}$(neat) 3215(bs), 2981(s), 1732(s), 1369(s), 1200(s), 1030(s), 772(s); $\delta_H$ ($CDCl_3$, 400 MHz), 1.26 (3H, t, $J = 7.1$, $OCH_2CH_3$), 1.32 (3H, t, $J = 7.1$, $OCH_2CH_3$), 1.64 (1H, m, C4*H*), 1.82 (1H, m, C4*H′*), 2.09 (2H, m, $C3H_2$), 2.8 (1H, bs, N*H*), 3.35 (1H, d, $J = 9.1$, $CH(CO_2Et)_2$), 3.53 (3H, s, $OCH_3$), 3.61 (1H, d, $CHPh$), 3.83 (1H, m, C5*H*), 4.19 (2H, q, $J = 7.1$, $OCH_2CH_3$), 4.28 (2H, q, $J = 7.1$, $OCH_2CH_3$), 5.17 (2H, m, $CH_2$=CH), 6.32 (1H, m, $CH{=}CH_2$), 7.15–7.25 (5H, m, Ar*H*); $\delta_C$(400, $CDCl_3$), 15.5 ($2 \times OCH_2CH_3$), 30 ($C4H_2$), 34.3 ($C3H_2$), 53.4 ($OCH_3$), 57.9 ($CHPh$), 58.3 (*C*5H), 60.3 ($CH(CO_2Et)_2$), 62.6 ($2 \times OCH_2CH_3$), 74.2 (*C*2), 118.9 ($CH_2$=CH), 128–129.5 (Ar*C*), 138.9 (ArC), 142.4 ($CH{=}CH_2$),169.5–169.8 ($2 \times CO_2Et$), 178 ($CO_2Me$), *m/z* ($ES^+$) 404 (M + $H^+$, 100%), 402 (M – $H^+$, 100%), 426 (M + $Na^+$, 85%): HRMS (M + $H^+$) accurate mass 426.1887, $C_{22}H_{29}NNaO_6$ requires 426.1995.
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