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Diastereoselective conjugate reduction with samarium diiodide: asymmetric synthesis of methyl (2*S*,3*R*)-*N*-acetyl-2-amino-2,3-dideuterio-3-phenylpropionate

Stephen G. Davies,* Humberto Rodríguez-Solla, Juan A. Tamayo, A. Christopher Garner and Andrew D. Smith

The Department of Organic Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA. E-mail: steve.davies@chem.ox.ac.uk

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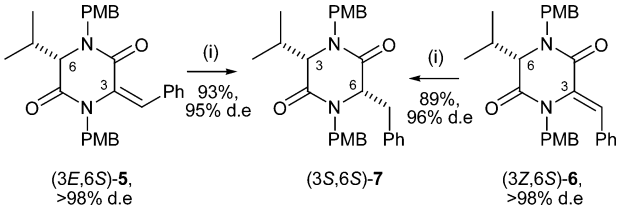
A highly diastereoselective conjugate reduction using SmI_2 and D_2O has been demonstrated on a homochiral benzylidene diketopiperazine template, giving methyl (2*S*,3*R*)-*N*-acetyl-2-amino-2,3-dideuterio-3-phenylpropionate 12 in 93% de and 90% ee after deprotection, hydrolysis and *N*-acetylation.

Samarium diiodide (SmI_2) is a versatile reagent in synthetic organic chemistry.[1] First introduced by Kagan,[2] SmI_2 has been used to effect a range of organic transformations, including the chemoselective reduction of a wide variety of functional groups such as organic halides, carbonyls and epoxides. This versatile reagent also promotes reductions of the C=C double bond of α,β-unsaturated esters and amides, and, while additives such as *N,N*-dimethylacetamide[3] or HMPA[4] are typically required to facilitate this reaction, Concellón *et al.* have recently shown that conjugate reductions can be carried out using SmI_2 and either H_2O or D_2O.[5,6] The diastereoselective conjugate reduction of α,β-unsaturated carbonyl systems using this methodology has received only minimal attention.[5c,7] SmI_2 has also been employed in various other enantioselective processes.[1h,8]

Previous work from this laboratory has demonstrated that protonation of metallated *bis*-*N*-4-methoxybenzyl-diketopiperazine enolates **1**, prepared by conjugate addition to the methylene diketopiperazine **2** or deprotonation of a substituted diketopiperazine **3**, proceed with high levels of diastereoselectivity and may be used for the asymmetric synthesis of either (*R*)- or (*S*)-α-amino acids depending upon the enantiomer of auxiliary utilised.[9] The excellent protonation selectivity observed using this template led us to investigate the diastereoselectivity upon protonation of the analogous samarium enolate, which it was envisaged could be generated by the SmI_2 promoted conjugate reduction of a 3-alkylidene substituted diketopiperazine template **4** (Fig. 1). We report herein our preliminary results in this area, in which protonation of the samarium enolate proceeds with high levels of diastereoselectivity under the stereocontrol of the chiral auxiliary and with excellent stereoselectivity in the formation of an exocyclic stereogenic centre, facilitating the first highly stereoselective SmI_2 promoted asymmetric synthesis of (2*S*,3*R*)-2,3-dideuterio-phenylalanine derivatives.

Initial investigations were concerned with the SmI_2 promoted reduction of the (3*E*,6*S*)-**5** and (3*Z*,6*S*)-**6** diastereoisomers of template **4**. Treatment of (3*E*,6*S*)-**5** with SmI_2 in THF and subsequent addition of deoxygenated H_2O led to clean reduction of the α,β-unsaturated enamide to afford the known *cis*-(3*S*,6*S*)-**7** in 95% de,[9c,e] and in 93% isolated yield. The effect of enamide geometry upon the diastereoselectivity of this reduction was next examined, with the diastereoisomeric benzylidene (3*Z*,6*S*)-**6** also giving *cis*-(3*S*,6*S*)-**7** in 96% de and 89% isolated yield (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) SmI_2, THF, H_2O, rt.

Encouraged by the high levels of *cis*-selectivity afforded by these reductions, consistent with the expected protonation selectivity for an intermediate samarium enolate, the mechanism and stereochemical course of these transformations was probed further through the incorporation of deuterium in these reactions. While the reduction of (*E*)- and (*Z*)-benzylidenes **5** and **6** with SmI_2 in THF–H_2O affords a single new stereogenic centre at C(6), the reductive deuteration of these substrates potentially generates, stereoselectively, two new stereogenic centres, at C(6) and C(1′). Treatment of either (3*E*,6*S*)-**5**, (3*Z*,6*S*)-**6**, or a 7 : 1 mixture of (3*E*,6*S*)-**5** : (3*Z*,6*S*)-**6** with a solution of SmI_2 in THF–D_2O gave C(1′),C(6)-dideuterated-diketopiperazine (3*S*,6*S*,1′*R*)-**8** with >99% incorporation of two deuterium atoms. Examination of the ^1H NMR spectrum of the crude material indicated a 92 : 8 ratio of (3*S*,6*S*,1′*R*)-**8** and combined diastereoisomers (3*S*,6*S*,1′*S*)-**9**, (3*S*,6*R*,1′*R*)-**10** and (3*S*,6*R*,1′*S*)-**11**, respectively and a 95.5 : 4.5 ratio of *cis*-(3*S*,6*S*) **8** + **9** to *trans*-(3*S*,6*R*) **10** + **11** diastereoisomers respectively, in all reductions investigated. Chromatographic removal of the samarium residues afforded **8** (92 : 8 mixture of **8** and minor diastereoisomers **9**–**11**) in 96% yield (Scheme 2).

The (3*S*,6*S*,1′*R*)-configuration within dideutero **8** was established by conversion to the known methyl (2*S*,3*R*)-*N*-acetyl-2-amino-2,3-dideuterio-3-phenylpropionate **12**.[10] *N*-Debenzylation of **8** with ceric ammonium nitrate afforded (3*S*,6*S*,1′*R*)-dideuteriodiketopiperazine **13** in 90% yield. Subsequent hydrolysis followed by esterification yielded a mixture of methyl (2*S*,3*R*)-2-amino-2,3-dideuterio-3-phenylpropionate **14** and (*S*)-valine methyl ester **15** as their hydrochloride salts which were separated by distillation of the free amino esters to afford (2*S*,3*R*)-2,3-dideutero-phenylalanine methyl ester **14** in 93% d.e and 90% ee[11] [consistent within experimental error with the 95.5 : 4.5 ratio of *cis* (**8** + **9**)/*trans* (**10** + **11**) diastereoisomers from the diketopiperazine reduction]. *N*-acetylation of **14** afforded, after chromatographic purification, *N*-acetyl (2*S*,3*R*)-**12** in 71% overall yield (Scheme 3).

The relative configuration within **12** was identified unambiguously by comparison with an authentic 1 : 1.4 mixture of racemic dideutero (2*SR*,3*RS*)-**12** and dideutero epimer (2*SR*,3*SR*)-**16**, derived from the D_2O promoted SmI_2 reduction of methyl (*Z*)-α-acetamido-cinnamate, and comparison with the ^1H NMR

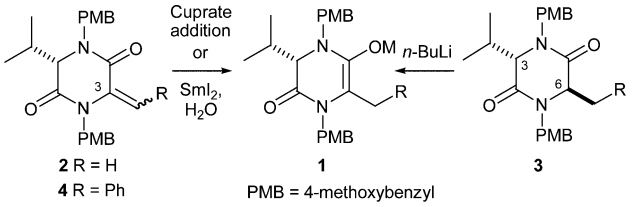


Fig. 1

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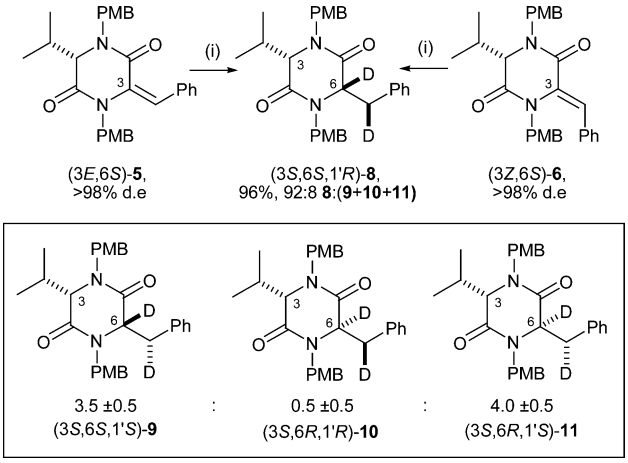
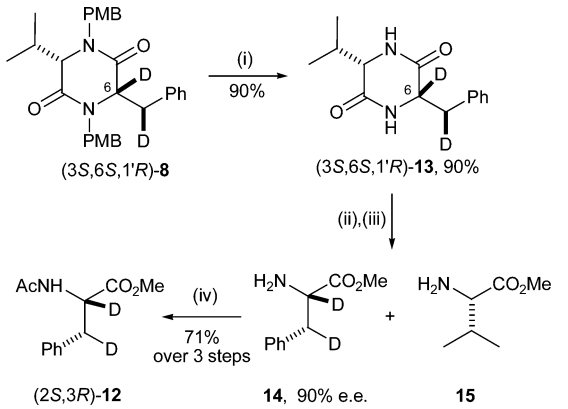


Scheme 2 *Reagents and conditions*: (i) SmI_2, THF, D_2O, rt.



Scheme 3 *Reagents and conditions*: (i) Ceric ammonium nitrate, H_2O, MeCN, rt; (ii) HCl conc., Δ; (iii) $SOCl_2$, MeOH, Δ; $NaHCO_3$; distillation (iv) Ac_2O, NEt_3, DMAP, DCM, rt.

spectroscopic data in the literature.[12] The absolute configuration of (3*S*,6*S*,1′*R*)-diketopiperazine **8** and the (2*S*,3*R*)-phenylalanine derivatives **12** and **14** follows from the configuration of the (*S*)-valine derived stereogenic centre of the starting auxiliary and was confirmed by the sign of the specific rotation of the hydrochloride salt of methyl (2*S*,3*R*)-2-amino-2,3-dideuterio-3-phenylpropionate **14** {$[\alpha]_D^{21}$ +29.9 (*c*, 0.70 in EtOH), lit.[13] $[\alpha]_D$ +35.7 (*c*, 1.06 in EtOH)}. The observed ee and de of **14** are consistent with a 92 : 3.5 : 0.5 : 4 ratio of **8** : **9** :**10** : **11** in the original reduction mixture (within an experimental error of ±0.5%) (Scheme 2).

The remarkable levels of stereoselectivity observed in the reduction of either (3*E*,6*S*)-**5** or (3*Z*,6*S*)-**6** to furnish the same product diastereoisomer indicates that this process is highly diastereoselective but completely non-stereospecific. To investigate further the mechanism of this transformation and to eliminate the possibility that these results derive from interconversion of (3*E*,6*S*)-**5** and (3*Z*,6*S*)-**6** by isomerisation prior to reduction, the partial reductions of (3*E*,6*S*)-**5** and (3*Z*,6*S*)-**6** were carried out. Treatment of either (3*E*,6*S*)-**5** or (3*Z*,6*S*)-**6** with a solution of SmI_2 (1 equiv.) in THF and D_2O proceeded to ~50% conversion giving the expected diketopiperazine (3*S*,6*S*,1′*R*)-**8** and only unchanged starting material in each case. Furthermore, treatment of a 50 : 50 mixture of (3*E*,6*S*)-**5**:(3*Z*,6*S*)-**6** under identical conditions proceeded to 50% conversion, furnishing (3*S*,6*S*,1′*R*)-**8** and returning a 50 : 50 mixture of (3*E*,6*S*)-**5** : (3*Z*,6*S*)-**6**, indicating that the rates of reduction of the two diastereoisomeric diketopiperazines are identical. The observed high levels of stereoselectivity in the generation of the C(6) stereogenic centre presumably arise from stereoselective protonation/deuteration of an intermediate samarium enolate, consistent with the previously observed *Re* face selective protonation of the corresponding lithium enolate.[9] The stereoselective incorporation of deuterium at C(1′), from both (*E*)- and (*Z*)-enamides **5** and **6**, is consistent with a configurationally labile radical anion intermediate in the reduction process.[14] Current studies are directed toward delineating fully the factors involved in this process.

In conclusion, an efficient and highly diastereoselective conjugate reduction using SmI_2 in THF and H_2O and D_2O has been demonstrated.

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12 ^1H NMR data for synthetic methyl (2*S*,3*R*)-[2,3-$^2H_2$]-*N*-acetyl-phenylalaninate **12** (400 MHz, DMSO) 1.81 (3H, s, CO*Me*), 2.97 (1H, s, C(3)H_S), 3.61 (3H, s, CO_2Me), 7.21–7.35 (5H, m, Ar*H*), 8.37 (1H, br s, N*H*). Selected literature data [reference 10*b*] for methyl (*RS*)-*N*-acetyl-phenylalaninate (^1H 400 MHz, DMSO) 2.86 (1H, dd, *J*13.7, 9.3, C(3)H_R), 3.00 (1H, dd, *J*13.7, 5.4, C(3)H_S), 4.44 (1H, ddd, *J*9.3, 7.3, 5.4, C(2)H); for methyl (2*S*,3*R*)-[3-^2H]-*N*-acetyl-phenylalaninate (^1H 800 MHz, DMSO) 2.98 (1H, d, *J*5.5, C(3)H_S); methyl (2*S*,3*S*)-[2,3-$^2H_2$]-*N*-acetyl-phenylalaninate (^1H 400 MHz, DMSO) 2.84 (1H, s, C(3)H_R).

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