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

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The asymmetric synthesis of (1*R*,2*S*,3*R*)-3-methyl-2-amino-cyclopentane 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 (1*R*,2*S*)-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 (1*R*,2*S*)-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 *tert*-butyl 3-methyl cyclopentene-1-carboxylate **1** with homochiral lithium amide **2** (Fig. 1).

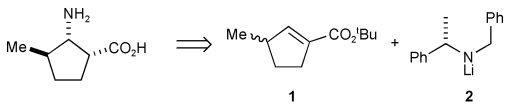
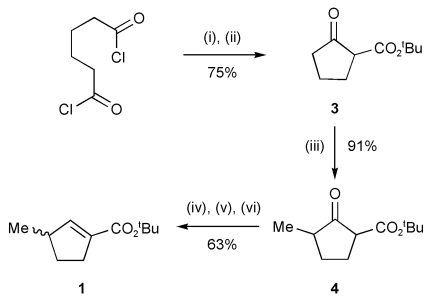


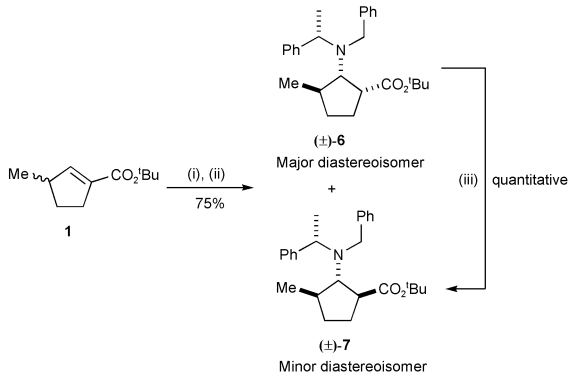
Fig. 1

The required conjugate acceptor for this approach was readily prepared on a multigram scale from adipoyl chloride. Esterification[5] and subsequent Dieckmann cyclisation[6] 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). $PhNMe_2$ (3.15 eq.), ^tBuOH (3.25 eq.), Et_2O, rt; (ii). NaH (1.05 eq.), ^tBuOH (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). $NaBH_4$, EtOH, 0 °C; (v). TsCl (1.1 eq.), pyridine, 0 °C to rt; (vi). DBU, DCM, 0 °C.

Initially the mutual kinetic resolution[7] of the racemic acceptor (±)-**1** and (±)-lithium *N*-benzyl-*N*-α-methylbenzylamide **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, (±)-**1** was added to a solution of (±)-**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 (±)-**6** and (±)-**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 diastereoisomeric product, γ-methyl-*cis*-pentacin (1*RS*,2*SR*,3*RS*,α*SR*)-**6**,[9] to homogeneity by column chromatography and subsequent complete conversion to the thermodynamic epimer, γ-methyl-*trans*-pentacin (1*SR*,2*SR*,3*RS*,α*SR*)-**7**, by treatment with KO^{t}Bu/^{t}BuOH (3 h at reflux) confirmed that the two diastereoisomers (±)-**6** and (±)-**7** were epimeric at C(1) (Scheme 2).



Scheme 2 *Reagents and conditions*: (i). (±)-lithium *N*-benzyl-*N*-α-methylbenzylamide (2 eq.), THF, −78 °C; (ii). 2,6-di-*tert*-butylphenol, THF, −78 °C to rt; (iii). KO^{t}Bu, ^{t}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.

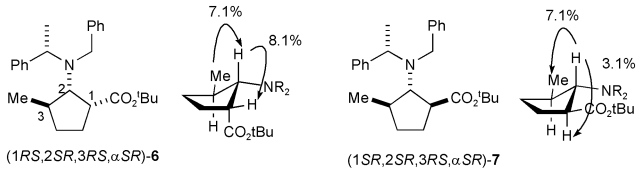


Fig. 2 Selected NOE difference enhancements for diastereoisomers (±)-**6** and (±)-**7**; other NOE enhancements omitted for clarity.

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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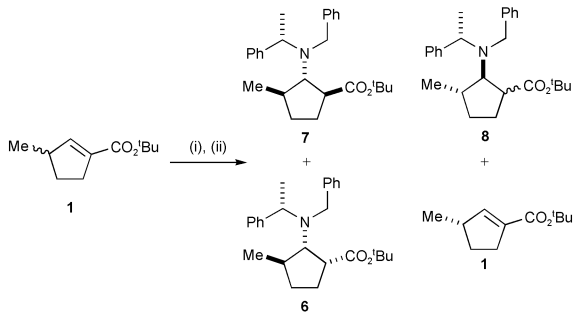
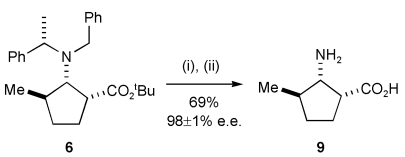
8.1% enhancement between C(1)H and C(2)H of the major diastereoisomer (±)-**6** was only 3.1% for the minor diastereoisomer (±)-**7**. This indicates that both diastereoisomers (±)-**6** and (±)-**7** have the same *anti*-configuration between C(2)H and C(3)Me, but while the major diastereoisomer has a *syn*-relationship between C(1)H and C(2)H, the minor diastereoisomer (±)-**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 (1*RS*,2*SR*,3*RS*,α*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 (±)-**1** with homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **2** was undertaken. Thus, treatment of (±)-**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** {$[\alpha]_D^{24}$ −84.7, (*c*. 1.1, $CHCl_3$)} 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 (1*R*,2*S*,3*R*,α*S*)-**6** and (1*S*,2*S*,3*R*,α*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 ± 0.5% de. As **6** has the (1*R*,2*S*) 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 *N*-debenzylation and treatment with TFA gave (1*R*,2*S*,3*R*)-3-methyl-2-aminocyclopentane carboxylic acid **9** in 69% yield and 98 ± 1% ee[12] after purification by ion exchange chromatography (Scheme 4).



Scheme 4 *Reagents and conditions*: (i). $Pd(OH)_2$ on C, MeOH, H_2 (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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9 Experimental procedure for the preparation of (±)-**6**: a solution of *tert*-butyl (±)-3-methylcyclopentene-1-carboxylate **1** (200 mg, 1.10 mmol) in anhydrous THF (0.5 ml) was added dropwise to a stirred solution of (±)-lithium *N*-benzyl-*N*-α-methylbenzylamide **2** (2.20 mmol) in THF (2ml) at −78 °C. After 3 h a precooled solution of 2,6-di-*tert*-butylphenol (453 mg, 2.20 mmol) in anhydrous THF (0.5 ml) was added slowly *via* cannula and allowed to warm to rt. The reaction mixture was partitioned between sat. $NH_4Cl_{(aq)}$ (5 ml) and Et_2O (3 × 50 ml), dried, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (2% Et_2O, *n*-pentane) gave (±)-**6** (324 mg, 75%); Found: C, 79.0; H, 9.3; N, 3.6%; $C_{26}H_{35}NO_2$ requires C, 79.3; H, 9.0; N, 3.6%; ν_{max} (film) 1712 (C=O), 1149 (C–O); δ_H (400 MHz, $CDCl_3$) 0.99–1.04 (1H, m, C(4)H_A), 1.02 (3H, d, *J*6.5, C(3)*Me*), 1.19 (3H, d, *J*6.9, C(α)*Me*), 1.51 (9H, s, OCMe_3), 1.52 (1H, m, C(5)H_A), 1.72 (1H, m, C(5)H_B), 1.97 (1H, m, C(4)H_B), 2.28 (1H, m, C(3)*H*), 2.53 (1H, ddd, *J*4.0, 7.7 and 7.7, C(1)*H*), 2.82 (1H, dd, *J*7.7 and 10.5, C(2)*H*), 3.96 and 4.16 (2 × 1H, d, *J*15.9, NCH_2Ph), 4.15 (1H, q, *J*6.9, C(α)*H*), 7.21–7.52 (10H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 19.5, 20.5, 26.9, 28.1, 30.7, 34.6, 46.7, 50.9, 60.1, 70.4, 80.0, 126.4, 127.0, 127.8, 127.9, 128.1 and 128.3, 143.6, 145.6, 176.5; *m*/*z* (CI^+) 394 (MH^+, 100%).

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