First asymmetric desymmetrisation of a centrosymmetric molecule: CBS reduction of a 2-pyridone [4 + 4]-photodimer derivative

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Received (in Liverpool, UK) 6th October 1999, Accepted 25th October 1999

The *B*-Me-(*S*)-CBS catalysed borane reduction of centrosymmetric bis-*N*-Boc tetrahydro photodimer 3 has been achieved with virtually complete enantiotopic group selectivity (>97% ee) and in good yield (76%).

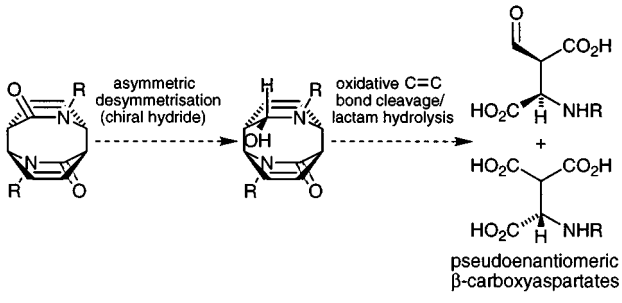
The exploitation of latent molecular symmetry to expedite synthesis is an attractive strategy in organic chemistry.[1] An exemplary tactic in this regard is the asymmetric desymmetrisation of *meso* intermediates,[2,3] *i.e.* compounds containing more than one stereocentre but which are achiral by virtue of overall molecular symmetry. This approach can provide access to enantiomerically pure compounds, often with a high degree of molecular complexity, in relatively few synthetic steps. The enantiotopic group differentiation can be achieved by either enzymatic[4] or synthetic[5] means.

However, to the best of our knowledge, this strategy has only been employed with *meso* compounds containing a mirror plane. We were intrigued by the possibility of asymmetric desymmetrisation of *meso* compounds containing a centre of symmetry, *i.e.* centrosymmetric compounds. Of particular interest to us was the prospect of desymmetrising centrosymmetric [4 + 4]-photodimer derivatives of 2-pyridone[6] as the key step in a conceptually new route to functionalised amino acids. Here we describe enantiotopic amide carbonyl group differentiation using 'chiral' hydride (Scheme 1).

Despite the plethora of literature pertaining to asymmetric carbonyl reduction by chiral hydride reagents,[7] the only work reported on amidic compounds has been the desymmetrisation of *meso* imides.[8] For example, Speckamp has described the catalytic asymmetric reduction of cyclic *meso* imides using the Corey–Bakshi–Shibata (CBS) method in 68–94% ee.[8]

For the CBS reduction of [4 + 4]-photodimers of 2-pyridone to be successful, we anticipated that 'activation' of the amide carbonyl groups towards reduction would be necessary and envisaged that *N*-Boc derivatisation would serve this purpose.[9] Furthermore, we decided to work initially on a saturated tetrahydro photodimer derivative so as to allow the optimisation of the CBS reduction without the potential complications of competing hydroboration.[10]

Irradiation (350 nm) of an aqueous solution of 2-pyridone **1** (20 g in 50 ml) in a Rayonet reactor over 5 days caused [4 + 4]-photodimer **2** to precipitate from solution as white crystals (10.4 g, 52%).[11] Treatment with BuLi/Boc_2O in THF gave the bis-*N*-Boc derivative, and subsequent bis-hydrogenation using Adams' catalyst[11] furnished the bis-*N*-Boc tetrahydro photodimer **3** in excellent yield (Scheme 2).

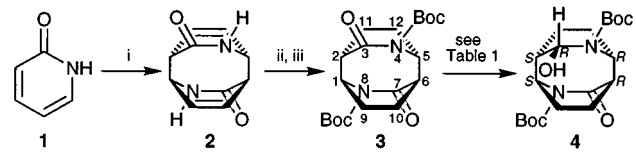


Scheme 1

Uncatalysed reaction of the bis-*N*-Boc tetrahydro photodimer **3** with $BH_3{\cdot}SMe_2$ was found to be slow, affording the racemic monolactamol† (±)-**4** in 16% yield after 22 h (entry 1, Table 1). Examination of the single crystal X-ray structure of this racemic monolactamol (±)-**4**‡ revealed it to have been formed by 'axial' attack of hydride at C3§ (this was expected as 'equatorial' attack of hydride at C3 is blocked by the C9, C10 ethylene bridge).

Using *B*-Me-(*S*)-CBS·BH_3 complex synthesised from (*S*)-proline,[12]¶ a systematic investigation of the asymmetric reduction of bis-*N*-Boc tetrahydro photodimer **3** was undertaken (Table 1).

Initial attempts at the asymmetric reduction in CH_2Cl_2 gave poor conversions and moderate ees, presumably due to the low catalyst loading and competing uncatalysed reduction by excess $BH_3{\cdot}SMe_2$ (entries 2, 3). A stoichiometric amount of catalyst and a 1:1 ratio of catalyst to borane gave significantly improved yields and ees (entries 4–6). Finally, performing the reaction at higher concentrations in $CHCl_3$ allowed for sub-stoichiometric amounts of catalyst to be used, producing the bis-*N*-Boc



Scheme 2 *Reagents and conditions*: i, hν = 350 nm, H_2O (52%); ii, BuLi (2.5 equiv.), Boc_2O (4 equiv.), THF (98%); iii, H_2 (3 bar), PtO_2 (0.2 equiv.), EtOAc (100%).

Table 1 Optimisation of the *B*-Me-(*S*)-CBS·BH_3 catalysed asymmetric reduction of bis-*N*-Boc tetrahydro photodimer **3**

					Monolactamol **4**	
Entry[a]	*B*-Me-(*S*)-CBS·BH_3/ equiv.	$BH_3{\cdot}SMe_2$/ equiv.	*t*/h	Solvent (ml)	Yield[b] (%)	Ee[c] (%)
1	0	1.2	22	CH_2Cl_2 (10)	16	0
2	0.2	1.2	22	CH_2Cl_2 (10)	34	66
3	0.2	1.2	6	CH_2Cl_2 (10)	16	64
4	1	1	6	CH_2Cl_2 (10)	41	86
5	1	1	14	CH_2Cl_2 (10)	57	94
6	1	1	14	$CHCl_3$ (5)	63	96
7	0.5	0.5	14	$CHCl_3$ (2)	49	97
8	0.5	0.5	22	$CHCl_3$ (1)	76	97

[a] All reactions were performed on a 100 mg scale. [b] Isolated yield after column chromatography; the mass balance consists of photodimer **3** and lesser amounts of over-reduced products. [c] Determined by chiral HPLC [Column: Chiralcel OD (25 × 0.46 cm), eluting with 99.2:0.8 hexane–Pr^iOH, 1.0 ml min^{-1}, 40 °C, UV detection at 225 nm].

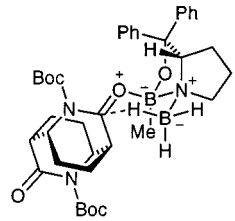


Fig. 1 Predicted transition state for the *B*-Me-(*S*)-CBS·BH_3 reduction of the bis-*N*-Boc tetrahydro-dimer **3** (NB. the larger *N*-Boc substituent is oriented equatorially and the smaller alkyl substituent is oriented axially in the chair transition state).

tetrahydro monolactamol in 76% yield and 97% ee (entries 7 and 8).

Based on the model proposed by Corey,[10] and corroborated by Speckamp for his imide reductions,[8] we predicted that the *B*-Me-(*S*)-CBS catalyst would deliver hydride selectively to the *Si*-face of the photodimer (Fig. 1).

To confirm this prediction we grew X-ray quality crystals of the enantiomerically pure monolactamol (+)-**4** {from entry 8, $[\alpha]_D$ +8.0, $[\alpha]_{365}$ +90.2 (*c* 0.5 $CHCl_3$)} and performed a single crystal X-ray structure determination using Cu-Kα irradiation.‖ This established the absolute configuration of monolactamol (+)-**4** as being (1*S*,2*S*,3*R*,5*R*,6*R*) as expected (Fig. 2, and as depicted in Scheme 2).

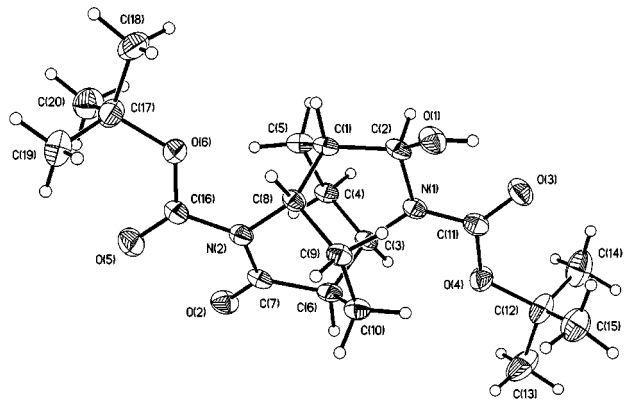


Fig. 2 ORTEP (50% probability ellipsoids) of the enantiomerically pure monolactamol (+)-**4**.‖

In conclusion, we have demonstrated that *B*-Me-(*S*)-CBS catalysed borane reduction of a bis-*N*-Boc tetrahydro photodimer can be achieved with virtually complete enantiotopic group selectivity (97% ee) and in good yield (76%). This provides efficient access to an enantiomerically pure product containing five chiral centres and represents the first asymmetric desymmetrisation of a centrosymmetric compound. It is also the first example of the asymmetric reduction of a *meso* diamide, and as such represents a significant extension of the scope and versatility of the CBS reduction process.

We are currently investigating the utility of related asymmetric desymmetrisations of unsaturated and more highly functionalised [4 + 4]-photodimer derivatives of 2-pyridone for the preparation of enantiomerically pure β-carboxyaspartic acid derivatives.

We thank the EPSRC and Pfizer for provision of a CASE studentship, and also the Nuffield Foundation and The Royal Society Equipment Fund for financial support of this work.

Notes and references

† We use the term lactamol in preference to cyclic hemiaminal (*cf.* lactone → lactol *vs.* lactam → lactamol).

‡ The single crystal X-ray structure for racemic monolactamol (±)-**4** is topologically superimposable on that of the enantiomerically pure compound (+)-**4**.‖

§ 'Axial' attack refers to the trajectory of hydride attack which results in an axial hydrogen in the 'double boat' structure of the photodimer product.

¶ The quality of the catalyst was confirmed by performing the asymmetric reduction of acetophenone to (*R*)-1-phenylethan-1-ol (ref. 13) in quantative yield and 95% ee using *B*-Me-(*S*)-CBS·BH_3 (0.1 equiv.), BH_3·SMe_2 (1.2 equiv.), CH_2Cl_2, room temp., 1 h.

‖ *Crystal data* for (+)-**4**: $C_{20}H_{32}N_2O_6$, M_r = 396.48, Rigaku AFC7R diffractometer, crystal dimensions 0.30 × 0.35 × 0.40 mm, T = 123(1) K, monoclinic, space group $P2_1$, a = 633.2(4), b = 2600.0(4), c = 672.0(3) pm, β = 112.63(4) °, V = 1.0211(8) nm^3, Z = 2, $\rho_{calc.}$ = 1.289 Mg m^{-3}, Cu-Kα radiation, (λ = 1.54178 Å), μ = 0.781 mm^{-1}, θ = 3.40–67.45°. 4008 reflections collected, 3589 were unique including one set of Bijvoet opposites (+h, +k, ±l and −h, −k, ±l) (R_{int} = 0.0140). Data were corrected for absorption by the method of ψ-scans, T_{min} and T_{max} = 0.916 and 0.999, repectively. Refinement by full-matrix least-squares on F^2, 295 refined parameters, 1 restraint gave R_1 = 0.0418, wR^2 = 0.1177 and GOF = 1.009 based on all 3589 data, absolute structure parameter = 0.14(19), residual density –0.22 and +0.19 e $Å^{-3}$. The structure was solved and refined using the SHELXTL suite of programs. All hydrogen atoms with the exception of the hydroxy, H(1B), were placed in geometric position, (U_{iso} freely refined). The hydroxy hydrogen was located in a difference map and its positional parameters and U_{iso} freely refined. CCDC 182/1471. See http://www.rsc.org/suppdata/cc/1999/2523/ for crystallographic data in .cif format.

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Communication 9/08059G