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Cycloadditions of chiral carbonyl ylides with imine dipolarophiles as a route to enantiomerically pure α-amino-β-hydroxy acids

Yu Gan [a,†], Laurence M. Harwood [a,*], Simon C. Richards [a], Ian E. D. Smith [b], Victoria Vinader [b,‡]

[a] *Department of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK*
[b] *GlaxoSmithKline, Gunnels Wood Road, Stevenage Herts SG1 2NY, UK*

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This paper is dedicated to Professor George Fleet, on the occasion of his 65th birthday

ABSTRACT

The preparation of enantiomerically pure *threo*-β-amino-α-hydroxy acids via 1,3-dipolar cycloadditions of imine dipolarophiles with the chiral isomünchnone derived from (5*R*)-5-phenylmorpholin-3-one **1** is described. The cycloadducts were obtained with excellent diastereofacial- and *exo*-selectivity. Subsequent hydrolysis and chemoselective exocyclic amide cleavage afforded the *threo*-β-amino-α-hydroxy acids with recovery of the initial chiral auxiliary.

1. Introduction

β-Amino-α-hydroxy acids are typically prepared by methods that utilise asymmetric epoxidation,[1] Sharpless asymmetric dihydroxylation,[2] and chiral auxiliary-based strategies.[3,4] They are an important component in many biologically active compounds,[5–8] in particular Taxol® and Taxotere®.[9,10] Previous work within the group has developed a carbonyl ylide system[11] based on the chiral auxiliary 5-phenylmorpholin-3-one **1**. Cycloadditions of this system with selected aldehyde dipolarophiles have been shown to afford cycloadducts with excellent diastereoselectivities, although the scope of the reaction was limited to electron-deficient aldehydes. Subsequent manipulation of the cycloadducts afforded enantiomerically pure α,β-dihydroxyacids, allowing the recovery of the initial chiral material.[12]

Herein, we report a significantly more reproducible and efficient synthesis of the key carbonyl ylide precursor **2**, its highly diastereoselective cycloadditions with a variety of imine dipolarophiles to afford cycloadducts in moderate to good yields and their subsequent efficient conversion into enantiomerically pure *threo*-β-amino-α-hydroxy acids.

2. Results and discussion

The carbonyl ylide precursor **2** was synthesised from auxiliary **1** via diamide **3** prepared in 84% yield following Sato's diketene methodology.[13] Compound **3** was subsequently treated with polystyrene-bound benzenesulfonyl azide,[14] for ease of purification, giving the diazo adduct **4** in a reproducible 91% yield. Finally, deacetylation[15] of **4** was achieved using pyrrolidine, to afford carbonyl ylide precursor **2** in 87% yield (Scheme 1). This synthesis represents a significant improvement over our earlier methodology.

Cycloadditions with the isomünchnone, derived from the rhodium-catalysed decomposition of **2**, with the imine dipolarophile **5a** were initially studied in order to optimise conditions. A range of solvents, temperatures and addition protocols for this cycloaddition were surveyed and it was found that use of nitromethane as solvent proved to be a key element, affording **6a** in 43% purified yield (Table 1).[16] Inspection of the crude reaction material revealed no other cycloadduct to be present. X-ray crystallographic analysis of **6a** showed cycloaddition to have occurred on the face of the carbonyl ylide *anti* to the phenyl substituent with the anisyl group in an *exo*-configuration (Fig. 1).[17]

Following this optimisation study, the scope of this conversion was studied using aromatic imine dipolarophiles bearing both electron-withdrawing and electron-donating substituents on the aromatic ring (Scheme 2). The highest yield was obtained for the reaction between **2** and the imine derived from benzaldehyde and benzylamine **6c** and all cycloadditions occurred with the same excellent diastereofacial- and *exo*-selectivity (Table 2), with only one diastereoisomer being identified in the crude material in all cases. Comparison of the NMR spectroscopic data for these cycloadducts with those of **6a**,[16] indicated that the additions had all occurred in the same *anti-exo* manner.

Cycloadducts **6a–e** were subjected to mild acid hydrolysis, using a THF/water mixture and *p*-toluenesulfonic acid catalyst (1 mol %). The hydrolysis products **7a–e** could not be purified by chromatography, as they appeared to exist as an equilibrium mixture of ring-chain tautomers; therefore the crude hydrolysis products **7a–e** were subjected to selective exocyclic amide bond

* Corresponding author. Tel.: +44 (0) 118 378 7417; fax: +44 (0) 118 378 6121.
E-mail address: l.m.harwood@reading.ac.uk (L.M. Harwood).
† Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1Ez, UK.
‡ Institute of Cancer Therapeutics, School of Life Sciences, University of Bradford, West Yorkshire BD7 1DP, UK.

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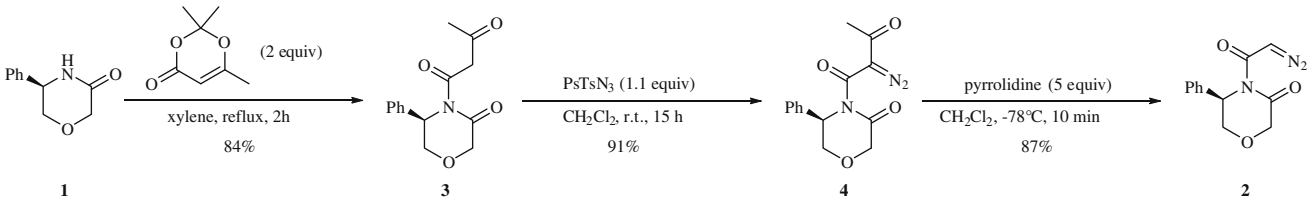


Scheme 1.

Table 1
Effect of temperature and solvent on cycloaddition

Solvent	Temperature	Yield (%)
CH_2Cl_2	−78 °C	0
CH_2Cl_2	0 °C	7
CH_2Cl_2	rt	12
CH_2Cl_2	Reflux	10
THF	rt	3
THF	Reflux	0
EtOAc	rt	0
$CHCl_3$	rt	2
MeOH	rt	0
CH_3NO_2	rt	43

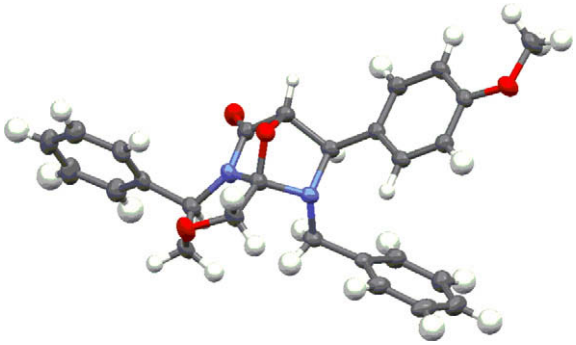


Figure 1. X-ray crystal structure of **6a**.

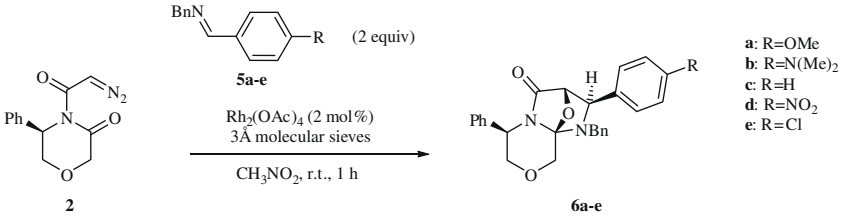
Table 2
Yields of cycloadducts

Entry	R	Yield (%)	Diastereoisomer
6a	OMe	43	*exo*-I
6b	NMe_2	21	*exo*-I
6c	H	70	*exo*-I
6d	NO_2	47	*exo*-I
6e	Cl	30	*exo*-I

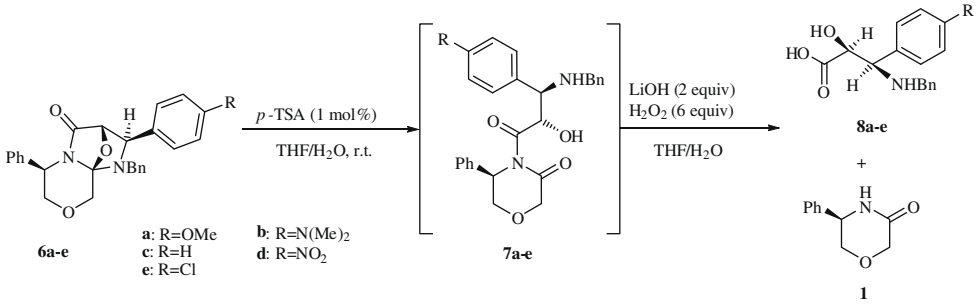
cleavage with lithium hydroperoxide following the methodology of Evans (Scheme 3).[18] Purification of products **8a–e** and recovery of the initial chiral auxiliary **1** were achieved through column chromatography.[17] The pure chiral auxiliary **1** was recovered in good to excellent yields, and the desired *threo*-β-amino-α-hydroxy acids were isolated in reasonable to good yields over the two-step sequence (Table 3). It is worth noting that both the methyl ester

Table 3
The preparation of β-amino-α-hydroxy acids and the recovery of the chiral auxiliary

Cycloadduct	R	Yield of **8** (%)	Recovery of **2** (%)
6a	OMe	59	90
6b	NMe_2	32	84
6c	H	80	95
6d	NO_2	65	71
6e	Cl	61	83



Scheme 2.



Scheme 3.

and the free amine derivatives of **8c** have been used to access the C-13 side chain of Taxol®.[19]

3. Conclusion

In conclusion, we have developed a highly diastereocontrolled synthesis of enantiopure β-amino-α-hydroxy acids, via the cycloadditions of imines with the carbonyl ylide derived from chiral precursor **1**. After cleavage, the chiral auxiliary **1** was recovered in excellent yield, with the β-amino-α-hydroxy acids **8a–e** isolated in reasonable to good yields. Optimisation studies of the carbonyl ylide generation/cycloaddition step demonstrated the dramatic effect of the use of nitromethane as a solvent.

Acknowledgements

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16. All novel compounds isolated gave spectroscopic data in accordance with their assigned structures. General experimental and selected data for key products are given below.
General cycloaddition procedure: To $Rh_2(OAc)_4$ (2 mol %) and 3 Å molecular sieves in nitromethane (1 mL) under an inert atmosphere, was added a 0.81 M solution of **5a–e** in nitromethane followed by the dropwise addition of a 0.27 M solution of **2** in nitromethane. The reaction was left to stir until TLC analysis showed no evidence of the ylide precursor. The molecular sieves were removed by filtration and washed with DCM (3 × 5 mL), the solvent was removed in vacuo and purification by gradient column chromatography eluting with diethyl ether/petroleum ether (30–40 °C) and triethylamine (2%) afforded **6a–e**.
General cycloadduct degradation procedure: To a 0.05 M solution **6a–e** of in THF/water (3:1) was added *p*-TSA (1 mol %). The reaction was monitored by TLC analysis and, when the cycloadduct was no longer observed, the solvents were removed in vacuo. The crude hydrolysis product was dissolved in THF/water (3:1) to make a 0.05 M solution, cooled to 0 °C and a hydrogen peroxide solution (30% w/w) (6 equiv) was added, followed by solid lithium hydroxide monohydrate (2 equiv). The solution was warmed to room temperature over 2 h and left to stir until the hydrolysis product was no longer present by TLC analysis. The reaction mixture was recooled to 0 °C and quenched by addition of a 1.5 M aqueous sodium thiosulfate solution (6.6 equiv). The solution was adjusted to pH 8 with 4 M aqueous hydrochloric acid and the solvents were removed in vacuo. Purification by gradient column chromatography eluting with chloroform/ethanol, gave **1** and **8a–e**.
Compound **6a**: mp 124–125 °C; *m*/*z* $C_{27}H_{26}N_2O_4$ requires 442.1893, found 442.1899; ν_{max} (thin film) 1728, 1609, 1511, 1454, 1421, 1336 and 1244 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41–6.65 (14H, m, ArH), 4.97 (1H, dd, *J* 5.0, *J*′ 9.5 Hz, 10α-H), 4.72 (1H, d, *J* 13.0 Hz, NC*H*HPh), 4.60 (1H, d, *J* 12.5 Hz, 7α-H or 7β-H), 4.48 (1H, s, 3-H), 4.32 (1H, d, *J* 12.5 Hz, 7α-H or 7β-H), 4.08 (1H, dd, *J* 5.0, *J*′ 12.0 Hz, 9α-H or 9β-H), 3.73, (3H, s, CH_3), 3.68 (1H, d, *J* 13.0 Hz, NCH*H*Ph), 3.59 (1H, s, 4H) and 3.54 (1H, dd, *J* 10.0, *J*′ 12.0 Hz, 9α-H or 9β-H); δ_C (101 MHz, $CDCl_3$) 171.5, 158.8, 137.2, 135.7, 132.4, 128.8, 128.7, 128.4, 128.0, 127.2, 127.0, 113.2, 101.0, 86.0, 73.1, 69.5, 65.6, 58.5, 55.2 and 55.1; $[\alpha]_D^{20} = -204.3$ (*c* 0.5 $CHCl_3$); Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 73.14; H, 5.99; N, 6.35. *Compound* **6c**: *m*/*z* $C_{26}H_{24}N_2O_3$ requires 412.1787, found 412.1787; ν_{max} (thin film) 1728, 1496, 1457, 1423, 1336 and 1071 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.44–7.05 (15H, m, ArH), 4.97 (1H, dd, *J* 4.5, *J*′ 9.5 Hz, 10α-H), 4.74 (1H, d, *J* 13.0 Hz, NC*H*HPh), 4.62 (1H, d, *J* 12.5 Hz, 7α-H or 7β-H), 4.50 (1H, s, 3-H), 4.32 (1H, d, *J* 12.5 Hz, 7α-H or 7β-H), 4.06 (1H, dd, *J* 4.5, *J*′ 12.0 Hz, 9α-H or 9β-H), 3.68 (1H, d, *J* 13.0 Hz, NCH*H*Ph), 3.62 (1H, s, 4H) and 3.53 (1H, dd, *J* 9.5, *J*′ 12.0 Hz, 9α-H or 9β-H); δ_C (62.8 MHz, $CDCl_3$) 171.9, 140.6, 137.5, 136.1, 129.4, 129.2, 129.1, 128.9, 128.5, 128.4, 128.3, 127.7, 127.0, 101.5, 86.4, 73.5, 69.9, 66.6, 58.9 and 55.7; $[\alpha]_D = -175.2$ (*c* 0.4 $CHCl_3$). *Compound* **8a**: mp 204–207 °C; *m*/*z* $C_{17}H_{19}NO_4$ requires 302.1392, found 302.1387; ν_{max} (thin film) 3389, 2918, 1602, 1507, 1247, 1177, 1113 and 1026 cm^{-1}; δ_H (400 MHz, D_2O); 7.56–7.10 (9H, m, ArH), 4.25 (1H, d, *J* 6.5 Hz N–C*H*), 4.14 (1H, d, *J* 6.5 Hz, O–C*H*), 3.95 (1H, d, *J* 13.5 Hz, NC*H*HPh), 3.94 (3H, s, OCH_3) and 3.84 (1H, d, *J* 13.5 Hz, NCH*H*Ph); δ_C (101 MHz, D_2O); 180.4, 161.7, 132.5, 131.9, 131.8, 131.6, 131.4, 130.9, 116.9, 77.1, 66.1, 58.1 and 51.6; $[\alpha]_D^{20} = -31.7$ (*c* 1.0 MeOH). *Compound* **8c**: mp 146–149 °C; *m*/*z* $C_{16}H_{17}NO_3$ requires 272.1286, found 272.1276; ν_{max} (thin film) 3399, 3058, 2845, 1600, 1454, 1369, 1124 and 697 cm^{-1}; δ_H (400 MHz, D_2O/MeOD); 7.44–7.10 (10H, m, ArH), 4.14 (1H, d, *J* 5.5 Hz N–C*H*), 4.10 (1H, d, *J* 5.5 Hz, O–C*H*), 3.92 (1H, d, *J* 13.5 Hz, NC*H*HPh) and 3.85 (1H, d, *J* 13.5 Hz, NCH*H*Ph); δ_C (101 MHz, D_2O/MeOD); 178.9, 135.1, 134.2, 132.3, 132.1, 131.9, 131.4, 130.7, 127.9, 75.4, 66.3 and 51.6; $[\alpha]_D^{20} = -51.9$ (*c* 0.95 MeOH).
17. *Crystal data for* **6a**: $C_{27}H_{26}N_2O_4$ *M* = 442.5, orthorhombic, $P2_12_12_1$, *a* = 9.5588(2), *b* = 10.2099(3), *c* = 22.1559(4) Å, *V* = 2162.29(9) $Å^3$, *Z* = 4, *D* = 1.359 g cm^{-3}, *F*(000) = 936. 3712 Independent reflections were collected on an Oxford Gemini S Ultra Image Plate System. The structures were solved by direct methods and refined on F^2 using SHELX97. Final *R* = 0.0417, weighted *R* = 0.1327. CCDC 717010 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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