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Stereocontrolled spirocyclic bislactams derived from pyroglutamic acid

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Abstract—The synthesis of rigid spirocyclic bislactams derived from pyroglutamic acid has been established.

Spirocyclic lactams have recently been of considerable interest, because of their occurrence in structurally complex and highly active natural products,[1] for example, in the spiropyrrolidinyloxindole alkaloids,[2,3] perophoramidine,[4] amathaspiramides[5] and azaspirene.[6] They have also come to prevalence in their use in conformationally controlled templates, scaffolds and bioisosteres as a result of their well-defined molecular architecture.[7] In particular, spiro-bis-δ-lactams based on the pyroglutamate[8] and proline[9] templates have recently been prepared for their potential as β-turn mimetics. The rapid asymmetric synthesis of spiro-2-pyrrolidin-5-ones has recently been reported,[10,11] and related spiro compounds have attracted considerable recently interest due to their resemblance to natural products.[12]

We have examined spirocyclic lactam systems derived from the bicyclic lactam system **2**, readily prepared using our published methodology.[13] Alkylation of ester **2** with several bromonitriles/NaH in THF gave products **3**, **4a**, **4b** and **4c** in yields of 65%, 68%, 42% and 30%, respectively (Scheme 1).[14] Lactam **3** was obtained as a 2:1 diastereomeric but inseparable mixture, for which the stereochemistry of the major isomer was assigned as 7*R*, arising by *exo*-attack of the electrophile; this assignment was made by comparison of the chemical shift difference of the C(6)H protons (Δδ 0.2) with the observed differences in previously reported compounds (bicyclic lactams formed via *exo*-alkylation reliably have a chemical shift difference for the C(6)H protons of Δδ 0.2, but those from *endo*-alkylation show a difference of Δδ 0.8).[15,13] Lactam **4a** was similarly assigned the 7*R* stereochemistry (Δδ 0.3), but was epimeric at C-1′ as shown by the doubling of the signals of C(1′)Me in the ^{13}C NMR spectrum; this analysis was confirmed by NOE results (Fig. 1). Lactam **4b** was obtained as a single crystalline diastereomer, and X-ray analysis allowed the unequivocal assignment as (7*R*,1′*S*); in this case, the chemical shift difference of the C(6)H protons (Δδ 0.3) was consistent with the protocol used for the other compounds for their stereochemical assignment. Lactam **4c** was obtained as a 1:1 mixture of *exo*- and *endo*-diastereomers, each of which exhibited the expected C(6)H chemical shift differences (Δδ 0.3 and Δδ 1.0, respectively); the *exo*-assignment of the former was confirmed by NOE analysis (Fig. 1). The alkylation reactions of **2** with substituted halonitriles therefore give high levels of *exo*-diastereoselectivity relative to bromoacetonitrile, and in the case of the phenyl substituted product **4b**, also excellent C-1′ stereoselectivity.

Reduction of nitriles **3**, **4a** and **4b** ($NaBH_4$, $CoCl_2{\cdot}H_2O$ or $NaBH_4$, $NiCl_2{\cdot}H_2O$) followed by in situ cyclisation of the resulting amine[16] gave the desired spirolactam systems **5a**,**b** and **6a**,**b** and **7**, albeit in low yields (25%, 20% and 21%, respectively); this is likely to be due to the strained spirobislactam system, but their very high polarity and water solubility (typically, a MeOH/EtOAc mixture is required for efficient elution in column chromatography) also complicated isolation. Spirocyclisation was accompanied by large changes in the chemical shifts of the C(6)H protons relative to the starting

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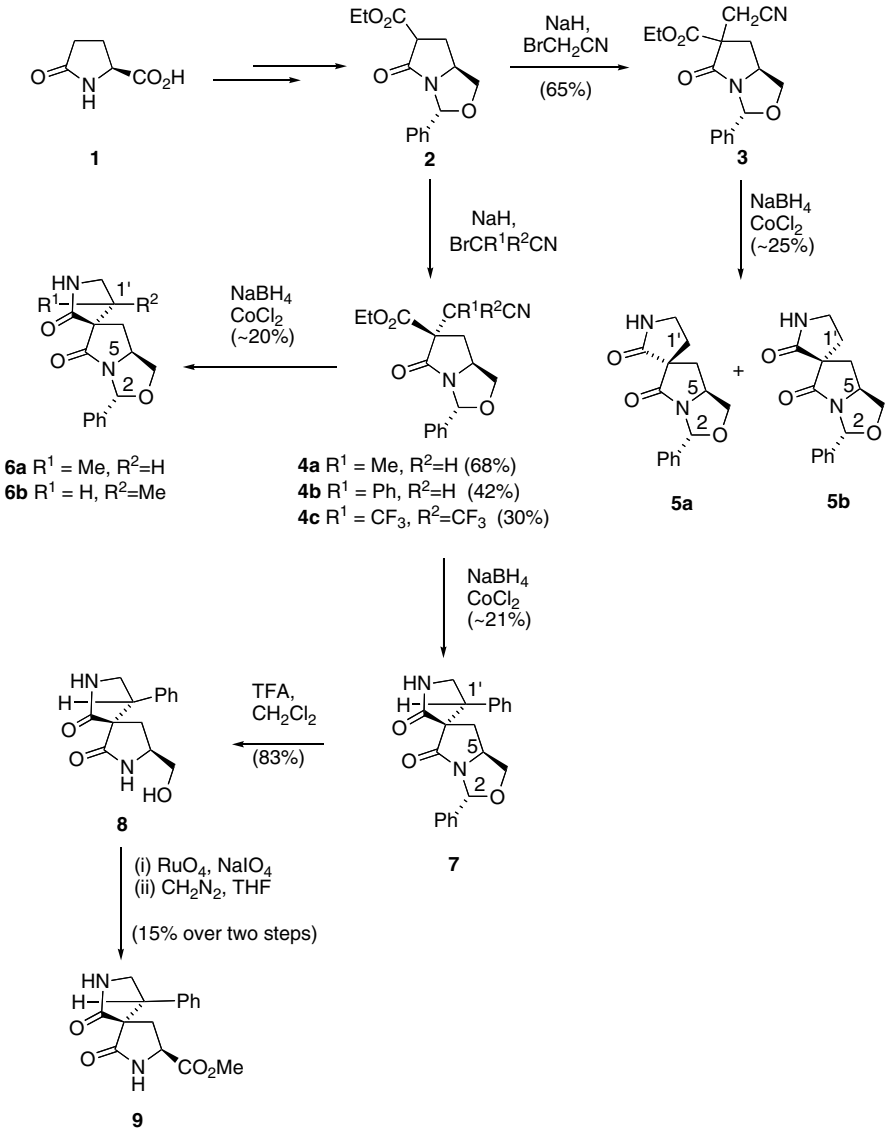

Scheme 1.

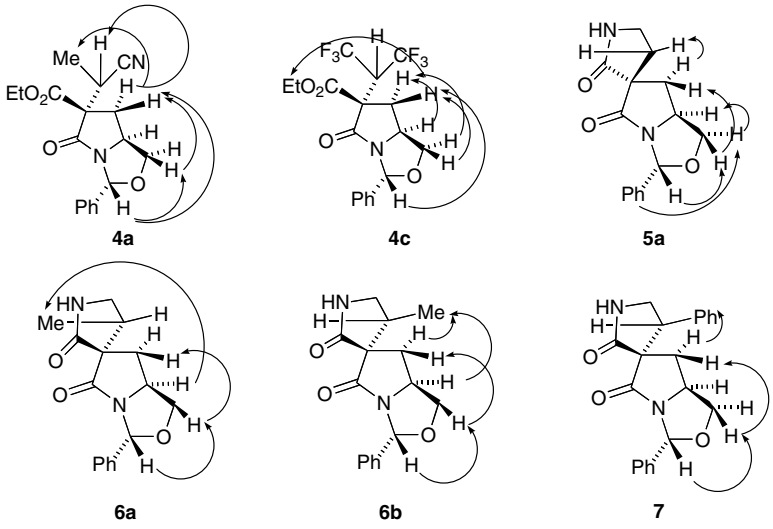

Figure 1.

lactams; for example, for **5a**, whose stereochemistry was established by NOE, the C(6)H protons exhibited $\Delta\delta$ 0.9, but for **5b**, the value was $\Delta\delta$ 0.5. Reduction and cyclisation of **4c** was not successful due to the instability of the starting material. Interestingly, despite their expected well-defined conformation, stereochemical assignment has been unexpectedly difficult. For lactams **6a**,**b**, the isomers were also obtained as a diastereomeric mixture (ratio **6a**:**6b** = 1:1) with C(6)H proton chemical shift difference values of $\Delta\delta$ 0.1 and $\Delta\delta$ 0.6, respectively; 2D-NOESY analysis convincingly indicated the proximal relationship of C-1′(Me), C(6)H_{exo} and C(5)H of lactam **6b**, with the C-1′(Me) substituent located under the pyroglutaminyl ring. Interestingly, however, a long range but weak NOE was observed in lactam **6a** from C(5)H to C-1′(Me). The stereochemistry of **7** follows from the unequivocal assignment of **4b**; the C-1′(*S*) configuration in which the phenyl substituent is located under the pyroglutaminyl ring was confirmed by NOE analysis (Fig. 1) and the fact that an anisotropic shielding effect from the nearby aromatic ring on C(6)H_{exo} was apparent (δ 1.95 as opposed to δ 2.8) in the unsubstituted lactam **5a**. Deprotection of **7** efficiently yielded the pyroglutaminyl system **8**; this compound is very polar (DMSO soluble only) and has not been purified, but was readily converted to the corresponding ester **9** in a two-step oxidation–esterification process in 15% overall yield. Bioassays of compounds **5a**,**b**, **6a** and **7** indicated weak activity against *Staphylococcus aureus* (hole plate method) at 30 μg ml^{-1}.

Acknowledgements

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References and notes

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14. The deprotonation was conducted at 0 °C, and then the reaction was heated to reflux after addition of the alkyl halide, except for **4c**, which was not stable and needed to be stirred at room temperature.
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16. The nitrile (3.8 mmol) was dissolved in methanol or ethanol (150 ml), and to this solution was added the Lewis acid (7.4 mmol). After 5 min of stirring, $NaBH_4$ (32 mmol) was added portion-wise and the mixture was allowed to stir for 16 h. The solvent was removed under vacuum, aq ammonium hydroxide (45 ml, 0.1 M) and ethyl acetate (150 ml) were added and this mixture was stirred for 30 min. After filtration through Celite®, the organic layer was washed with water, dried and the solvent removed; purification by chromatography (MeOH/EtOAc, 1:19) gave the desired product.
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