(5*R*)-7,8 : 9,10-Di-*O*-isopropylidene-2,6-dioxa-4-azaspiro[4,5]decan-3-one: a New Chiral Spirooxazolidin-2-one derived from D-(+)-Galactose for use in Asymmetric Transformations

Malcolm R. Banks,[a] Alexander J. Blake,[a] J. I. G. Cadogan,[b] Ian M. Dawson,[a] Suneel Gaur,[a] Ian Gosney,[a] Robert O. Gould,[a] Keith J. Grant[a] and Philip K. G. Hodgson[b]

[a] *Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, Scotland EH9 3JJ*
[b] *BP International Ltd., Sunbury Research Centre, Chertsey Road, Sunbury-on-Thames, Middlesex, England TW16 7LN*

Starting from D-(+)-galactose, the crystalline spirooxazolidin-2-one **2** can be readily prepared in an optically pure state by a nitrene-mediated four-step sequence, and serves to control both aldol and Diels–Alder reactions with high chiral efficiency, being easy to remove after use.

We, together with others, have recently reported the synthesis of the terpenoid-derived chiral oxazolidin-2-one **1**, although in our case[1] we adopted a more straightforward approach based on intramolecular nitrene insertion, whereas the other groups[2] employed classical cyclocarbamation of the corresponding β-amino alcohol. We have now extended our nitrene approach to the carbohydrate series and report here the synthesis of the first chiral spirooxazolidin-2-one **2** from D-(+)-galactose and demonstrate its powerful topological bias in asymmetric transformations involving aldol and Diels–Alder cycloaddition reactions.

The title compound **2** is easily synthesised on a preparative scale in 53% overall yield by the simple four-step sequence outlined in Scheme 1. It is isolated as a colourless, highly crystalline solid [m.p. 169–170 °C; $[\alpha]_D^{22}$ −88.4 (*c* 5.00, $CHCl_3$)]† whose X-ray crystal structure has been determined and is shown in Fig. 1(*a*), together with some pertinent bond lengths and angles.‡

In this structure, the pyranose ring of the molecule adopts a slightly twisted boat conformation, which reflects the hydrogen-bonding between H(4) on the nitrogen of the oxazolidinone ring and an oxygen atom of the 7,8-di-*O*-isopropylidene group. This strong association is lost when the nitrogen is functionalised as exemplified by the *N*-propionyl derivative **3** [m.p. 186–187 °C; $[\alpha]_D^{22}$ + 16.4 (*c* 2.58, CH_2Cl_2).§ Its single X-ray structure is shown in Fig. 1(*b*) (and pictorially in Scheme 2) and confirms the pyranose ring to be present in a twisted boat conformation.¶ The result is a shielding of the oxazolidinone ring by the 9,10-di-*O*-isopropylidene group such that reactions of the corresponding enolate, generated under kinetic conditions, proceed with an excellent π-face discrimination in aldol reactions without recourse to the use of hazardous and expensive di-n-butylboron triflate as a mediating agent; this aspect has been a characteristic drawback with other chiral auxiliaries reported so far.[3]

Thus, of the four possible diastereoisomeric aldol products (**E**$_1$, **E**$_2$, **T**$_1$, **T**$_2$) from the reaction of **3** with benzaldehyde ($LiNPr^i_2$, THF at −78 °C) (Scheme 2), only three are formed in the ratio of 89 : 6 : 5 (d.e. 78%) based on ^{1}H NMR analysis of the alcohol resonances. The absolute configuration of the predominating *erythro* aldol stereoisomer (**E**$_2$) was confirmed by X-ray analysis as well as by cleavage with lithium borohydride to afford, after recrystallisation, (1*S*,2*R*)-1-phenyl-2-methylpropane-1,3-diol as colourless flakes [83%; m.p. 74–75 °C; $[\alpha]_D^{22}$ −62.5 (*c* 0.48, $CHCl_3$); lit.[4] 75–76 °C; +57.8 (*c* 0.45, $CHCl_3$) for (1*R*,2*S*) enantiomer]. By comparison when using the established (*S*)-valinol-derived oxazolidinone **4**,[5] in our hands three of the four possible diastereoisomeric products were obtained in the ratio 24 : 10 : 66, giving a diastereoisomeric excess of only 32%. The exceptional quality of diastereocontrol exhibited by **3** is

† *Selected spectral data for* **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.34 (1H, br s, NH), 5.47 (1H, d, *J* 4.2 Hz, 7-H), 4.69 (1H, ddd, *J* 7.3, 1.6, 0.4 Hz, 9-H), 4.44 (1H, d, *J* 10.1 Hz, 1-H), 4.32 (1H, d, *J* 7.3 Hz, 10-H), 4.25 (1H, dd, *J* 10.1, 0.5 Hz, 1-H), 4.20 (1H, dd, *J* 4.2, 1.6, 8-H), 1.60 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.33 (3H, s, CH_3) and 1.31 (3H, s, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 156.69 (C=O), 109.86 (quat C), 109.78 (quat C), 94.50 (CH), 84.88 (quat C), 73.91 (CH_2), 73.72 (CH), 71.41 (CH), 69.84 (CH), 26.01 (CH_3), 25.83 (CH_3), 24.75 (CH_3) and 24.00 (CH_3); IR (nujol) 3380 (NH) and 1785 (C=O) cm^{-1}.

‡ *Crystal data for* **2**: $C_{13}H_{19}NO_7$, *M* = 301.3, orthorhombic, space group $P2_12_12_1$, *a* = 7.1559(10), *b* = 9.6106(4), *c* = 20.5508(12) Å, *V* = 1413.3 Å^3 [from 2θ values of 27 reflections measured at ±ω (2θ = 30–32°, λ = 0.71073 Å), *T* = 298 K], *Z* = 4, D_c = 1.416 g cm^{-3}, μ(Mo-Kα) = 0.11 mm^{-1}. A colourless column (0.31 × 0.47 × 0.78 mm) was mounted on a Stadi-4 four-circle diffractometer. Data collection using Mo-Kα X-radiation gave 1137 unique reflections ($2\theta_{max}$ 45°) of which 977 with $F \geq 4\sigma(F)$ were used in all calculations. Following solution by automatic direct methods [SHELXS-86, program for crystal structure solution, G. M. Sheldrick, University of Göttingen, Germany, 1986], the structure was refined by full-matrix least-squares analysis (on *F*), with anisotropic parameters for all non-H atoms (SHELX-76, program for crystal structure refinement, G. M. Sheldrick, University of Cambridge, England, 1976). Except for the hydrogen which was constrained to lie 1.00 Å from the nitrogen, H-atoms were included in fixed, calculated positions. At final convergence, *R* = 0.0374, *wR* = 0.0525, *S* = 0.578 for 193 parameters and the final Δ*F* synthesis showed no feature outwith the range ±0.22 e Å^{-3}. Atomic coordinates, bond lengths, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

§ *Selected spectral data for* **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.33 (1H, d, *J* 2.6 Hz, 7-H), 4.95 (1H, d, *J* 5.4 Hz, 9-H), 4.61 (1H, d, *J* 5.4 Hz, 10-H), 4.52 (1H, d, *J* 10.4 Hz, 1-H), 4.27 (1H, d, *J* 10.4 Hz, 1-H), 3.98 (1H, dd, *J* 2.6, 0.4 Hz, 8-H), 2.98–2.80 (2H, symm. m, CH_3CH_2C=O), 1.40 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.35 (3H, s, CH_3) and 1.09 (3H, t, *J* 7.3 Hz, CH_3CH_2C=O); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.56 (C=O), 153.01 (C=O), 111.50 (quat C), 108.69 (quat C), 94.26 (CH), 88.92 (quat C), 78.68 (CH), 75.98 (CH), 73.41 (CH), 69.01 (CH_2), 29.89 (CH_2), 27.41 (CH_3), 26.92 (CH_3), 25.72 (CH_3), 25.46 (CH_3) and 7.96 (CH_3); IR (nujol) 1785 (oxazolidinone C=O), 1780 (C=O), 1310, 1225 and 1080 cm^{-1}.

¶ *Crystal data for* **3**: $C_{16}H_{23}NO_7$, *M* = 341.33, monoclinic, space group $P2_1$, *a* = 6.750(5), *b* = 8.674(7), *c* = 15.201(9) Å, β = 90.07(2)°, *V* = 890.0 Å^3, (from setting angles for 16 *h*0*l* and 4 0*k*0 data, 2θ = 20–35°, λ = 0.71073 Å, *T* = 295 K), *Z* = 2, D_c = 1.273 g cm^{-3}, μ(Mo-Kα) = 0.09 mm^{-1}. A colourless needle (1.2 × 0.24 × 0.4 mm) was mounted on a Stöe Stadi-2 diffractometer, mounting about [010]. Data collection using Mo-Kα X-radiation gave 1720 unique reflections ($2\theta_{max}$ = 50°), of which 1590 unique data with $|F| \geq 6(F)$ were used in all calculations. Following solution by automatic direct methods [SHELXS-86], the structure was refined by full-matrix least-squares analysis (on *F*), with anisotropic parameters for all non-H atoms [SHELX-76]. H-atoms were included in fixed, calculated positions. At final convergence, *R* = 0.049, *wR* = 0.067, *S* = 1.8 for 225 parameters and the final Δ*F* synthesis showed no feature above 0.20 or below −0.29 e Å^{-3}. Atomic coordinates, bond lengths, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

further highlighted when compared with our *endo*-borneol-derived oxazolidinone **1**, which affords a mixture of all four diastereoisomers in the ratio 55:29:10:6 (d.e. 10%) for the same aldol condensation.‖ Indeed, an equally low level of asymmetric induction (d.e. 30%) was found for condensation of isobutyraldehyde with the latter, whereas with **3** a diastereoisomeric excess of 82% is obtained.

The high level of asymmetric induction imparted by auxiliary **2** is further reflected in Lewis-acid mediated asymmetric Diels–Alder reactions of its acrylate derivatives **5a–c** with cyclopentadiene to prepare optically-active norbornenes **6** (Scheme 3). The crotonate dienophile **5b** and the cinnamate dienophile **5c** can be prepared smoothly and in good yields (80% and 71% respectively) by treatment of oxazolidinone **2** sequentially with n-butyllithium and the relevant acid chloride. This procedure failed in the case of the acrylate dienophile **5a** due to polymerisation which could be avoided by metallation of **2** with methylmagnesium bromide,[6] followed by treatment with acryloyl chloride to yield **5a** in 63% yield (together with small amounts of the corresponding *O*-acrylate ester).

The outcome of the Et_2AlCl-mediated cycloadditions of the acrylate dienophiles **5a–c** with excess cyclopentadiene are given in Table 1, and from these results it is evident that auxiliary **2** induces very high levels of diastereofacial differen-

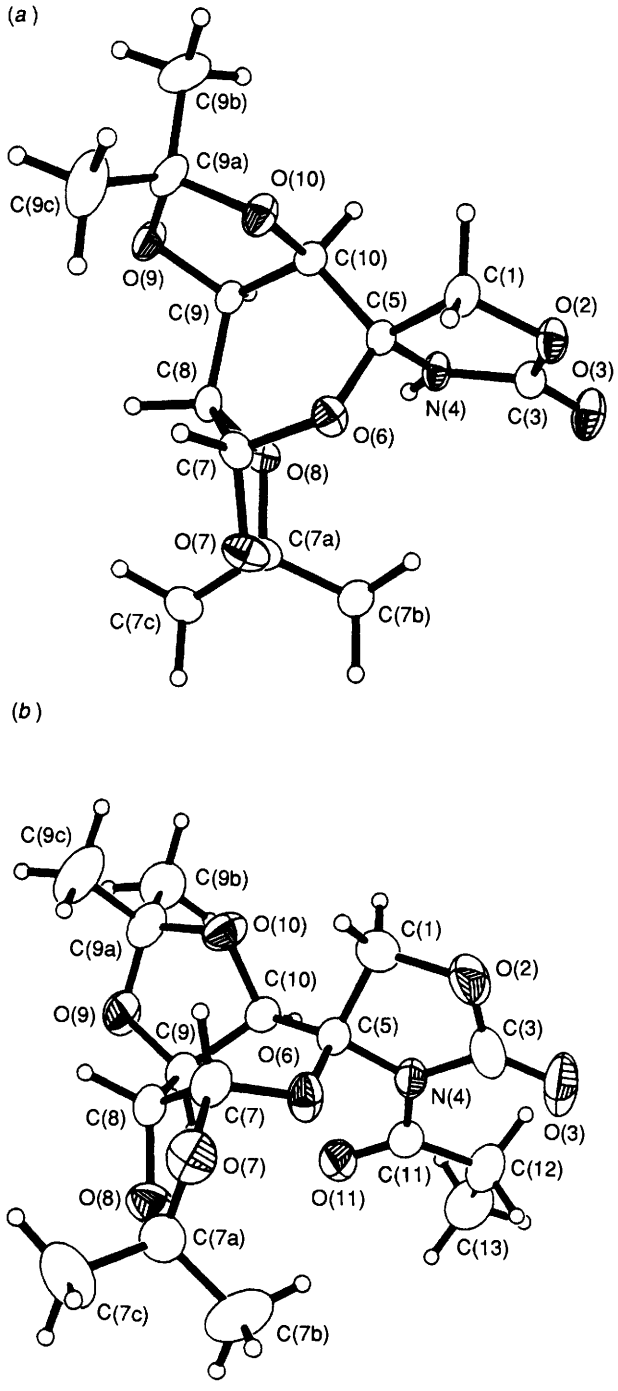
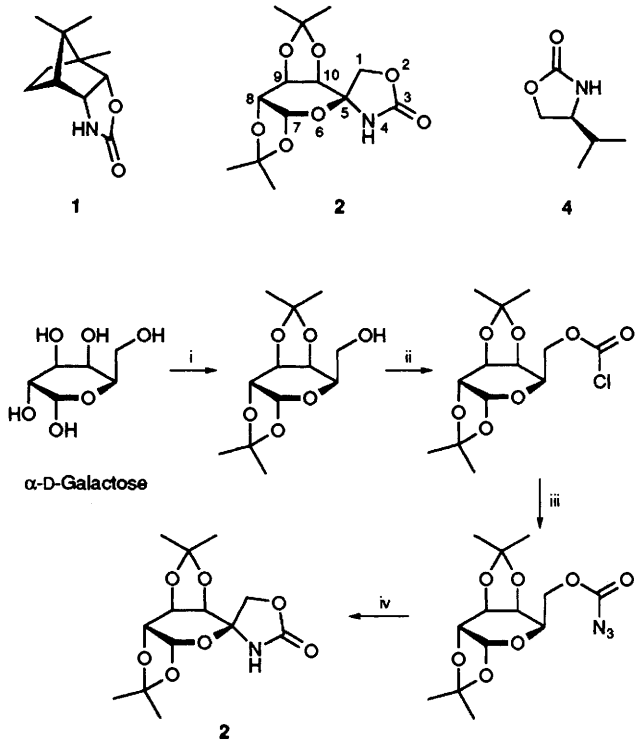
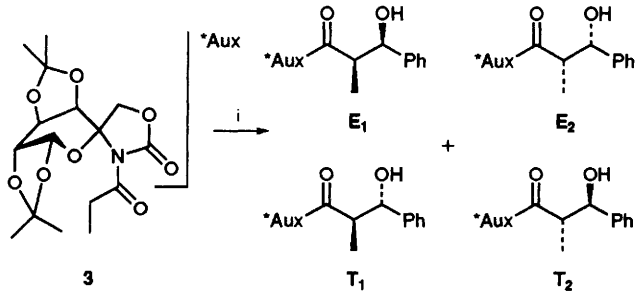


Fig. 1 ORTEP diagrams of (*a*) spirooxazolidin-2-one **2** and (*b*) its *N*-propionyl derivative **3**. Selected bond lengths (Å) and angles (°) for **2** and **3**. Estimated standard deviations of all values are 0.005 Å or 0.3°: C(1)–O(2): 1433, 1.450; O(2)–C(3): 1.363, 1.346; C(3)–O(3): 1.187, 1.198; C(3)–N(4): 1.342, 1.401; N(4)–C(5): 1.423, 1.465; N(4)–C(11):—, 1.403; C(1)–C(5): 1.524, 1.523; O(2)–C(1)–C(5): 104.9, 103.9; C(1)–O(2)–C(3): 109.5, 108.6; O(2)–C(3)–O(3): 122.5, 122.6; O(2)–C(3)–N(4): 108.6, 108.7; O(3)–C(3)–N(4): 128.9, 128.7; C(3)–N(4)–C(5): 113.2, 109.2; C(3)–N(4)–C(11):—, 126.7; C(5)–N(4)–C(11):—, 123.7; C(1)–C(5)–N(4): 100.8, 98.6.

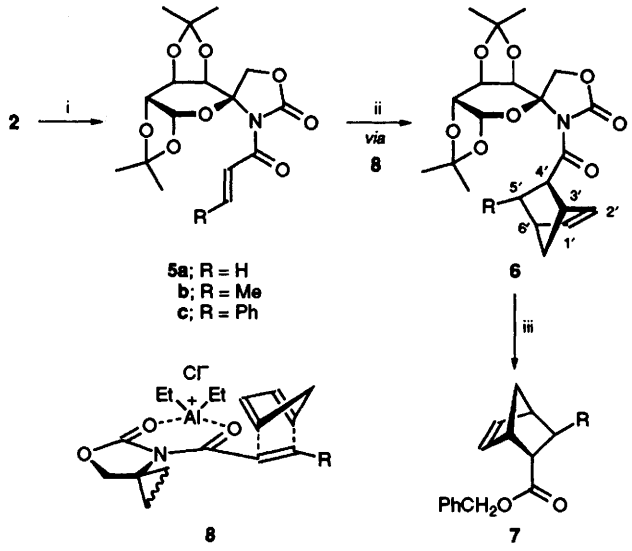
‖ A similar aldol reaction involving Oppolzer's camphor sultam is reported[4] to form all four diastereoisomers in the ratio 76:10:9:5 (d.e. 52%).



Scheme 1 *Reagents and conditions*: i, acetone, $ZnCl_2$, H_2SO_4 (catalyst), room temp., 97%; ii, $COCl_2$ (3 equiv.), pyridine, toluene–diethyl ether, 0 °C to room temp., 99%; iii, NaN_3 (2 equiv.), tetrabutylammonium bromide (catalyst), CH_2Cl_2, room temp., 92%; iv, $C_2H_2Cl_4$, reflux, 147 °C, 60%



Scheme 2 *Reagents and conditions*: i, (*a*) $LiNPr^i_2$, THF, −78 °C, (*b*) PhCHO, THF, 2 min



Scheme 3 *Reagents and conditions*: i, MeMgBr, THF, 0 °C, acryloyl chloride (for R = H); alternatively, Bu^nLi, THF, −78 °C, acid chloride (for R = Me, Ph); ii, cyclopentadiene, Et_2AlCl (1.4 equiv.), CH_2Cl_2, −78 °C (for R = H, Me), −20 °C (for R = Ph); iii, $LiOCH_2Ph$, THF, −78 °C to room temp.

tiation. In each case the *endo*/*exo* ratios for cycloadducts **6** are extremely high with *endo*-diastereoselection in the range 80–92%. Because of the highly crystalline nature of the adducts (imparted by **2**), the diastereoisomeric purity can be raised to >99% in each case by simple recrystallisation from diisopropyl ether.

Also shown in Table 1 (in parenthesis) are the levels of *endo*-diastereoselection obtained by us for the corresponding Diels–Alder reactions mediated by the (*S*)-valinol-derived oxazolidinone **4**. For **6a** the outcome is comparable; however there is a significant drop in diastereoselection (12%) provided by **4** for the cycloaddition of its (*E*)-crotonyl imide relative to that of **6b** bearing the auxiliary **2**. The efficiency of **2** as a chiral control element in Diels–Alder reactions is further highlighted when compared to the *endo*-diastereoselectivity brought about by the aforementioned terpenoid-based auxiliary **1** for its acryloyl (d.e. 59%) and crotonyl imide (d.e. 71%) under strictly analogous reaction conditions.

The origin of the high diastereofacial selectivity with **2** can be rationalised by reference to structure **8** in which cyclopentadiene approaches the intermediate chelated aluminium complex from the Cα-*re* face (top face as drawn) with high preference. Examination of Dreiding models show that this face is indeed the less hindered face of the acrylate, with the other face being shielded by the 9,10-di-*O*-isopropylidene grouping. The configuration of adducts **6** was determined *via* the optical rotations of benzyl esters **7** obtained by cleavage with lithium benzyloxide.** These values allowed the absolute configuration for adducts **6** to be assigned (Table 1) and is as shown in Scheme 3. For **6a** the stereostructural assignment was also confirmed by X-ray analysis, full details of which will be published elsewhere.

** *Optical rotations of benzyl esters*: **7a**, $[\alpha]_D$ −125 (*c* 1.10, CH_2Cl_2); **7b**, −127 (*c* 1.96, $CHCl_3$); **7c**, −118 (*c* 1.65, CH_2Cl_2). These values are of equal magnitude albeit of opposite sign to those reported for oxazolidinone **4**.[6]

Table 1 Et_2AlCl-mediated asymmetric Diels–Alder reactions of chiral unsaturated carboximides **5a–c** and cyclopentadiene[a]

		Cycloadduct **6**[b]		
Dienophile	*T*/°C	Yield (%)	*endo*:*exo*	*endo* d.e./%[c,d]
5a	−78	83 (88)	98:2 (98:2)	80 (79)
5b	−78	98 (91)	99:1 (98:2)	89 (77)
5c	−78 to −20	99	98:2	92

[a] Reactions run at −78 °C in methylene chloride using 1.4 equiv. of Et_2AlCl. [b] Figures in parentheses for corresponding reactions with (*S*)-valinol-derived oxazolidinone **4** under identical reaction conditions. [c] Ratios determined by 360 MHz ^1H NMR spectroscopy. [d] Absolute configuration of the preferred diastereoisomer: **6a**, 4′*S*; **6b**, 4′*S*,5′*R*; **6c**, 4′*R*,5′*R*.

Finally, we also note the broad spectrum of chromatographic separability conferred by **2** as reflected in the high separation factors (α) obtained by HPLC for the normally difficult resolution of racemic amines, carboxylic acids, *etc.* For example, an α-value of 1.50 is found for the separation of racemic 1-phenylethylamine *via* diastereoisomeric ureas (prepared from **2** by deprotonation with n-butyllithium, treatment with phosgene to generate the carbamoyl chloride, and reaction with amine), well in excess of 1.09 reported for the corresponding commercially available FLEC [(+)-1-(9-fluorenyl)ethyl chloroformate].[7] Likewise, analysis of the corresponding diastereoisomeric amides derived from carboxylic acids (following addition of the acid chloride to lithiated **2**) by HPLC gave α-values well in excess of 2.0, *i.e.* 2.70 for (±)-2-chloropropanoic acid, and of such magnitude as to ensure straightforward effective resolution of sizeable quantities of material by flash silica chromatography. In both these cases the resolved compounds, together with **2** for re-use, can be recovered by cleavage of the resultant diastereoisomers using conventional methods.

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