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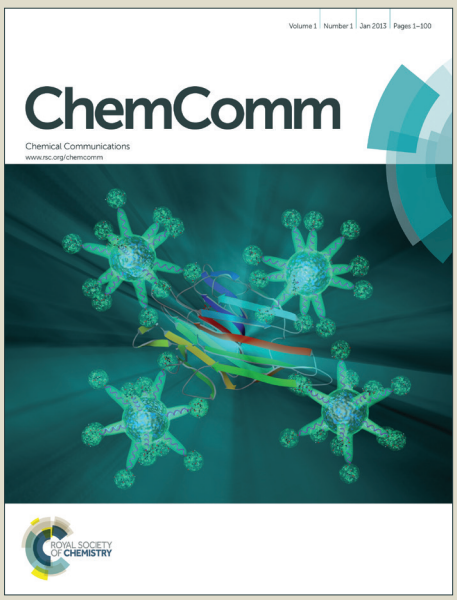

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Rhodium(II)-catalysed tandem aziridination and ring-opening: stereoselective synthesis of functionalised tetrahydrofurans

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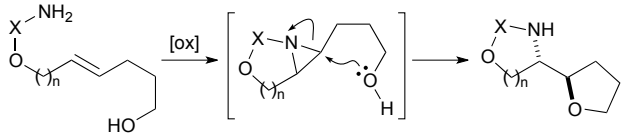
William P. Unsworth,[a,b] Nicola Clark,[a] Thomas O. Ronson,[a,b] Kiri Stevens,[a] Amber L. Thompson,[a] Scott G. Lamont[c] and Jeremy Robertson*[a]

Aziridines formed upon treatment of allylic carbamates and homoallylic sulfamates with Rh(II) carboxylate catalysts under oxidative conditions are trapped by suitably-disposed hydroxyl groups to give functionalised tetrahydrofurans.

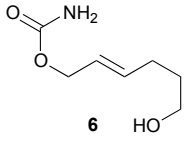
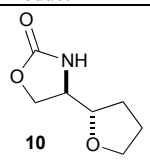
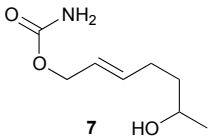
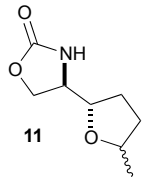
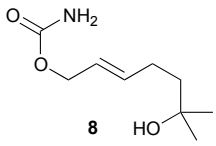
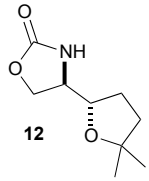
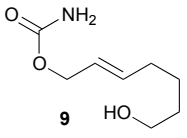
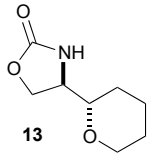
The stereospecific 1,2-functionalisation of alkenes by oxygen and nitrogen functionality occupies a central position in strategic route development to natural products, pharmaceuticals, and other molecules of interest. Classical concerted epoxidation coupled to S_N2-like delivery of a nitrogen-centred nucleophile delivers overall 1,2-*anti*-oxyamination. More recent single-step equivalents[1] such as Sharpless' asymmetric aminohydroxylation[2] and Donohoe's tethered aminohydroxylation[3] provide an overall *syn*-stereospecific transformation in which both oxygen and nitrogen functionality are delivered from the metal centre to the same face of the alkene. Complementary to this, aziridine intermediates generated from the intramolecular reaction of Rh(II)-nitrenoids and tethered alkenes[4] suffer regio- and stereoselective ring-opening by acetate, liberated from $PhI(OAc)_2$ during the formation of the nitrenoid.[5] This method is predominantly *anti*-selective and only the nitrogen functionality is delivered from the rhodium catalyst, opening the possibility of aziridine capture by a range of nucleophiles. The current paper describes a potentially valuable realisation of this idea: consecutive aziridination and *O*-cyclisation resulting in 2-(1-amino-2-hydroxyethyl)tetrahydrofurans (Scheme 1).[6]



Scheme 1 A tandem aziridination *O*-cyclisation approach to functionalised tetrahydrofurans. [X = CO, SO_2; n = 1, 2]

Initially, four substrates were prepared, each bearing a 3-hydroxypropyl substituent on the distal end of the alkene. Cross metathesis of allyl carbamate **1** (Scheme 2) with the requisite alkenol **2**–**5** delivered test substrates **6**–**9** effectively, enriched in the *E*-isomer (dr = 4–7:1). The unoptimised reactions of these substrates, under the standard conditions,[7] are summarised in Table 1. In all cases inspection of NMR spectra of the crude reaction mixtures revealed excellent conversion to the desired products of aziridination and 5-*exo*- mode *O*-cyclisation. The moderate isolated yields in these reactions are attributable, at least in part, to the small scales involved; later, larger scale reactions with more complex substrates (see below) were more efficient. An increase in steric encumbrance at the hydroxyl centre had little impact on the yield but the stereoselectivity dropped off progressively in the 2°- and 3°-alcohol substrates (entries 2 and 3, respectively).

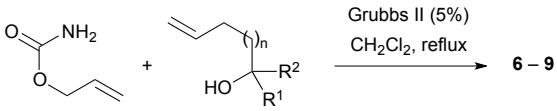
Table 1 Rh(II)-mediated tandem aziridination and *O*-cyclisation

Entry	Substrate[a]	Product[b]	Yield, dr
1	 **6**	 **10**	(a) 48%, 9:1 (b) 68%, >10:1[c] (c) 42%, >10:1[d]
2	 **7**	 **11**	54%, ~5:1[e]
3	 **8**	 **12**	51%, 3:1
4	 **9**	 **13**	20%, >10:1

[a] *E*-/*Z*- ratios: **6**, dr = 7:1; **7**, dr = 4:1; **8**, dr = 5.5:1, **9**, dr = 4:1; [b] the assumed relative stereochemistry for the major diastereomer is depicted; [c] performed on the *N*-*para*-toluenesulfonyloxy derivative of **6** with $Rh_2(OAc)_4$ (5 mol%), K_2CO_3, acetone; [d] as (b) but using $Cu(pyr)_4(OTf)_2$ (5 mol%); [e] four diastereomers 1.0:0.8:0.2:0.15 (see text).

Depiction of the major product as the *anti*- isomer in each case is based on both mechanistic expectation and confirmed

outcomes in more complex substrates, see below. The product **11** (entry 2) was obtained as a mixture of four diastereomers, assumed to be the two *anti*-diastereomers (as depicted, major) and two *syn*-diastereomers (minor), both as ~1:1 mixtures at the methyl group. An increased tether length reduced the efficiency of the *O*-cyclisation and the reaction in entry 4 gave a complex product mixture from which the desired product was isolated in low yield. Lebel's conditions for nitrenoid generation were tested (entry 1(b) & (c));[8] here, the carbamate substrate **6** is introduced 'pre-oxidised' as its *N*-sulfonyloxy derivative, with Rh(II)- or Cu(II)-mediated aziridination effected under basic conditions in the absence of an external oxidant. Both procedures gave high stereoselectivity but the original (oxidative) procedure was more effective overall, taking into account preparation of the substrates.



1

2, n = 1, $R^1 = R^2 = H$ 88%
3, n = 1, $R^1 = CH_3$, $R^2 = H$ 60%
4, n = 1, $R^1 = R^2 = CH_3$ 44%
5, n = 2, $R^1 = R^2 = H$ 46%

Scheme 2 Preparation of simple ω-hydroxyalkyl-substituted allylic carbamates.

This study established a direct route to the 2-(1-amino-2-hydroxyethyl)tetrahydrofuran motif, a core structural feature of a variety of secondary metabolites including ezomycin A2,[9] malayamycin A (Fig. 1),[10] dysiherbaine,[11] and furanodictines A and B (Fig. 1).[12] These molecules all have interesting and potentially exploitable biological activity; ezomycin A2 and malayamycin A possess antifungal activity, dysiherbaine shows selective neuroexcitotoxicity, and furanodictine B potently induces neurite outgrowth. Therefore, more complex substrates were assembled to probe the performance of the aziridination/*O*-cyclisation in a target-relevant setting. Scheme 3 illustrates the assembly and reaction of a model substrate for an approach to malayamycin A. Cross metathesis of alkenes **14**[13] and **15**,[14] formation of the carbamate,[15] and stereoselective reduction[14a] gave substrate **16** efficiently. Application of the standard aziridination/*O*-cyclisation conditions on ~1.0 g scale gave a 60% yield of the oxazolidinone as a 57:43 ratio of diastereomers **17** and **18**. Efforts to elaborate these products to a phenyl analogue of malayamycin A, by connection of the starred oxygen and carbon, will be described elsewhere.

Scheme 4 illustrates a second series of cyclisations that, through a combination of NOE studies and single crystal X-ray diffraction studies of the products,[†] supported our previous stereochemical assignments based on mechanistic expectations. Here, *Z*- and *E*- esters[16] **19** and **23** were converted into carbamates **20** and **24**, respectively. In this work, we found that

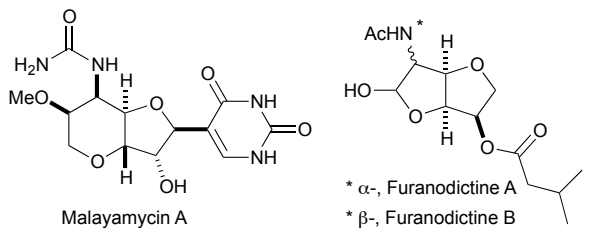


Fig. 1 Biologically-active natural products containing the 2-(1-amino-2-hydroxyethyl)tetrahydrofuran motif.

there was no advantage to using $Rh_2(oct)_4$ as the catalyst, and switching to $Rh_2(OAc)_4$ with the conditions otherwise unaltered afforded good results on ~300 mg scale. The initial aziridinations exhibited some facial selectivity; *Z*-substrate **20** gave diastereomers **21** and **22** with dr ~75:25, and diastereomers **25** and **26** were obtained from *E*-substrate **23** with dr ~65:35. The major diastereomers **21** and **25** have the correct stereochemistry for elaboration to furanodictines A and B, respectively. In a conformation in which the adjacent dioxolane C–H and alkenyl C–H bonds are *anti*-periplanar, aziridination from the 'rear' face avoids the dioxolane ring and potentially benefits from coordination of -N=$Rh_2(OAc)_4$ to the free hydroxyl group (Fig. 2); subsequent aziridine opening by invertive *O*-cyclisation from the 'front' face delivers the major diastereomers in each series.

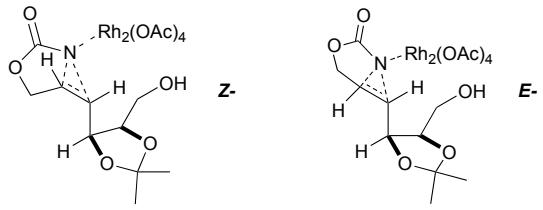
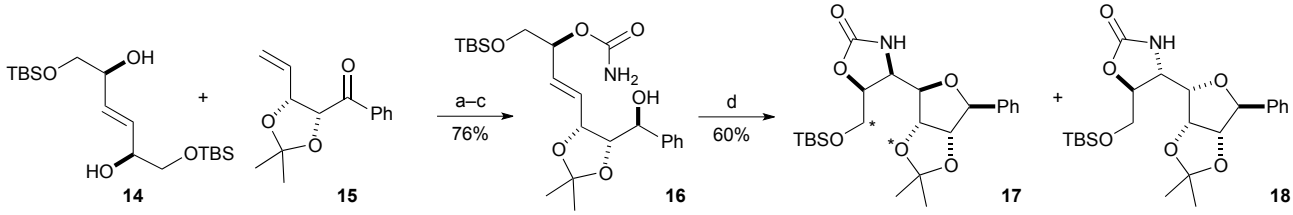


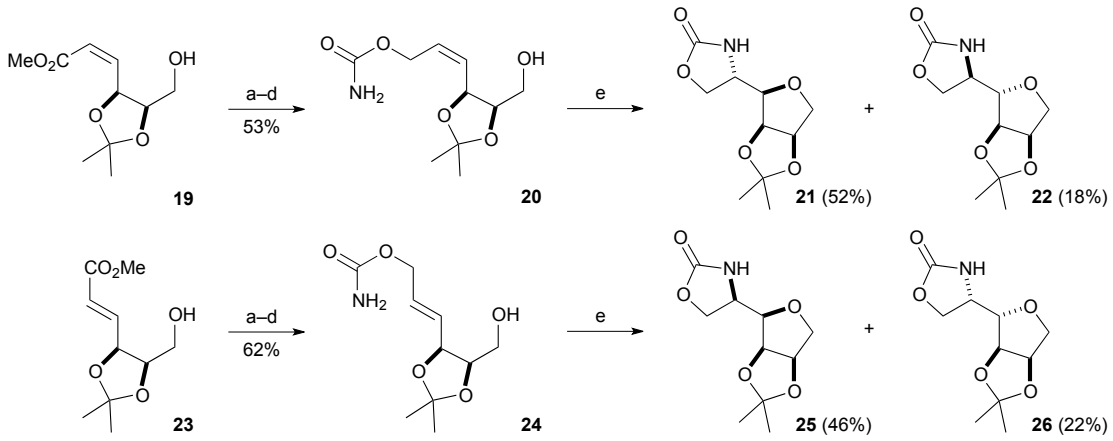
Fig. 2 Working model for stereocontrol in the aziridination leading to major diastereomers **21** (from *Z*-**19**) and **25** (from *E*-**23**).

Finally, we briefly investigated the reactions of homoallylic *sulfamates* as a comparison with the carbamates and to test whether the derived aziridines would follow the known preference for *endo*-C–N bond cleavage[17] or if, when presented with an *internal* nucleophile, conformational constraints would bias the reaction towards cleavage of the *exo*-C–N bond. In two preliminary examples, reaction of *E*-**27** (Scheme 5) followed the expected pathway, giving the *trans*-fused 7,5-bicyclic sulfamate **28**.[18] In contrast, reaction of the corresponding *Z*-**27** afforded two products, the (major) *cis*-fused 7,5-bicyclic sulfamate **29** being accompanied by some of the '*exo*-mode' ring-opening product **30** (stereochemistry assigned on mechanistic grounds).

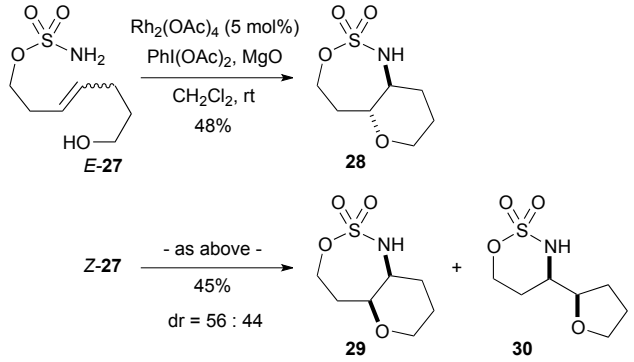


14 **15** **16** **17** **18**

Scheme 3 *Reagents and conditions.* (a) Hoveyda–Grubbs II (8 mol%), CH_2Cl_2, reflux, 20 h; (b) $Cl_3CCONCO$, CH_2Cl_2, 0 °C, 1 h then Al_2O_3; (c) L-Selectride, $ZnCl_2$, CH_2Cl_2-Et_2O-THF, –78 °C, 1.5 h; (d) $Rh_2(oct)_4$ (5 mol%), $PhI(OAc)_2$, MgO, CH_2Cl_2, 50 °C (sealed tube), 18 h.



Scheme 4 *Reagents and conditions.* (a) TBSCl, imidazole, DMF, 35 °C, 15 h; (b) $LiAlH_4$, THF, rt, 40 min; (c) $Cl_3CCONCO$, CH_2Cl_2, 0 °C, 1 h then K_2CO_3, MeOH, rt, 3 h; (d) TBAF, THF, rt, 15 min; (e) $Rh_2(OAc)_4$ (5 mol%), $PhI(OAc)_2$, MgO, CH_2Cl_2, 50 °C (sealed tube), 18 h.



Scheme 5 Aziridination and *O*-cyclisation of homoallylic sulfamates.

In conclusion, Rh(II)-mediated amino-cycloetherification provides a one-step regio- and *anti*-stereoselective route to functionalised tetrahydrofurans. Applications of this process in the synthesis of biologically-active natural products will be reported in due course.

Notes and references

[a] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK.
[b] Current address: Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK.
[c] AstraZeneca Global R&D, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

Electronic Supplementary Information (ESI): Selected experimental procedures and spectroscopic data. See DOI: 10.1039/c000000x/

† Diffraction data were collected at 150 K using a Nonius Kappa CCD Diffractometer (λ = 0.71073Å). Data were reduced using DENZO/SCALEPACK.[19] The structure was solved with SuperFlip[20] and refined by full-matrix least squares on *F2* using CRYSTALS.[21] See the ESI/CIF for full refinement details; crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1015840 (**21**), 1015841 (**25**), 1015842 (**26**)) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

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