Asymmetric synthesis of (1R, 2S, 3R)- γ -methyl-*cis*-pentacin by a kinetic resolution protocol

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The asymmetric synthesis of (1R,2S,3R)-3-methyl-2-aminocyclopentane carboxylic acid has been achieved *via* kinetic resolution of racemic *tert*-butyl 3-methyl-cyclopentene-1-carboxylate with homochiral lithium (S)-N-benzyl-N- α methylbenzylamide.

The cyclic α -alkyl- β -amino acid (1R,2S)-2-aminocyclopentane carboxylic acid (cis-pentacin) has aroused much commercial and synthetic interest as a result of its potent antifungal activity.1 The synthesis and screening of a number of derivatives and analogues of cis-pentacin has demonstrated that the saturated 5-membered ring backbone is essential for biological activity, as is the (1R, 2S)-absolute configuration.² We have previously shown that the conjugate addition of homochiral lithium amides derived from α -methylbenzylamine to α,β unsaturated esters represents a versatile methodology for the asymmetric synthesis of β -amino acid derivatives,³ as demonstrated for the preparation of homochiral cis-pentacin.⁴ In order to extend this methodology to the asymmetric synthesis of the homochiral 3-methyl analogue, the simplest route would be to employ the unprecedented kinetic resolution of racemic tertbutyl 3-methyl cyclopentene-1-carboxylate 1 with homochiral lithium amide 2 (Fig. 1).



The required conjugate acceptor for this approach was readily prepared on a multigram scale from adipoyl chloride. Esterification⁵ and subsequent Dieckmann cyclisation⁶ afforded β -keto ester **3**, which underwent regioselective γ -methylation to furnish **4** as a 5:2 mixture of diastereoisomers. Sequential reduction, tosylation and elimination furnished (±)-*tert*-butyl 3-methyl cyclopentene-1-carboxylate **1** (Scheme 1).



Scheme 1 Reagents and conditions: (i). PhNMe₂ (3.15 eq.), 'BuOH (3.25 eq.), Et₂O, rt; (ii). NaH (1.05 eq.), 'BuOH (cat), PhMe, Δ ; (iii). NaH (1.05 eq.) then *n*-BuLi (1.0 eq.), then MeI (1.1 eq.), -78 °C to 0 °C; (iv). NaBH₄, EtOH, 0 °C; (v). TsCl (1.1 eq.), pyridine, 0 °C to rt; (vi). DBU, DCM, 0 °C.

Initially the mutual kinetic resolution⁷ of the racemic acceptor (\pm) -**1** and (\pm) -lithium *N*-benzyl-*N*- α -methylbenzyla-mide **2** was performed to assay the level of enantiorecognition between the two reactants. This racemic/racemic strategy

allows a rapid evaluation of the stereoselectivity factor (E) for the reaction, which in this case is identical to the diastereoselectivity (since the effects of mass action are eliminated) on the assumption that there are no non-linear effects operating.8 Thus, (\pm) -1 was added to a solution of (\pm) -2 at -78 °C and quenched by addition of 2,6-di-tert-butylphenol. ¹H NMR spectroscopic analysis of the crude reaction mixture indicated the presence of the two C(1) epimeric diastereoisomers (\pm) -6 and (\pm) -7 (95:5) together with <1.5% of a third diastereoisomer, consistent with >98.5% control at the β -centre during the conjugate addition. Purification of the major diasterγ-methyl-cis-pentacin eoisomeric product, $(1RS, 2SR, 3RS, \alpha SR)$ -6,9 to homogeneity by column chromatography and subsequent complete conversion to the thermodynamic epimer, γ -methyl-trans-pentacin (1SR,2SR,3RS, α SR)-7, by treatment with KO^tBu/^tBuOH (3 h at reflux) confirmed that the two diastereoisomers (\pm) -6 and (\pm) -7 were epimeric at C(1) (Scheme 2).



Scheme 2 Reagents and conditions: (i). (\pm)-lithium N-benzyl-N- α -methylbenzylamide (2 eq.), THF, -78 °C; (ii). 2,6-di-*tert*-butylphenol, THF, -78 °C to rt; (iii). KO'Bu, 'BuOH, Δ , 3 h.

The configuration at C(2) within (±)-6 and (±)-7 relative to the *N*- α -methylbenzyl stereocentre was assigned by analogy with previous models developed to explain the stereoselectivity observed during addition of lithium amide **2** to α , β -unsaturated acceptors.¹⁰ ¹H NOE difference analysis subsequently gave enhancements consistent with the (1*RS*,2*SR*,3*RS*, α *SR*) configuration of diastereoisomer (±)-6 and the (1*SR*,2*SR*,3*RS*, α *SR*) configuration of diastereoisomer (±)-7, consistent with the expected thermodynamics of the system, as described in Fig. 2.



Fig. 2 Selected NOE difference enhancements for diastereoisomers (\pm)-6 and (\pm)-7; other NOE enhancements omitted for clarity.

Notably, while both diastereoisomers exhibited a 7.1% NOE enhancement between their C(2)H and C(3)Me protons, the

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8.1% enhancement between C(1)H and C(2)H of the major diastereoisomer (\pm) -6 was only 3.1% for the minor diastereoisomer (\pm) -7. This indicates that both diastereoisomers (\pm) -6 and (\pm) -7 have the same *anti*-configuration between C(2)H and C(3)Me, but while the major diastereoisomer has a synrelationship between C(1)H and C(2)H, the minor diastereoisomer (\pm) -7 has the anti-relationship between C(1)H and C(2)H. Thus, the nucleophilic lithium amide adds to the α , β unsaturated acceptor anti to the C(3) methyl group, while protonation of the resultant enolate occurs anti to the amine, resulting in the preferential formation of γ -methyl-*cis*-pentacin $(1RS, 2SR, 3RS, \alpha SR)$ -6. As measurement of the diastereoisomeric product ratios in a mutual kinetic resolution reaction allows the magnitude of the stereoselectivity factor to be assessed, the magnitude of the stereoselectivity factor, E could be quantified as >70. Having established the high level of recognition between the γ -methyl conjugate acceptor 1 and racemic lithium amide 2, the kinetic resolution of (\pm) -1 with homochiral lithium (S)-N-benzyl-N- α -methylbenzylamide 2 was undertaken. Thus, treatment of (\pm) -1 with 0.7 eq. of (S)-2 at -78 °C for three hours before the addition of 2,6-di-tert-butyl phenol gave, at approximately 51% conversion, a 95.5:1.7:2.8 mixture of diastereoisomers 6:7:8, consistent with E > 130, and (S)-1 { $[\alpha]_{\rm D}^{24}$ -84.7, (c. 1.1, CHCl₃)} in 99 ± 0.5% ee.¹¹ (Scheme 3).



Scheme 3 Reagents and conditions: (i). (S)-lithium N-benzyl-N- α -methylbenzylamide (0.7 eq.), THF, -78 °C; (ii). 2,6-di-*tert*-butylphenol, THF, -78 °C to rt.

With the relative configurations within 6 and 7 known in the racemic series from the mutual recognition studies, the absolute configurations of $(1R, 2S, 3R, \alpha S)$ -6 and $(1S, 2S, 3R, \alpha S)$ -7 derive from the known configuration of the N- α -methylbenzyl stereocentre. The C(1) configuration of the third minor diastereoisomeric product 8 arising from the kinetic resolution protocol is presently unknown. Purification by column chromatography and recrystallisation gave 6 in 39% yield (78% of theoretical maximum) and 99 \pm 0.5% de. As 6 has the (1R,2S) configuration of cis-pentacin required for biological activity, deprotection to the β -amino acid was undertaken to prepare the γ -methyl analogue of the natural product. Thus, Pd mediated Ndebenzylation and treatment with TFA gave (1R, 2S, 3R)-3-methyl-2-aminocyclopentane carboxylic acid 9 in 69% yield and $98 \pm 1\%$ ee¹² after purification by ion exchange chromatography (Scheme 4).



Scheme 4 *Reagents and conditions*: (i). Pd(OH)₂ on C, MeOH, H₂ (5 atm); (ii). TFA:DCM (1:1) then Dowex 50W-X8.

In conclusion, this protocol allows for the diastereoselective synthesis of γ -methyl *cis*- and *trans*-pentacin analogues, which are of interest for pharmacological evaluation and for β -peptide structural studies respectively.¹³ Furthermore, the asymmetric synthesis of (1*R*,2*S*,3*R*)-3-methyl-2-aminocyclopentane carboxylic acid has been achieved by kinetic resolution of (±)-*tert*-butyl 3-methylcyclopentene-1-carboxylate with a homochiral lithium amide and subsequent deprotection. The extension of this methodology to the preparation of other homochiral *cis*-and *trans*-pentacin analogues from (±)-*tert*-butyl γ -alkyl cyclopentene-1-carboxylates is currently under investigation.

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Notes and references

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