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The Origin of the Stereoselectivity in the Aldol Reactions of β-Boronate Carbonyl Derivatives.

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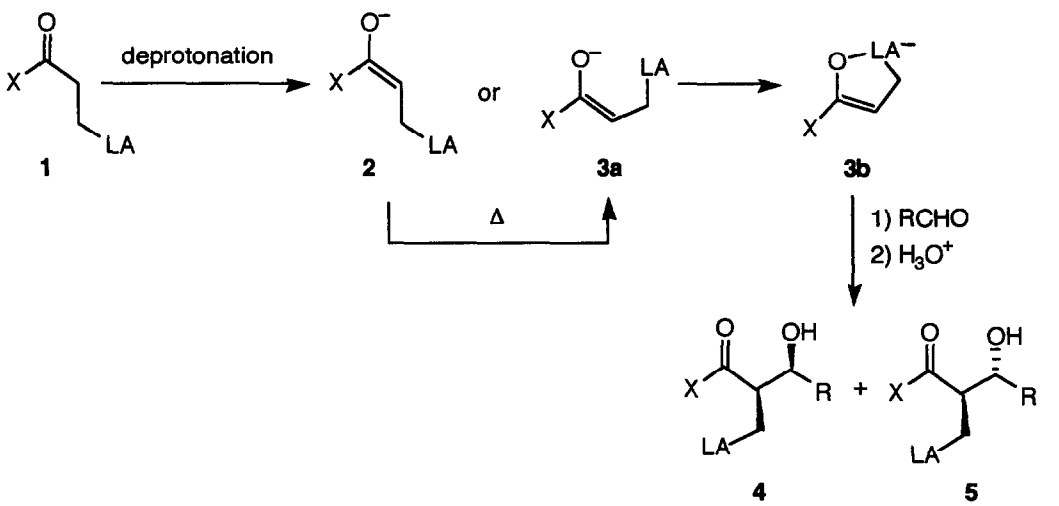
Abstract: β-Boronate carbonyl derivatives can be readily deprotonated using LDA and reaction of the resulting enolates with aldehydes gives the corresponding aldol products, with high *syn*-selectivity for *Z*-enolates with both benzaldehyde and pivaldehyde. Moderate to good *syn*-selectivity is observed for *E*-enolates. These results are consistent with chelation enhanced stabilisation of the enolate geometry via the boronate moiety and chelation enhanced locking of the resulting aldolate stereochemistry

The aldol reaction has found countless applications in organic synthesis for the preparation of natural products[1] and the control of the enolate geometry has a profound effect upon the stereochemistry of the final aldol products[2,3]; as does the nature of the metal[3,4]. With a view to finding new methods for achieving stereoselectivity in the aldol reaction, we wished to investigate the effect of an intramolecular Lewis-acidic group upon the stereochemical outcome of an aldol reaction, as exemplified in **Scheme 1**[5].

Scheme 1.

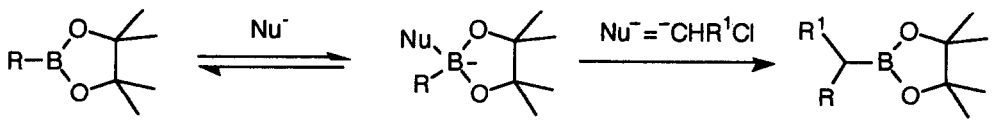


Thus, a group (LA) in structure **1** might intramolecularly stabilise the *Z*-enolate of **1**, i.e. *via* complex **3b**. Assuming that the stabilised enolate **3b** could be prepared at the expense of enolate **2**, a subsequent aldol reaction with an aldehyde should afford *syn*-aldol **4** rather than *anti*-aldol **5**.

It was our hope that for any X substituent in structure **1**, the *cis*- or *Z*-enolate **3** would be accessible directly by kinetic deprotonation[4] (if X = Ar, alkyl or NR_2) or indirectly by equilibration of the *trans*-enolate (or E-enolate) **2** using the intramolecular stabilisation of **3** to trap the *cis*-enolate, as shown in **Scheme 1**. Hence an ensuing *syn*-selective aldol reaction should result when enolates of type **3b** are reacted with aldehydes, providing a stereoselective route to aldol products **4**, rather than **5**. Herein we report the full details of our endeavours towards realising the application of an intramolecular Lewis-acid[6,7] for assisting stereoselection in the aldol reaction[8,9].

After considering the possible types of Lewis-acidic functions (LA) that may be applicable to the chemistry envisaged in **Scheme 1**, we decided that an alkyl boronate such as pinacol ester **6** would serve most usefully (**Scheme 2**). This conclusion was based upon the fact that hindered boronates are reasonably stable under thermal, basic, and acidic conditions[10]. Also, boronate esters can be treated with hard nucleophiles to give intermediate "ate"-complexes such as **7**[11], which can be collapsed to the corresponding homologated derivatives **8**, if the incoming nucleophile possesses a leaving group such as chloride.

Scheme 2.

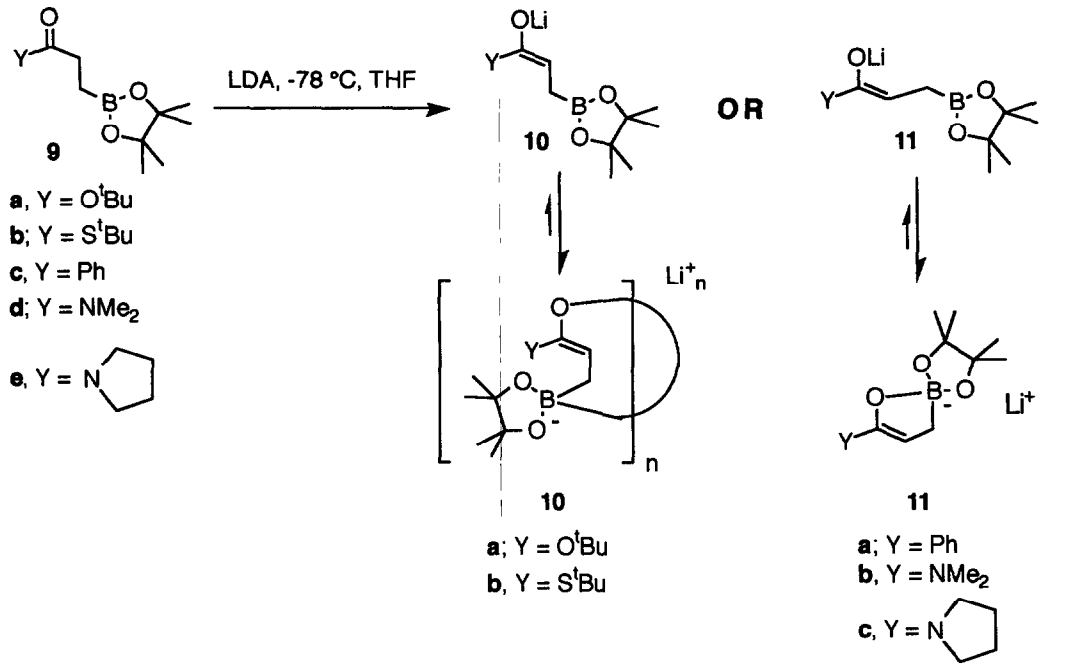


6 **7** **8**

We therefore required a general route to derivatives of type **1** where LA = boron[3], i.e. the β-boronate derivatives **9**, and subsequently reported a general process for conveniently preparing these compounds[6,7]. We also found that the deprotonation of boronates **9** with lithium diisopropylamide (LDA) gave the same kinetic enolates **10** (≥ 90 % *E*-enolate) and **11** (≥ 95 % *Z*-enolate) (**Scheme 3**) that would be expected for the corresponding propionate compounds[8,2], and both enolates **10** and **11** are thermally stable, e.g. kinetic *E*-enolate **10a** does not interconvert into the thermodynamic *Z*-enolate, as had been envisaged in **Scheme 1**, upon allowing the enolate to warm to room temperature. Both enolates **10** and **11** behave similarly to normal three coordinate boron enolates, which are generally quite stable at room temperature and can often be isolated[12]. On the basis of this information and observation of the ^{11}B n.m.r. spectrum of examples of both the *E*- and *Z*-enolates (all appear at δ ~0; ext. ref. $BF_3.Et_2O$)[13,6], we propose that *deprotonation of ester and thioester compounds* ***9a*** *and* ***9b*** *with LDA afford intermolecularly complexed E-enolates* ***10a*** *and* ***10b*** *respectively. Whereas phenone and amide compounds* ***9c-e*** *afford intramolecularly complexed enolates* ***11a-c*** *respectively.*

Having established that deprotonation of boronates **9** occured smoothly, we turned to the aldol reactions of the resulting enolates **10** and **11**, firstly with benzaldehyde[8] and then with pivaldehyde, as shown in **Equation 1**. For each of the examples shown in **Equation 1**, we deprotonated under standard conditions with LDA and then added benzaldehyde or pivaldehyde.

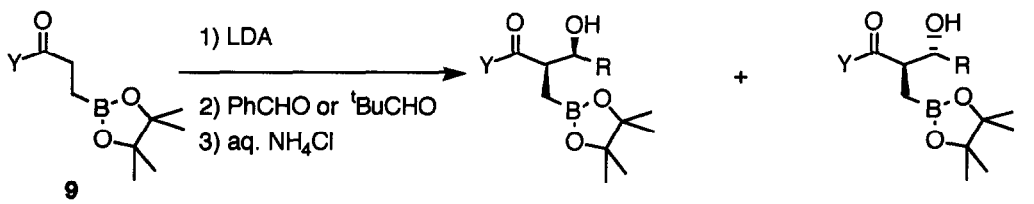
Scheme 3.



The ensuing aldol reactions were slower than normal lithium mediated reactions, i.e. approxmately 1 hour versus a few minutes at -78 °C[14]. After quenching the reactions with aqueous ammonium chloride at -78 °C[15], we could isolate the free aldol products in each case but attempts to purify the crude aldol products by chromatographic techniques proved unsuccessful due to deesterification of the boronate ester. We therefore determined the diastereomeric ratio of the aldol products on the crude reaction mixtures by 300 MHz ^{1}H n.m.r. after removing exchangeable hydrogens with D_2O. The diastereomeric ratios[16] observed are shown in **Equation 1**, the identification of the *syn*- and *anti*-diastereoisomers was accomplished as shown in **Equation 2**, i.e. by oxidation of the boron-carbon bond followed by isopropylidenation to afford derivatives **14** and **15**.

From the results shown above (**Equation 1**), it is clear that ester and thioester enolates derived from compounds **9a** and **9b** give poor stereoselection, in a comparable way to normal lithium enolates with benzaldehyde[17]. However in contrast to normal alkali metal aldolate[18] products, the boron containing aldol products obtained (i.e. **12a / 13a** and **12b / 13b**) are stable in their aldolate form, even at elevated temperatures. For example, when an approximately 1:1 mixture of aldol products **12a** and **13a** was treated with an excess of sodium hydride at room temperature in tetrahydrofuran, no noticeable change in the ratio of **12a** to **13a** or quantity of material recovered (after acidification, aqueous ammonium chloride) was observed even after 24 h.

Equation 1.



9

a; Y = O^{t}Bu
b; Y = S^{t}Bu
c; Y = Ph
d, Y = NMe_2
e; Y = N

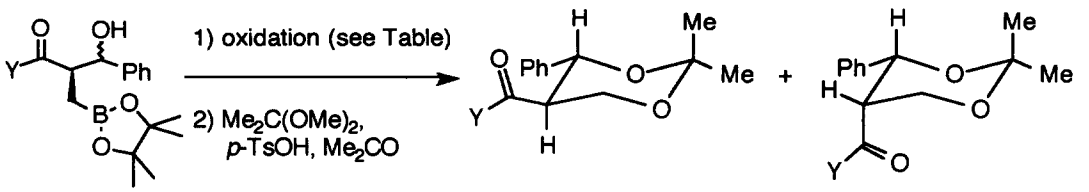
12	*syn* : *anti*	13
a; Y = O^{t}Bu, R = Ph	60 · 40	**a**, Y = O^{t}Bu, R = Ph
b; Y = S^{t}Bu, R = Ph	53 . 47	**b**; Y = S^{t}Bu, R = Ph
c, Y = Ph, R = Ph	96 · 4	**c**; Y = Ph, R = Ph
d; Y = NMe_2, R = Ph	95 . 5	**d**, Y = NMe_2, R = Ph
e; Y = O^{t}Bu, R = ^{t}Bu	88 · 12	**e**; Y = O^{t}Bu, R = ^{t}Bu
f; Y = S^{t}Bu, R = ^{t}Bu	82 · 18	**f**, Y = S^{t}Bu, R = ^{t}Bu
g; Y = Ph, R = ^{t}Bu	≥96 4	**g**; Y = Ph, R = ^{t}Bu
h; Y = NMe_2, R = ^{t}Bu	≥91 : 9	**h**; Y = NMe_2, R = ^{t}Bu
i, Y = N, R = ^{t}Bu	≥93 : 7	**i**; Y = N, R = ^{t}Bu

Therefore, aldol products **12** and **13** do not undergo thermodynamically driven equilibration of the *syn*- to the *anti*-diastereoisomers, presumably due to formation of internal chelates **16** and **17** respectively, in which the boronate strongly coordinates the aldolate oxygen in both *syn*- and *anti*-aldolates. Their non-boron substituted normal lithium aldolate counterparts differ in that the *syn*-aldolates may exist in forms **18a** or **19a** and the *anti*-aldolates in forms **20a** and **21a** or open-chain chelates[2], which can undergo equilibration

By comparison normal boron aldolate products are thermodynamically stable[19] due to strong oxygen to boron chelation, again in both *syn*- and *anti*-configurations, i e **18b** and **19b** versus **20b** and **21b**. Hence, by analogy, the boronate aldolates **16** and **17** behave more like normal boron aldolates **18b-21b** rather than lithium enolates **18a-21a**

Although it is possible to understand how the β-boronate aldol products **12** and **13** are configurationally stable once prepared, the origin of the stereoselectivity is less clear. The enhanced *syn*-selectivity for the E-enolates **10** with pivaldehyde versus benzaldehyde is surprising (**12a** and **12b** versus **12e** and **12f**, **Equation 1**), we had expected enhanced *anti*-selectivity upon changing the aldehyde from benzaldehyde to the more hindered pivaldehyde, as observed for lithium E-enolates by Heathcock[20]. The high *syn*-selectivity for the Z-enolates **11** can be explained by a Zimmerman-Traxler like transition-state[21] of type **22**, i e the boronate moiety is axially arranged and can move from the enolate oxygen to the aldolate oxygen as the reaction procedes and hence equilibration is unable to take place

Equation 2.



12 and / or **13**

a; Y = O^{t}Bu
b; Y = S^{t}Bu
c; Y = Ph
d; Y = NMe_2

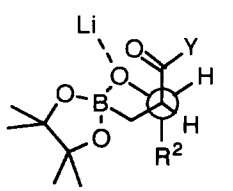
14

a; Y = O^{t}Bu
b; Y = S^{t}Bu
c; Y = Ph
d; Y = NMe_2

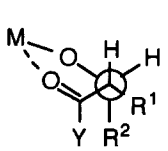
15

a; Y = O^{t}Bu
b; Y = S^{t}Bu
c; Y = Ph
d; Y = NMe_2

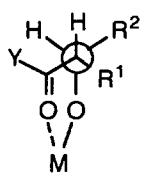
A similar transition-state to **22** is unlikely for the E-enolates **10**, since enhanced *anti*-selectivity is not observed[8]. It is more likely that the E-enolates may reversibly complex the aldehydes as shown in **Equation 3**, leading to two possible transition-states **23** and **24**, resembling the acyclic aldol transition-states proposed by Mulzer and Noyori[22]. When benzaldehyde is used, these two transition-states are of similar energy and we observe roughly equal amounts of both aldol products **12a** and **12b** versus **13a** and **13b**. However, when the more hindered pivaldehyde is used, transition-state **23** becomes more favoured due to orientation of the *tert*-butyl group away from the enolate *tert*-butyloxy or *tert*-butylthio substituents.



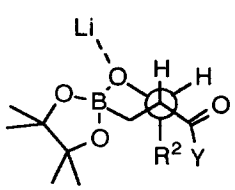
16



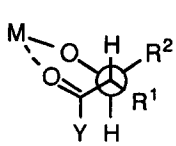
18



19



17



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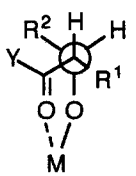
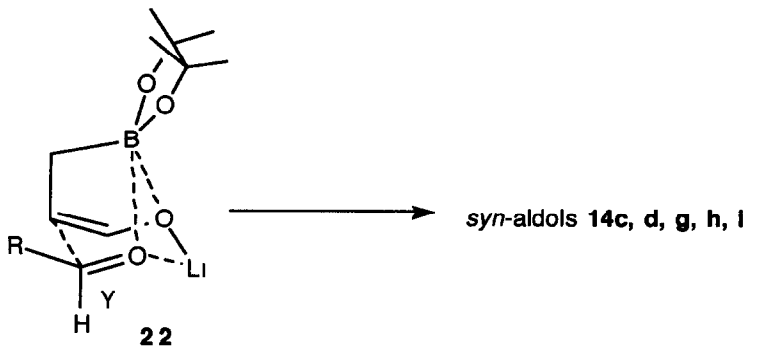


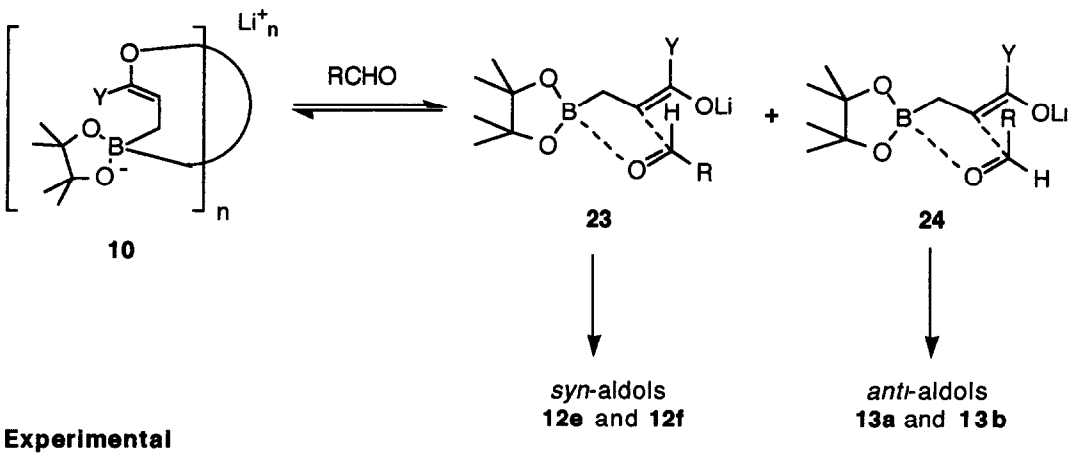
21

a; M = Li
b; M = BR^3_2

Equation 3.



Equation 4.



Experimental

n-Butyllithium was purchased as a solution in hexanes from Aldrich or Janssen Chimica Diisopropylamine was purchased from Aldrich or Janssen Chimica and stored under argon, over KOH pellets Dry tetrahydrofuran was freshly distilled from benzophenone and sodium, under argon, immediately prior to use Dichloromethane was distilled over calcium hydride Light petroleum refers to the fraction boiling in the range 40-60 °C Pivaldehyde was purchased as 99.8 % + purity reagent and used directly as purchased and stored under argon. Benzaldehyde was distilled from calcium hydride and stored under argon

T.l.c. was performed on Merck plastic or aluminium sheets coated with silica gel 60 F_{254} (Art. 5735), the chromatograms were initially examined under u.v. light and then developed either with iodine vapour or an ethanolic anisaldehyde (1.0 %) solution containing sulfuric acid (9%) used as a spray and visualised by heating with a heat gun Column chromatography was achieved under medium pressure, using Merck Kieselgel H (Type 60).

All anhydrous, low temperature reactions were carried out in glassware which was dried prior to use by storage in a glass oven maintained at 140 °C and cooled under a stream of argon Evaporations were carried out using a Buchi rotary evaporator or Buchi cold-finger rotary evaporator. Kugelruhr distillations were carried out using a Buchi GKR-51 Kugelruhr apparatus. M.p 's were determined using an Electrothermal melting point apparatus and were uncorrected. ^1H spectra were recorded at 200 or 300 MHz on a Bruker AC200 or AC300 n m.r. spectrometer. ^{13}C spectra were recorded at 75.6 MHz on a Bruker AC300 Both ^1H and ^{13}C spectra were recorded

using $CDCl_3$ and $CHCl_3$ as internal standards respectively. ^{11}B N.m.r. spectra were recorded at either 25.7 MHz Bruker WP80 n.m.r. spectrometer or at 64.2 MHz on a Bruker AC200 n.m.r. spectrometer and resonances are quoted upfield of $BF_3.Et_2O$ as external standard. I r. spectra were recorded on a Perkin-Elmer 783 equiped with a PE600 data station and u.v. spectra were recorded on a Perkin-Elmer λ15 spectrometer. Electron impact (e.i) (70 e.v.) and chemical ionisation (c.i.) spectra were recorded with a Kratos MS25. Fast atom bombardment (f.a.b.) spectra were recorded on a Kratos MS50, using a *meta*-nitrobenzylalcohol matrix and accurate mass determinations were carried out on a Kratos Concept IS spectrometer Microanalyses were performed using a Carlo-Erba 1106 elemental analyser.

Method 1. Preparation of aldol products 12a and 13a. To a stirred solution of LDA [prepared from diisopropylamine (0.383 ml, 2 75 mmol), n-BuLi (1.10 ml of a 2.5 M solution in hexanes, 2.75 mmol), and dry, redistilled tetrahydrofuran (4.0 ml) at 0 °C] at -78 °C under argon, was added neat boronate **9a** (0.640 g, 2.50 mmol). After 1h, benzaldehyde (0.279 ml, 2.75 mmol) was added and the mixture stirred for a further 2-3 h at -78 °C. The mixture was quenched with saturated ammonium chloride, allowed to warm to room temperature, extracted with ethyl acetate, dried ($MgSO_4$) and evaporated. Crude aldol products **12a** and **13a** were isolated in essentially quantitive crude yield and the diastereomeric ratios were determined from the D_2O exchanged 300 MHz ^1H n.m r. spectrum[16]; υ_{max} (film) *inter alia* 3450 br (OH), and 1730 (C.O) cm^{-1}; λ_{max} (EtOH) 208 (ε 8,370), 252 (ε 340), 258 (ε 370), 264 (ε 340), and 282 (ε 250) nm, δ (^1H, $CDCl_3$, 300MHz) major diastereoisomer. 1.22 (12H, s, 2 x C.Me_2), 1.20-1 30 and 1.40-1.50 (each 1H, m, B.CH_2), 1 37 (9H, s, C.Me_3), 2.82-2.92 (1H, m, O C CH), 5.00 (1H, d, J = 5.3 Hz, Ph C<u>H</u>), and 7 28-7.36 (5H, m, Ph); minor diastereoisomer. 1 21 (12H, s, 2 x C.Me_2), 1.20-1.30 and 1.40-1.50 (each 1H, m, B.CH_2), 1 38 (9H, s, C.Me_3), 2.82-2.92 (1H, m, O·C CH), 4.80 (1H, d, J = 6.5 Hz, Ph C<u>H</u>), and 7 28-7.36 (5H, m, Ph), ratio of major · minor = 57 43; m/z (+ve c i.) 363 (M^++ H), 262 (M^+ - $C_6H_{12}O$), and 58 (base peak, C_3H_6O).

Preparation of aldol products 12b and 13b via Method 1. Prepared as above using LDA [from diisopropylamine (0.383 ml, 2.75 mmol), n-BuLi (1.10 ml of a 2 5 M solution in hexanes, 2 75 mmol), tetrahydrofuran (4.0 ml)], boronate **9b** (0 680 g, 2 50 mmol), and benzaldehyde (0.279 ml, 2.75 mmol). Crude aldol products **12b** and **13b** were isolated in essentially quantitive crude yield and the diastereomeric ratios were determined from the D_2O exchanged 300 MHz ^1H n m r spectrum[9]; υ_{max} (film) *inter alia* 3475 br (OH), and 1760 (C.O) cm^{-1}; λ_{max} (EtOH) 206 (ε 10,205), 238 (ε 5,200), and 276 (ε 3,520) nm, δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer 1 26 (12H, s, 2 x C.Me_2), 1 20-1 30 and 1 40-1 50 (each 1H, m, B CH_2), 1.41 (9H, s, C Me_3), 2 95-3.05 (1H, m, O·C.CH), 4 85 (1H, d, J = 6 5 Hz, Ph C<u>H</u>), and 7 28-7.36 (5H, m, Ph); minor diastereoisomer 1.21 (12H, s, 2 x C.Me_2), 1.20-1 30 and 1 40-1.50 (each 1H, m, B CH_2), 1.40 (9H, s, C Me_3), 2 82-2.92 (1H, m, O C CH), 5 05 (1H, d, J = 5 3 Hz, Ph C<u>H</u>), and 7 28-7 36 (5H, m, Ph), ratio of major . minor = 57 43, m/z (f a b.) 379 (base peak, M^+ + H), 361 (M^+ - HO), and 305 (base peak, M^+ - $C_3H_6O_2$).

Preparation of aldol products 12c and 13c via Method 1. Prepared as above using LDA [from diisopropylamine (0 383 ml, 2.75 mmol), n-BuLi (1 10 ml of a 2.5 M solution in hexanes, 2.75 mmol), tetrahydrofuran (4.0 ml)], boronate **9c** (0 650 g, 2 50 mmol), and benzaldehyde (0 279 ml, 2 75 mmol) Crude aldol product **12c** was isolated in essentially quantitive crude yield and the diastereomeric ratio was determined by the D_2O exchanged 300 MHz ^1H n m r spectrum[9], υ_{max} (film) *inter alia* 3400 br (OH), and 1680 (C.O) cm^{-1}, λ_{max} (EtOH) 203 (ε 20,730), and 242 (ε 10,440) nm; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer 1 25 (12H, s, 2 x C Me_2), 1.10-1 30 (2H, m, B CH_2), 4.00-4.15 (1H, m, O·C CH), 5.18 (1H, d, J = 4 6 Hz, Ph C<u>H</u>), and 7 20-7 55 (10H, m, 2 x Ph), m/z (f a b.) 367 (M^+ + H), 249 (M^+ - HO), 261 (M^+ - C_7H_6O), and 161 (base peak, M^+ - $C_{13}H_{18}O_2$).

Preparation of aldol products 12d and 13d via Method 1. Prepared as above using LDA [from diisopropylamine (0.383 ml, 2 75 mmol), n-BuLi (1 10 ml of a 2 5 M solution in hexanes, 2.75 mmol), tetrahydrofuran (4.0 ml)], boronate **9d** (0 568 g, 2 50 mmol), and benzaldehyde (0 279 ml, 2 75 mmol) Crude aldol product **12d** was isolated in essentially quantitive yield and the

diastereomeric ratio was determined from the D_2O exchanged 300 MHz ^1H n m.r. spectrum[9]; υ_{max} (film) *inter alia* 3380 br (OH), and 1630 (C:O) cm^{-1}; λ_{max} (EtOH) 205 (ε 13,480), 217 (ε 4,820), 252 (ε 340), 258 (ε 350), and 264 (ε 310) nm; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer. 1.19 and 1.21 (each 6H, s, 2 x C.Me_2), 1.10-1.30 (1H, m, B.C<u>H</u>H), 1.32 (1H, dd, *J* = 16.4 and 8.2 Hz, B.CH<u>H</u>), 2.66 and 2.80 (each 3H, s, N.Me_2), 3.20 (1H, ddd, *J* = 8.2, 6.7 and 4.2 Hz, O:C.CH), 4.77 (1H, d, *J* = 4.3 Hz, Ph.C<u>H</u>), and 7.30-7.38 (5H, m, Ph); m/z (f.a.b.) 334 (M^+ + H), 316 (M^+ - HO), and 228 (M^+ - C_6H_6CO).

Preparation of aldol products 12e and 13e via Method 1. Prepared as above using LDA [from diisopropylamine (0.199 ml, 1.40 mmol), n-BuLi (0.57 ml of a 2.5 M solution in hexanes, 1.40 mmol), tetrahydrofuran (3.0 ml)], boronate **9a** (0.331 g, 1.30 mmol), and pivaldehyde (0.155 ml, 1.40 mmol). Crude aldol product **12e** and **13e** was isolated in ca.73 % crude yield and the diastereomeric ratio was determined by the D_2O exchanged 300 MHz ^1H n.m.r. spectrum[9]; υ_{max} (film) *inter alia* 3470 br (OH), 1730 (C:O) cm^{-1}, δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer 0.87 (9H, s, C.C.Me_3), 0.90-0.99 (1H, m, B C<u>H</u>H), 1.22 (12H, s, 2 x C.Me_2), 1.39-1.47 (1H, m, B.CH<u>H</u>), 1.43 (9H, s, O.CMe_3), 2.75 (1H, ddd, *J* = 6.8, 8.2, and 9.7 Hz, O:C.CH), 4.11 (1H, d, *J* = 6.8 Hz, ^{t}Bu.C<u>H</u>); m/z (+ve c i.) 360 (M^++NH_3), 343 (M^++ H), and 300 (M^+-C_3H_7).

Preparation of aldol products 12f and 13f via Method 1. Prepared as above using LDA [from diisopropylamine (0.170 ml, 1 21 mmol), n-BuLi (0 49 ml of a 2.5 M solution in hexanes, 1 21 mmol), tetrahydrofuran (3.0 ml)], boronate **9b** (0.251 g, 1.11 mmol), and pivaldehyde (0.133 ml, 1.22 mmol). Crude aldol product **12f** and **13f** was isolated in 79 % crude yield and the diastereomeric ratio was determined by the D_2O exchanged 300 MHz ^1H n.m.r. spectrum[9]; υ_{max} (film) *inter alia* 3450 br (OH), and 1685 (C:O) cm^{-1}; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer 0 88 (9H, s, C.C.Me_3), 0 88-0 95 (1H, m, B.C<u>H</u>H), 1 23 (12H, s, 2 x C.Me_2), 1.19-1.27 (1H, m, B.CH<u>H</u>), 1.45 (9H, s, S.CMe_3), 3.01 (1H, ddd, *J* = 6 4, 7.7 and 9.7 Hz, O:C CH), 4 18 (1H, d, *J* = 6.4 Hz, ^{t}Bu.C<u>H</u>); m/z (f a b) 359 (M^+ + H), 269 (M^+ - C_4H_9S), and 169 (base peak, M^+ - $C_{10}H_{21}OS$)

Preparation of aldol products 12g and 13g via Method 1. Prepared as above using LDA [from diisopropylamine (0.796 ml, 5.70 mmol), n-BuLi (2 27 ml of a 2.5 M solution in hexanes, 5.70 mmol), tetrahydrofuran (5 0 ml)], boronate **9c** (1.342 g, 5.20 mmol), and pivaldehyde (0.621 ml, 5.70 mmol). Crude aldol product **12g** was isolated in 34 % crude yield and the diastereomeric ratio was determined by the D_2O exchanged 300 MHz ^1H n m r spectrum[9]; υ_{max} (film) *inter alia* 3440 br (OH), and 1680 (C:O) cm^{-1}; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer: 0.88 (9H, s, C Me_3), 1 20-1 30 (1H, m, B.C<u>H</u>H), 1.24 (12H, s, 2 x C Me_2), 1 53 (1H, dd, *J* = 8 5 and 16 8 Hz, B.CH<u>H</u>), 3.88 (1H, ddd, *J* = 6.9, 8.5 and 10 3 Hz, O.C CH), 4 59 (1H, d, *J* = 6.9 Hz, ^{t}Bu.C<u>H</u>), 7.42-7 62 and 7 95-8.00 (3 and 2H respectively, each m, Ph), m/z (f.a.b) 347 (base peak, M^+ + H), 329 (M^+ - HO), and 229 (M^+ - $C_6H_{13}O_2$).

Preparation of aldol products 12h and 13h via Method 1. Prepared as above using LDA [from diisopropylamine (0.170 ml, 1.21 mmol), n-BuLi (0.49 ml of a 2 5 M solution in hexanes, 1.21 mmol), tetrahydrofuran (3.0 ml)], boronate **9d** (0.251 g, 1.11 mmol), and pivaldehyde (0.133 ml, 1 22 mmol) over 3h. Crude aldol product **12h** was isolated in 79 % crude yield and the diastereomeric ratio was determined by the D_2O exchanged 300 MHz ^1H n.m r. spectrum[9]; υ_{max} (film) *inter alia* 3400 br (OH), and 1634 (C·O) cm^{-1}, λ_{max} (EtOH) (ε), and (ε) nm; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer· 0.86 (9H, s, C Me_3), 1.03 (1H, dd, *J* = 8 6 and 16 9 Hz, B.C<u>H</u>H), 1 24 (12H, s, 2 x C.Me_2), 1.33 (1H, dd, *J* = 9 8 and 16 8 Hz, B.CH<u>H</u>), 2 95 and 3.07 (each 3H, s, N.Me_2), 2 96 (1H, m, O C CH), 4 47 (1H, d, *J* = 7 0 Hz, ^{t}Bu.C<u>H</u>); m/z (f a b.) 314 (M^+ + H), and 214 (M^+ - $C_6H_{11}O$)

Preparation of aldol products 12i and 13i via Method 1. Prepared as above using LDA [from diisopropylamine (0 170 ml, 1 21 mmol), n-BuLi (0 49 ml of a 2.5 M solution in hexanes, 1.21

mmol), tetrahydrofuran (4 0 ml)], boronate **9e** (0.279 g, 1.11 mmol) in dry tetrahydrofuran (0.5 ml), and pivaldehyde (0.133 ml, 1.22 mmol) over 3h. Crude aldol product **12l** was isolated in 70 % crude yield and the diastereomeric ratio was determined by the D_2O exchanged 300 MHz ^1H n.m.r. spectrum[9]; υ_{max} (film) *inter alia* 3380 br (OH), and 1620 (C·O) cm^{-1}; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer: 0.87 (9H, s, C.Me_3), 0.88-0.97 (1H, m, B.CHH), 1.21-1.29 (1H, m, B.CHH) 1.24 (12H, s, 2 x C.Me_2), 1.80-2.00 (4H, m, N.CH_2.CH_2.CH_2), 2.85-3 19 (1H, m, O:C.CH), 3.40-3.50 (4H, m, H_2C.N CH_2) 4.40 (1H, d, J = 7.2 Hz, ^{t}Bu.CH), m/z (f.a.b.) 340 (M^+ + H), and 284 (base peak, M^+ - C_4H_7).

Method 2. Preparation of acetonides 14a and 15a. To a stirred mixture of the crude aldol product **12a** and **13a** (1.094 g, ca. 2.5 mmol), tetrahydrofuran (12 ml), and sodium hydroxide (0.132 g, 3.3 mmol) in water (2.5 ml) at 0 °C, was added 30 % hydrogen peroxide (0.4 ml). After 4 h the mixture was diluted with water, extracted with ethyl acetate (2 x), dried ($MgSO_4$), and evaporated to give 0.793 g of a light yellow oil. This oil was then dissolved in 2,2-dimethoxypropane (2 5 ml) and analar acetone (2.5 ml), and treated with *para*-toluenesulphonic acid monohydrate (ca 20 mg) After 24 h, the reaction mixture was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, dired ($MgSO_4$), and evaporated to give 0.639 g of a crude light yellow oil. Purification of the oil by silica gel chromatography (petroleum ether . ethyl acetate, 9 : 1, as eluant) gave two fractions. The first fraction (0.462 g) was identified as the *syn*-diastereoisomer **14a** (63 % overall including the aldol reaction): υ_{max} (film) *inter alia* 1720 (C:O) cm^{-1}; λ_{max} (EtOH) 207 (ε 8,357), 251(ε 263), 257(ε 288), and 263(ε 235) nm; δ (^1H, $CDCl_3$, 300 MHz) 1.22 (9H, s, C.Me_3), 1 49 and 1 61 (each 3H, s, C.Me_2), 2.81 (1H, ddd, J = 5.1, 10.5 and 11.2 Hz, O·C.CH), 4.02 (1H, dd, J = 5.1 and 11.4 Hz, O.CHH), 4.16 (1H, dd, J = 11.2 and 11 4 Hz, O CHH), 5 01 (1H, d, J = 10.5 Hz, Ph.CH) and 7 27-7.41 (5H, m, Ph); m/z (c.i) 310 (M + NH_4^+), 263 (M^+ - C_2H_5), 252 (M + NH_4^+ - C_3H_6O), 222 (M + NH_4^+ - C_4H_8O), and 58 (base peak, $C_3H_6O^+$); Accurate m.s $C_{17}H_{28}BNO_4$ requires m/z 310.2018, peak at m/z 310.1994 The second fraction (0 170 g) was identified as the *anti*-diastereoisomer **15a** (23 % overall including the aldol reaction). υ_{max} (film) *inter alia* 1720 (C:O) cm^{-1}, λ_{max} (EtOH) 209 (ε 9,678), 252 (ε 346), 257 (ε 371), and 263 (ε 296) nm; δ (^1H, $CDCl_3$, 300 MHz) 1 12 (9H, s, C Me_3), 1.51 and 1.57 (each 3H, s, C.Me_2), 2 79 (1H, q, J = 4.1 Hz, O·C.CH), 4 19 (2H, d, sep 3 9 Hz, O.CH_2 CH), 5.19 (1H, d, J = 4.3 Hz, Ph.CH), and 7,21-7.40 (5H, m, Ph), m/z (c i) 310 (M + NH_4^+), 293 (M + H^+), 263 (M^+ - C_2H_5), 252 (M + NH_4^+ - C_3H_6O), 222 (M + NH_4^+ - C_4H_8O), 58 (base peak, $C_3H_6O^+$); Accurate ms, $C_{17}H_{28}NO_4$ requires m/z 310 2018, peak at m/z 310 2014.

Method 3. Preparation of acetonides 14b and 15b To a stirred mixture of the crude aldol product **12b** and **13b** (0 980 g, ca 2 5 mmol), dichloromethane (20 ml), and sodium hydrogen carbonate (0.462 g, 5 50 mmol), was added *meta*-chloroperoxybenzoic acid (0.680 g of ca. 70 % pure peroxide). After 3 h the mixture was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution (2 x), dried ($MgSO_4$), and evaporated to give a crude light yellow syrup. This syrup was then dissolved in 2,2-dimethoxypropane (2 5 ml) and analar acetone (2.5 ml), and treated with *para*-toluenesulphonic acid monohydrate (ca 20 mg). After 24 h, the reaction mixture was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated to give 0.590 g of a crude light yellow syrup. Purification of the syrup by silica gel chromatography (hexane · ethyl acetate, 9 1, as eluant) gave 0 391 g (66 % overall including the aldol reaction) of a mixture of the*syn*-product **14b** and the *anti*-product **15b** as a light yellow waxy solid υ_{max} (film) *inter alia* 1735 (C O) cm^{-1}, λ_{max} (EtOH) 210 (ε 8,060), and 235 (ε 4,320) nm; δ (^1H, $CDCl_3$, 300 MHz) major diastereoisomer **14b**: 1 29 (9H, s, C Me_3), 1 49 and 1.60 (each 3H, s, C.Me_2), 2 97 (1H, dt, J = 4.8 and 10 6 Hz, O:C.CH), 3.99 (1H, dd, J = 5.0 and 11 5 Hz, O·C·CH·CHH), 4 16 (1H, t, J = 11.3 Hz, O·C·CH·CHH), 5 09 (1H. d, J = 10 2 Hz. Ph CH), and 7.20-7.35 (5H, m, Ph); minor diastereoisomer **15b**: 1 22 (9H, s, C Me_3), 1 53 and 1 61 (each 3H, s, C Me_2), 2.86 (1H, m, O.C CH), 4.06-4 11 and 4 22-4 30 (each 1H, m, O·C.CH.CH_2), 5.19 (1H, d, J = 5 5 Hz, Ph CH), and 7 20-7 35 (5H, m, Ph), ratio of major minor = 74 : 26, m/z

(f.a.b.) 309 (M^++ H), 251 (M^+ - C_4H_9), and 195 (base peak, M^+ - $C_7H_{13}O$); Accurate m.s. $C_{17}H_{24}SO_3$ requires m/z 308.1446, peak at m/z 308.1448.

Preparation of acetonide 14c. The preparation of acetonide **14c** was carried out as for **14a** and **15a** (**Method 2**). Crude aldol product **12c** (0.90 g, ca. 2.5 mmol), tetrahydrofuran (10 ml), sodium carbonate (1.5 ml of a 2 M solution), and 30 % hydrogen peroxide (0.2 ml) gave 0.717 g of a light yellow oil. 2,2-Dimethoxypropane (2.0 ml), analar acetone (2.0 ml), *para*-toluenesulphonic acid monohydrate (ca. 20 mg). Gave 0.655 g of a crude light yellow solid. Purification of the solid by silica gel chromatography (petroleum ether : ethyl acetate, 9 . 1, as eluant) gave 0 473 g (64 % overall including the aldol reaction) of *syn*-product **14c** as an of white solid. Recrystallisation from hexane provided pure acetonide **14c** (0.271 g, 37 % overall): m.p. 123-124 °C; υ_{max} (film) *inter alia* 1680 (C:O) cm^{-1}; λ_{max} (EtOH) 207 (ε 18,218), and 249 (ε 13,447) nm; δ (^1H, $CDCl_3$, 300 MHz) 1.56 and 1.68 (each 3H, s, C.Me_2), 3.95-4.07 (2H, m, O:C.C<u>H</u>.C<u>H</u>H), 4.19-4.27 (1H, m, O:C.CH.CH<u>H</u>), 5.33 (1H, d, *J* = 9.8 Hz, Ph.C<u>H</u>), 7.13-7.49 and 7.65-7.68 (8 and 2H respectively, 2 x Ph); m/z (f.a.b.) 297 (M^+ + H), 239 (M^+ - C_3H_5O), 209 (M^+ - $C_4H_8O_2$), and 135 (base peak, $C_9H_{11}O$), Accurate m.s: $C_{19}H_{21}O_3$ requires m/z 297.1491, peak at m/z 297.1481.

Preparation of acetonide 14d. The preparation of acetonide **14d** was carried out as for **14b** and **15b** (**Method 3**). Crude aldol product **12d** and **13d** (0.736 g, ca. 2.5 mmol), dichloromethane (10 ml), sodium hydrogen carbonate (0.30 g, 7.90 mmol), and *meta*-chloroperoxybenzoic acid (0.95 g of ca 55 % pure peroxide) for 3 h gave 0.563 g of a light yellow solid 2,2-Dimethoxypropane (2.5 ml), analar acetone (2 5 ml), *para*-toluenesulphonic acid monohydrate (ca. 20 mg), gave 0.593 g of a crude light yellow syrup. Purification of the syrup by silica gel chromatography (petroleum ether . ethyl acetate, 9 · 1, as eluant) gave 0.280 g (43 % overall from the aldol reaction) of *syn*-product **14d** as a colorless syrup: υ_{max} (film) *inter alia* 1630 (C.O) cm^{-1}; λ_{max} (EtOH) 205 (ε 13,590), 210 (ε 9,430), 250 (ε 840), 257 (ε 810), 263 (ε 740), and 281 (ε 620) nm; δ (^1H, $CDCl_3$, 300 MHz) 1.53 and 1.65 (each 3H, s, C.Me_2), 2.44 and 2.75 (each 3H, s, N.Me_2), 3.09 (1H, dt, *J* = 4.8 and 10.6 Hz, O.C.CH), 3.88 (1H, dd, *J* = 4.8 and 11.7 Hz, O:C.CH.C<u>H</u>H), 4.35 (1H, t, *J* = 11.4 Hz, O:C.CH.CH<u>H</u>), 5.17 (1H, d, *J* = 10.0 Hz, Ph.C<u>H</u>), and 7.24-7.39 (10H, m, 2 x Ph); m/z (f.a.b.) 264 (M^+ + H), 206 (M^+ - C_3H_5O), 176 (base peak, M^+ - C_4H_9NO); Accurate m.s: $C_{15}H_{21}NO_3$+H requires m/z 264.1600, peak at m/z 264.1602

Preparation of acetonides 14e via Method 2. Crude aldol product **12e** (1.341 g, 3 9 mmol), tetrahydrofuran (8 ml), sodium hydroxide (0.176 g) in water (1 ml), and 30 % hydrogen peroxide (0.5 ml) gave 0.717 g of a light yellow oil after 4h. 2,2-Dimethoxypropane (7.0 ml), *para*-toluenesulphonic acid monohydrate (ca. 10 mg), gave 0.743 g of a crude light brown oil. Purification of the oil by silica gel chromatography (hexane . ethyl acetate, 95 · 5, as eluant) gave 0.412 g (39 %) of the *syn*-product **14e**: υ_{max} (film) *inter alia* 1730 (C.O) cm^{-1}; δ (^1H, $CDCl_3$, 300 MHz) 0.88 (9H, s, C C.Me_3), 1 33 and 1.42 (each 3H, s, C Me_2), 1 44 (9H, s, O C.Me_3), 2 56 (1H, ddd, *J* = 5.9, 6.6 and 9 6 Hz, O:C CH), 3.82 (1H, d, *J* = 9 6 Hz, ^{t}Bu.C<u>H</u>), 3.82 (1H, dd, *J* = 6.6 and 11.5 Hz, O.CH<u>H</u>), and 3.88 (1H, dd, *J* = 5 9 and 11 3 Hz, O CH<u>H</u>), δ (^{13}C, $CDCl_3$) 25 5 (C.C.<u>Me</u>$_3$), 20 6 and 27.5 (C.<u>Me</u>$_2$), 27 9 (C.C.<u>Me</u>$_3$), 34 6 (O C.<u>Me</u>$_3$), 44 3 (O C.<u>C</u>H), 61.7 (O CH_2), 75.6 (O.<u>C</u>H.C.Me_3), 80.7 (O.<u>C</u>.Me_3), 89.6 (<u>C</u>.Me_2), and 172.6 (O.C:O), m/z (f a.b) 297 (M^+ + H), 239 (M^+ - C_3H_5O), 209 (M^+ - $C_4H_8O_2$), and 135 (base peak, $C_9H_{11}O$), Analysis, $C_{15}H_{28}O_4$ reqiures C, 66 1; H, 10 4; found C, 65.9; H, 10 1 %

Preparation of acetonide 14f via Method 3. Crude aldol product **12f** (0 500 g, 1.5 mmol), dichloromethane (10 ml), sodium hydrogen carbonate (0.146 g) , and *meta*-chloroperoxybenzoic acid (0.505 g of ca. 55 % pure peroxide) gave 0 401 g of a light yellow oil after 4h. 2,2-Dimethoxypropane (4.0 ml), *para*-toluenesulphonic acid monohydrate (ca. 5 mg), gave 0.541 g of a crude light brown oil which solidified on standing. Purification of the solid by silica gel chromatography (hexane . diethyl ether, 95 · 5, as eluant) gave 0.190 g (22 %) of the *syn*-product **14f** m.p 59.5 °C, υ_{max} (KBr disc) *inter alia* 1680 (C O) cm^{-1}, δ (^1H, $CDCl_3$, 300 MHz) 0 89 (9H, s,

C.C.Me_3), 1.33 and 1.43 (each 3H, s, C.Me_2), 1.44 (9H, s, S.C.Me_3), 2.83 (1H, ddd, J = 5.8, 7.4 and 9.9 Hz, O.C.CH), 3.81 (1H, dd, J = 7.5 and 11.5 Hz, O.C<u>H</u>H), 3.88 (1H, d, J = 9.8 Hz, ^{t}Bu.CH), and 3.89 (1H, dd, J = 6.0 and 11.5 Hz, O.CH<u>H</u>); δ (^{13}C, $CDCl_3$) 25.7 (C.C.<u>Me</u>$_3$), 20.1 and 27.6 (C.<u>Me</u>$_2$), 29.5 (S.C.<u>Me</u>$_3$), 34.7 (C.<u>C</u>.Me$_3$), 48.1 (S.<u>C</u>.Me$_3$), 52.3 (O:C.<u>C</u>H), 62.4 (O.CH_2), 76.4 (O.<u>C</u>H.C.Me$_3$), 89.6 (<u>C</u>.Me$_2$), and 199.9 (S.C:O); m/z (f.a.b.) 289 (M^+ + H), 231 (M^+ - C_3H_5O), and (base peak, $C_9H_{11}O$); Accurate m.s: $C_{15}H_{28}O_3S$ requires m/z 289.1837, peak at m/z 289.1826.

Preparation of acetonide 14g via Method 3. Crude aldol product **12g** (0.885 g, 2.6 mmol), dichloromethane (8 ml), sodium hydrogen carbonate (0 255 g) , and *meta*-chloroperoxybenzoic acid (0.880 g of ca. 55 % pure peroxide) gave 1 791 g of a light yellow solid after 4h. 2,2-Dimethoxypropane (7.0 ml), *para*-toluenesulphonic acid monohydrate (ca. 10 mg), gave 1.236 g of a crude light brown solid. Purification of the solid by silica gel chromatography (hexane : diethyl ether, 95 : 5, as eluant) gave 0.161 g (21 %) of the *syn*-product **14g**: m.p. 94-96 °C; υ_{max} (KBr disc) *inter alia* 1680 (C:O) cm^{-1}; δ (^{1}H, $CDCl_3$, 300 MHz) 0.82 (9H, s, C.C.Me_3), 1.40 and 1.52 (each 3H, s, C.Me_2), 3.80-4.00 (3H, m, O:C.CH.CH_2), 4.18 (1H, d, J = 9.0 Hz, ^{t}Bu.C<u>H</u>), 7.33-7.50 (2H, m, Ar-H's), 7 59 (1H, t, J = 7.3 Hz, Ar-H), and 7.90 (2H, dd, J = 1.0 and 8.3 Hz, Ar-H's); δ (^{13}C, $CDCl_3$) 26.7 (C.<u>Me</u>$_3$), 20.8 and 29.0 (C.<u>Me</u>$_2$), 35.6 (<u>C</u>.Me$_3$), 45.0 (O:C.<u>C</u>H), 63 2 (O.CH_2), 77.3 (<u>C</u>H.C Me$_3$), 99.4 (<u>C</u>.Me$_2$), 128.9, 129.6, 134.1 and 137.1 (Ar-C's), and 200.7 (Ph.C:O); m/z (f.a.b.) 277 (M^++H), 219 (base peak, M^+ - C_3H_5O), and 201 (M^+ - $C_3H_7O_2$); Analysis, $C_{17}H_{24}O_3$ requires C, 73.9, H, 8.8; found C, 73 6; H, 9.0 %

Preparation of acetonide 14h. To a stirred mixture of the crude aldol product **12h** (0 255 g, ca. 0.86 mmol), 1,4-dioxane (4.6 ml) and water (1 4 ml) was added sodium perborate tetrahydrate (0 264 g, 1.72 mmol). After refluxing for 1.25 h the mixture was cooled, diluted with diethyl ether, washed with saturated ammonium chloride , dried ($MgSO_4$), and evaporated to give 0.151 g of a yellow oil. This oil was then dissolved in 2,2-dimethoxypropane (0.2 ml) and analar acetone (1.5 ml), and treated with *para*-toluenesulphonic acid monohydrate (ca. 20 mg). After 24 h, the reaction mixture evaporated and purified of by silica gel chromatography (heptane : ethyl acetate, 9 : 1, as eluant) to give 0.064 g (33 % overall from the aldol reaction) of the *syn*-diastereoisomer **14h** as a colourless solid· m.p. 98-99 °C; υ_{max} (film) *inter alia* 1630 (C:O) cm^{-1}; δ (^{1}H, $CDCl_3$, 300 MHz) 0.84 (9H, s, C.Me_3), 1.36 and 1.49 (each 3H, s, C.Me_2), 2.01 and 3.10 (each 3H, s, N.Me_2), 2.95 (1H, dt, J = 5.4 and 9 9 Hz, O:C.CH), 3.75 (1H, dd, J = 5.4 and 11.5 Hz, O C<u>H</u>H), 3.90 (1H, dd, J = 10 0 and 11 5 Hz, O CH<u>H</u>), and 4.03 (1H, d, J = 9 8 Hz, ^{t}Bu C<u>H</u>); δ (^{13}C, $CDCl_3$) 25.9 (C C <u>Me</u>$_3$), 19.5 and 29 1 (C <u>Me</u>$_2$), 34.7 (<u>C</u>.Me$_3$), 35.7 and 37 3 (N.Me_2), 38.8 (O.C.<u>C</u>H), 62 1 (O.CH_2), 77.2 (<u>C</u>.Me$_3$), 98 2 (<u>C</u>.Me$_2$), and 172 0 (N.C:O), m/z (f a.b) 244 (base peak, M $^+$ + H), and 186 (M^+ - C_3H_5O), Analysis, $C_{13}H_{25}NO_3$ requires C, 64.2, H, 10.4, N, 5 8; found C, 63.9; H, 10.2; N, 6.0 %

Preparation of acetonide 14i via Method 3. Crude aldol product **12i** (0 297 g, ca. 1 1 mmol), dichloromethane (5 ml), sodium hydrogen carbonate (0.101 g) , and *meta*-chloroperoxybenzoic acid (0 379 g of ca. 55 % pure peroxide) gave 0 398 g of a light yellow waxy solid after 4h. 2,2-Dimethoxypropane (5.0 ml), *para*-toluenesulphonic acid monohydrate (ca. 10 mg), gave a crude yellow solid Purification of the solid by silica gel chromatography (heptane · ethyl acetate, 95 : 5, as eluant) gave 0.055 g (18 %) of the *syn*-product **14i** as a white solid: m p. 96 8 °C, υ_{max} (KBr disc) *inter alia* 1630 (C.O) cm^{-1}; δ (^{1}H, $CDCl_3$, 300 MHz) 0.85 (9H, s, C.Me_3), 1 35 and 1 48 (each 3H, s, C.Me_2), 1 80-2.00 (4H, m, N.CH_2.CH_2.CH_2), 2 76 (1H, dt, J = 5.2 and 10 5 Hz, O:C.CH), 3 30-3.60 (4H, m, CH_2 N CH_2), 3 78 (1H, dd, J = 5 2 and 11 4 Hz, O C<u>H</u>H), 3.99 (1H, dd, J = 10 5 and 11 4 Hz, O CH<u>H</u>), and 4 04 (1H, d, J = 10.1 Hz, ^{t}Bu.C<u>H</u>), δ (^{13}C, $CDCl_3$) 19 4 and 29.1 (C <u>Me</u>$_2$), 24 2 (N.CH_2 <u>C</u>H_2 <u>C</u>H_2), 26 0 (<u>C</u> <u>Me</u>$_2$), 41 2 (O:C <u>C</u>H), 45 8 and 46 7 (H_2<u>C</u> N <u>C</u>H_2), 62 1 (O <u>C</u>H_2), 76.7 (<u>C</u> Me$_3$), 98.1 (<u>C</u>.Me$_2$), and 170.5 (N.C.O), m/z (f.a.b.) 270 (base peak, M^+ + H), 212 (M^+ - C_3H_5O), and 182 (M^+ - C_4H_9NO); Analysis, $C_{15}H_{27}NO_3$ requires C, 66 9; H, 10 1, N, 5 2, found C, 66 6, H, 10 0, N, 5 2 %

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