

Application of Enantiopure Templated Azomethine Ylids to β -Hydroxy- α -amino Acid Synthesis

David Alker,^a Giles Hamblett,^b Laurence M. Harwood,^{c*} Sarah M. Robertson,^c David J. Watkin^b and C. Eleri Williams.^d

^aPfizer Central Research, Sandwich CT13 9NJ, UK.

^bChemical Crystallography Laboratory, Parks Road, University of Oxford, Oxford OX1 3PD, UK.

^cDepartment of Chemistry, University of Reading, Whiteknights, Reading RG6 6AD, UK.

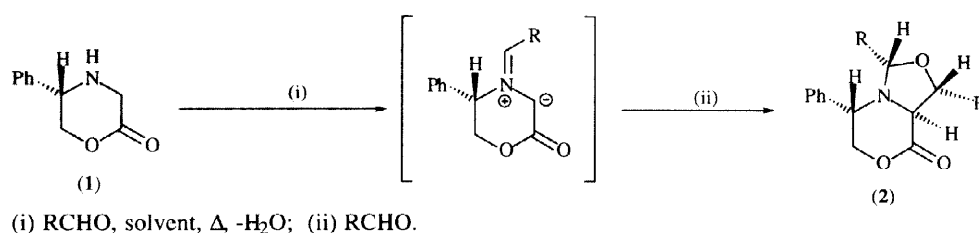
^dDyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK.

Received 12 February 1998; revised 1 April 1998; accepted 2 April 1998

Abstract: Chiral stabilised azomethine ylids derived from the reaction of (5*S*)-5-phenylmorpholin-2-one (**1**) with aldehydes undergo efficient and highly diastereocontrolled cycloaddition with a second molecule of aldehyde to furnish products (**2**) which may be converted into enantiomerically pure *threo* (2*S*,3*R*) β -hydroxy- α -amino acids (**3**) in excellent yield. © 1998 Elsevier Science Ltd. All rights reserved.

β -Hydroxy- α -amino acids are natural products and constituents of more complex organic compounds, often with interesting biological properties.^{1,2} The stereoselective synthesis of the β -hydroxy- α -amino acids has been approached in a variety of ways including Sharpless epoxidation,³ synthesis *via* oxazoline,⁴ imidazolidinone⁵ and oxazolidine intermediates,⁶ and also by using chiral catalysts⁷ and enzymatic transformations.⁸ However given the wide spread use of such acids in industry, further rapid and efficient methods need to be investigated. In this communication we wish to report the application of chirally templated azomethine ylids for the rapid and enantiocontrolled synthesis of β -hydroxy- α -amino acids.

In a series of papers we have reported that (5*S*)-5-phenylmorpholin-2-one (**1**) reacts with aldehydes under both thermal^{9a–h} or Lewis-acid catalysed conditions,⁹ⁱ generating azomethine ylid species capable of undergoing highly diastereoselective cycloadditions. Subsequent trapping of the reactive intermediate is possible with a range of electron deficient alkene or alkyne dipolarophiles whilst, in the absence of such a dipolarophile, a second molecule of aldehyde will participate in diastereocontrolled 1,3-dipolar cycloaddition with *E*-ylid to form cycloadducts (**2**) in good to excellent yields. The mechanism involves initial generation of an azomethine ylid possessing a single geometry, followed by cycloaddition of a second equivalent of aldehyde (Scheme 1).¹⁰



Scheme 1

These cycloadducts (**2**) represent fully and differentially pure β -hydroxy- α -amino acids and it was therefore decided to study the scope and limitations of this 1,3-dipolar cycloaddition reaction as a means of access to such targets. A range of aromatic and aliphatic aldehydes was reacted with (**1**) to furnish highly crystalline, bicyclic materials in good to excellent yields (**2a** – **h**) in each case. The results are summarised in **Table 1**.

R	Solvent	Cycloadduct (2)	Cycloadduct Yield (%)	$[\alpha]_D(\text{CHCl}_3)$
	toluene	a	69	-87.5
	toluene	b	61	-108.1
	toluene	c	45	-145.2
	toluene	d	50	-110.4
	toluene	e	51	-17.5
	benzene	f	86	+18.1
	benzene	g	80	+13.7
	toluene	h	80	-26.8

Table 1

In this instance three stereogenic centres have been constructed with high stereocontrol under the influence of the C-5 stereogenic atom in the morpholinone. The relative stereochemistry was initially deduced by n.O.e. difference measurements (mutual enhancements amongst H2, H7 and H9 proving particularly diagnostic) and subsequently in the case of (**2d**) and (**2g**), the *exo*-stereochemistry was verified by single crystal X-ray analysis (**Figure 1**).¹¹

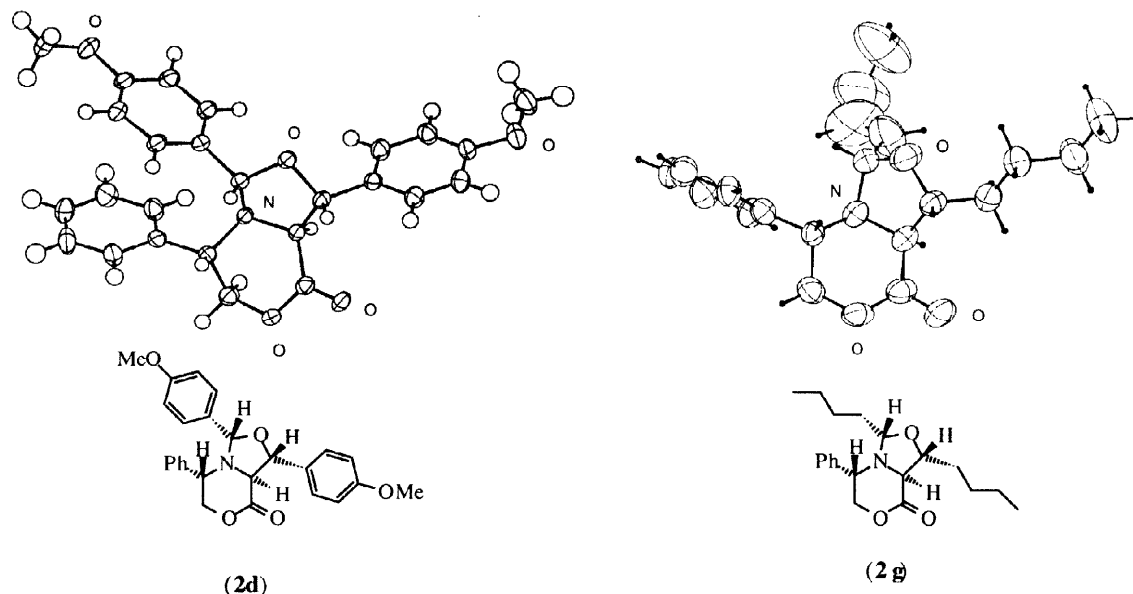


Figure 1

The rationale behind the observed stereocontrol in both ylid generation–trapping sequences invokes cycloaddition of the aldehyde dipolarophile with the least hindered geometric isomer of the azomethine ylid from the face opposite the 5-phenyl substituent (Figure 2).¹⁰

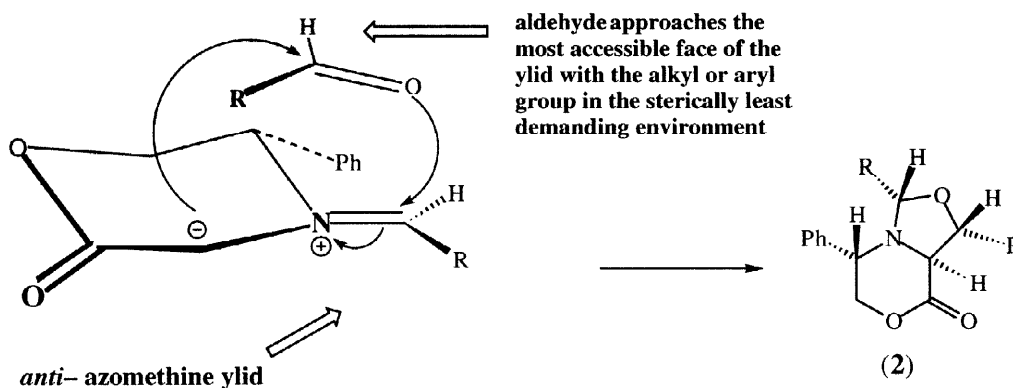
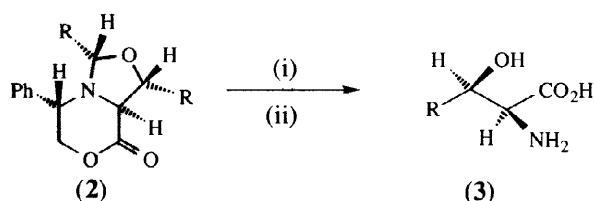


Figure 2

Recognising that cycloadducts (2a - h) prepared from aromatic and aliphatic aldehyde cycloadditions are differentially and orthogonally protected β -hydroxy- α -amino acids, it was proposed that subsequent removal of the morpholinone template under standard conditions developed in our laboratory¹² would generate *threo* (2*S*,3*R*) β -hydroxy- α -amino acids. The cycloadducts derived from aromatic aldehydes were subjected to hydrogenolysis conditions of 5 atm pressure in the presence of Pearlman's catalyst and TFA and furnished enantiopure amino acids (3a - d) directly and in good yield, purification being achieved by basic ion-exchange chromatography on Dowex® 1X8-200 (Dowex-1-chloride) (Scheme 2). Hydrogenolysis of cycloadduct (2c) afforded the free amino acid (3c) in which the aromatic nitro group had also been reduced. Unfortunately, hydrogenolysis of cycloadduct (2e) resulted in the degradation of starting material, probably involving reduction of the furan ring. The results are summarised in Table 2.



(i) Hydrogen (5 atm.), Pd(OH)₂/C, TFA (1 equiv.), aq. methanol;
(ii) Basic ion-exchange column.

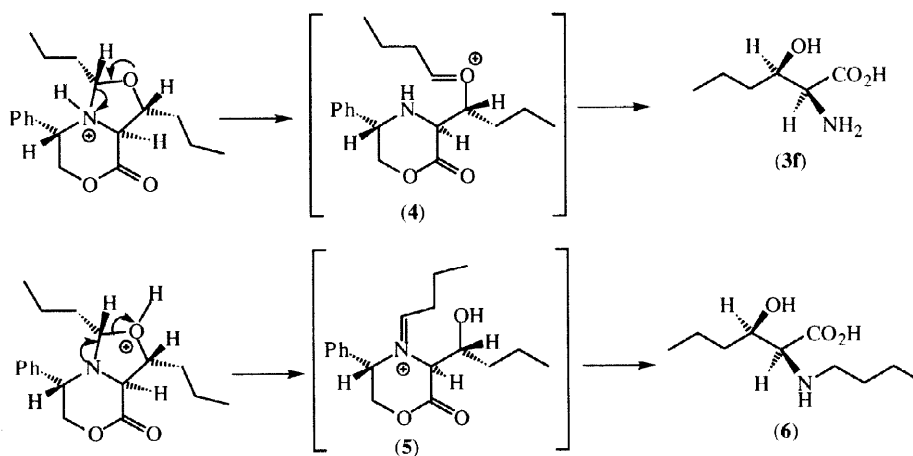
Scheme 2

Cycloadduct (2)	R	Isolated yield of amino acid (3) (%)	$[\alpha]_D^{25}(\text{H}_2\text{O}/\text{MeOH})$
a		65	-20.0
b		75	-22.2
c		84*	-7.5
d		76	-20.8
e		0	

* Concomitant reduction of the nitro-group occurred during hydrogenolysis.

Table 2

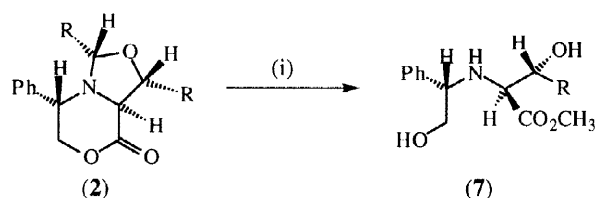
Subjecting cycloadduct (2f) to hydrogenolysis conditions led to the formation of two chromatographically inseparable products which were identified as the free amino acid and its *N*-alkylated counterpart (**Scheme 3**). Formation of the two products can be rationalized by a consideration of the order of bond cleavage of the oxazolidine ring generating either oxocarbenium species (4) which is susceptible to hydrolysis resulting in formation of the free amino acid (3f) or iminium species (5) which yields the *N*-alkylated product (6).



Scheme 3

Consequently it was decided to liberate the free amino acids in a two-step process involving hydrolysis of the oxazolidine ring followed by hydrogenolysis. A variety of conditions was assessed using cycloadduct

(**2d**) and it was found that refluxing the cycloadduct in methanol in the presence of 1 M HCl led to opening of the lactone with concomitant esterification to form amino ester (**7d**) and 4-methoxybenzaldehyde. Applying these optimum hydrolysis conditions to cycloadducts (**2e – h**) resulted in formation of amino esters (**7e – h**) as a single product in each instance (**Scheme 4**). The results are summarised in **Table 3**.



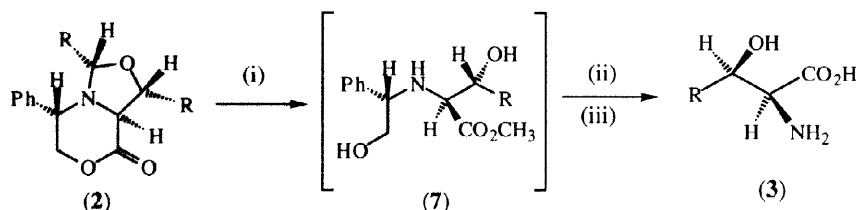
(i) 1M HCl, Methanol, Δ .

Scheme 4

Cycloadduct (2)	R	Isolated yield of amino ester (7) (%)	$[\alpha]_D(\text{CHCl}_3)$
d		40	+66.9
e		50	+46.5
f		43	+27.4
g		46	+31.2
h		50	+33.3

Table 3

The amino esters (**7**) were isolated for the purpose of characterisation but were obtained in disappointingly low yields. In all cases, tlc monitoring suggested the cycloadduct was converted to a single new product and we therefore suspected the amino ester was lost during work-up. In an attempt to resolve this problem, we investigated hydrogenolysis of the crude-hydrolysis reaction mixture, avoiding reaction work-up after the hydrolysis step. Thus, cycloadducts (**2a – d**) were refluxed in methanol in the presence of 1M HCl and, after complete consumption of starting material, the solvent was removed *in vacuo*. The crude reaction mixture was transferred directly into a Fischer–Porter Bottle and subjected to the previously optimised hydrogenolysis conditions. Pleasingly, the desired *threo* (2*S*,3*R*) β -hydroxy- α -amino acids (**3d – h**) were isolated in quantitative yield, after purification by basic ion-exchange chromatography and possessed specific rotations in accord with values reported in the literature (**Scheme 5**). In the case of cycloadduct (**2e**), concomitant reduction of the furan-ring during hydrogenolysis furnished amino acid (**3e**) as an inseparable 3 : 1 mixture of diastereoisomers (**Table 4**).



(i) 1 M HCl, MeOH, Δ ; (ii) Hydrogen (5 atm.), Pd(OH₂)/C, TFA (1 equiv.), aq. methanol; (iii) Basic ion-exchange column.

Scheme 5

Cycloadduct (2)	R	(3) $[\alpha]_D$ (H ₂ O/MeOH)
d		-19.8 (lit ¹³ -20.3)
e		*
f		+4.9 (lit ¹⁴ +4.5)
g		+7.8 (lit ¹⁵ +7.95)
h		+3.0

* Obtained as 3:1 mixture of diastereoisomeric tetrahydrofuran reduction products.

Table 4

In conclusion, we have demonstrated that aromatic and aliphatic aldehydes will undergo condensation with (*S*)-(1) to furnish chiral azomethine ylids which undergo diastereocontrolled 1,3-dipolar cycloadditions to furnish cycloadducts (2) in good to excellent yields. These cycloadducts are masked (2*S*,3*R*) β -functionalised α -amino acids and hydrogenolytic cleavage releases the enantiopure amino acids (3) in high yield where the 3*R*- group is an aryl moiety; whereas the hydrogenolysis of cycloadducts derived from aliphatic aldehydes is complicated by the formation of two inseparable products; the free amino acid and its *N*-alkylated counterpart. This can be circumvented by initial acid-catalysed hydrolysis of the oxazolidine ring of the cycloadduct to generate the amino ester (7) and subjecting the crude amino ester to hydrogenolysis, furnishing the corresponding *threo* (2*S*,3*R*) β -hydroxy- α -amino acid (3) in quantitative yield over the two steps.

Having achieved a flexible means of carrying out the diastereo- and enantiocontrolled synthesis of β -substituted α -amino acids we are in a position to capitalise upon this protocol to explore syntheses of specific target molecules. We will report further studies on the synthetic applications of this system in due course.

ACKNOWLEDGEMENTS

We thank Pfizer Central Research, E.P.S.R.C. and DTI for financial support of this work under the auspices of the Asymmetric LINK Scheme (to C. E. W.) and the University of Reading for postgraduate support under the R.E.T.F framework (to S. M. R.)

EXPERIMENTAL

General procedures Melting points were recorded using a Kofler heated-stage microscope. Mass spectrometric data were recorded on a VG Autospec or ZAB1F or TRIO-1 G.C. mass spectrometer under conditions of chemical ionisation (CI), or desorption chemical ionisation (DCI) using ammonia as the ionising source. Mass spectra are quoted in the form m/z (relative intensity). Microanalyses were performed on a Carlo Erba 1106 elemental analyser in the Dyson Perrins Laboratory, Oxford by Mrs V. Lamburn. Infra-red spectra were recorded on a Perkin Elmer 1750 FT-IR spectrometer as thin films or KBr discs as stated. ^1H NMR spectra were recorded in deuteriochloroform or deuterium oxide using a Jeol JNM EX400 (400MHz) and a Bruker AM500 (500 MHz). Peak positions were recorded in δ p.p.m., with the abbreviations s, d, t, dd, dt, m and b denoting singlet, doublet, double doublet, double triplet, multiplet and broad respectively. Nuclear Overhauser effect (n. O. e.) difference experiments were recorded on a Bruker AM500 spectrometer in the Dyson Perrins Laboratory by Mrs E. McGuinness. Optical rotation measurements were obtained using a Perkin Elmer 241 polarimeter. Column chromatography used Merck 60 silica gel and head pressure according to the method of Still.¹⁶ All reaction and chromatography solvents were distilled before use.

General method for the preparation of adducts from aldehyde cycloaddition (2)

Freshly distilled/recrystallised aldehyde (6 mmol, 3 equiv.) was added to a solution of the morpholin-2-one (**1**) (177 mg, 1 mmol, 1 equiv.) in calcium hydride dried toluene (for **a**, **b**, **c**, **d**, **e**, and **h**) or sodium dried benzene (for **f** and **g**) (60 mL). The flask was fitted with a magnetic stirrer bar, a Soxhlet extractor containing activated 3 Å sieves and a condenser. The reaction mixture was heated to reflux for 48 hours under nitrogen and solvent removed *in vacuo* to yield a pale yellow oil which solidified on cooling in the refrigerator. Recrystallisation from ether furnished the main crop of cycloadduct. Column chromatography of the mother liquor, eluting with ether–light petroleum 1 : 4, gave the remainder of the cycloadduct as well as permitting recovery of the excess starting aldehyde in the case of involatile aldehydes.

(2S,6S,7R,9S)-2,7,9-Triphenyl-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (**2a**)¹⁰

Colourless needles (256 mg, 69 %), m.p. 153–154 °C; ν_{max} (KBr disc) 1748 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.70–6.80 (m, 15H), 5.60 (d, J 7.0 Hz, 1H), 5.02 (s, 1H), 3.84 (d, J 7.0 Hz, 1H), 3.66 (dd, J 11.5, J' 9.9 Hz, 1H), 3.65 (dd, J 11.5, J'' 4.6 Hz, 1H) and 3.49 (dd, J 9.9, J' 4.6 Hz, 1H); m/z (DCI) 372 (100%, MH^+), 266 and 104; $[\alpha]_{\text{D}}^{23}$ -87.5 (c 1.0, CHCl_3).

(2S,6S,7R,9S)-2-Phenyl-7,9-di(4-fluorophenyl)-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (**2b**)

Colourless needles (248 mg, 61 %), m.p. 123–127 °C; $\text{C}_{24}\text{H}_{19}\text{NO}_3$ requires C, 70.7, H, 4.70, N, 3.4 %, found C, 70.8, H, 4.60, N, 3.2 %; ν_{max} (KBr disc) 1757 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.43–7.39 (m, 2H), 7.34–7.31 (m, 2H), 7.25–7.20 (m, 5H), 7.05 (m, 2H), 6.87 (m, 2H), 5.43 (d, J 7.6 Hz, 1H), 5.40 (s, 1H), 4.42 (t, J 11.2 Hz, 1H), 4.34 (dd, J 3.6, J' 11.7 Hz, 1H), 4.17 (d, J 7.5 Hz, 1H) and 4.15 (dd, J 3.6, J'' 10.7 Hz, 1H); m/z (DCI) 408 (100%, MH^+) and 284; $[\alpha]_{\text{D}}^{24}$ -108.1 (c 0.95, CHCl_3).

(2S,6S,7R,9S)-2-Phenyl-7,9-di(4-nitrophenyl)-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (**2c**)

Colourless needles (207 mg, 45 %), m.p. 188–190 °C; $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_7$ requires C, 62.5, H, 4.15, N, 9.1 %, found C, 62.3, H, 3.90, N, 9.2 %; ν_{max} (KBr disc) 1750 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 8.23 (d, J 8.8 Hz, 2H), 8.08 (d, J 8.8 Hz, 2H), 7.62 (d, J 8.7 Hz, 2H), 7.54 (d, J 8.7 Hz, 2H), 7.27–7.20 (m, 5H), 5.58 (s, 1H), 5.54 (d, J 8.0 Hz, 1H), 4.49 (dd, J 10.8, J' 11.7 Hz, 1H), 4.40 (dd, J 3.4, J' 11.8 Hz, 1H), 4.24 (dd, J 3.4, J' 10.8 Hz, 1H) and 4.19 (d, J 8.0 Hz, 1H); n.O.e. **H2** → **H7** (4.1%) → **H9** (8.3%), **H3** → **H2** (5.6%) → **H3** (12.8%), **H7** → **H2** (3.2%) → **H9** (5.4%), **H9** → **H2** (8.8%) → **H7** (6.0%); m/z (DCI) 462 (100%, MH^+) and 311; $[\alpha]_{\text{D}}^{20}$ -145.2 (c 0.54, CHCl_3).

(2S,6S,7R,9S)-2-Phenyl-7,9-di(4-methoxyphenyl)-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonane-5-one (**2d**)

Colourless needles (215 mg, 50 %), m.p. 170–172 °C; $\text{C}_{26}\text{H}_{25}\text{NO}_5$ requires C, 72.4, H, 5.85, N, 3.2%, found C, 72.2, H, 5.55, N, 3.1 %; ν_{max} (KBr disc) 1747 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.31–7.20 (m, 9H), 6.86 (d, J 8.4 Hz, 2H), 6.72 (d, J 8.4 Hz, 2H), 5.39 (s, 1H), 5.36 (d, J 7.7 Hz, 1H), 4.41 (dd, J 10.6, J' 11.4 Hz, 1H), 4.32 (dd, J 3.7, J' 11.7 Hz, 1H), 4.17 (dd, J 3.6, J' 10.6 Hz, 1H), 4.16 (d, J 7.7 Hz, 1H), 3.80 (s, 3H) and 3.75 (s, 3H); n.O.e. **H2** → **H7** (5.8%) → **H9** (10.5%), **H3** → **H6** (4.0%), **H7** → **H9** (3.8%), **H9** → **H7** (5.8%); δ_{C} (100 MHz, CDCl_3) 168.8, 159.7, 159.5, 136.3, 131.0, 130.4, 128.9, 128.5, 128.4, 128.3, 128.0, 127.8, 113.8, 113.6, 113.4, 97.1, 80.6, 72.0, 65.5, 59.4, and 55.2; m/z (CI) 432 (MH^+), $\text{C}_{26}\text{H}_{26}\text{NO}_5$ requires 432.1811, found 432.1821; $[\alpha]_{\text{D}}^{20}$ -110.4 (c 1.0, CHCl_3).

(2S,6S,7R,9S)-2-Phenyl-7,9-di(2-furyl)-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (**2e**)

Colourless needles (180 mg, 51 %), m.p. 174–177 °C; $\text{C}_{20}\text{H}_{17}\text{NO}_5$ requires C, 68.3, H, 4.90, N, 4.0 %, found C, 68.1, H, 4.70, N, 3.8 %; ν_{max} (KBr disc) 1750 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.46–7.31 (m, 7H), 6.33 (d, J 1.5 Hz, 2H), 6.29 (d, J 3.3 Hz, 1H), 6.24 (dd, J 1.8, J' 3.3 Hz, 1H), 5.57 (s, 1H), 5.30 (d, J 8.8 Hz, 1H), 4.67 (d, J 8.8 Hz, 1H), 4.40 (t, J 11.2 Hz, 1H), 4.31 (dd, J 3.1, J' 11.5 Hz, 1H) and 4.20 (dd, J 3.1, J' 10.9 Hz, 1H); n.O.e. **H2** → **H7** (6.6%) → **H9** (5.3%), **H7** → **H2** (4.2%) → **H9** (1.0%), **H9** → **H2** (3.4%); δ_{C} (100 MHz, CDCl_3) 166.7, 151.1, 150.5, 143.2, 142.8, 135.5, 129.0, 128.9, 128.0, 110.6, 110.0, 109.8, 108.5, 91.2, 91.1,

74.2, 74.1, 73.1, 62.7, 62.6 and 59.0; m/z (CI) 352 (MH^+ , 30 %) and 256, $C_{20}H_{18}NO_5$ requires 352.1185, found 352.1183; $[\alpha]_D^{25}$ -17.5 (c 0.6, $CHCl_3$).

(2S,6S,7R,9S)-2-Phenyl-7,9-dipropyl-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (2f)

Colourless needles (261 mg, 86 %), m.p. 77–80 °C; $C_{18}H_{25}NO_3$ requires C, 71.2, H, 8.30, N, 4.6 %, found C, 71.5, H 8.25, N 4.5 %; ν_{max} (KBr disc) 1 740 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.43–7.32 (5H, m), 4.36 (dd, J 4.7, J' 5.9 Hz, 1H), 4.31 (t, J 11.0 Hz, 1H), 4.23 (dd, J 3.3, J' 11.4 Hz, 1H), 4.17 (dt, J 3.2, J' 8.4 Hz, 1H), 3.92 (dd, J 3.5, J' 10.7 Hz, 1H), 3.82 (d, J 8.1 Hz, 1H), 1.95 (m, 1H), 1.59 (m, 2H), 1.48 (m, 1H), 1.23 (m, 4H), 0.98 (t, J 7.0 Hz, 3H) and 0.72 (t, J 7.0 Hz, 3H); n.O.e. $H_2 \rightarrow H_7$ (3.5%) $\rightarrow H_9$ (3.2%), $H_3 \rightarrow H_6$ (2.5%), $H_7 \rightarrow H_2$ (2.7%) $\rightarrow H_9$ (2.0%), $H_9 \rightarrow H_2$ (5.1%) $\rightarrow H_7$ (2.7%); δ_C (100 MHz, $CDCl_3$) 169.3, 137.1, 128.8, 128.1, 96.7, 78.5, 72.4, 63.3, 59.6, 37.6, 19.4, 14.0 and 13.7; m/z (CI) 304 (MH^+ , 28 %), 260 and 232, $C_{18}H_{26}NO_4$ requires 304.1913, found 304.1918; $[\alpha]_D^{24}$ +18.1 (c 1.0, $CHCl_3$).

(2S,6S,7R,9S)-2-Phenyl-7,9-dibutyl-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (2g)

Colourless needles (265 mg, 80%), m.p. 68–71 °C; $C_{20}H_{29}NO_3$ requires C, 72.5, H, 8.80, N, 4.2 %, found C, 72.3, H, 8.70, N, 4.0 %; ν_{max} (KBr disc) 1 733 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.40–7.31 (m, 5H), 4.36 (dd, J 10.3, J' 6.2 Hz, 1H), 4.31 (t, J 11.0 Hz, 1H), 4.22 (dd, J 3.5, J' 11.5 Hz, 1H), 4.16 (dt, J 3.3, J' 8.4 Hz, 1H), 3.92 (dd, J 3.3, J' 10.6 Hz, 1H), 3.82 (d, J 8.4 Hz, 1H), 2.01–1.94 (m, 1H), 1.64–1.53 (m, 2H), 1.50–1.32 (m, 3H), 1.31–1.01 (m, 6H), 0.93 (t, J 7.2 Hz, 3H) and 0.76 (t, J 7.2 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 169.3, 137.1, 128.8, 128.7, 128.3, 128.1, 96.9, 78.8, 72.4, 63.3, 59.7, 35.2, 34.6, 28.3, 26.5, 22.6, 22.3, 14.0 and 13.9; m/z (CI) 332 (MH^+ , 22 %) and 274, $C_{20}H_{30}NO_3$ requires 332.2226, found 332.2266; $[\alpha]_D^{24}$ +13.7 (c 1.0, $CHCl_3$).

(2S,6S,7R,9S)-2-Phenyl-7,9-dicyclohexyl-1-aza-4,8-dioxabicyclo[4.3.0]^{1,6}nonan-5-one (2h)¹⁰

Colourless needles (307 mg, 80 %), m.p. 164–165 °C; ν_{max} (KBr disc) 1 754 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.32–7.24 (m, 5H), 4.26 (dd, J 11.4, J' 10.8 Hz, 1H), 4.16 (dd, J 11.4, J' 3.7 Hz, 1H), 4.04 (dd, J 7.3, J' 4.2 Hz, 1H), 3.95 (d, J 4.8 Hz, 1H), 3.84 (d, J 7.7 Hz), 3.82 (dd, J 3.7, J' 10.6 Hz, 1H) and 1.81–0.67 (m, 22H); δ_C (100 MHz, $CDCl_3$) 169.9, 137.3, 128.6, 128.5, 128.3, 100.2, 100.1, 81.8, 71.8, 71.7, 59.8, 40.9, 40.7, 30.3, 29.5, 27.2, 26.5, 26.2, 26.1 and 25.6; m/z (CI) 384 (MH^+ , 100%), 300, 272, $C_{24}H_{34}NO_3$ requires 384.2539, found 384.2536; $[\alpha]_D^{20}$ -26.8 (c 0.6, $CHCl_3$).

General hydrolysis method for the preparation and isolation of amino esters (7)

To a solution of *bis*-aldehyde cycloadduct (**2d** – **h**) (0.2 mmol) in methanol (4 mL) was added 1 M HCl (1 mL) and the reaction mixture heated to reflux under nitrogen until reaction monitoring indicated the absence of starting material after 1–2 hours and the presence of a new compound. The solvent was removed *in vacuo* to yield a yellow oil which was poured into sodium carbonate (10 mL), extracted with ethyl acetate (6 x 15 mL), the combined organic extracts washed with brine (10 mL) and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield a colourless or pale yellow oil (in the case of cycloadduct (**2d**) the reaction mixture was purified by column chromatography to separate amino ester (**7d**) and 4-methoxybenzaldehyde).

Methyl (2S,3R,1'S)-2-(N-2'-hydroxy-1'-phenylethylamino)-3-hydroxy-3-(4-methoxyphenyl)propanoate (7d)
Colourless oil (28 mg, 40 %), ν_{max} (film) 1 736 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.78–7.75 (m, 5H), 7.18 (d, J 8.4 Hz, 2H), 6.93 (d, J 8.4 Hz, 2H), 4.67 (d, J 5.5 Hz, 1H), 3.72 (s, 3H), 3.56 (d, J 6.2 Hz, 2H), 3.40 (t, J 6.0 Hz, 1H), 3.30 (d, J 5.9 Hz, 1H), 3.26 (s, 3H) and 2.59 (bs, 2H); δ_C (100 MHz, $CDCl_3$) 172.4, 159.4, 138.4, 131.9, 128.7, 128.3, 127.6, 127.4, 113.8, 73.6, 66.5, 66.0, 64.9, 55.3 and 52.1; m/z (CI) 346 (5%, MH^+), 211, 178, 137, $C_{19}H_{24}NO_5$ requires 346.1655, found 346.1661; $[\alpha]_D^{20}$ +66.9 (c 1.0, $CHCl_3$). 4-Methoxybenzaldehyde (16 mg, 55 %) also recovered.

Methyl (2S,3R,1'S)-2-(N-2'-hydroxy-1'-phenylethylamino)-3-hydroxy-3-(2-furyl)propanoate (7e)

Yellow oil (30 mg, 50 %), ν_{max} (film) 1 736 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.41–7.15 (m, 6H), 6.35 (m, 2H), 4.90 (d, J 4.0 Hz, 1H), 3.65 (d, J 4.4 Hz, 1H), 3.60 (m, 2H), 3.55 (s, 3H) and 3.33 (m, 1H); δ_C (100 MHz, $CDCl_3$) 172.8, 153.7, 142.1, 139.8, 128.5, 127.9, 126.9, 110.6, 107.4, 68.6, 66.7, 64.0, 62.6 and 52.4; m/z (CI) 306 (MH^+ , 45 %), 288, 210, 178, $C_{16}H_{20}O_5N$ requires 306.1341, found 306.1356; $[\alpha]_D^{24}$ +46.5 (c 1.0, $CHCl_3$).

Methyl (2S,3R,1'S)-2-(N-2'-hydroxy-1'-phenylethylamino)-3-hydroxyhexanoate (7f)

Colourless oil (24 mg, 43 %), ν_{max} (film) 1 736 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.36–7.24 (m, 5H), 3.78–3.75 (m, 1H), 3.71–3.65 (m, 3H), 3.47 (s, 3H), 3.17 (d, J 5.1 Hz, 1H), 2.59 (bs, 2H), 1.54–1.43 (m, 2H), 1.40–1.34 (m, 2H) and 0.93 (t, J 7.1 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 174.0, 139.7, 128.6, 127.9, 127.3, 72.0, 66.4, 64.9, 64.1, 52.0, 35.9, 18.8, and 13.9; m/z (CI) 282 (MH^+ , 100 %), 250, 232, 210, $C_{15}H_{24}NO_4$ requires 282.1705, found 282.1710; $[\alpha]_D^{24}$ +27.4 (c 1.0, $CHCl_3$).

Methyl (2S,3R,1'S)-2-(N-2'-hydroxy-1'-phenylethylamino)-3-hydroxyheptanoate (7g)

Colourless oil (27 mg, 46 %), ν_{max} (film) 1 738 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.35–7.26 (m, 5H), 3.78–3.74 (m, 1H), 3.71–3.63 (m, 3H), 3.47 (s, 3H), 3.17 (d, J 5.1 Hz, 1H), 2.60 (bs, 2H), 1.49–1.48 (m, 3H), 1.32 (m, 3H) and 0.90 (t, J 7.0 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 174.3, 140.1, 128.7, 128.0, 127.3, 72.3, 66.5, 64.8, 64.0,

52.0, 33.5, 27.8, 22.6 and 14.0; m/z (CI) 296 (MH^+ , 75 %), 264, 210, 178, $C_{16}H_{26}NO_4$ requires 296.1862, found 296.1859; $[\alpha]_D^{24} +31.2$ (c 1.0, $CHCl_3$).

Methyl (2S,3R,1'S)-2-(N-2'-hydroxy-1'-phenylethylamino)-3-hydroxy-3-cyclohexyl-propanoate (7h)

Colourless oil (32 mg, 50 %), ν_{max} (film) 1 736 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.28–7.17 (m, 5H), 3.69–3.66 (m, 1H), 3.64–3.59 (m, 2H), 3.40 (s, 3H), 3.36–3.33 (m, 1H), 3.17 (d, J 4.4 Hz, 1H), 2.55 (bs, 2H) and 1.84–0.95 (m, 11H); δ_C (100 MHz, $CDCl_3$) 174.8, 140.2, 128.5, 127.8, 127.3, 66.5, 64.6, 60.9, 51.9, 40.2, 29.7, 27.7, 26.5, 26.1 and 25.9; m/z (CI) 332 (MH^+ , 30 %), 290, 210, 178, $C_{18}H_{28}NO_4$ requires 322.2018, found 322.2026; $[\alpha]_D^{23} +33.3$ (c 1.0, $CHCl_3$).

General method for the preparation of threo-(2S, 3R)-3-hydroxy-2-amino acids

Method 1:

The *bis*-aldehyde adduct (**2a – d**) (0.5 mmol) was suspended in 10% aqueous methanol (5 mL) in a Fischer–Porter bottle. TFA (0.5 mmol, 1 equiv.) and Pearlman's catalyst (1 equiv. by mass) were added to the stirring suspension, the solution degassed, subjected to hydrogen at 5 atm and left to stir for 48 hours. The solution was then centrifuged to remove the catalyst, the solvent removed *in vacuo* and the crude mixture purified on a Dowex® basic ion-exchange column and the washings concentrated *in vacuo* to yield a homogeneous product in each case.

Method 2:

To a solution of *bis*-aldehyde cycloadduct (**2d – h**) (0.2 mmol) in methanol (4 mL) was added 1 M HCl (1 mL) and the reaction mixture heated to reflux under nitrogen. Reaction monitoring indicated the absence of starting material after 1–2 hours and the presence of a new compound. The solvent was removed *in vacuo* and transferred to a Fischer Porter bottle. TFA (0.2 mmol, 1 equiv.), Pearlman's catalyst (1 equiv. by mass) and 2 mL methanol / 0.2 mL water were added to the reaction vessel and the solution degassed and subjected to hydrogen at 5 atm. for 48 hours. The solution was then centrifuged to remove the catalyst, the solvent removed *in vacuo* and the crude mixture purified on a Dowex® basic ion-exchange column.

(2S, 3R)-2-Amino-3-hydroxy-3-phenylpropanoic acid (3a)

Colourless solid (59 mg, 65 % Method 1); δ_H (500 MHz, CD_3OD) 7.51–7.29 (m, 5H), 5.23 (d, J 4.1 Hz, 1H) and 4.21 (d, J 4.3 Hz, 1H); δ_C (125.7 MHz, D_2O) 169.9, 142.4, 129.8, 129.1, 127.2, 60.7 and 53.7; m/z (DCI) 182 (100%, MH^+), $C_{10}H_{14}NO_3$ requires 182.0817, found 182.0834; $[\alpha]_D^{22} -20.0$ (c 0.8, MeOH).

(2S, 3R)-2-Amino-3-hydroxy-3-(4-fluorophenyl)propanoic acid (3b)

Colourless solid (74 mg, 75% Method 1), m.p. 195–198 °C (dec.); δ_H (500 MHz, D_2O) 7.50 (dd, J 8.6 Hz, J' 5.4 Hz, 2H), 7.10 (t, J 8.8 Hz, 2H), 5.28 (d, J 3.5 Hz, 1H) and 3.66 (d, J 3.6 Hz, 1H); m/z (DCI) 200 (100%, MH^+) and 182 (70%); $[\alpha]_D^{26} -22.2$ (c 1, H_2O).

(2S, 3R)-2-Amino-3-hydroxy-3-(4-aminophenyl)propanoic acid (3c)

Yellow powder (82 mg, 84 % Method 1), m.p. 203–206 °C; δ_H (500 MHz, D_2O) 7.31 (d, J 8.3 Hz, 2H), 6.98 (d, J 8.3 Hz, 2H), 5.19 (d, J 4.8 Hz, 1H) and 3.86 (d, J 4.8 Hz, 1H); δ_C (125.7 MHz, D_2O) 171.1, 131.1, 129.6, 126.3, 117.0, 70.2 and 59.9; $[\alpha]_D^{24} -7.5$ (c 1, H_2O).

(2S, 3R)-2-Amino-3-hydroxy-3-(4-methoxyphenyl)propanoic acid (3d)¹³

Colourless powder (80 mg, 76 % Method 1 and 42 mg, quant. Method 2), m.p. 182–184 °C; ν_{max} (KBr disc) 3 547, 3 156, 1 660 and 1 613 cm^{-1} ; δ_H (400 MHz, D_2O) 7.02 (d, J 8.8 Hz, 2H), 6.69 (d, J 8.8 Hz, 2H), 4.87 (d, J 4.8 Hz, 1H), 3.51 (d, J 4.8 Hz, 1H) and 3.49 (s, 3H); δ_C (100 MHz, D_2O) 172.9, 159.7, 132.5, 128.2, 115.1, 71.8, 61.7 and 56.2; m/z (CI) 212 (MH^+ , 20 %), 194, 166, 150, 137, $C_{10}H_{14}NO_4$ requires 212.0924, found 212.0923; $[\alpha]_D^{24} -20.8$ (c 1.0, H_2O) (lit.¹³ -20.3 (c 1.0, H_2O)).

(2S,3R)-2-Amino-3-hydroxy-(2-tetrahydrofuran)propanoic acid (3e)

Colourless powder (35 mg, quant. Method 2), m.p. 162–165 °C; ν_{max} (KBr disc) 3 405, 3242, 2 961, 2 876, 2 362, 2 330 and 1 674 cm^{-1} ; δ_H (400 MHz, D_2O) 3.86 (m, 3H), 3.72 (m, 1H), 3.65 (m, 1H) and 1.80 (m, 4H); δ_C (100 MHz, D_2O) 173.7, 81.4, 70.8, 69.6, 58.9, 28.2 and 26.1, m/z (CI) 176 (MH^+ , 100 %), 130, and 114, $C_7H_{14}NO_4$ requires 176.0923, found 176.0919.

(2S,3R)-2-Amino-3-hydroxyhexanoic acid (3f)¹⁴

Colourless powder (29 mg, quant. Method 2), m.p. 181–183 °C; ν_{max} (KBr disc) 3 381, 3 133, 1 669 and 1 620 cm^{-1} ; δ_H (400 MHz, D_2O) 3.91 (m, 1H), 3.47 (d, J 4.7 Hz, 1H), 1.42 (m, 1H), 1.38 (m, 1H), 1.25 (m, 2H) and 0.77 (t, J 7.3 Hz, 3H); δ_C (100 MHz, D_2O) 173.9, 70.2, 60.1, 36.1, 19.2 and 13.7; m/z (CI) 148 (MH^+ , 100 %), 130, 102, $C_6H_{14}NO_3$ 148.0974, found 148.0972; $[\alpha]_D^{25} +4.9$ (c 1.0, H_2O) (lit.¹⁴ +4.5 (c 2.0, H_2O)).

(2S,3R)-2-Amino-3-hydroxy-heptanoic acid (3g)¹⁵

Colourless powder (32 mg, quant. Method 2), m.p. 208–210 °C; ν_{max} (KBr disc) 3 439, 3 275, 3 140, 1 669 and 1 620 cm^{-1} ; δ_H (400 MHz, D_2O) 3.89 (m, 1H), 3.46 (d, J 4.7 Hz, 1H), 1.42 (m, 2H), 1.25 (m, 1H), 1.18 (m, 3H) and 0.72 (t, J 7.1 Hz, 3H); δ_C (100 MHz, D_2O) 173.9, 70.5, 60.2, 33.8, 28.0, 22.5, and 14.1; m/z (CI)

162 (MH⁺, 100 %), 141, 128, 116, 100, C₇H₁₆NO₃ requires 162.1130, found 162.1138; [α]_D²⁴ +7.8 (c 0.9, H₂O) (lit.¹⁵ +7.95 (c 0.9, H₂O)).

(2S,3R)-2-Amino-3-cyclohexyl-3-hydroxypropanoic acid (3h)¹⁷

Colourless powder (37 mg, quant. Method 2), m.p. 199–202 °C; $\nu_{\max}$ (KBr disc) 3 446, 3 254, 3 095, 1 653 and 1 635 cm⁻¹; δ_{H} (400 MHz, D₂O) 3.69 (d, *J* 3.3 Hz, 1H), 3.65 (d, *J* 3.5, *J'* 8.2 Hz, 1H) and 1.79–0.94 (m, 11H); δ_{C} (100 MHz, D₂O) 174.0, 75.4, 57.9, 41.9, 31.0, 30.0, 27.5 and 27.4; *m/z* (CI) 188 (MH⁺, 92 %), 170, 142, 126, C₉H₁₈NO₃ requires 188.1287, found 188.1287; [α]_D²⁰ +3.0 (c 1.0, MeOH).

REFERENCES

- 1 Saeed, A. and Young, D.W.; *Tetrahedron*, 1992, **48**, 2507 and references therein.
- 2 Kimura, T.; Vassilev, V. P.; Shen, G.-J. and Wong, C.-H.; *J. Am. Chem. Soc.*, 1997, **119**, 11734–11742.
- 3 Jung, M. E. and Jung, Y. H.; *Tetrahedron Lett.*, 1989, **30**, 6637–6640.
- 4 Aebi, J. D. and Seebach, D.; *Tetrahedron Lett.*, 1983, **24**, 3311–3314.
- 5 Seebach, D.; Juaristi, E.; Miller, D.; Schickli, C. and Weber, T.; *Helv. Chim. Acta.*, 1987, **70**, 287.
- 6 Aebi, J. D. and Seebach, D.; *Tetrahedron Lett.*, 1984, **25**, 2545–2548.
- 7 Ito, Y.; Sawamura, M. and Hayashi, T.; *J. Am. Chem. Soc.*, 1986, **108**, 6405–6406.
- 8 Vassilev, V. P.; Uchiyama, T.; Kajimoto, T. and Wong, C.-H.; *Tetrahedron Lett.*, 1995, **36**, 4081–4084.
- 9 (a) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. J.; *Tetrahedron Asymmetry*, **1991**, **2**, 169–172. (b) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. J.; *Tetrahedron Asymmetry*, **1991**, **2**, 997–1000. (c) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. J.; Wong, L. F.; *Tetrahedron Asymmetry*, **1991**, **2**, 1343–1358. (d) Harwood, L. M.; Lilley, I. A.; *Tetrahedron Lett.*, **1993**, 537–540. (e) Harwood, L. M.; Kitchen, L. C.; *Tetrahedron Lett.*, **1993**, 6603–6606. (f) Harwood, L. M.; Lilley, I. A.; *Tetrahedron Asymmetry*, **1995**, **6**, 1557–1560. (g) Anslow, A. S.; Cox, G. G.; Harwood, L. M.; *Chemistry of Heterocyclic Compounds*, **1995**, **10**, 1393–1401. (h) Anslow, A. S.; Harwood, L. M.; Lilley, I. A.; *Tetrahedron Asymmetry*, **1995**, **6**, 2465–2568. (i) Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D. J.; Williams, C. E.; *Synlett*, **1993**, 777–780.
- 10 Harwood, L. M.; Macro, J.; Watkin, D. J.; Williams, C. E.; Wong, L. F.; *Tetrahedron Asymmetry*, **1992**, **3**, 1127–1130.
- 11 Crystal data for (2d); C₂₆H₂₅NO₅, monoclinic, P2₁, *a*=13.385, *b*=5.922, *c*=15.180 Å, β =115.14 °, *V*=1089.08 Å³, *z*=2, *D_x*=1.32 Mg m⁻³. 2772 independent reflections with *I*>3 σ (*I*) were used in the analysis. Data for crystallographic analysis were measured ($\theta_{\max}$ =72 °) on an Enraf Nonius CAD-4 diffractometer using Cu K α radiation and 2 θ / ω scans. Crystal data for (2g); C₂₀H₂₉NO₃, monoclinic, P1₁, *a*=5.466, *b*=11.021, *c*=17.188 Å, β =108.57 °, *V*=966.50 Å³, *z*=2, *D_x*=1.390 g cm⁻³. 1727 independent reflections with *I*>3 σ (*I*) were used in the analysis. Data for crystallographic analysis were measured ($\theta_{\max}$ =144 °) on an Enraf Nonius CAD-4 diffractometer using Cu K α radiation and 2 θ / ω scans. Both structures were solved using the CRYSTAL package. and atomic co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.
- 12 Cox, G. G. and Harwood, L. M.; *Tetrahedron Asymmetry*, 1994, **5**, 1669–1672.
- 13 Blaser, D. and Seebach, D.; *Liebigs Ann. Chem.*, 1991, 1067–1078.
- 14 Ariyoshi, Y.; Yasuda, N. and Yamatani, T.; *Bull. Chem. Soc. Jpn.*, 1974, **47**, 326–330.
- 15 Stucky, G. and Seebach, D.; *Chem. Ber.*, 1989, **122**, 2365–2375.
- 16 Still, W. C.; Khan, M.; Mitra, A.; *J. Org. Chem.*, 1978, **43**, 2923–2925.
- 17 Guanti, G.; Banfi, L.; Narisano, E.; *Tetrahedron*, 1988, **44**, 5553–5567.