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Preparation of Enantiomerically Pure Fructose-Derived 1,3-Oxazin-2-one by INIR Methodology and its Application as a Chiral Auxiliary in Some Model Asymmetric Reactions

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Abstract: A newly developed fructose-based homochiral 1,3-oxazin-2-one reagent prepared *via* a regioselective and stereoselective intramolecular nitrene insertion reaction (INIR) exerts smooth stereocontrol resulting in high levels of asymmetric induction and chemical yield in various synthetic transformations including aldol, Diels-Alder cycloaddition and α-bromination reactions. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Further to previous studies by ourselves[1,2] and others[3] relating to the use of carbohydrate-based chiral auxiliaries for the synthesis of homochiral fragments, we now report a valuable new addition in (-)-D- fructose derived 1,3-oxazin-2-one chiral auxiliary **1**. Previously, similar investigations carried out and communicated by us on (+)-D-galactose derived oxazolidin-2-one **2**[1] and gulonic-acid derived 1,3-oxazin-2-one **3**[2] had achieved high levels of stereoselection. The use of oxazinones as auxiliaries in this field has, as recently reported by us[2], been insignificant in relation to oxazolidinones. However, others[3,4] have now reported successful usage and chiral auxiliary **1** is complementary to this emerging class of reagent. The synthetic route taken to develop **1** was in keeping with previous experimental work carried out by us in the preparation of **2** and **3** and involved the widely known, although rarely employed stereospecific intramolecular nitrene insertion reaction (INIR) in a four-step procedure. Inspection of oxazin-2-one **1** reveals key features which are hallmarks of many chiral systems, *e.g.* Evans' auxiliary **4** ,[5] *viz.* an easily functionalisable nitrogen atom, a carbonyl group which can be utilised for bidentate chelation control, inherent conformational rigidity and protecting groups on the sugar

We dedicate this paper to Professor Alan Katritzky, FRS in recognition of his enormous and unflagging contributions to heterocyclic chemistry still delivered both 'on-and-off the field' with unstinted stentorian enthusiasm and newly found septuagenarian vigour.

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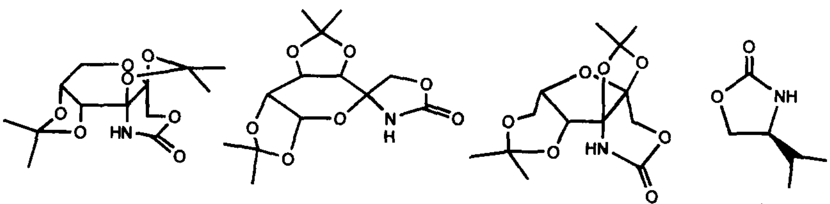
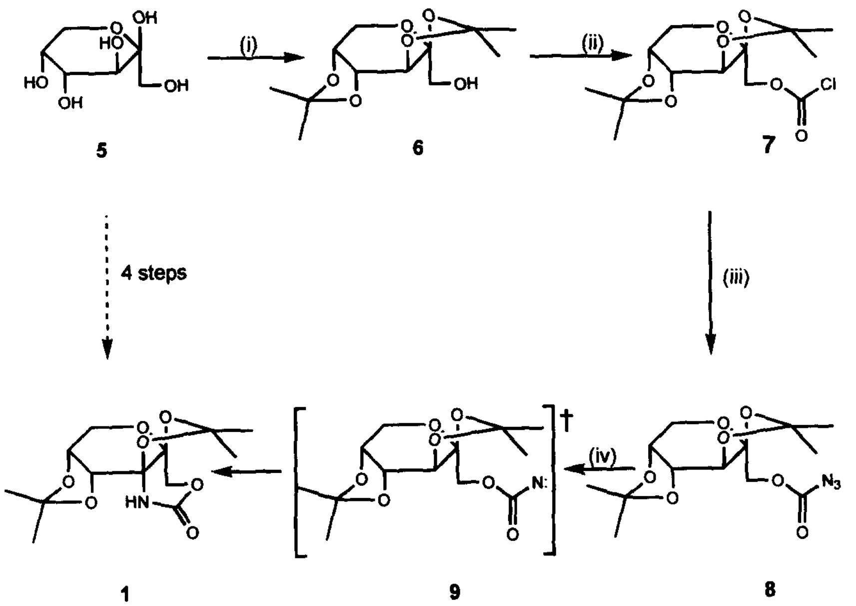
skeleton that can provide steric overload to a reacting face and in doing so induce a stereofacial bias which results in dictated diastereoselectivity. As in the case of auxiliaries **2** and **3**, and of considerable benefit in conducting these investigations, the highly crystalline nature of oxazin-2-one **1** imparted excellent crystallinity to its derivatives thereby often allowing facile purification by fractional crystallisation. In addition, the aldol and a-bromination procedures resulted in high levels of stereocontrol *via* lithium mediated (Z)-enolates as opposed to the precarious and costly boron enolate systems. Following each asymmetric conversion cleavage of the chiral fragment was achieved in high yield by mild hydrolysis and without compromising the newly created centres of asymmetry.



1 **2** **3** **4**

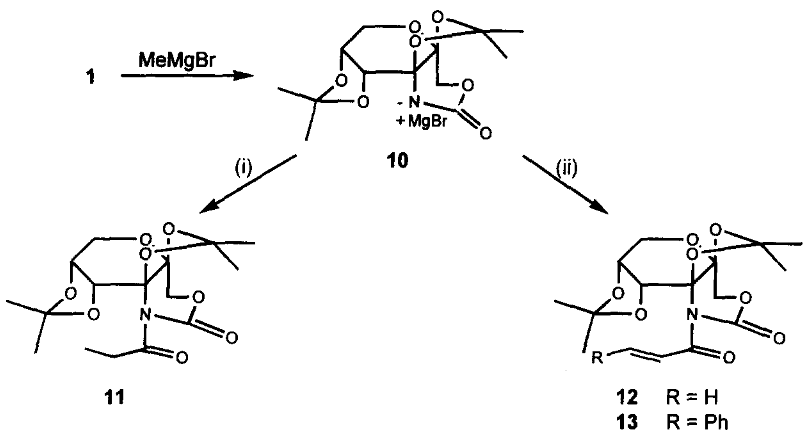
RESULTS AND DISCUSSION

The synthesis of 1,3-oxazin-2-one **1** was carried out by a four-step process as shown in Scheme 1. The first step involved protection of the starting sugar, D-fructose **5**, by condensation with acetone in the presence of acid catalyst to furnish the 2,3:4,5 ß-D-fructopyranose protected derivative **6** in 90% yield. It is worth noting that the concentration of acid in this step is important since at lower concentrations formation of the 1,2:4,5 protected isomer is predominant. Subsequent conversion of **6** into the corresponding chloroformate **7** in quantitative yield was achieved by reaction with phosgene in the presence of pyridine as base catalyst. In the next step, the chloroformate **7** was transformed into the corresponding azidoformate **8** in similar yield by reaction with sodium azide under phase-transfer catalysis conditions (DCM/H_2O, tetrabutylammonium bromide). The final step of the synthesis involved decomposition of the latter *via* solution thermolysis in boiling 1,1,2,2-tetrachloroethane (TCE) to generate the nitrene intermediate **9** which inserted regiospecifically from the lower face into C(3)-H to give oxazin-2-one **1** exclusively. Further purification by flash chromatography followed by fractional crystallisation furnished **1** as a colourless highly crystalline solid (mp 219°C, yield 55%), whose structure was confirmed by microanalysis, mass spectral and NMR data. Interestingly, X-ray crystallographic studies have shown that in the solid state, the tetracyclic structure of **1** exists in two slightly different conformations. Fig. 1(a) depicts only one conformation in which the six-membered parent carbohydrate ring adopts a distorted twist-boat structure whilst the oxazinone ring adopts a chair-like arrangement.



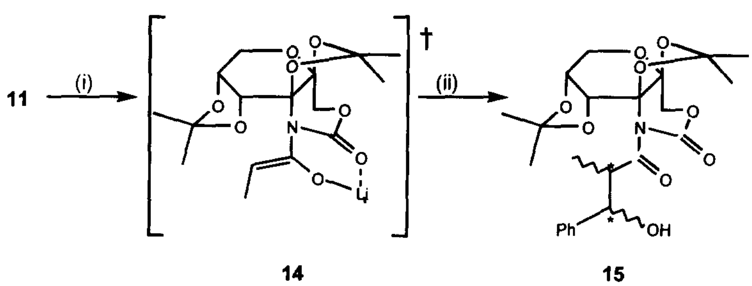
Scheme 1. *Reagents and conditions:* (i), acetone/conc.H_2SO_4; (ii), Cl_2CO/pyridine; (iii), NaN_3/TBAB; (iv), TCE/reflux 147°C.

A pivotal step *en route* to the determination of the utility of **1** as a chiral control element in promoting asymmetric induction is its conversion into the appropriate *N*-acyl carboximide derivative for use in asymmetric aldol and Diels-Alder reactions. In general, the protocol depicted in Scheme 2 was adopted, whereby oxazin-2-one **1** was reacted with freshly prepared methylmagnesium bromide at 0°C (Evans' procedure) to generate the *N*-bromomagnesium species **10**. Subsequent acylation with propionyl chloride returned the *N*-propionyl derivative **11** in 97% yield, a procedure that was repeated with acryloyl chloride and cinnamoyl chloride to furnish α,β- unsaturated derivatives **12** (22% yield) and **13** (90% yield), respectively. It is worth noting in passing that attempts to functionalise **1** by treatment with other bases led to the concomitant *O*-acylation of the desired product **11**, which was formed with some degree of difficulty. For example, with *n*-butyllithium as base (in THF at -78°C) only 10% yield of **11** was isolated, the major product (42%) being its *O*-acylated derivative as verified by the characteristic ^{13}C NMR signal for the unsaturated *C*H linkage at 120 ppm. Nonetheless, the low chemical yield returned from the preparation of the acryloyl dienophile **12** is disappointing, but is attributed to a propensity of the latter to polymerise despite the use of Evans' procedure which was highly successful (82% yield) with the corresponding oxazin-2-one **3** derived from gulonic acid.[2]



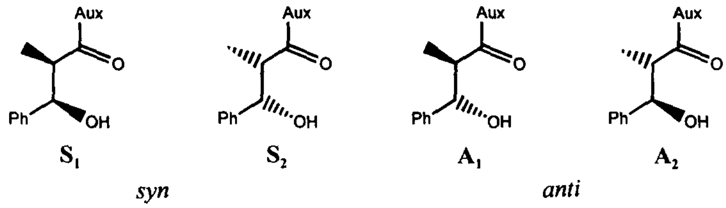
Scheme 2. *Reagents and conditions:* (i), MeMgBr, Et_2O, 0°C; (ii), THF, -78°C, EtCOCl; (iii), THF, -78°C, RCH=CHCOCl.

The ability of oxazinone **1** to impart chiral induction in an asymmetric transformation was demonstrated initially by the relatively high level of selectivity achieved in a lithium-mediated aldol condensation of the propionyl derivative **11** with benzaldehyde, *i.e.* without recourse to the use of hazardous and expensive di-*n*-butylboron triflate as a mediating agent.. The reaction proceeded *via* a lithium enolate intermediate **14**, which upon subsequent treatment at low temperature with benzaldehyde in anhydrous THF, delivered the aldol product **15** in 85% yield (Scheme 3).

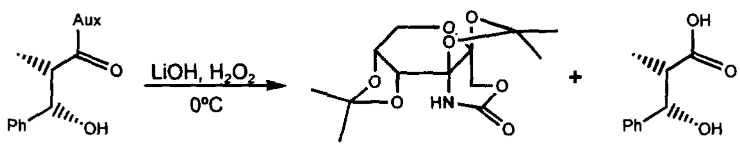


Scheme 3. *Reagents and conditions:* (i), $LiNPr_2^i$, THF, 0°C; (ii), PhCHO, THF, 0°C.

Thus, TLC analysis of the reaction indicated the presence of only two out of the four possible isomers ($\mathbf{S_1}$, $\mathbf{S_2}$, $\mathbf{A_1}$, $\mathbf{A_2}$), a fact that was confirmed by an examination of the 360 MHz ^{1}H NMR spectrum of the crude material. From studies by Heathcock[6] it has been established that the relative configuration (*syn versus anti*) in an aldol product containing two asymmetric carbons, each bearing a hydrogen, can be determined *via* coupling constant values using ^{1}H NMR spectroscopy. Upon engaging the theory to this particular case, the relevant signals arising from the doublet of protons (PhC*H*OH) in the region δ 3.40-4.10 ppm showed the coupling constant value to be J = 3.2 Hz which is consistent with the configuration of both diastereomers formed being *syn* (S_1,S_2). Integration of the ^{1}H NMR signals showed that the two *syn* isomers had been formed in the ratio of 8:1, giving a diastereomic excess (de) of 78% (*cf.* 82% for **3**).



Following purification by fractional crystallisation the major diastereomer was subjected to hydrolytic cleavage[7] using lithium hydroperoxide as shown in Scheme 4 to furnish without racemisation both the β-hydroxy carboxylic acid fragment **16** and oxazinone **1** in high chemical yield (>95%). Comparison of the optical rotation value of the acid fragment ($[\alpha]_D^{25}$ = -28.7°) with literature[8] precedent established the absolute configuration to be S_2 (*2S,3S*). In addition, examination of the X-ray crystal structure of benzaldehyde aldol adduct **15** allowed visual confirmation of the absolute stereochemistry as depicted in Fig. 1(b).



Scheme 4

The preponderance of the *syn*-aldol product **16** can be explained by the difference in steric congestion at opposite faces of the Z-enolate system **14** such that approach by the aldehyde is sterically less imposing from the upper C_α-*re* face (*vide infra*). An attempt to bring about a reversal in the sense of induction, *i.e.* formation of S_1, by use of a boron-mediated enolate system instead of the lithium-based enolate **14** ended in failure with no evidence of any reaction having taken place. The reason may arise from added chelation by the ketal and/or pyranose ring oxygens within the boron enolate that prevents reaction. Nonetheless, the outcome from the lithium-enolate **14** is worthy of note, especially when compared to the result obtained from use of Evans'

(a) (b)

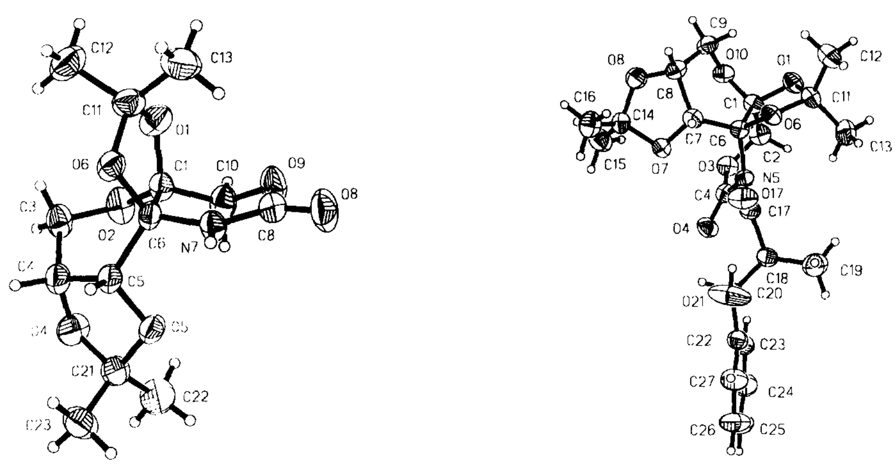
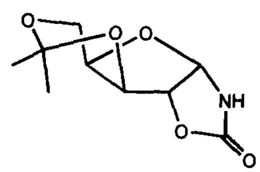


Figure 1. (a) View of the X-ray crystal structure of 1,3-oxazin-2-one **1** and (b) of aldol-adduct **15**. The molecules of **1** and **15** are shown as 40% thermal ellipsoid plots.

auxiliary **4** for the same reaction which resulted in a mixture of three diastereomers in the ratio 24 : 10 : 66 (de 32%) in a chemical yield of 88%. More recently in an analogous reaction, Luntzen and Köll[9] reported formation of the principal product in a diastereomeric ratio of 5:3 (inseparable isomers) upon using the chiral oxazolidin-2-one **17** which is prepared from D-xylose by a two-step potassium cyanate methodology. This noticeable decrease in diastereoselectivity compared to **1** (and **3**[2]) presumably arises from poorer chelation control from the furanoid/ketal oxygens.



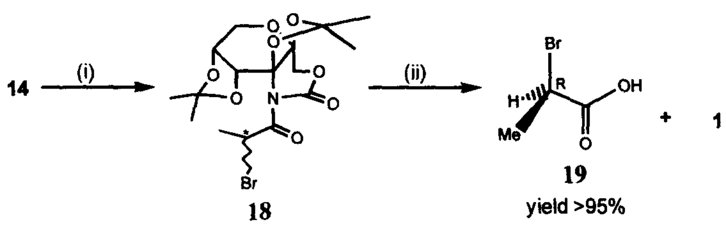
17

Following the success of the reaction involving benzaldehyde, the experiment was repeated with two other aldehydes, *viz.* acetaldehyde and isobutyraldehyde; the results for these reactions are shown in Table 1.

Table 1. Stereoselectivity of aldol reactions of the lithium enolate **14** with aldehydes, RCHO.

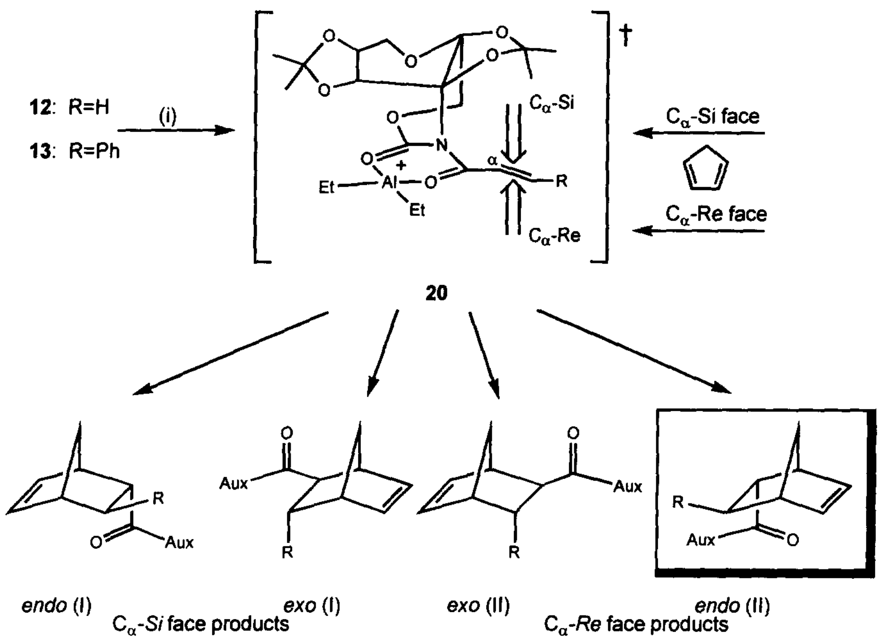
R	% yield	% de	configuration
Ph	85	78	(2*S*,3*S*)
$CH(CH_3)_2$	95	78	(2*S*,3*R*)
Me	85	single isomer	(2*S*,3*R*)

The *N*-acyl propionate **11** was also utilised in an α-bromination reaction. By generating the lithium mediated enolate complex **14** as in the aldol reactions and subsequent treatment with *N*-bromosuccinimide (NBS), the α-brominated compound **18** was furnished in quantitative yield (Scheme 5). Cleavage of the isolated product with lithium hydroperoxide led to the isolation of the α-brominated carboxylic acid **19** in high yield (>95%) with a similar high return of oxazinone **1**. An examination of the 200 MHz ^{1}H NMR spectrum of the crude reaction mixture showed almost total asymmetric stereocontrol, but upon analysis of an expansion of the least complicated region in the spectrum (δ 5.00-5.20 ppm) the presence of two isomers were found in the ratio of 25:1 (de 92%). Comparison of the optical rotation value of **19** (+27.9°) with a literature[10] value determined the absolute configuration about the newly formed chiral carbon to be designated *(R)*.



Scheme 5. *Reagents and conditions:* (i), THF, NBS, -78°C; (ii), LiOH, H_2O_2, 0°C.

For continued judgment of the asymmetric inducting powers of oxazin-2-one chiral auxiliary **1**, the α,β-unsaturated *N*-acyl derivatives **12** and **13** were utilised in Lewis-acid catalysed Diels-Alder cycloaddition reactions. Each procedure was carried out at low temperature by the addition of a large excess of cyclopentadiene to a solution of each dienophile in dry dichloromethane followed by immediate treatment with diethylaluminium chloride (DEAC) as Lewis-acid (Scheme 6). Consideration of the intermediate Lewis-acid/dienophile complex **20** formed in each reaction shows that the cycloaddition process can occur at either the C_α-*re* face or the C_α-*si* face of the olefin. Consequently, attack at each of the two faces can lead to either the kinetically favoured *endo*-product or the thermodynamically favoured *exo*-product, *i.e.* there are four conceivable products in all. In fact, evidence of an *exo*-isomer could only be detected with **13** owing to the increase in temperature (-20°C) required for complete reaction. For both dienophiles, reaction occurred at the relatively unhindered Cα-*re* face *via* the bidentate complex **20** to produce *endo* (II) adduct as shown in Scheme 6; concomitant attack at the Cα-*si* face led to formation of the minor *endo* (I) adduct.



Scheme 6. *Reagents and conditions:* (i), CH_2Cl_2, cyclopentadiene (10 eq), Et_2AlCl (1.4 eq) **12**: -78°C, **13**: -20°C

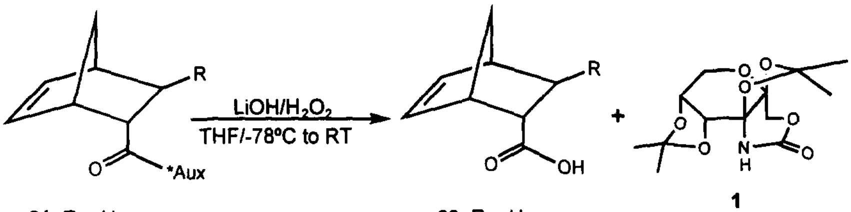
The outcome for each transformation is given in Table 2, which includes for direct comparison the results obtained with Evans' auxiliary **4** in parallel reactions. All stereochemical data are fully consistent with the sense of asymmetric induction illustrated in Scheme 7. Following each asymmetric conversion, the major

Table 2. Lewis-acid catalysed Diels-Alder cycloaddition reactions of **12** and **13** with cyclopentadiene.

Dienophile	% yield	*endo:exo*	*endo* de %
12	95 (81)	*endo* only (100:1)	87 (86)
13	95 (83)	4:1 (*endo* only)[b]	63 (86)

[a]Figures in parentheses represent results obtained using Evans' auxiliary **4** (see ref.11); [b]*endo* (I) 15%, *exo* (I) 5%: *exo* (II) 15%, *endo* (II) 65%.

cycloadducts **21** and **22** (*endo* II) were cleaved by standard lithium hydroperoxide hydrolysis to produce the diastereomerically pure acid fragments **23** and **24**, which were returned in quantitative yield with complementary recovery of auxiliary **1**. The absolute stereochemistry of the phenyl derivative **24** was confirmed to be 2*S*,3*R* by cleavage of adduct **22** with lithium benzyloxide to produce the corresponding benzyl ester and comparison of its optical rotation with literature values [11].

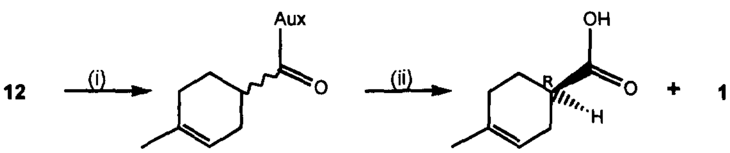


21: R = H
22: R = Ph

23: R = H
24: R = Ph

Scheme 7

In addition to the above Lewis-acid catalysed reactions with cyclopentadiene, a supplementary cycloaddition reaction employing an acyclic diene was carried out. Accordingly, the acrylate **12** was matched with isoprene under identical conditions adopted for the reaction with cyclopentadiene (Scheme 8). The resulting cycloadduct **25** was returned in very high yield (> 95%) and the major isomer *(R)*, which was formed in conjunction with its antipode in the ratio of 7:1, was isolated by flash chromatography. Subsequent hydrolysis with lithium hydroperoxide yielded the desired carboxylic acid **26** with *R* -stereochemistry (see experimental) in high yield and with concomitant return of oxazinone **1**.



25
> 95%
(*R*) 7:1(S)

26

Scheme 8. *Reagents and conditions:* (i), CH_2Cl_2, isoprene (10 eq), Et_2AlCl (1.4 eq), -78°C; (ii), LiOH, H_2O_2, 0°C.

In all of the asymmetric conversion reactions detailed above, diastereofacial selectivity is present and preference is for the relatively unhindered C_α-*re* face as is evident in Lewis-acid/dienophile complex **20**. The inherent predilection for the C_α-*re* face is due to steric shielding of the C_α-*si* face by the isopropylidene protecting groups on the sugar skeleton and a topographical relationship between the two reacting faces transpires. As a consequence of the steric encumberment to the C_α-*si* face, a more accessible route to the C_α-*re* face prevails and dictated diastereoselectivity occurs as observed.

CONCLUSION

The studies conducted herein concern chiral oxazin-2-one auxiliary **1**, whose ease of preparation and quality of stereocontrol in model asymmetric transformation reactions qualify it to be a potentially valuable addition to the current arsenal of carbohydrate-based auxiliaries in this field. Moreover, it is a complementary import to the six-membered oxazinone category which hitherto is largely underdeveloped in relation to the five-membered oxazolidinones. Oxazin-2-one **1** has participated in aldol, α-bromination and Lewis-acid catalysed Diels-Alder cycloaddition reactions. In these transformations it has demonstrated excellent dictated diastereofacial selectivity in high chemical yield and the chiral fragment is easily removed from the parent auxiliary by mild hydrolysis. We are currently finalising the investigation of fructose-based oxazin-2-one **1** in other asymmetric reactions and intend to report the findings and details of these studies in due course.

EXPERIMENTAL

Melting points were measured on a digital Gallenkamp capillary tube apparatus and are uncorrected. Proton NMR spectra were obtained either on a 200 MHz or 360 MHz instrument in $CDCl_3$ and ^{13}C NMR on a 50.3 MHz instrument in $CDCl_3$. Infra-red spectra were recorded on a Perkin-Elmer 781 spectrometer. Mass spectra (FAB and accurate mass) were determined on a Kratos MS-50 TC mass spectrometer. Polarimetry measurements were obtained with an Optical Activity AA 1000 polarimeter using sodium-D-line. Solvents THF and diethyl ether were distilled prior to use from sodium/benzophenone ketyl and methylene chloride was distilled from finely divided calcium hydride. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) plates and component spots were visualised by ultra-violet light, iodine vapour or charring using a 5-10% concentrated sulfuric acid/ethanol solution. Flash column chromatography was conducted using silica gel 60 (220-240 mesh) and elution aided pressure of 10 psi. X-ray crystallographic structures were determined on a Stoe STADI-4, four circle diffractometer. Crystal Data: **1**: $C_{13}H_{19}NO_7$, M = 301.3, tetragonal, a = 12.8375(8), c = 36.736(6)Å, V = 6054.1Å^3, T = 293(2) K, space group $P4_12_12$, Z = 16, D_c = 1.322 Mg m^{-3}, μ = 0.108 mm^{-1}. **2**: $C_{23}H_{29}NO_9$, M = 463.5, orthorhombic, a = 8.9092(6), b = 12.3596(6), c = 21.220(2)Å, V = 2336.7Å^3, T = 293(2)

K, space group $P2_12_12_1$, Z = 4, D_c = 1.317 Mg m^{-3}, μ = 0.102 mm^{-1}. Data collection and processing: Stoë STADI-4 diffractometer, graphite monochromated Mo-Kα radiation, $\omega/2\theta$ scans, $5 < 2\theta < 50°$. **1** gave 3143 independent data and **15** 1769. Both structures solved by DIRDIF[12], using initially a theoretically constructed fragment, and refined anisotropically (SHELXL [13]) to give **1**: R_1 = 0.041 for 1860 data with $F > 4\sigma(F)$, wR_2 (all data) 0.132. **15**: R_1 = 0.033 for 1369 data with $F > 4\sigma(F)$, wR_2 (all data) 0.107. All hydrogen atoms were placed in calculated positions.

Preparation of *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose* 6. In accordance with the method described by Brady[14], D-fructose (36.0g, 0.20mol) was added in *ca.* 6g proportions at regular intervals over 15 minutes to a stirring solution of acetone (700ml) and concentrated sulfuric acid (35ml) at 0°C under a flushing inert argon atmosphere. The contents were allowed to warm with stirring to room temperature then vigorously stirred for a further 90 minutes. The solution was subsequently re-cooled to 0°C before gradually adding an ice-cold solution of sodium hydroxide (110g, 2.75mol) in water (500ml). Following filtration of the reaction mixture, the acetone solvent was removed from the filtrate by *in vacuo* evaporation at the pump. The resultant pale yellow liquid layer was extracted into dichloromethane (3 x 100ml) and the combined organic extracts were then washed with water (100ml), dried ($MgSO_4$) and evaporated to yield a yellow crystalline solid which after recrystallisation from a diethyl ether (5ml/g) : n-pentane (5ml/g) mixture provided the target product **6** as a colourless crystalline solid (46.8g, 90%). **Mp** = 92°C; **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 4.57 (1H, dd, *J*=7.9, 2.6 Hz, C$\underline{H}$), 4.30 (1H, d, *J*=2.6 Hz, C$\underline{H}$), 4.19 (1H, ddd, *J*=7.9, 1.9, 1.1 Hz, C$\underline{H}$), 3.87 (1H, dd, *J*=13.0, 1.1 Hz, C$\underline{H}$), 3.71 (1H, dd, *J*=13.0, 1.1 Hz, C$\underline{H}$), 3.63 (2H, s, C$\underline{H}_2$), 2.60 (1H, broad s, O$\underline{H}$), 1.50 (3H, s, C$\underline{H}_3$), 1.43 (3H, s, C$\underline{H}_3$), 1.35 (3H, s, C$\underline{H}_3$), 1.30 (3H, s, C$\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 108.86 (quat C), 108.33 (quat C), 102.87 (quat C), 70.72 (CH), 70.58 (CH), 69.83 (CH), 65.21 (CH_2), 61.03 (CH_2), 26.26 (CH_3), 25.56 (CH_3), 25.14 (CH_3), 23.76 (CH_3) ppm; **IR** (thin film) ν_{max} 3290 (OH) cm^{-1}; **Accurate mass** (FAB), Found: 261.13381, ($C_{12}H_{21}O_6$) (M+H), Requires: 261.13382.

Preparation of *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose-10-chloroformate* 7. A solution of *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose* **6** (28.0g, 0.108mol) and pyridine (9.30g, 0.117mol, 1.1eq) in dry diethyl ether (280ml) was added dropwise over 30 minutes to a rapidly stirred solution of phosgene (264ml, 20%w/v in toluene, 0.333mol, 3eq) under argon at 0°C. Upon warming to ambient temperature the solution was stirred overnight then filtered. The resultant precipitate was washed thoroughly with dry ether and the combined filtrate and washings were evaporated to yield *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose-10-*

chloroformate **7** as a yellow viscous oil (34.73g, 100%). **Note!** the chloroformate hydrolyses readily and should therefore be used *immediately* for next stage.

^{1}**H NMR** (200.13MHz,$CDCl_3$) δ 4.60 (1H, dd, *J*=7.8, 2.7 Hz, CH), 4.56 (1H, d, *J*=11.2 Hz, CH), 4.31 (1H, d, *J*=2.7 Hz, CH), 4.21 (1H, dd, *J*=7.8, 1.8 Hz, CH), 4.19 (1H, d, *J*=11.2 Hz, CH), 3.89 (1H, dd, *J*=13.0, 1.8 Hz, CH), 3.74 (1H, d, *J*=13.0 Hz, CH), 1.53 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm; ^{13}**C NMR** (50.3MHz,$CDCl_3$) δ 150.05 (C=O), 109.08 (quat C), 108.93 (quat C), 100.38 (quat C), 70.34 (CH), 70.30 (CH), 70.03 (CH), 69.60 (CH_2), 61.16 (CH_2), 26.23 (CH_3), 25.61 (CH_3), 24.80 (CH_3), 23.75 (CH_3) ppm; **IR** (thin film) ν_{max} 1780 (C=O) cm^{-1}; **MS** (ei) m/z 44 (base), 60 (62%), 113 (20%), 307 (48%, ^{35}Cl $(M-15)^+$), 309 (16%, ^{37}Cl $(M-15)^+$), 322 (96%, ^{35}Cl, M^+), 324 (32%, ^{37}Cl, M^+); **Accurate mass** (FAB), Found: 323.08973, ($C_{13}H_{20}{}^{35}ClO_7$) (M+H), Requires: 323.08974.

Preparation of *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose-10-azidoformate* 8. A solution of sodium azide (14.13g, 0.217mol) and tetrabutylammonium bromide, TBAB, (3g) in distilled water (500ml) was added in one aliquot to a rapidly stirred solution of *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose-10-chloroformate* **7** (34.73g, 0.108mol) in dichloromethane (500ml). The reaction mixture was stirred vigorously for 4 hours, separated and the aqueous layer then extracted with dichloromethane (3 x 100ml). The combined organic layers were washed with water (100ml), dried with powdered $MgSO_4$, filtered and evaporated *in vacuo* to yield a brown viscous oil. The crude mixture was extracted with hot hexane to yield a brown viscous residue of (*2,3:4,5-di-O-isopropylidene-β-D-fructopyranose-10-azidoformate*) **8** (33.66g, 95%).

^{1}**H NMR** (200.13MHz, $CDCl_3$) δ 4.52 (1H, dd, *J*=7.9, 2.6 Hz, CH), 4.40 (1H, d, *J*=11.5 Hz, CH), 4.22 (1H, d, *J*=2.6 Hz, CH), 4.15 (1H, ddd, *J*=7.9, 1.8, 0.8 Hz, CH), 4.05 (1H, d, *J*=11.5 Hz, CH), 3.80 (1H, dd, *J*=13.0, 1.8 Hz, CH), 3.65 (1H, dd, *J*=13.0, 0.8 Hz, CH), 1.44 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.24 (3H, s, CH_3) ppm; ^{13}**C NMR** (50.3MHz,$CDCl_3$) δ 157.03 (C=O), 108.80 (quat C), 108.70 (quat C), 100.70 (quat C), 70.34 (CH), 70.07 (CH), 69.92 (CH), 67.71 (CH2), 60.99 (CH_2), 26.14 (CH_3), 25.49 (CH_3), 24.74 (CH_3), 23.70 (CH_3) ppm; **IR** (thin film) ν_{max} 2160 (N_3), 1740 (C=O) cm^{-1}; **MS** (ei) m/z 44 (base), 60 (70%), 70 (52%), 85 (36%), 113 (42%), 314 (79%, $(M-15)^+$), 330 (20%, M^+); **Accurate mass** (FAB), Found: 330.13012, ($C_{13}H_{20}NO_7$) (M+H), Requires: 330.13013.

Preparation of *5-aza-1S,6S:7R,8R-di-O-isopropylidene-3,10-dioxa-[4,4,01,6]-decan-4-one* 1 *via* solution thermolysis of azidoformate 8. A solution of *2,3:4,5-di-O-isopropylidene-β-D-fructopyranose-10-azidoformate* **8** (33.66g, 0.102mol) in dry 1,1,2,2-tetrachloroethane, TCE, (100ml) was added dropwise *via* syringe pump over 20 minutes into boiling dry 1,1,2,2-tetrachloroethane (bp=147°C) (1500ml) under a flushing argon atmosphere. Upon complete addition the contents were heated under reflux for a further 60 minutes at which point TLC analysis indicated all starting material had been consumed. The solution was allowed to cool followed by removal of the reaction solvent by evaporation *in vacuo* (fume cupboard) to yield a thick viscous brown oil. The crude material was subjected to flash column chromatography using gradient elution (100% hexane to 100% ether) to yield after recrystallisation from ethyl acetate (5ml/g) the desired product *5-aza-1S,6S:7R,8R-di-O-isopropylidene-3,10-dioxa-[4,4,01,6]-decan-4-one* **1** as a colourless highly crystalline solid (16.9g, 55%); **mp** = 219°C; $[\alpha]^{26}$ = +57.1°; ^{1}**H NMR** (200.13MHz,$CDCl_3$) δ 7.51 (1H, br s, N<u>H</u>), 4.46 (1H, d, *J*=7.9 Hz, C<u>H</u>), 4.25 (1H, dd, *J*=7.9, 1.8 Hz, C<u>H</u>), 4.18 (1H, d, *J*=11.7 Hz, C<u>H</u>), 4.16 (1H, d, *J*=11.7 Hz, C<u>H</u>), 3.92 (1H, dd, *J*=13.1, 1.8 Hz, C<u>H</u>), 3.75 (1H, d, *J*=13.1 Hz, C<u>H</u>), 1.44 (3H, s, $C\underline{H}_3$), 1.38 (3H, s, $C\underline{H}_3$), 1.29 (3H, s, $C\underline{H}_3$), 1.25 (3H, s, $C\underline{H}_3$) ppm; ^{13}**C NMR** (50.3MHz,$CDCl_3$) δ 153.87 (C=O), 111.12 (quat C), 109.46 (quat C), 98.16 (quat C), 85.68 (quat C), 71.84 (CH), 71.04 (CH), 67.83 (CH_2), 62.41 (CH_2), 28.25 (CH_3), 27.48 (CH_3), 25.86 (CH_3), 24.31 (CH_3) ppm; **IR** (thin film) ν_{max} 3300 (N-H), 1680 (C=O) cm^{-1}; **MS** (ei) m/z 32 (80%), 44 (base), 60 (90%), 186 (56%), 201 (95%), 244 (50%), 286 (61%, $(M-15)^+$), 302 (20%, M^+), 603 (95%); **Accurate mass** (FAB), Found: 302.12395, ($C_{13}H_{20}NO_7$) (M+H), Requires: 302.12396.

Preparation of N-acyl derivatives for asymmetric conversion reactions

General procedure for the preparation of *N*-functionalised derivatives 11, 12, 13 *via* Grignard reagent methylmagnesium bromide. An ice-cold solution of auxiliary **1** (6g, 0.020mol) in dry tetrahydrofuran (60ml) was added over 10 minutes to a prepared solution* of methylmagnesium bromide (2eq) in dry diethyl ether under argon. The reaction temperature was maintained at 0°C and the mixture stirred for 15 minutes before cooling to -78°C at which time a pre-cooled (-78°C) solution of freshly distilled acyl chloride (0.030mol, 1.5eq) in dry tetrahydrofuran (30ml) was added in small portions *via* syringe. Stirring was continued for 60 minutes then quenched by adding a saturated solution of aqueous ammonium chloride (50ml). After stirring vigorously for 10 minutes the reaction solvent was removed at the pump and the product extracted into dichloromethane (3 x 40ml). The combined organic extracts were washed with water (40ml), dried (powdered $MgSO_4$), filtered under gravity and evaporated to yield a pale/deep yellow solid/oil. The crude material was subjected to flash chromatography using gradient elution to return each of the products as a colourless crystalline solid. (*Magnesium turnings were added to a reaction vessel and immersed under dry diethyl ether in an argon atmosphere. Following the addition of a few drops of iodomethane (initiator) the contents were cooled to 10-15°C whereupon bromomethane solution in dry diethyl ether (one small portion *via* syringe) was added. Hand warming of the reaction vessel and gentle agitation by tapping helps to start the reaction which is indicated by the production of bubbles. When underway the reaction is sustained by adding the remaining bromomethane in small portions until completion which is signified by cessation of bubble production. Excess halide was driven off from the reaction mixture by heating the reaction vessel in warm water then the resulting solution was cooled to 0°C in preparation for the addition of the auxiliary).

Preparation of *N-propionyl-5-aza-1S,6S:7R,8R-di-O-isopropylidene-3,10-dioxa-[4,4,01,6]-decan-4-one* 11. Spectral analysis of **11** (returned as colourless crystalline solid, yield 97%): **Mp** = 130-131°C; $[\alpha]^{24}$ = -16.6°; ^{1}**H NMR** (200.13MHz,$CDCl_3$) δ 5.11 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.28 (1H, ddd, *J*=8.1, 1.8, 1.0 Hz, C<u>H</u>), 4.25 (1H, d, J=11.6 Hz, C<u>H</u>), 4.18 (1H, d, J=11.6 Hz, C<u>H</u>), 3.87 (1H, dd, J=13.2, 1.8 Hz, C<u>H</u>), 3.79 (1H, dd, J=13.2, 1.0 Hz, C<u>H</u>), 2.73 (2H, q, J=7.5 Hz, $C\underline{H}_2$), 1.57 (3H, s, $C\underline{H}_3$), 1.44 (3H, s, $C\underline{H}_3$), 1.41 (3H, s, $C\underline{H}_3$), 1.27 (3H, s, $C\underline{H}_3$), 1.16 (3H, t, J=7.5 Hz, $C\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 179.09 (C=O), 152.29 (C=O), 111.88 (quat C), 109.11 (quat C), 101.04 (quat C), 89.82 (quat C), 70.54 (CH), 70.30 (CH), 68.41 (CH_2), 61.15 (CH_2), 32.52 (CH_2), 27.74 (CH_3), 27.30 (CH_3), 25.61 (CH_3), 23.94 (CH_3), 9.63 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1720 (C=O) cm-1; **MS** (ei) m/z 31 (32%), 43 (76%), 57 (base), 244 (38%), 302 (95%), 342 (80%, $(M-15)^+$), 358 (75%, M^+) 414 (40%); **Accurate mass** (FAB), Found: 358.15019, ($C_{16}H_{24}NO_8$) (M+H), Requires: 358.15018.

Preparation of *N-acryloyl-5-aza-1S,6S:7R,8R-di-O-isopropylidene-3,10-dioxa-[4,4,01,6]-decan-4-one* 12. Spectral analysis of **12** (returned as colourless crystalline solid, yield 22%, all unreacted starting material **1** recovered intact): **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 6.44 (1H, dd, J=16.9, 9.7 Hz, C<u>H</u>), 6.34 (1H, dd, J=16.9, 1.8 Hz, C<u>H</u>), 5.70 (1H, dd, J=9.7, 1.8 Hz, C<u>H</u>), 5.11 (1H, d, J=8.1 Hz, C<u>H</u>), 4.26 (1H, dd, J=8.1, 1.8 Hz, C<u>H</u>), 4.24 (1H, d, J=11.7 Hz, C<u>H</u>), 4.18 (1H, d, J=11.7 Hz, C<u>H</u>), 3.82 (1H, dd, J=13.2, 1.8 Hz, C<u>H</u>), 3.76 (1H, d, J=13.2, Hz, C<u>H</u>), 1.56 (3H, s, $C\underline{H}_3$), 1.42 (3H, s, $C\underline{H}_3$), 1.39 (3H, s, $C\underline{H}_3$), 1.24 (3H, s, $C\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,CDCl3) δ 168.74 (C=O), 152.23 (C=O), 131.20 (CH), 129.28 (CH_2), 112.10 (quat C), 109.35 (quat C), 101.28 (quat C), 89.97 (quat C), 70.79 (CH), 70.34 (CH), 68.92 (CH_2), 61.27 (CH_2), 27.66 (CH_3), 27.31 (CH_3), 25.60 (CH_3), 24.02 (CH_3) ppm; **MS** (ei) m/z 43 (36%), 55 (base), 103 (33%), 340 (28%, $(M-15)^+$), 356 (32%, M^+); **Accurate mass** (FAB), Found: 356.13452, ($C_{16}H_{22}NO_8$) (M+H), Requires: 356.13453.

Preparation of *N-cinnamoyl-5-aza-1S,6S:7R,8R-di-O-isopropylidene-3,10-dioxa-[4,4,01,6]-decan-4-one* 13. Spectral analysis of **13** (returned as colourless crystalline solid, yield 90%): **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.73 (1H, d, J=15.6 Hz, CH=C<u>H</u>), 7.54 (5H, m, Ph), 6.83 (1H, d, J=15.6 Hz, C<u>H</u>), 5.25 (1H, d, J=8.1 Hz, C<u>H</u>), 4.32 (1H, d, J=11.7 Hz, C<u>H</u>), 4.30 (1H, dd, J=8.1, 1.3 Hz, C<u>H</u>), 4.29 (1H, d, J=11.7 Hz, C<u>H</u>), 3.91 (1H, dd, J=13.2, 1.9 Hz, C<u>H</u>), 3.84 (1H, d, J=13.2, Hz, C<u>H</u>), 1.61 (3H, s, C<u>H</u>3), 1.49 (3H, s, $C\underline{H}_3$), 1.43 (3H, s, $C\underline{H}_3$), 1.28 (3H, s, $C\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 168.74 (C=O), 152.33 (C=O), 143.78 (CH), 134.09 (quat C), 130.18 (CH), 128.52 (2xCH), 128.17 (2xCH), 121.29 (CH), 111.78 (quat C), 111.78 (quat C), 101.40 (quat C), 89.88 (quat C), 70.97 (CH), 70.19 (CH), 68.86 (CH_2), 61.09 (CH_2), 27.46 (CH_3), 27.09 (CH_3), 25.43 (CH_3), 23.89 (CH_3) ppm; **MS** (ei) m/z 43 (40%), 131 (base), 302 (60%), 374 (42%), 416 (64%, $(M-15)^+$), 432 (92%, M^+); **Accurate mass** (FAB), Found: 432.16585, (C22H26NO8) (M+H), Requires: 432.16583.

Application of auxiliary 1 in model asymmetric transformations

Asymmetric aldol reaction using benzaldehyde to furnish adduct 15 (S_2). [The aldol reactions involving aldehydic reagents, *viz.* isobutyraldehyde and acetaldehyde were conducted in accordance with that used for benzaldehyde which is described in detail below.]

To an ice-cold solution of diisopropylamine (0.93g, 1.1eq) in dry THF (15ml) was added butyllithium (6ml, 1.6M, 1.1eq) dropwise *via* syringe. After leaving the contents to stir for 20 minutes, the solution was cooled to -78°C whereupon a pre-cooled solution (-78°C) of the propionate **11** (3g, 8.4mmol) in dry THF (25ml) was added. The mixture was left to stir for 60 minutes then freshly distilled benzaldehyde (1g, 1.1eq) in dry THF (10ml) was added. After allowing to stir for 20 minutes the reaction mixture was quenched with a saturated aqueous ammonium chloride solution (15ml) then warmed to room temperature before removing the reaction solvent at the pump. Separation of the two-layer mixture was followed by extraction with dichloromethane (3 x 40ml). The organic layer and extracts were combined, washed with water (40ml), dried with powdered magnesium sulphate, filtered and evaporated to yield the aldol product **15** as a pale yellow foam (3.3g, 85%). Examination of the 360 MHz ^{1}H NMR spectrum revealed the presence of two diastereomers (both *syn*) in the ratio of 8:1. The stereochemical assignment of the two diastereomers was determined from the coupling constant values obtained for the appropriate doublets of the PhC$\underline{H}$OH and CH_3CH(C=O) vicinal protons (values were approximately 3.2 Hz). From a single crystallisation (methylene chloride/hexane) the major diastereomer was isolated for which full spectrophotometric data was obtained and is given below.

$[\alpha]^{25}$ = -18.2°; **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.42-7.22 (5H, m, Ph), 5.26 (1H, d, *J*=8.1 Hz, C$\underline{H}$), 4.37 (1H, dd, *J*=8.1, 1.2 Hz, C$\underline{H}$), 4.28 (2H, s, 2xC$\underline{H}$), 4.12 (1H, d, *J*=1.7 Hz, C$\underline{H}$), 3.93 (1H, dd, *J*=13.3, 2.0 Hz, C$\underline{H}$), 3.86 (1H, d, *J*=13.3 Hz, C$\underline{H}$), 3.62 (1H, dq, *J*=6.9, 1.7 Hz, C$\underline{H}$), 1.63 (3H, s, C$\underline{H}_3$), 1.50 (3H, s, C$\underline{H}$3), 1.48 (3H, s, C$\underline{H}_3$), 1.35 (3H, s, C$\underline{H}_3$), 1.01 (3H, d, *J*=6.9 Hz, C$\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 181.35 (C=O), 152.10 (C=O), 141.07 (quat C), 127.71 (Phenyl CH), 126.69 (Phenyl CH), 125.33 (Phenyl CH), 112.02 (quat C), 109.29 (quat C), 100.79 (quat C), 90.25 (quat C), 72.14 (CH), 70.27 (CH), 70.25 (CH), 67.89 (CH_2), 60.89 (CH2), 49.12 (CH), 27.87 (CH3), 27.10 (CH3), 25.38 (CH3), 23.78 (CH3), 8.57 (CH3) ppm; **IR** (thin film) ν_{max} 3540 (OH), 1770 (C=O), 1720 (C=O) cm-1; **MS** (ei) m/z 44 (64%), 58 (70%), 145 (base), 244 (44%), 286 (40%), 302 (86%); **Accurate mass** (FAB), Found: 464.19202, ($C_{23}H_{30}NO_9$) (M+H), Requires: 464.19203.

Hydrolytic cleavage of the chiral fragment from the parent auxiliary following each asymmetric transformation was effected by adopting the general procedure as described in detail for the cleavage of benzaldehyde-derived aldol product 15 to generate α-alkyl, *β*-hydroxy acid fragment 16. To an ice-cold solution of the substrate **15** (0.90g, 1.94mmol) in tetrahydrofuran/water mixture (40ml, 3:1) was added hydrogen peroxide (1.47ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide(0.17g, 2.0eq). After allowing to warm to ambient temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulfite solution (1.5M, 8ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 30ml), the auxiliary **1*** was recovered as a white foam in high yield (0.56g, >95%). The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 30ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid fragment **16** as a thin colourless oil (0.34g, >95%). *Analysis by ^1H and ^{13}C NMR spectroscopy confirmed the identity of the organic matrix as auxiliary **1**.

Spectral analysis of acid fragment **16**: (-)-(*2S,3S*)-3-hydroxy-2-methyl-3-phenylpropanoic acid, $[\alpha]^{25}$ = -28.7°; **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.30-7.22 (5H, m, Ph), 6.75 (1H, br s, OH), 5.16 (1H, d, *J*=3.9 Hz, PhC$\underline{H}$OH), 2.82 (1H, dq, *J*=7.2, 3.9 Hz, CH3C$\underline{H}$), 1.13 (3H, d, *J*=7.2 Hz, C$\underline{H}$3) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 180.50 (C=O), 140.93 (quat C), 128.21 (Phenyl CH), 127.50 (Phenyl CH), 125.82 (Phenyl CH), 73.24 (CHOH), 46.01 (CHC=O), 14.99 (CH_3) ppm.

Preparation of α-bromo substituted product 18. Butyllithium (2.0ml, 1.6M, 1.1eq) was added dropwise *via* syringe to an ice-cold solution of diisopropylamine (0.31g, 1.1eq) in dry THF (15ml). Upon leaving the contents to stir for 20 minutes, the solution was cooled to -78°C at which time a pre-cooled solution (-78°C) of the propionate **11** (1.0g, 2.8mmol) in dry THF (20ml) was added. The mixture was left to stir for 60 minutes then a solution of *N*-bromosuccinimide (NBS, 1.00g, 5.6mmol, 2eq) in dry THF (25ml) was added dropwise. The temperature was maintained at -78°C and the reaction mixture allowed to stir whilst supervising reaction progress by TLC at regular 2 minute intervals. After a period of 12 minutes all starting material had been consumed and the reaction was immediately quenched by adding a saturated solution of aqueous ammonium chloride (40ml). The quenched solution was allowed to warm to room temperature whereupon the THF reaction solvent was removed *in vacuo* and the resultant aqueous layer extracted with diethyl ether (3 x 30ml). The extracts were combined, washed with water (30ml), dried with powdered $MgSO_4$, filtered and evaporated to return a pale yellow viscous oil in quantitative yield. The crude product was flushed down a chromatographic column with a mixture of hexane/ether (1:1) to remove reaction contaminants. A sample of the returned product **18** was analysed by high resolution ^1H NMR to reveal the existence of two isomers in a ratio of 25:1. The refined material was then subjected to flash chromatography using an elution ratio of hexane/ether (3:1, 1000ml) to separate the two isomers. The first fraction yielded an approximately 5-10% return of the minor isomer as a thin oil and the second fraction returned the major isomer as colourless crystals in an overall yield of 90%.

Spectral data relating to major isomer **18**: **Mp** = 134-135 °C; $[\alpha]^{24}$ = +46.6°; **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 5.07 (1H, q, *J*=6.7 Hz, BrC$\underline{H}$), 4.95 (1H, d, *J*=8.1 Hz, C$\underline{H}$), 4.29 (1H, d, *J*=11.6 Hz, C$\underline{H}$), 4.29 (1H, dd, *J*=7.9, 1.8 Hz, C$\underline{H}$), 4.22 (1H, d, *J*=11.6Hz, C$\underline{H}$), 3.89 (1H, dd, *J*=13.2, 1.8 Hz, C$\underline{H}$), 3.79 (1H, d, *J*=13.2 Hz, C$\underline{H}$), 1.87 (3H, d, *J*=6.7 Hz, BrCHC$\underline{H}_3$), 1.60 (3H, s, C$\underline{H}_3$), 1.43 (3H, s, C$\underline{H}_3$), 1.41 (3H, s, C$\underline{H}_3$), 1.28 (3H, s, C$\underline{H}_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 173.86 (C=O), 152.83 (C=O), 112.38 (quat C), 109.41 (quat C), 103.73 (quat C), 90.67 (quat C), 72.93 (CH), 70.83 (CH_2), 69.93 (CH), 60.93 (CH_2), 43.30 (CH-Br), 28.23 (CH_3), 26.96 (CH_3), 25.29 (CH_3), 24.28 (CH_3), 21.41 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1700 (C=O) cm-1; **MS** (ei) m/z 43 (85%), 57 (70%), 73 (40%), 244 (base), 302 (25%), 421 (40%, $(M-15)^+$), 437 (60%, M^+); **Accurate**

mass (FAB), Found: 436.06078, ($C_{16}H_{23}79BrNO_8$) (M+H), Requires: 436.06074, Found: 438.05880, ($C_{16}H_{23}81BrNO_8$) (M+H), Requires: 438.05877.

Hydrolytic cleavage of major isomer of α-brominated product 18 to furnish (+)-2-(*R*)-bromopropionic acid 19. To an ice-cold solution of the substrate **18** (0.5g, 1.15mmol) in tetrahydrofuran/water mixture (40ml, 3:1) was added hydrogen peroxide (0.9ml, 6.0eq, assay 27%) followed by hydrated lithium hydroperoxide(0.10g, 2.0eq). After allowing the mixture to warm to ambient temperature and stirring for 60 minutes, the excess peroxide was quenched with sodium sulfite solution (1.5M, 6ml, 1.1eq) and then buffered to pH 9-10 with saturated aqueous sodium bicarbonate. Upon removal of organic volatiles by rotary evaporation and subsequent work-up by separation and extraction from the aqueous layer with dichloromethane (3 x 30ml), the auxiliary **1*** was recovered as a white foam in high yield (0.33g, >95%). The aqueous phase was acidified to pH 1-2 by the dropwise addition of concentrated hydrochloric acid, extracted with ethyl acetate (3 x 30ml), then separated, dried ($MgSO_4$), filtered and evaporated to yield the carboxylic acid fragment as a colourless oil (0.16g, >90%). The absolute configuration of the fragment was later identified from literature comparison of its optical rotation value as being (+)-2-(*R*)-bromopropionic acid **19** in a yield of >85%. $[\alpha]^{24}$ = +27.9°, [lit.[10] = -27.6° for (2*S*) enantiomer].

*Analysis by ^{1}H and ^{13}C NMR spectroscopy confirmed the identity of the organic matrix as auxiliary **1**.

Lewis-acid catalysed Diels-Alder cycloaddition reactions

The general procedure for the asymmetric cycloaddition reactions was conducted as detailed below.

To a solution of dienophile **12** and **13** (0.85mmol) in dry methylene chloride (20ml) at -78°C under argon was added a pre-cooled solution of freshly cracked diene (8.50mmol, 10eq) in dry methylene chloride (10ml). Diethylaluminium chloride (1.6M, 1.4eq) was promptly added *via* syringe and resulted in the transient appearance of a distinct yellow colour. The contents of the reaction vessel were stirred at -78°C for 10 minutes then quenched by the addition of a saturated solution of ammonium chloride (15ml) and allowed to warm to room temperature. The reaction mixture was poured into a combination of methylene chloride/water (40ml, 1:1), then separated and the aqueous layer extracted with methylene chloride (3 x 30ml). The organic layer and extracts were combined, washed with both aqueous $NaHCO_3$ (30ml) and water (30ml), then dried $MgSO_4$, filtered and evaporated to yield a viscous oil. Excess cyclopentadiene was removed from the crude material by column chromatography (elution ratio: hexane/ether, 7:1, 500ml) to furnish the refined products **21**, **22**, and **25**.

Cycloaddition reaction of acrylate 12 with cyclopentadiene to generate cycloadduct 21. Examination of the ^{1}H NMR spectrum of a sample of the purified product **21** revealed the presence of two isomers (both *endo*) in a ratio of 14:1 giving a diastereomeric excess of 87%. This value was determined by integration of the doublet signal obtained from an auxiliary proton which lies in an uncomplicated region in the spectrum at δ=5.00-5.10 ppm.

Spectral analysis of compound **21** (returned as colourless crystals, **mp** = 134-135°C yield 95%): **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 6.15 (1H, dd, *J*=5.6, 3.1 Hz, CH=C<u>H</u>), 5.96 (1H, dd, *J*=5.6, 2.8 Hz, C<u>H</u>=CH), 5.05 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.29 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.26 (1H, ddd, *J*=8.0, 1.9, 0.8 Hz, C<u>H</u>), 4.15 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.87 (1H, dd, *J*=13.2, 1.9 Hz, C<u>H</u>), 3.78 (1H, dd, *J*=13.2, 0.8 Hz, C<u>H</u>), 3.68 (1H, ddd, *J*=9.3, 4.9, 3.3 Hz, C<u>H</u>C=O), 3.24 (1H, br s, bridgehead C<u>H</u>), 2.89 (1H, br s, bridgehead C<u>H</u>), 2.06 (1H, m, C<u>H</u>), 1.58 (1H, m, C<u>H</u>), 1.56 (3H, s, C<u>H</u>$_3$), 1.45 (3H, s, C<u>H</u>$_3$), 1.40 (3H, s, C<u>H</u>$_3$), 1.31 (3H, s, C<u>H</u>$_3$), 1.26 (1H, m, C<u>H</u>$_2$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 179.62 (C=O), 152.57 (C=O), 137.35 (CH=CH), 132.89 (CH=CH), 111.92 (quat C), 109.26 (quat C), 101.74 (quat C), 90.11 (quat C), 71.04 (CH), 70.43 (CH), 68.69 (CH_2), 61.36 (CH_2), 49.48 (bridgehead CH_2), 47.79 (CH), 46.84 (CH), 42.66 (CH), 32.29 (CH_2), 28.02 (CH_3), 27.27 (CH_3), 25.69 (CH_3), 24.22 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1730 (C=O) cm^{-1}; **MS** (ei) m/z 32 (65%), 44 (base), 57 (60%), 73 (45%), 91 (70%), 121 (65%), 302 (70%), 396 (20%, $(M-15)^+$), 422 (30%, M^+); **Accurate mass** (FAB), Found: 422.18148, ($C_{21}H_{28}NO_8$) (M+H), Requires: 422.18147.

Cycloaddition reaction of cinnamate 13 with cyclopentadiene to generate cycloadduct 22. Yield 95%; $[\alpha]^{26}$ = -41.0°; **^{1}H NMR** (360.13MHz,CDCl3) δ 7.29-7.11 (5H, m, Phenyl C<u>H</u>), 6.40 (1H, dd, *J*=5.6, 3.1 Hz, C<u>H</u>=CH), 6.12 (1H, dd, *J*=5.5, 2.7 Hz, CH=C<u>H</u>), 5.09 (1H, d, *J*=8.1 Hz, C<u>H</u>), 4.26 (1H, dd, *J*=8.1, 1.7 Hz, C<u>H</u>), 4.23 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.07 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.88 (1H, dd, *J*=13.2, 2.1 Hz, C<u>H</u>), 3.87 (1H, d, *J*=13.2, 2.0 Hz, C<u>H</u>), 3.86 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.35 (1H, br s, bridgehead C<u>H</u>), 3.10 (1H, m, C<u>H</u>-CH=CH), 3.05 (1H, m, C<u>H</u>), 3.00 (1H, m, CH=CH-C<u>H</u>), 2.84 (1H, br s, bridgehead C<u>H</u>), 1.76 (1H, m, C<u>H</u>Ph), 1.52 (3H, s, C<u>H</u>$_3$), 1.46 (3H, s, C<u>H</u>$_3$), 1.32 (3H, s, C<u>H</u>$_3$), 1.24 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,CDCl3) δ 178.36 (C=O), 152.43 (C=O), 144.49 (Ar quat C), 139.26 (CH=CH), 133.10 (CH=CH), 129.72 (Phenyl CH), 128.61 (Phenyl CH), 127.73 (Phenyl CH), 112.11 (quat C), 109.35 (quat C), 100.81 (quat C), 90.14 (quat C), 70.76 (CH), 67.49 (CH_2), 61.88 (CH_2), 55.80 (CH), 49.90 (CHC=O), 48.56 (CHPh), 46.68 (bridgehead CH_2), 43.12 (CH), 40.36 (CH), 28.46 (CH_3), 27.62 (CH_3), 25.91 (CH_3), 24.35 (CH_3) ppm; **IR** (thin film) ν_{max} 1760 (C=O), 1710 (C=O) cm-1; **Accurate mass** (FAB), Found: 498.21276, ($C_{27}H_{32}NO_8$) (M+H), Requires: 498.21277.

Cycloaddition reaction of acrylate 12 with isoprene to generate cycloadduct 25.

Spectral data relating to major isomer **25**: Yield 95%; **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 5.35-5.33 (1H, br dd, *J*=3.4, 1.7 Hz, C<u>H</u>=CH2), 5.09 (1H, d, *J*=8.0 Hz, C<u>H</u>), 4.28 (1H, dd, *J*=8.1, 1.7 Hz, C<u>H</u>), 4.21 (1H, d, *J*=11.6 Hz, C<u>H</u>), 4.18 (1H, d, *J*=11.6 Hz, C<u>H</u>), 3.88 (1H, dd, *J*=13.2, 2.1 Hz, C<u>H</u>), 3.80 (1H, d, *J*=13.2 Hz, C<u>H</u>), 3.08-3.00 (1H, symm m {dddd}, *J*=14.2, 11.6, 5.4, 2.3 Hz, C<u>H</u>C=O), 2.32-1.98 (6H, br m, 3C<u>H</u>$_2$), 1.62 (3H, s, C=CC<u>H</u>$_3$), 1.57 (3H, s, C<u>H</u>$_3$), 1.44 (3H, s, C<u>H</u>$_3$), 1.41 (3H, s, C<u>H</u>$_3$), 1.27 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 181.74 (C=O), 152.28 (C=O), 133.31 (quat C {C=C}), 119.01 (<u>C</u>H=C), 111.91 (quat C), 108.93 (quat C), 100.79 (quat C), 89.79 (quat C), 71.31 (CH), 70.89 (CH), 67.85 (CH_2), 61.30 (CH_2), 43.16 (<u>C</u>HC=O), 29.35 (CH_2), 29.15 (CH_2), 28.05 (CH_3), 27.26 (CH_3), 25.79 (CH_2), 25.64 (CH_3), 23.92 (CH_3) 23.07

(CH_3) ppm; **MS** (ei) m/z 43 (base), 57 (55%), 95 (90%), 123 (35%), 201 (30%), 244 (50%), 302 (75%), 422 (95%, M+); **Accurate mass** (FAB), Found: 424.19709, ($C_{21}H_{30}NO_8$) (M+H), Requires: 424.19710.

Cleavage of major cycloadduct of acrylate reaction with cyclopentadiene to generate carboxylic acid 23. Analysis by ^{1}H and ^{13}C NMR spectroscopy confirmed the identity of the organic matrix as auxiliary **1**. Spectral analysis of acid fragment **23** (returned as a thin colourless oil yield >95%): **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 7.11 (1H, br s, O<u>H</u>), 6.25 (1H, dd, *J*=5.6, 3.0 Hz, CH=C<u>H</u>), 6.04 (1H, dd, *J*=5.6, 3.0 Hz, C<u>H</u>=CH), 3.77 (1H, m, C<u>H</u>C=O), 3.32-3.24 (1H, br s, bridgehead C<u>H</u>), 2.96 (1H, br s, bridgehead C<u>H</u>), 2.17 (1H, m, CH<u>H</u>), 1.68 (1H, m, C<u>H</u>H), 1.33 (2H, m, C<u>H</u>$_2$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 179.46 (C=O), 137.30 (CH=CH), 132.82 (CH=CH), 49.76 (CH_2), 47.72 (CH), 46.78 (CH), 42.54 (CH), 32.16 (CH_2) ppm; **IR** (thin film) ν_{max} 1750 (C=O), 1670 (C=C) cm^{-1}.

Cleavage of major cycloadduct of cinnamate reaction with cyclopentadiene to generate carboxylic acid 24. Analysis by ^{1}H and ^{13}C NMR spectroscopy confirmed the identity of the organic matrix as auxiliary **1**. The resulting acid fragment **24,** obtained as a colourless solid in >95% yield: **mp** = 108-109°C, was identified as 2*S*, 3*R* -3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid *via* its benzyl ester; $[\alpha]_D$ = -119° (*cf.* +121° for antipode[11]): **^{1}H NMR** (360.13MHz,$CDCl_3$) δ 7.36-7.20 (5H, m, Phenyl C<u>H</u>), 6.90 (1H, br s, O<u>H</u>), 6.46 (1H, dd, *J*=5.6, 3.1 Hz, CH=C<u>H</u>), 6.20 (1H, dd, *J*=5.6, 2.8 Hz, C<u>H</u>=CH), 3.43 (1H, m, C<u>H</u>C=O), 3.23-3.11 (1H, br s, bridgehead C<u>H</u>), 3.06-2.92 (1H, br s, bridgehead C<u>H</u>), 2.82-2.70 (1H, m, C<u>H</u>Ph), 1.91-1.73 (2H, m, C<u>H</u>$_2$) ppm; **^{13}C NMR** (50.3MHz,CDC13) δ 179.73 (C=O), 144.61 (Ar quat C), 139.32 (CH=CH), 133.18 (CH=CH), 129.76 (Phenyl CH), 128.66 (Phenyl CH), 127.80 (Phenyl CH), 49.96 (CHC=O), 48.71 (CHPh), 46.66 (CH_2), 43.22 (CH), 40.49 (CH) ppm; **IR** (thin film) ν_{max} 1730 (C=O), 1650 (C=C) cm-1.

Cleavage of major cycloadduct of acrylate reaction with isoprene to generate carboxylic acid 26. Analysis by ^{1}H and ^{13}C NMR spectroscopy confirmed the identity of the organic matrix as auxiliary **1**. The resulting acid fragment **26** obtained as a colourless oil in >95% yield, was identified as (+)-(*R*)-4-methyl-3-cyclohexenecarboxylic acid; $[\alpha]_D$ = + 102° (C= 0.41, 95% ethanol), lit.[15] $[\alpha]_D$ = -107° (*S*-isomer): **^{1}H NMR** (200.13MHz,$CDCl_3$) δ 7.11 (1H, br s, O<u>H</u>), 5.91 (1H, m, C=C<u>H</u>), 3.44 (1H, m, C<u>H</u>C=O), 2.46 (2H, m, C<u>H</u>$_2$), 2.38 (2H, m, C<u>H</u>$_2$), 2.18 (2H, m, C<u>H</u>$_2$), 1.68 (3H, s, C<u>H</u>$_3$) ppm; **^{13}C NMR** (50.3MHz,$CDCl_3$) δ 180.58 (C=O), 134.20 (quat C=C), 119.22 (CH=), 42.69 (CH), 31.08 (CH_2), 27.83 (CH_2), 26.46 (CH2), 23.54 (CH_3) ppm; **IR** (thin film) ν_{max} 1740 (C=O) cm-1.

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