Highly enantioselective organocatalysis of the Hajos–Parrish–Eder–Sauer–Wiechert reaction by the β-amino acid cispentacin

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The β-amino acid cispentacin promotes the Hajos–Parrish–Eder–Sauer–Wiechert reaction with levels of enantioselectivity comparable to or higher than proline.

Organocatalysis is at the forefront of much current research, fuelled by the search for efficient reactions that do not rely upon the use of metals for their promotion.[1] Among the array of catalysts that promote enamine based organocatalysis, proline[2] and its derivatives[3] have received the most attention for a range of asymmetric transformations such as the aldol, Mannich and Michael reactions. The first widely recognised catalytic asymmetric application of proline concerned the enantioselective intramolecular aldol reaction of triketone **1** to the bicyclic alcohol **2** in quantitative yield and 93% e.e. (commonly known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction).[4] Proline has remained unrivalled as the most efficient catalyst for this often studied reaction,[5] with enantioselectivity thought to be due to the constraints of transition state **4**. Key to the stability of this transition state is the preference for reaction *via* the *s-trans* rather than the *s-cis* geometry,[6] and intramolecular acid catalysis due to hydrogen bonding of the carboxylic acid proton to the carbonyl undergoing nucleophilic attack.[7] As an extension of our research concerned with the synthesis and chemistry of enantiomerically pure β-amino acids,[8] their ability to promote asymmetric organocatalysis was probed. Limited previous studies detailing β-amino acid catalysis of the cyclisation of triketone **1** have been reported, with (*S*)-homoproline[9] and (*S*)-3-amino-4-phenylbutanoic acid[10] reported to give enone (*R*)-**3** in 58% and 83% optical yield respectively. In our hands however, the cyclisation of triketone **1** using the enantiomerically pure β-amino acids (*S*)-homoproline and (*R*)-3-amino-4-phenylbutanoic acid gave enone (*R*)-**3** in 36% e.e. and (*S*)-**3** in 64% e.e. respectively; under identical conditions L-proline gave enone (*S*)-**3** in 93% e.e., consistent with the literature.[4b]

It is well recognised that the pyrrolidine ring within proline is necessary to enforce conformational rigidity and impart high enantiocontrol in this reaction.[7] Following this analysis, we proposed that a β-amino acid capable of providing a fixed orientation of the carboxylic acid and amino functionalities should also be able to provide high enantiocontrol in this reaction manifold. Comparison with the proposed transition state for the cyclisation of triketone **1** using proline as the catalyst[11] led to the prediction that the conformationally constrained α-substituted-β-amino acid (1*R*,2*S*)-cispentacin[12] would also promote the Hajos–Parrish–Eder–Sauer–Wiechert reaction with high selectivity. The *cis*-relative orientation of the carboxylic acid and amine functionalities within cispentacin was predicted to provide a defined asymmetric environment, with the reaction proceeding preferentially *via* the *s-cis* enamine geometry and hydrogen bonding activation of the carbonyl as shown in transition state **5** [Fig. 1, illustrated for D-proline and (1*R*,2*S*)-cispentacin for ease of comparison].

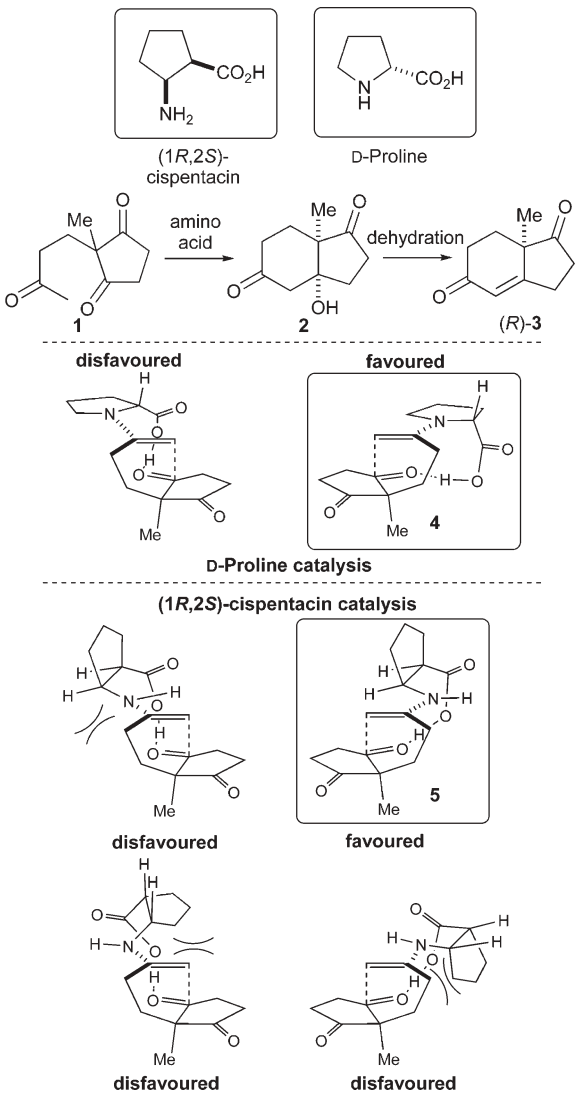

Fig. 1 Proposed transition state models for the reaction of D-proline and (1*R*,2*S*)-cispentacin with triketone **1**.

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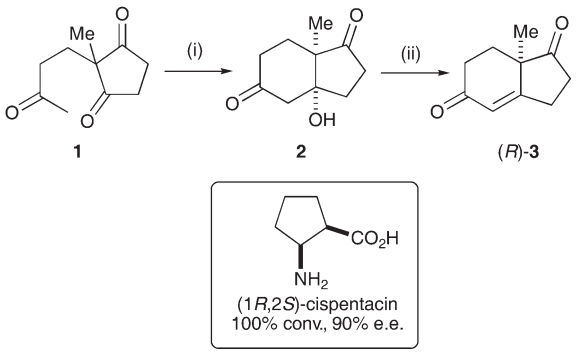
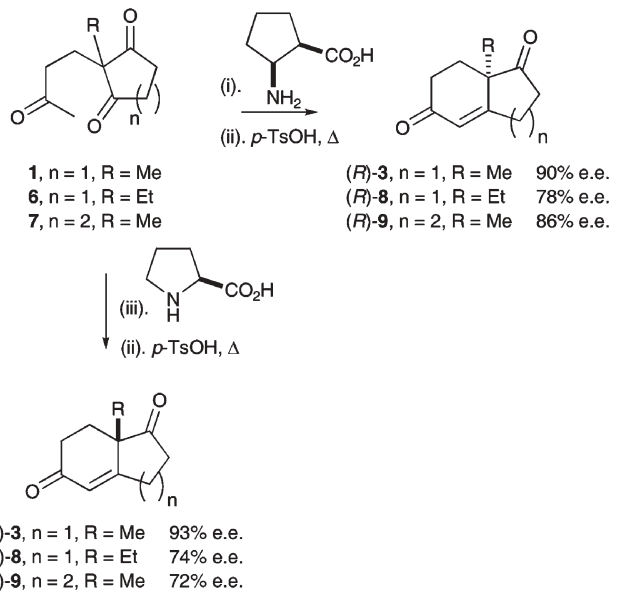
As a model substrate, treatment of triketone **1** with (1*R*,2*S*)-cispentacin (30 mol%) promoted complete conversion to the corresponding alcohol **2** after 48 hours,[13] which after dehydration upon treatment with *p*-TsOH, gave as predicted enone (*R*)-**3** in 90% e.e.[14] The e.e. of (*R*)-**3** was established unambiguously by GC analysis and comparison with an authentic racemic sample, while the absolute configuration of **3** was established both by comparison of specific rotation {$[\alpha]_D^{22}$ −282 (*c* 1.00 in $CHCl_3$), (*ent*). $[\alpha]_D^{22}$ + 287 (*c* 0.40 in $CHCl_3$)} and chiral GC data with an authentic sample of enone (*S*)-**3** (93% e.e.), prepared using L-proline (30 mol%). The high stereoselectivity using (1*R*,2*S*)-cispentacin (90% e.e.) is comparable to that using L-proline (93% e.e.) and is the highest enantioselectivity reported to date for this particular transformation using an amino acid containing a primary amino functionality (Scheme 1).



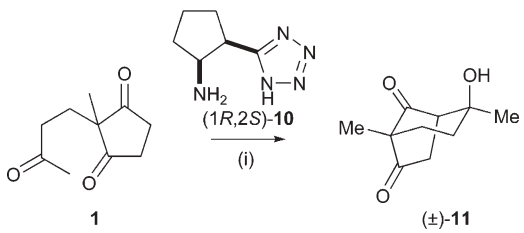
Scheme 1 *Reagents and conditions*: (i). (1*R*,2*S*)-cispentacin, (30 mol%), DMF, rt; (ii). *p*-TsOH, toluene, Δ.

The generality of this protocol with (1*R*,2*S*)-cispentacin was next established through the enantioselective cyclisation of triketones **6** and **7**, that differ in both alkyl substitution and ring size; the same cyclisation using L-proline was also evaluated under the same conditions to afford a direct comparison of the stereoselectivity of the reaction. The cyclisations promoted by (1*R*,2*S*)-cispentacin proceeded to complete conversion, giving the corresponding enones (*R*)-**8** and (*R*)-**9** respectively after dehydration. In each case, higher levels of enantioselectivity using the β-amino acid (1*R*,2*S*)-cispentacin were noted than using the α-amino acid L-proline for the same cyclisation {formation of **8**; cispentacin 78% e.e. [(*R*)], L-proline 74% e.e. [(*S*)]; formation of **9**, cispentacin 86% e.e. [(*R*)], L-proline 72% e.e. [(*S*)]} (Scheme 2).[15]

A spate of recent publications has demonstrated that tetrazole equivalents of amino acids (proline and homoproline) are enhanced organocatalysts for a range of transformations,[3b,3c,16] with the tetrazole considered an efficient mimic for the carboxylic acid. As part of our investigations within this area, the ability of the tetrazole equivalent of cispentacin (1*R*,2*S*)-**10** to promote the cyclisation of triketone **1** was examined. Notably, the reaction of triketone **1** with tetrazole (1*R*,2*S*)-**10** proceeded with a marked rate enhancement in comparison to cispentacin (100% conversion, 1 day) and with a remarkable change in product distribution, giving only the racemic bicyclic species **11**[17] (Scheme 3). It is apparent that the incorporation of the tetrazole moiety within this framework completely changes the reaction manifold; the incorporation of the tetrazole motif within organocatalysts as a carboxylic acid replacement should not therefore be regarded as a panacea strategy.



Scheme 2 *Reagents and conditions*: (i). (1*R*,2*S*)-cispentacin (30 mol%), DMF, rt; (ii). *p*-TsOH, toluene, Δ; (iii). L-proline, (30 mol%), DMF, rt.



Scheme 3 *Reagents and conditions*: (i). (1*R*,2*S*)-**10** (30 mol%), DMF, rt.

In conclusion, the conformational constraints offered by the homochiral β-amino acid cispentacin confer high efficiency and enantioselectivity during the promotion of the Hajos–Parrish–Eder–Sauer–Wiechert reaction. Further applications of the use of β-amino acids and their derivatives as organocatalysts for a range of synthetic transformations are currently under investigation in this laboratory.

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Notes and references

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13 The cyclisation of **1** to **2** is slower with (1*R*,2*S*)-cispentacin than L-proline; for example 30 mol% L-proline promotes the cyclisation of triketone **1** to **2** in 24 hours; 70% conversion to **2** is seen with 30 mol% of (1*R*,2*S*)-cispentacin after 24 hours. In MeCN, no reaction was observed using (1*R*,2*S*)-cispentacin for the cyclisation of **1** to **2**; (1*R*,2*S*)-*N*-methyl-cispentacin was inactive as a catalyst in this reaction manifold.
14 Typical experimental protocol: (1*R*,2*S*)-cispentacin (26 mg, 0.20 mmol) was added to a stirred solution of triketone **1** (124 mg, 0.68 mmol) in anhydrous DMF (1.0 mL). After 48 hours, the reaction mixture was filtered through a short plug of silica (eluent DMF) then concentrated *in vacuo* (Genevac™). The residue was then re-dissolved in toluene and treated with *p*-TsOH (13 mg, 0.07 mmol). The resultant mixture was heated at reflux for 5 hours before being allowed to cool to ambient temperature. Addition of sat. aq. $NaHCO_3$ solution, followed by extraction with EtOAc gave an organic solution which was dried over $MgSO_4$ and concentrated *in vacuo* to furnish enone (*R*)-**3** (104 mg, 94%); {$[\alpha]_D^{22}$ −282 (*c* 1.00 in $CHCl_3$), (*ent*). $[\alpha]_D^{22}$ + 287 (*c* 0.40 in $CHCl_3$)}. The e.e. of (*R*)-**3** was determined using a ThermoQuest TRACE GC fitted with a Cydex-β column; 120 °C isotherm, 120 min, (*R*)-**3** t_R = 91.5 min and (*S*)-**3** t_R = 100.5 min and comparison with an authentic racemic sample.
15 In the literature, the cyclisations of **6** to furnish (*S*)-**8** and **7** to give (*S*)-**9** using L-proline have been reported, but optical yields rather than e.e.s of the initial products were determined; see references 2, 4(a) and 4(b).
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17 The bicyclic species **11** was shown to be racemic by ^{1}H NMR studies in the presence of *O*-acetyl mandelic acid.

