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Highly Regio- and Stereo-specific Preparation of a New Carbohydrate-based 1,3-Oxazin-2-one by the INIR Method and its Applications in Some Asymmetric Transformations

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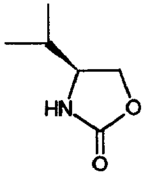
Abstract: Preliminary experiments show that a new gulonic acid-derived 1,3-oxazin-2-one, prepared by an intramolecular nitrene insertion reaction (INIR) method, serves to control both asymmetric aldol and Diels-Alder reactions with excellent stereo-selection.

INTRODUCTION

Following the seminal work of Evans[1] on the development of chiral oxazolidin-2-ones, *e.g.* **1**, as auxiliaries in asymmetric reactions, there have been numerous efforts[2] to design more efficient variants including some recent reports by us on the promising use of oxazolidin-2-ones **2** and **3** derived from terpenes such as [(1S)-*endo*]-(-)-borneol[3], (+)- and (-)- camphene[4,5]. Unlike the Evans' approach which employed direct cyclocarbamation of relatively expensive optically pure β-amino alcohols, we used the INIR (Intramolecular Nitrene Insertion Reaction) method, a powerful albeit little used tool in organic synthesis, to construct the oxazolidin-2-one ring in a three-step sequence involving phosgenation, azidination and thermolysis (Scheme 1). This process has also been extended to the carbohydrate series and starting from D-(+)-galactose we recently reported the synthesis of the first chiral spirooxazolidin-2-one[6] **4** whose highly crystalline nature imparted excellent crystallinity to derivatives. This auxilary also served to control Diels-Alder as well as aldol reactions with high chiral efficiency. The benefit of **4** as an achiral control element in aldol reactions was highlighted by the fact that such processes proceeded with excellent π-face discrimination *via* a lithium-chelated (Z)-enolate, *i.e.* without recourse to the use of hazardous and expensive di-*n*-butylboron triflate as a mediating agent. However, contrary to our earlier claim[6], more detailed studies have shown that the recovered galactose-derived chiral auxiliary **4** undergoes epimerisation to varying degrees about the spiro-carbon atom upon cleavage of its adducts with lithium borohydride or lithium benzyloxide.



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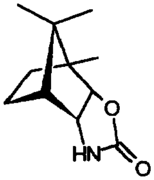

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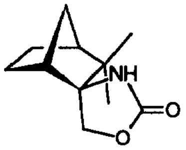

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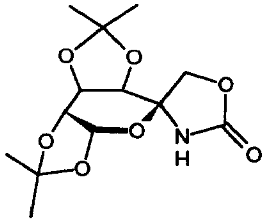

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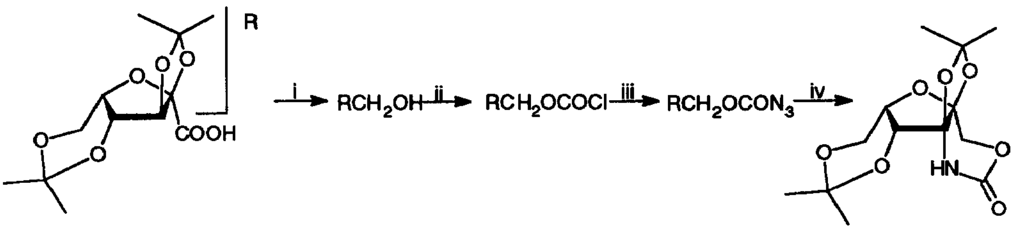
In an effort to circumnavigate this epimerisation process but retain the lithium-chelate behaviour we have applied the same synthetic methodology to prepare a new chiral auxiliary from 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid **5**. In this particular case the nitrene insertion reaction occurred solely at *C*-3 due to steric constraints to produce an 1,3-oxazin-2-one ring system and not an oxazolidin-2-one as the main chiral control element. The use of oxazinones as chiral auxilaries has received scant attention to date[7,8] but in a fused ring system they possess the essential features necessary to control asymmetric transformations, *viz.* an easily functionalised nitrogen atom, a carbonyl group for chelation control, conformational immobility to provide a stereochemical bias, and importantly, little propensity for chemical modification under mild cleavage conditions such that the stereochemical integrity of the auxiliary and the newly created chiral centres are maintained.

RESULTS AND DISCUSSION

The strategy for the synthesis of oxazinone **9** involved four reactions in sequence as outlined in Scheme 1. Firstly, the protected gulonic acid **5** was reduced with $LiAlH_4$ to afford alcohol **6** in 89% yield. This crude material was then converted into its chloroformate **7** (82%) by treatment with phosgene in the presence of pyridine and used immediately in the next stage.

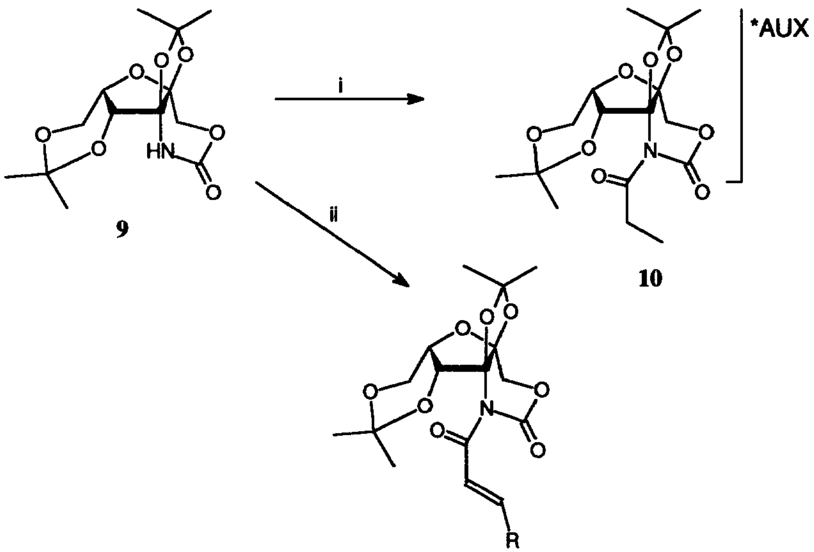


5 6 7 8 9

Scheme 1. ***Reagents and conditions***: (i), $LiAlH_4$, THF, 0°C; (ii), $3Cl_2CO$, pyridine, toluene/ether; (iii), $2NaN_3$, tetrabutylammonium bromide, DCM/H_2O; (iv), thermolysis in TCE (15 m.).

Under phase-transfer conditions (DCM/H_2O, tetrabutylammonium bromide) chloroformate **7** was transformed into azidoformate **8** (90%) by treatment with NaN_3. In the final step of the synthesis thermal decomposition of **8** in 1,1,2,2-tetrachloroethane (TCE) under reflux furnished after flash chromatography the highly crystalline oxazinone **9** (m.p. 187-188°C) in 55% yield.

In order to test the efficiency of **9** as a chiral control element we prepared a few key *N*-acyl derivatives, including *N*-propionyl imide **10** in 83% yield for use in asymmetric aldol reactions, by treatment of oxazinone **9** with *n*-butyl lithium followed by addition of propionyl chloride (Scheme 2). A similar protocol yielded the *N*-((*E*)-crotonyl) derivative **11** in 80% yield as a dienophile for Lewis-acid mediated Diels-Alder reactions. Attempts to prepare the corresponding acrylate dienophile **12** under similar conditions were frustrated by polymer formation but the compound could be obtained in 82% yield by treatment of oxazinone **9** with methylmagnesium bromide followed by acylation of the resulting magnesium anion with acryloyl chloride.



9

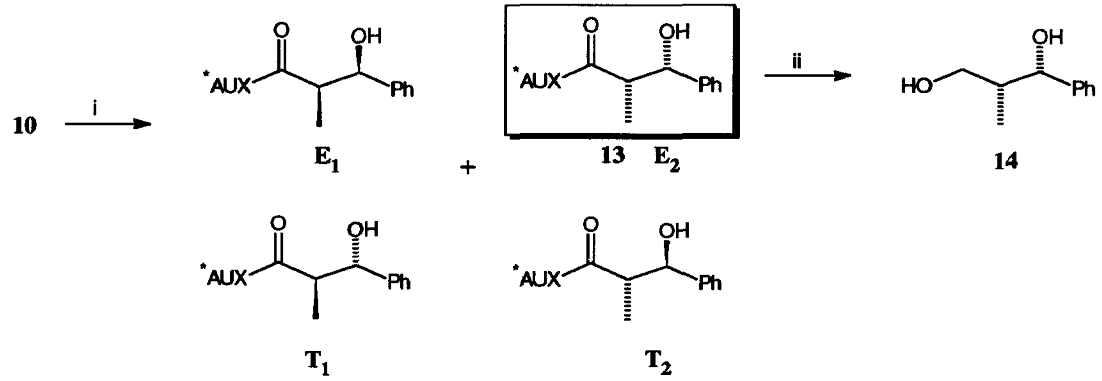
10

11 (R = CH_3)
12 (R = H)

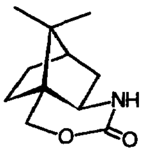
Scheme 2. *Reagents and conditions*: (i), Bu^{n}Li, hexane/THF, -78°C, EtCOCl; (ii), **11**: Bu^{n}Li, hexane/THF, -78°C, MeCH:CHCOCl; **12**: MeMgBr, THF, CH_2:CHCOCl.

The first asymmetric reaction to be investigated involved the lithium enolate mediated aldol reaction of *N*-propionyl imide **10** with benzaldehyde (Scheme 3). The imide **10** was deprotonated with lithium diisopropyamide (LDA) and immediately treated with freshly distilled benzaldehyde at -78°C to give the aldol product **13** in 88% yield. The diastereoselective outcome of the reaction was determined by ^{1}H NMR analysis of the aldol product; in particular by integration of the doublets in the range δ 4.70-5.00 ppm arising from the PhC*H*OH protons. This revealed that out of a possible four diastereomeric products only two *erythro* isomers

(${}^3J$ = 2.3 Hz) had been formed in the ratio of 91:9 giving a diastereomeric excess of 82%. In order to establish its absolute configuration, the major *erythro* aldol stereoisomer **13** was subjected to reductive cleavage using $LiBH_4$ from which the *erythro* diol **14** (78% yield) and the auxiliary **9** (64% yield) were obtained after flash chromatography. The optical rotation of **14** was found to be -53.5 and by comparison with literature values[9] established that the absolute configuration of the major diastereomer **13** to be (2S, 3S) which is the same stereochemical outcome as that obtained with the galactose-derived auxiliary **4**[6] although with the latter a diastereomeric excess of only 78% was obtained. Significantly the cleavage of the major product occurred without any measurable racemisation of the auxiliary **9** which imparted considerably greater diastereoselection to that obtained for the reaction with the camphor-based oxazinone[8] **15** for which a mixture of three aldols (44:4:52 E_2:E_1:T_2) was obtained with the corresponding lithium enolate.



Scheme 3. ***Reagents and conditions***: (i), $LiNPr^i_2$, THF, -78°C, PhCHO, 2m; (ii), $LiBH_4$, H_2O, THF, 0°C.



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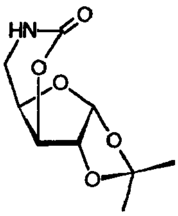

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The high level of asymmetric induction imparted by oxazinone **9** in the model aldol reaction is also reflected in the Lewis-acid catalysed asymmetric Diels-Alder reaction of α,β-unsaturated *N*-acyloxazinones **11** and **12** with freshly cracked cyclopentadiene. Both reactions were carried out at low temperatures in anhydrous DCM by addition of excess cyclopentadiene (10 equiv.) followed by immediate treatment with diethylaluminium chloride (1.4 equivs.) (Table 1).

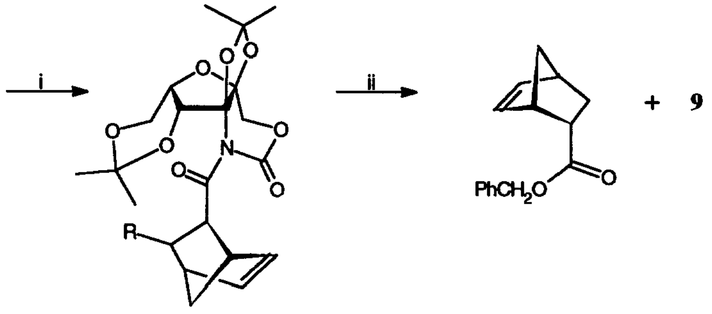
Table 1 Lewis-acid catalysed Diels-Alder reaction between α,β-unsaturated *N*-acyloxazinones **11** and **12** and cyclopentadiene

Dienophile	Temp/°C	Yield/%	*endo*:*exo*	*endo* de%
11	-20 (-78)[a]	89 (98)	98:2 (99:1)	94 (89)
12	-78 (-78)	74 (83)	97:3 (98:2)	82 (80)

[a] Figures in parenthese for corresponding reactions with galactose-derived auxiliary **4** using the same protocol.

In each case cycloaddition proceeded smoothly and the diastereomeric product ratios were ascertained by 200 MHz ^{1}H NMR analysis of the crude reaction mixture. These ratios were determined by integration of the doublet of doublet signals in the range δ 5.50-6.50 ppm arising from the alkenic protons in the cycloadducts **17** and **18** (Scheme 4). As can be seen from Table 1 *endo*-diastereoselection is excellent in both cases as is the *endo/exo* selectivity. Given that these reactions have not been optimised these results compare well to those reported for the galactose-derived auxiliary[6] **4** and are in sharp contrast to the disappointing result obtained by Kunz[10] with the related xylofuranose-oxazinone **16** for the corresponding cycloaddition The absolute stereochemistry of the one of the products from these model reactions was determined by subjecting acrylate adduct **17** to cleavage using lithium benzyloxide. The resulting benzyl ester **19** and unchanged auxiliary **9** were readily separated by flash chromatography in 97% and 93% yields respectively, and the optical rotation of **19** was determined to be -114 which is the same stereochemical outcome as that obtained in the galactose case[6].

11; (R = CH$_3$)
12; (R = H)



17; (R = H)
18; (R = CH$_3$)

19

Scheme 4. *Reagents and conditions*: (i), 10 cyclopentadiene, 1.4 Et$_2$AlCl, (**11**) -20°C, (**12**) -78°C; (ii), LiOCH$_2$Ph, THF, -78°C to ambient temp.

CONCLUSION

The results obtained in these model experiments clearly establish that there is considerable potential for chiral 1,3-oxazin-2-ones in the rapidly developing field of substrate-controlled asymmetric synthesis. The experiments described herein confirm that oxazinone **9** constitutes a structurally well organised chiral control element with excellent facial bias in both aldol reactions and Lewis-acid catalysed Diels-Alder reactions. Moreover, unlike the spirooxazolidin-2-one **4** it can be recovered in enantiomerically pure form following cleavage of the resultant diastereomers using conventional methods. We are currently investigating further chiral-mediated reactions with **9** together with the preparation of other likewise carbohydrate-based 1,3-oxazin-2-ones, and details will be published in due course.

EXPERIMENTAL

Melting points are uncorrected. All ^{1}H NMR spectra were run on a 200 MHz instrument in $CDCl_3$, and all ^{13}C NMR on a 50.3 MHz instrument in $CDCl_3$ unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 781 spectrometer and accurate mass measurements determined on a Kratos MS 50TC mass spectrometer. Elemental analysis was determined on a Carlo-Erba 1106 analyser and polarimetry measurements were carried out on an Optical Activity Ltd. instrument using sodium light. THF and diethyl ether were distilled prior to use from sodium/benzophenone ketyl and DCM was distilled from finely divided calcium hydride. Thin-layer chromatography was carried out on silica gel 60 F_{254} (Merck) plates and visualised by UV irradiation and/or dipping the plate into a solution of 5% concentrated sulphuric acid in ethanol followed by gentle flaming. Flash chromatography was conducted using silica gel 60 (220-240 mesh).

PREPARATION OF CHIRAL AUXILIARY 9

Preparation of 2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulofuranose-2-methanol 6.

To a stirred suspension of lithium aluminium hydride (3.99g, 0.103 mol., 1.5 equivs.) in dry tetrahydrofuran (THF) (200 ml) under argon at 0°C was added dropwise a solution of 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid **5** (20.0g, 68.5 mmol) in THF (200 ml). After addition was complete the reaction mixture was stirred at room temperature for 5 h, cooled in an icebath and carefully quenched by dropwise addition of H_2O until a granular precipitate had formed, filtered, dried ($MgSO_4$), and evaporated *in vacuo* to yield *2,3:4,6-di-O-isopropylidene-2-keto-L-gulofuranose-2-methanol* **6** as a colourless syrup (15.82g, 89%); FAB-MS (M^++1) 261.13369 $C_{12}H_{21}O_6$ requires 261.13370; ^{1}H NMR δ 4.12 (1H, d, J = 11.5 Hz, C*H*HOH), 4.36 (1H, s, C*H*-O), 4.32 (1H, d, J = 1.6 Hz, C*H*-O), 4.33 (1H, d, J = 11.5 Hz, CH*H*OH), 4.09-4.05 (1H, m, C*H*-O), 3.98-3.76 (2H, m, C*H*-O), 1.41 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.30 (3H, s, CH_3) ppm; IR (thin film) ν_{max} 3480 (br, OH), 1450, 1380 cm^{-1}.

Preparation of 2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulofuranose-2-methylchloroformate 7.
A solution of 2,3:4,6-di-O-isopropylidene-2-keto-L-gulofuranose-2-methanol **6** (13.5g, 51.9 mmol) and pyridine (4.10g, 51.9 mmol) in dry ether (200 ml) was added dropwise to a rapidly stirred solution of phosgene (77 ml of 20% solution in toluene, 156 mmol, 3 equivs.) at 0°C under argon. When addition was complete the reaction mixture was stirred at room temperature overnight, filtered and evaporated *in vacuo* to yield *2,3:4,6- di-O-isopropylidene-2-keto-L-gulofuranose-2-methylchloroformate* **7** as a viscose yellow syrup (13.89g, 82%) which rapidly darkened on exposure to air was used immediately in the next stage. FAB-MS (M^++1) 323.08971 $C_{13}H_{20}ClO_7$ requires 323.08974; ^1H NMR δ 4.71 (1H, d, J = 11.5 Hz, C-1H), 4.41 (1H, s, C-3H), 4.28 (1H, d, J = 1.7 Hz, C-4H), 4.21 (1H, d, J = 11.5 Hz, C-1H*H*), 4.09-4.05 (1H, m, C-5H), 3.98-3.74 (2H, m, C-6H_2), 1.45 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.29 (3H, s, CH_3) ppm; IR (thin film) ν_{max} 1780 (C=O), 1455, 1380 cm^{-1}.

Preparation of 2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulofuranose-2-methylazidoformate 8.
A solution of NaN_3 (5.60g, 86.1 mmol, 2 equivs.) and tetrabutylammonium bromide (0.5g) in H_2O (300 ml) was added to a rapidly stirred solution of 2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulofuranose-2-methylchloroformate **7** (13.9g, 43.1 mmol) in dichloromethane (DCM) (300 ml). The reaction mixture was stirred for 4 h and the two layers were separated. The aqueous fraction was extracted with DCM (3x50 ml). The combined organic fractions were washed with H_2O (20 ml), dried ($MgSO_4$) and evaporated to yield *2,3:4,6-di-O-isopropylidene-2-keto-L-gulofuranose-2-methylazidoformate* **8** as a pale-orange viscous syrup (12.80g, 90%). A sample was purified for analysis by flash chromatography using hexane:ether (3:1) as eluent to afford a colourless oil; $[\alpha]_D$ = -47.1 (c = 1.94, DCM, 24°C); FAB-MS (M^++1) 330.130089 $C_{13}H_{20}N_3O_7$ requires 330.130089; EI-MS m/z 43 (base), 59 (30%), 113 (32%), 315 (36%), no M^+; ^1H NMR δ 4.60 (1H, d, J = 11.6 Hz, C-5H), 4.39 (1H, s, C-3H), 4.30 (1H, d, J = 1.6 Hz, C-2H), 4.25 (1H, d, J = 11.6 Hz, C-5H), 4.09-4.07 (1H, m, C-1H), 4.00-3.75 (2H, m, C-6H), 1.46 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm; ^{13}C NMR δ 157.07 (C=O), 112.5 (quat. C), 111.86 (quat. C), 97.25 (quat. C), 84.27 (CH), 72.86 (CH), 72.44 (CH), 66.15 (CH_2), 59.93 (CH_2), 28.64 (CH_3), 27.22 (CH_3), 26.06 (CH_3), 18.41 (CH_3) ppm; IR (thin film) ν_{max} 2140 (N_3), 1735 (C=O), 1450, 1380, 750 cm^{-1}.

Solution Thermolysis of 2,3:4,6-Di-*O*-isopropylidene-2-keto-L-gulofuranose-2-methylazidoformate 8. A solution 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulofuranose-2-methylazidoformate **8** (2.00g, 6.08 mmol) in dry TCE (100ml) was added dropwise onto boiling TCE (bp = 147°C) (200 ml) under argon. After addition was complete the solution was heated for 15 m, allowed to cool to room temperature and the TCE removed *in vacuo* to yield a brown tar which was subjected to flash chromatography (100g, SiO_2) using hexane:ether (1:3) as eluent. *(5S,9S)-4-Aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0.]nonan-3-one* **9** was recrystallised from diisopropyl ether (1.01g, 55%); mp = 187-188°C; $[\alpha]_D$ = +21.6 (c = 2.26, DCM, 25°C); FAB-MS (M^++1) 302.12396 $C_{13}H_{20}NO_7$ requires 302.12395; EI-MS m/z 43 (70%), 59 (base), 114 (60%), 286 (58%, $[M-15]^+$). no M^+; C, 51.5; H, 6.29; N, 4.61% $C_{13}H_{19}NO_7$ requires C, 51.8; H, 6.31; N, 4.65%: ^1H NMR δ

6.78 (1H, br s, NH), 4.31 (2H, ABq, *J* = 11.5 Hz, C-1H$_2$), 4.24-4.20 (2H, m, C-7H, C-6H), 4.06 (1H, dd, *J* = 13.9, 2.0 Hz, C-*10H*H), 3.96 (1H, dd, *J* = 13.8, 0.9 Hz, C-*10H*H), 1.49 (3H, s, CH$_3$), 1.44 (3H, s, CH$_3$), 1.39 (3H, s, CH$_3$), 1.36 (3H, s, CH$_3$) ppm; ^{13}C NMR δ 153.31 (C=O), 114.84 (quat. C), 106.03 (quat. C), 97.79 (quat. C), 97.41 (quat. C), 73.08 (CH), 71.91 (CH), 67.74 (CH$_2$), 60.04 (CH$_2$), 28.72 (CH$_3$), 28.27 (CH$_3$), 27.82 (CH$_3$), 18.60 (CH$_3$) ppm; IR (nujol) ν_{max} 3290 (NH), 1750 (d, C=O), 1110, 1075, 900 cm^{-1}.

PREPARATION OF N-ACYL DERIVATIVES FOR ASYMMETRIC TRANSFORMATION REACTIONS

Preparation of (5S, 9S)-*N*-propionyl-4-aza-5,9:6,10-di-*O*-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 10. A solution of *n*-butyl lithium (2.2 ml of 1.6 M solution in hexane, 3.44 mmol) was added dropwise *via* a syringe to a stirred solution of (5S,9S)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one **9** (1.00g, 3.32 mmol) in dry THF (50 ml) at -78°C under argon. After 30 m a solution of freshly distilled propionyl chloride (0.58g, 6.25 mmol, 2 equivs.) was added dropwise *via* a syringe and stirring was continued for a further 30 m and quenched by addition of aqueous 1M Na$_2$CO$_3$ solution (10 ml). The reaction mixture was stirred vigorously for 15 m, the THF was removed *in vacuo* and the aqueous residue was extracted with ether (3x20 ml). The combined ether extracts were washed with H$_2$O, dried (MgSO$_4$) and evaporated to yield *(5S, 9S)-N-propionyl-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one* **10** as a colourless syrup which partially crystallised on standing (0.98g, 83%); $[\alpha]_D$ = +36.6 (c = 2.14, DCM, 25°C); FAB-MS (M$^+$+1) 358.15015 C$_{16}$H$_{24}$NO$_8$ requires 358.15017; ^{1}H NMR δ 4.76 (1H, d, *J* = 2.4 Hz, CH-O), 4.37 (2H, ABq, *J* = 11.4 Hz, CH$_2$O), 4.28-4.27 (1H, m, CH), 4.02-3.95 (2H, ABqd, *J* = 13.9, 2.3, 1.7 Hz, CH$_2$-C=O), 2.97-2.78 (2H, symm m, CH$_3$C*H$_2$*), 1.54 (3H, s, CH$_3$), 1.38 (3H, s, CH$_3$), 1.30 (3H, s, CH$_3$), 1.25 (3H, s, CH$_3$), 1.12 (3H, t, *J* = 7.1 Hz, C*H$_3$*CH$_2$) ppm; ^{13}C NMR δ 173.41 (C=O), 153.12 (C=O), 116.10 (quat. C), 108.19 (quat. C), 100.27 (quat. C), 97.81 (quat. C), 73.84 (CH), 71.94 (CH), 67.01 (CH$_2$), 59.97 (CH$_2$), 30.01 (CH$_2$), 28.53 (CH$_3$), 28.46 (CH$_3$), 27.91 (CH$_3$), 18.31 (CH$_3$), 7.96 (CH$_3$) ppm; IR (thin film) ν_{max} 1740 (C=O) 1720 (C=O) cm^{-1}.

Preparation of (5S, 9S)-*N*-((E)-crotonyl)-4-aza-5,9:6,10-di-*O*-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 11. *N*-Lithio-(5S,9S)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0.]nonan-3-one (1.00g, 3.32 mmol) was treated with freshly distilled crotonyl chloride (0.694g, 6.64 mmol, 2 equivs.) in the manner just descibed. The crude product was subjected to flash chromatography using hexane:ether (1:3) as eluent to afford *(5S, 9S)-N-((E)-crotonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one* **11** as a colourless foam (0.98g, 80%); FAB-MS (M$^+$+1) 370.15017 C$_{17}$H$_{24}$NO$_8$ requires 370.15018; ^{1}H NMR δ 6.98 (1H, *J* = 15.1, 7.0 Hz, =CHCH$_3$), 6.35 (1H, dq, *J* = 15.2, 1.5 Hz, CH=), 4.77 (1H, d, *J* = 2.3 Hz, CH-O), 4.33 (2H, d, *J* = 1.1 Hz, CH$_2$-O), 4.27-4.24 (1H, m, CH), 4.01 (2H, ABqd, *J* = 13.8, 2.3, 1.5 Hz, C*H$_2$*-C=O), 2.97-2.78 (2H, symm m, CH$_3$C*H$_2$*), 1.54 (3H, s, CH$_3$), 1.38 (3H, s, CH$_3$), 1.30 (3H, s, CH$_3$), 1.25 (3H, s, CH$_3$), 1.12 (3H, t, *J* = 7.1 Hz, C*H$_3$*CH$_2$) ppm; ^{13}C NMR δ 168.14 (C=O), 151.02 (C=O), 144.35 (CH=), 124.59 (CH=), 115.77 (quat. C), 108.20 (quat. C), 100.16 (quat. C), 97.95 (quat. C), 73.56 (CH), 71.99 (CH), 66.93 (CH_2), 60.04 (CH_2), 28.58 (CH_3), 28.42 (CH_3), 27.81 (CH_3), 18.27 (CH_3), 18.06 (CH_3) ppm; IR (nujol) ν_{max} 1745 (C=O) 1710 (C=O), 1640 (C=C), 770 cm^{-1}.

Preparation of (5S, 9S)-*N*-(acryloyl)-4-aza-5,9:6,10-di-*O*-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 12. Methyl magnesium bromide was freshly prepared from magnesium (0.088g, 3.66 mmol) and methyl bromide (10 ml of 2M solution in ether, 1.9g, 20 mmol) in the manner descibed by Evans[x]. The Grignard solution was cooled to 0°C and treated with a solution of (5S,9S)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0.]nonan-3-one **9** (1.00g, 3.32 mmol) in THF (20 ml) *via* a syringe. The reaction mixture was stirred for 15 m, cooled to -78°C, and treated with a solution of freshly distilled acryloyl chloride (0.45g, 4.98 mmol, 1.5 equivs.) in THF (10 ml). The reaction was stirred for 5 m, warmed to room temperature, allowed to stir for a further 15 m and quenched with 1M Na_2CO_3 solution. THF was removed *in vacuo* and the aqueous residue was extracted with ether (3x50 ml). The combined ether fractions were washed with H_2O (3x50 ml), dried ($MgSO_4$), and evaporated. The crude product was subjected to flash chromatography using hexane:ether (1:2) as eluent to yield *(5S, 9S)-N-(acryloyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one* **12** as a colourless solid (0.97g, 82%); FAB-MS (M^+) 355.12669 $C_{16}H_{21}NO_8$ requires 355.12670; ^{1}H NMR δ 6.62 (1H, dd, *J* = 16.8, 10.1 Hz, $=CHCH_2$), 6.36 (1H, dd, *J* = 16.8, 1.7 Hz, =C*H*H), 5.74 (1H, dd, *J* = 10.1, 1.7 =CH*H*), 4.78 (1H, d, *J* = 2.3 Hz, CH-O), 4.34 (2H, d, *J* = 11.51 Hz, CH_2-O), 4.29-4.26 (1H, m, CH), 4.08-3.90 (2H, ABqd, *J* = 13.8, 2.3, 1.6 Hz, CH_2O-C=O), 1.54 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.28 (3H, s, CH_3) ppm; ^{13}C NMR δ 168.19 (C=O), 150.83 (C=O), 129.94 (CH=), 129.32 (CH_2=), 115.90 (quat. C), 108.14 (quat. C), 100.16 (quat. C), 97.98 (quat. C), 73.60 (CH), 71.88 (CH), 67.03 (CH_2), 60.03 (CH_2), 28.53 (CH_3), 28.42 (CH_3), 27.79 (CH_3), 18.25 (CH_3), ppm; IR (nujol) ν_{max} 1740 (C=O) 1710 (C=O), 1635 (C=C), 770 cm^{-1}.

APPLICATION OF AUXILIARY 9 IN SOME SELECTED ASYMMETRIC TRANSFORMATIONS

Asymmetric aldol reaction

n-Butyl lithium (0.63 ml of a 1.6 M solution in hexane, 1.01 mmol) was added to a solution of diisopropylamine (0.102g, 1.01 mmol) in dry THF (2 ml) at 0°C under argon, the mixture was stirred for 15 m, and the temperature was lowered to -78°C. The LDA solution was treated with a solution of (5S, 9S)-*N*-propionyl-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one **10** (0.328g, 0.919 mmol) in THF (10 ml), stirred for 30 m to produce a lithium enolate complex which was treated rapidly with a solution of freshly distilled benzaldehyde (0.146g, 1.38 mmol, 1.5 equivs.) in THF (5 ml). The reaction mixture was quenched after 2 m with saturated NH_4Cl solution (5 ml) and allowed to come to room temperature, THF was removed under vacuum and the aqueous residue was extracted with ether (3x20 ml). The combined ether fractions were washed (H_2O), dried ($MgSO_4$) and evaporated. The viscous gum obtained was subjected to flash chromatography (50g, SiO_2, hexane:ether 1:2) afforded the aldol product as a colourless solid (0.38g, 88%). Examination of the 200 MHz ^{1}H NMR spectrum of this product indicated that only two *erythro* diastereomers (^3J = 2.3 Hz) had been formed in the ratio of 91:9 (diastereomeric excess = 82%). The major diastereomer was identified as *(5S, 9S)-N-((2'S, 3'S)-3'-hydroxy-2'-methyl-3'-phenylpropionyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one* **13**; FAB-MS (M^++1) 464.19202 $C_{24}H_{30}NO_9$ requires 464.19203; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40-7.22 (5H, m, Ph), 5.12 (1H, dd, *J* = 3.5, 1.7 Hz, PhC*H*OH), 4.88 (1H, d, *J* = 2.3 Hz, CH-O), 4.42 (2H, ABq, *J* = 11.5 Hz, CH_2-O), 4.33 (1H, dd, *J* = 3.7, 2.2 Hz, CH), 4.13-4.01 (2H, ABq, *J* = 13.9, 2.2, 1.2 Hz, O-C*H*$_2$CH), 3.68-3.64 (1H, symm m, C*H*CH_3), 3.30 (1H, d, *J* = 1.7 Hz, oh),), 1.60 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.41 (6H, s, 2xCH_3), 1.06 (3H, d, *J* = 6.9 Hz, CH_3) ppm; ^{13}C NMR δ 181.38 (C=O), 150.73 (C=O), 140.26 (quat. C), 128.06 (Ar CH), 127.16 (Ar quat. C), 125.65 (Ar CH), 116.20 (quat. C), 108.08 (quat. C), 100.23 (quat. C), 98.60 (quat. C), 73.54 (CH), 72.88 (CH), 72.35 (CH), 66.82 (CH_2), 59.98 (CH_2), 47.74 (CH), 28.64 (2xCH_3), 27.85 (CH_3), 18.48 (CH_3), 8.58 (CH_3) ppm.

Reductive Cleavage of (5S, 9S)-N-((2'S, 3'S)-3'-hydroxy-2'-methyl-3'-phenylpropionyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 13: Solid $LiBH_4$ (0.036g, 1.66 mmol) and H_2O (30 μl, 1.66 mmol, 1.1equivs.) were added to a stirred solution of (5S, 9S)-N-((2'S, 3'S)-3'-hydroxy-2'-methyl-3'-phenylpropionyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one **13** (0.70g, 1.51 mmol) in dry THF (20 ml) at 0°C under argon. The reaction mixture was stirred for 1.5 h at 0°C, quenched with by the dropwise addition of H_2O (10 ml) and THF was removed by evaporation. The aqueous fraction was extracted with ether (3x20 ml) and the product obtained as a clear viscous oil following washing (H_2O) and drying ($MgSO_4$) of the combined ether fractions. Flash chromatography (50g, SiO_2, hexane:ether 1:1) of the crude product furnished *(1S, 2R)-1-phenyl-2-methylpropane-1,3-diol* **14** as a viscous oil which was crystallised from hexane/ether as colourless flakes (0.195g, 78%); mp = 70-74°C, (lit. = 75-76°C[9]); $[\alpha]_D$ = -53.5 (c = 0.48, $CHCl_3$, 25°C) (lit. $[\alpha]_D$ = +57.8 (c = 0.45, $CHCl_3$)[9] for (1R, 2S) isomer); Further elution gave the recovered auxiliary (5S,9S)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0.]nonan-3-one **9** (0.29g, 64%).

Asymmetric Lewis acid catalysed Diels-Alder reactions.

Using (5S, 9S)-N-(acryloyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 12: Freshly cracked cyclopentadiene (0.74g, 11.3 mmol, 10 equivs.) was added to a solution of (5S, 9S)-N-(acryloyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one **12** (0.4g, 1.13 mmol) in dry DCM (30 ml) at -78°C under argon followed immediately by diethylaluminium chloride (0.88 ml of 1.8M solution in toluene, 1.58 mmol, 1.4 equivs.). A transient yellow colour was noted. The reaction was stirred for a further 15 m at -78°C then quenched with saturated NH_4Cl solution (10 ml), allowed to warm to room temperature then poured onto a DCM/H_2O (1:1) mixture, separated and the aqueous layer was extracted with DCM (3x20 ml). The DCM fractions were combined, wash with H_2O , dried ($MgSO_4$), and evaporated. The product was obtained, after flash chromatography (hexane:ether 5:1), as a viscous oil which crystallised on standing. The major diastereomer was identified as *(5S, 9S)-N-((3'S, 4'S, 6'S)-bicyclo[2.2.1]heptane-4'-carbonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one* **17**; FAB-MS (M^++1)

422.18146 $C_{21}H_{28}NO_8$ requires 422.18147; ^{1}H NMR δ 6.17 (1H, dd, *J* = 5.5, 3.0 Hz, =*CH*CH$_2$), 5.86 (1H, dd, *J* = 5.5, 2.8 Hz, CH =*CH*), 4.76 (1H, dd, *J* = 2.2 Hz, CH-O), 4.35 (2H, ABq, *J* = 13.8, 2.0 Hz, -OC*H*$_2$-O), 4.02 (1H, dd, *J* = 13.8, 1.0 Hz,O-CH$_2$*CH*), 3.96-3.88 (1H, m, CH-C=O), 3.10 (1H, br s, bridgehead CH), 2.88 (1H, br s, bridgehead CH), 2.04-1.92 (1H, symm m, C*H*H), 1.53 (3H, s, CH$_3$), 1.48-1.28 (3H,m, CH$_2$, CH*H*), 1.41 (3H, s, CH$_3$), 1.40 (3H, s, CH$_3$), 1.38 (3H, s, CH$_3$) ppm; ^{13}C NMR δ 178.00 (C=O), 151.24 (C=O), 137.37 (CH=), 131.67 (CH=), 115.58 (quat. C), 108.14 (quat. C), 100.23 (quat. C), 98.04 (quat. C), 73.47 (CH), 72.33 (CH), 66.48 (CH$_2$), 60.00 (CH$_2$), 49.73 (CH$_2$), 46.88 (CH$_2$), 45.29 (CH), 42.62 (CH), 30.95 (CH), 28.84 (CH$_3$), 28.56 (CH$_3$), 27.79 (CH$_3$), 18.55 (CH$_3$), ppm.

Using (5S, 9S)-N-((E)-crotonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 11: This reaction was carried out between (5S, 9S)-N-((E)-crotonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one **11** (0.3g, 0.813 mmol) and cyclopentadiene (0.537g, 8.13 mmol, 10 equivs.) in the manner just descibed. The product obtained after flash chromatography (0.31g, 89%) was analysed by 360 MHz ^{1}H NMR spectroscopy and the *endo:exo* ratio was found to be 98:2 with an *endo* diastereomeric excess of 94%. The major diastereomer was identified as *(5S, 9S)-N-((3'S, 4'S, 5'R, 6'S)-5'-methylbicyclo[2.2.1]heptane-4'-carbonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one* **18** which crystallised from hexane as colourless needles; FAB-MS (M$^+$+1) 436.19711 $C_{22}H_{30}NO_8$ requires 436.19712; ^{1}H NMR δ 6.25 (1H, dd, *J* = 5.6, 3.1 Hz, =*CH*=CH), 5.79 (1H, dd, *J* = 5.6, 2.7 Hz, CH =*CH*), 4.71 (1H, dd, *J* = 2.1 Hz, CH-O), 4.33 (2H, s, C*H*$_2$-O), 4.23 (1H, d, *J* = 4.2 Hz, CH), 4.10-3.92 (2H, Abq, *J* = 13.8, 2.1, 0.9 Hz, -O-CH$_2$CH), 3.39 (1H, dd, *J* = 4.6, 3.4 Hz, CH-C=O), 3.01 (1H, br s, bridgehead CH), 2.45 (1H, br d, *J* = 1.2 Hz, bridgehead CH), 1.95-1.85 (1H, m), 1.51 (3H, s, CH$_3$),) 1.40 (6H, s, 2xCH$_3$), 1.36 (3H, s, CH$_3$) 1.15 (3H, d, *J* = 7.0 Hz, CH$_3$CH) ppm.

Cleavage of Diel-Alder adduct-(5S, 9S)-N-((3'S, 4'S, 6'S)-bicyclo[2.2.1]heptane-4'-carbonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one 17: *n*-Butyl lithium (0.24 ml of 1.6M solution in hexane, 0.391 mmol) was added to a solution of benzyl alcohol (0.077g, 0.711 mmol, 2 equivs.) in dry THF at -78°C under argon. After 10 m a solution of (5S, 9S)-N-((3'S, 4'S, 6'S)-bicyclo[2.2.1]heptane-4'-carbonyl)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0]nonan-3-one **17** (0.15g, 0.355 mmol) in THF (5 ml) was added dropwise *via* a syringe. The reaction was stirred for 10 m warmed to room temperature, and stirred for a further 10 m, quenched with saturated NH$_4$Cl solution (5 ml), and THF was removed *in vacuo*. The aqueous residue was extracted with ether (3x20 ml) and discarded. The ether fractions were combined washed (H$_2$O), dried (MgSO$_4$), and evaporated. The resulting crude residue was subjected to flash chromatography (50g, SiO$_2$, hexane:ether 5:1) to yield *benzyl (3S, 4S, 6S)-bicyclo[2.2.1]heptene-4-carboxylate* **19** as a colourless viscous oil (0.079g, 97%); $[\alpha]_D$ = -114 (c = 0.41, DCM, 22°C), (lit. $[\alpha]_D$ = -129 (c = 1.37, CHCl$_3$, 22°C)^{11}); Further elution with hexane:ether (3:1) yielded benzyl alcohol and finally elution with pure ether gave the recovered auxiliary (5S,9S)-4-aza-5,9:6,10-di-O-isopropylidene-2,8-dioxabicyclo[4.3.0.]nonan-3-one **9** (0.101g, 93%).

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