Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4917-4920, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01058-7

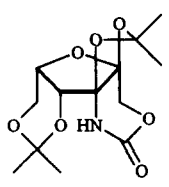
Intramolecular Ring Cleavage of Chiral Terpenoid-derived Oxazinone *via* Asymmetric *anti*-Aldol Reaction : Unexpected Entry to a *N*-Substituted Tetrahydro-1,3-oxazine-2,4-dione Derivative

Tariq R. Abbas[a], J.I.G. Cadogan[b], Allan A. Doyle[a], Ian Gosney[a], Philip K.G. Hodgson[c], Garnet E. Howells[a], Alison N. Hulme[a], Simon Parsons[a] and Ian H. Sadler[a]

[a] Department of Chemistry, The University of Edinburgh,
West Mains Road, Edinburgh EH9 3JJ, Scotland
[b] Department of Chemistry, Imperial College of Science, Technology and Medicine,
South Kensington, London SW7 2AY, England
[c] B.P.Chemicals Ltd, Research Laboratory, Dunstan Building, Chertsey Road, Sunbury-on-Thames,
Middlesex TW16 7LN, England

Abstract : In the presence of excess Bu_2BOTf to promote *anti*-selectivity, an asymmetric aldol reaction with a homochiral terpenoid-derived 1,3-oxazin-2-one as the chiral control element results unexpectedly in ring cleavage by an intramolecular process to form a *N*-substituted tetrahydro-1,3-oxazine-2,4-dione in virtually quantitative yield. © 1997 Elsevier Science Ltd.

Compared to homochiral oxazolidin-2-ones[1], the use of the six-membered 1,3-oxazin-2-one ring system as a stoichiometric chiral control element has received scant attention[2] despite having the essential features necessary to control asymmetric transformations, *viz.* an easily functionalised nitrogen atom, carbonyl group for chelation control, and importantly, conformational immobility to provide the necessary stereochemical bias . So far, mainly carbohydrates have provided the necessary stereogenic centres for construction of chiral 1,3-oxazin-2-ones, *e.g.* 2-keto-L-gulonic acid for **1**[3], and xylofuranose which serves as a chiral source for the variant **2**[4]. The only terpenoid-based oxazinone to be used as a chiral auxiliary is camphor-derived **3**[5],



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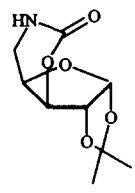

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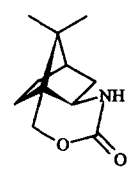

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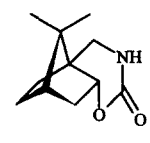

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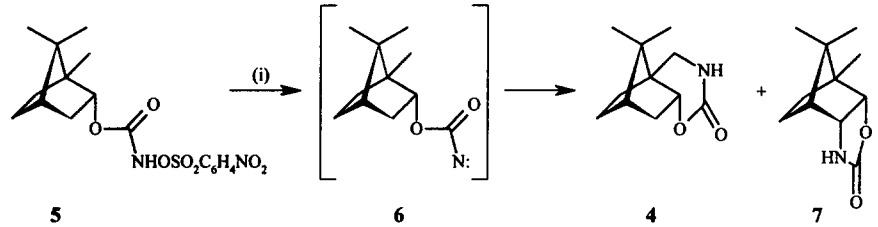
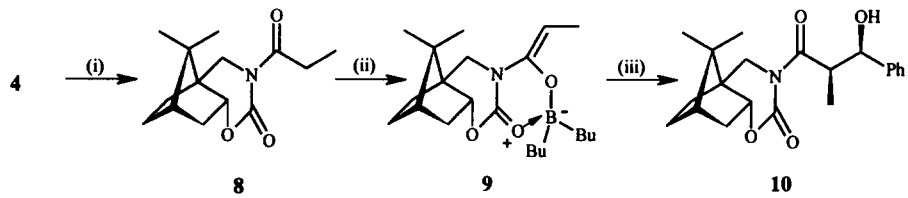
which imparted considerable diastereoselectivity in titanium-mediated "chelation-controlled" aldol reactions to give only *syn*-products. In this Letter, we wish to report the use of the 1,3-oxazin-2-one **4**, a structural isomer of **3**, as a chiral control element, and secondly, the unexpected cleavage of the fused ring system during attempts to stereoregulate the aldol reaction of its *N*-propionyl imide derivative leading to a tetrahydro-1,3-oxazine-2,4-dione[6] by a novel rearrangement process.

The oxazinone auxiliary **4** was synthesised as a *ca.* 1:1 mixture with the tricyclic oxazolidin-2-one **7**[7] by application of the INIR (Intramolecular Nitrene Insertion Reaction) method to the optically-active nitrene **6** which was generated from carbamate precursor **5** as shown in Scheme 1 in a two-phase system.



Scheme 1. *Reagents and conditions:* (i), benzyltriethylammonium chloride, sodium hydrogen carbonate, CH_2Cl_2-water, 25°C.

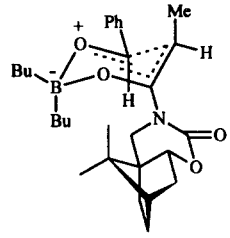
Separation of the isomeric products was easily achieved by flash chromatography on silica (cyclohexane:ethylacetate) which furnished well-formed crystals of the chiral oxazinone **4** in an enantiomerically pure form [(mp 170-171°C; $[\alpha]_D^{23}$= +72.1°; c = 5.1(ethanol) (*cf.* **3**, mp 240-242°C; $[\alpha]_D$= -155°; c = 0.85 (chloroform)] in 36% yield. The stereochemical control imparted by **4** in diastereoselective aldol processes with the enolate **9** derived from the *N*-propionyl imide **8** is reflected in the realisation of nearly complete asymmetric induction in boron-mediated aldol reaction[8] with benzaldehyde (Scheme 2).



Scheme 2. *Reagents and conditions:* (i), EtMgBr, then CH_3CH_2COCl, THF, -78°C; (ii), Bu_2BOTf, Pr^i_2NEt, CH_2Cl_2, 0°C; (iii), PhCHO, CH_2Cl_2, -78°C.

^{13}C-NMR spectroscopy showed unequivocally that only one product had been formed, whilst *syn*-stereochemistry was assigned on the basis of its small ^{1}H-NMR (250 MHz) vicinal coupling constants (J =2.6Hz) and only one doublet at 5.27 ppm arising from the PhC*H*(OH) proton[9]. The X-ray structure shown in **Fig.1a** confirms the absolute stereochemistry of the two newly formed chiral centres to be *syn* as depicted in compound **10**. This sense of diastereofacial selectivity is similar to that reported for the corresponding aldol reaction of **3** *via* the boron enolate under the original Evans' conditions[5], but in this case, *anti*-isomers were also formed. The high level of asymmetric induction imparted by oxazinone **4** in the

model aldol reaction can be explained by formation of the six-membered Zimmerman-Traxler transition state **11** with tetraco-ordinate boron in which attack of the aldehyde occurs on the C_α-*re* face of the enolate since the bulk of auxiliary shields the C_α-*si* face.



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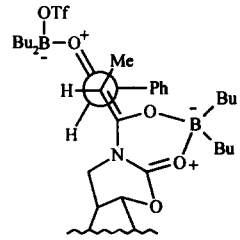

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In an attempt to induce *anti*-selectivity with well defined facial bias, we had occasion to investigate the outcome of the same aldol reaction using Heathcock's protocol[10] with an excess of dibutylboron triflate (2.2 equiv). Indeed, the same behaviour gratifyingly seemed to occur under these conditions, but to our surprise, the product isolated in virtually quantitative yield proved to be the rearranged compound **14** (Scheme 3). Further crystallisation from cyclohexane furnished colourless crystals of the enantiopure tetrahydro-1,3-oxazine-2,4-dione **14** (mp 125-127°C) whose structure was confirmed by microanalysis, mass spectral and NMR data[11]. X-Ray diffraction analysis confirmed the stereochemical integrity of **14** and has shown that the absolute configuration of the chiral centres at C(3) and C(4) is (5*S*,6*R*) (**Fig.1b**).

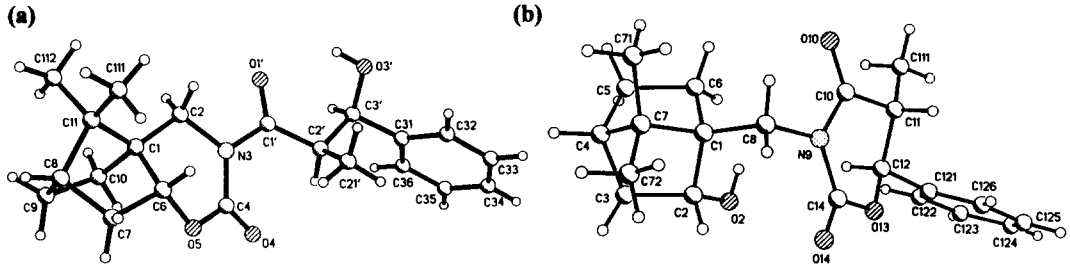
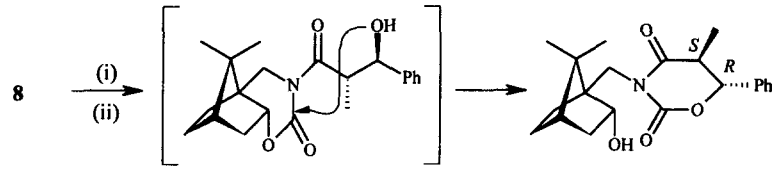


Figure 1. (a) Molecular structure of *syn*-aldol **10**, and **(b)** of tetrahydro-1,3-oxazine-2,4-dione **14**

From a mechanistic viewpoint, such an outcome provides strong support for the intermediacy of the *anti*-adduct **13** arising from a transition state like **12** where the enolate boron is chelated to the oxazinone carbonyl to give not only the correct sense of diastereofacial selectivity, but also to facilitate ring cleavage of the oxazinone ring. To our knowledge, this seems to be the first example of such a transformation and it is conceivable that the reaction may be extended to related systems under the influence of a Lewis acid. Further work in this area is in progress and will be reported in due course. In the meantime, it is worth noting that treatment of the *syn*-aldol product **10** with excess boron triflate under Heathcock's conditions gave 1,3-oxazine-2,4-dione **14** with *anti*-stereochemistry exclusively, pointing to realisation of a *retro*-aldol reaction or else α-epimerisation before rearrangement.



13 **14**

Scheme 3. *Reagents and conditions:* (i), excess Bu_2BOTf, Pr^i_2NEt, CH_2Cl_2, 0°C; (ii), PhCHO, CH_2Cl_2, -78°C.

References and notes

1. For a review, see Cadogan, J.I.G.; Doyle, A.A.; Gosney, I.; Hodgson, P.K.G.; Thorburn, P.; *Enantiomer*, **1997**, *2(2)*, 81-98.
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3. Banks, M.R.; Cadogan, J.I.G.; Gosney, I.; Gaur, S.; Hodgson, P.K.G.; *Tetrahedron Asymmetry*, **1994**, *5*, 2447-2458.
4. Ref. 2, page 346.
5. Anh, H.K.; Lee, S.; Lim, A.; *J. Org. Chem.*, **1992**, *52*, 5065-5066.
6. For pertinent references to the synthesis of tetrahydro-1,3-oxazine-2,4-diones, see Barton, D.H.R.; Liu, W.; *J. Chem. Soc. Chem. Commun.*, **1997**, 571-572.
7. Banks, M.R.; Blake, A.J.; Cadogan, J.I.G.; Dawson, I.M.; Gosney, I.; Grant, K.J.; Gaur, S.; Hodgson, P.K.G.; Knight, K.S.; Smith, G.W.; Stevenson, D.E.; *Tetrahedron*, **1992**, *48*, 7979-8006.
8. See ref. 6, and references cited therein.
9. All compounds exhibited spectral data consistent with their structures. Selected spectroscopic data for compound **10** : FTIR (nujol) ν_{max} : 3560(OH), 1732(C=O), 1674(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44-7.20(5H, cm, Ph), 5.27(1H, d, *J* =2.6Hz, C*H*OH), 4.56-4.49(1H, ddd, *J* =4.0,2.4,2.0Hz, C*H*O), 4.10(1H, dq, *J* =7.1, 2.6Hz, C*H*CH_3), 3.59(1H, d, *J* =12.2Hz, CH_2N), 3.48(1H, d, *J* =12.2Hz, CH_2N), 2.73(1H, broad s, O*H*), 2.31-2.21(1H, m, C*H* bridgehead), 1.99-1.24(6H, cm, 3CH_2), 1.02(3H, d, *J* =7.1Hz, CH_3CH), 1.02(3H, s, CH_3), 0.99(3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 181.16(C=O), 152.67(C=O), 141.26(Ar C), 127.94(Ar 2CH), 127.01(Ar CH), 125.95(Ar 2CH), 80.84(CH), 72.64(CH), 48.34(CH_2), 46.99(quat C), 46.38(CH), 45.85(quat C + CH), 32.48(CH_2), 27.44(CH_2), 25.00(CH_2), 19.75(CH_3), 18.61(CH_3), 10.58(CH_3) ppm; MS(FAB) m/z 55(29%), 95(11), 117(64), 135(80), 145(base), 178(7), 240(3), 296(12), 340(68), 358(11); Accurate mass (FAB); Found : 358.20073; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.
10. Danda, H.; Hansen, M.M.; Heathcock, C.H.; *J. Org. Chem.*, **1990**, *55*, 173-181.
11. Selected spectroscopic data for compound **14** : FTIR (nujol) ν_{max} : 3485(OH), 1765(C=O), 1677(C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.25(5H, cm, Ph), 4.99(1H, d, *J* =11.6Hz, PhC*H*O), 4.24(1H, dd, *J* =8.9,2.1Hz, C*H*OH), 3.96(2H, s, CH_2N), 2.88(1H, dq, *J* =11.6,7.0Hz, C*H*CH_3), 2.31-2.13(2H, cm, O*H* and C*H* bridgehead), 2.06-1.70(2H, cm, CH_2), 1.59-1.23(4H, cm, 2CH_2), 1.06(3H, d, *J* =7.0Hz, CH_3CH), 1.02(3H, s, CH_3), 0.90(3H, s, CH_3) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.87(C=O), 152.07(C=O), 135.09(Ar C), 129.50(Ar CH), 128.79(Ar CH), 128.62(Ar CH), 126.97(Ar CH), 125.28(Ar CH), 80.84(CH), 73.76(CH), 52.59(quat C), 48.54(quat C), 46.04(CH), 42.18(CH_2), 41.81(CH), 37.82(CH_2), 27.75(CH_2), 23.45(CH_2), 20.08(CH_3), 18.99(CH_3), 11.43(CH_3) ppm; MS(FAB) m/z 41(base), 55(53%), 95(20), 117(50), 135(44), 145(97), 178(27), 240(6), 296(11), 340(68), 358(13); Accurate mass (FAB); Found : 358.20129; $C_{21}H_{28}NO_4$ (M+H) requires 358.20183.

(*Received in UK* 28 *April* 1997; *revised* 27 *May* 1997; *accepted* 30 *May* 1997)