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Rapid Entry to Enantiopure Polycyclic β-Lactams *via* Intramolecular Nitrone-Alkene Cycloaddition of 2-Azetidinone-tethered Alkenylaldehydes

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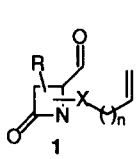
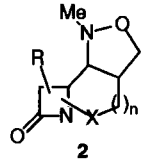
Abstract: New enantiomerically pure fused **2** or bridged **3** polycyclic β-lactam systems are regio- and stereoselectively prepared *via* intramolecular nitrone-alkene cycloaddition of 2-azetidinone-tethered alkenyl-aldehydes **1**. The regioselectivity of the cycloaddition can be tuned by moving the alkene substituent from N1 to C3 on the 2-azetidinone ring.

Since the pioneering work by LeBel,[2] the intramolecular nitrone-alkene cycloaddition (INAC) reaction has experienced impressive growth and found broad application in organic synthesis.[3] This wide research has been fostered by its operational simplicity and the fact that it proceeds usually with high degrees of regio- and stereocontrol. In our ongoing project directed to develop efficient routes to prepare bi- and polycyclic β-lactam systems,[4] we recently introduced 2-azetidinone-tethered alkenylaldehydes (type **1**) as starting materials for the synthesis of fused tricyclic β-lactams, by using both stereoselective allylation and IMDA reactions.[5] We envisaged that nitrones formed from such aldehydes might undergo INAC reaction to the alkene substituent on the 2-azetidinone ring thus providing a novel, rapid access to unusual, chiral polycyclic β-lactams (types **2** and/or **3**).[6, 7] Our interest in such reactions was further stimulated by the possibility of a selective functionalization of the fused bicyclic β-lactam systems by ring cleavage of the isoxazolidine moiety.[8] We report here our preliminary results in this area, that include the unique behaviour of 2-azetidinone-tethered alkenylaldehydes **1** which under standard INAC reaction conditions regio- and stereoselectively give either fused **2** or bridged **3** cycloadducts, or products **4** derived from intramolecular retro-Cope elimination.



1

(X = O, CH_2; n = 1, 2)



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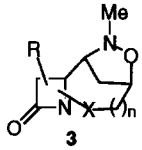

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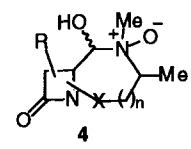

4

The substrates necessary for this study, enantiopure alkenylaldehydes **1a-d**, were conveniently synthesised from readily available *cis*-2-azetidinones **5a-d** following simple standard transformations. Compounds **5** were easily prepared as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylideneropanal, through Staüdinger reactions with the corresponding acid chlorides in the presence of Et_3N.[9]

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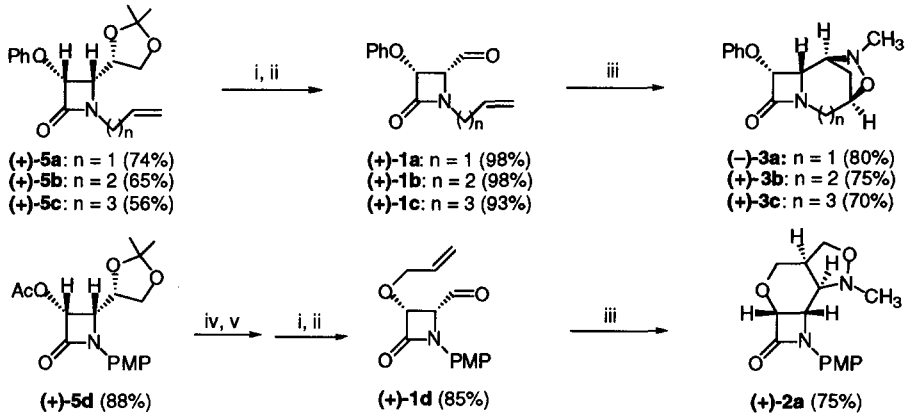
The reaction of 1-allyl-4-formyl-2-azetidinone **1a** with *N*-methylhydroxylamine proceeded smoothly in refluxing benzene to provide exclusively the bridged cycloadduct with a carbacepham structure, **3a**, in excellent yield as the pure product (80%). The constitution and the stereochemistry of **3a** were unequivocally established by X-ray crystallography (Figure).[10] The INAC reaction was also useful in the conversion of the homologous 1,4-tethered alkenylaldehydes **1b** and **1c** into the corresponding bridged tricyclic β-lactams with similar efficiency [**3b** (75%), **3c** (70%)] although in the case of **3b** with lower selectivity (mixture of two diastereoisomers in a ratio 95:5). Isomeric fused isoxazolidines could not be detected in the cycloaddition of nitrones derived from **1a-c**. Formation of the bridged-ring products **3** is worthy of note because only fused-ring products have been found in the INAC reactions of related N-alkenyl-2-prolinaldehyde and related cyclic-bridged alkenylaldehydes.[11] It is possible that , because of the rigid angular disposition imparted by the planar lactam group, the fused-ring transition state increases in energy thereby becoming uncompetitive with the usually unfavored bridged-ring transition state.

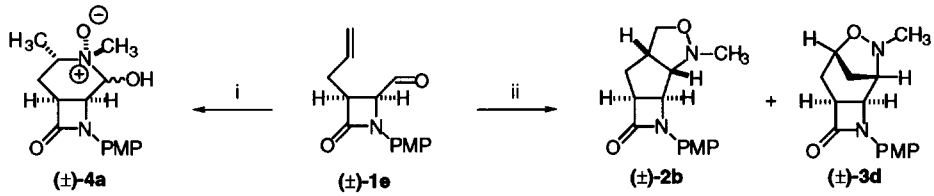


Key: i) PTSA, THF/H_2O, Δ. ii) $NaIO_4$, CH_2Cl_2, $NaHCO_3$, rt. iii) MeNHOH-HCl, Et_3N, benzene/Δ. iv) NaOMe, HOMe, rt. v) $Bu_4N^+Br^-$, NaOH, $BrCH_2CH{=}CH_2$.

Scheme 1

An interesting and useful aspect of the regioselectivity of this cycloaddition was subsequently discovered when the alkene substituent was moved from N1 to C3, as in the 3,4-tethered alkenylaldehyde **1d**. A dramatic change in the regioselectivity was observed when the fused cycloadduct **2a** was formed as the exclusive product (75% yield in pure form) from compound **1d**. This result prompted us to investigate the cycloaddition of the nitrone derived from racemic *cis*-3-allyl-4-formyl-2-azetidinone **1e**,[12] which would allow a direct comparison with the 1-allyl derivative **1a**. We were pleased to find that stirring an equimolar mixture of **1e**, MeHNOH.HCl and Et_3N, at room temperature in benzene under argon for 5h, afforded a 1.5:1 mixture of *N*-oxides **4a**, in excellent yield. *N*-Oxides **4a** are the products of a formal retro-Cope elimination reaction of the intermediate α-hydroxy-hydroxylamine.[13] The major isomer of **4a** was obtained in pure form by column chromatography. Next, we used a completely different base/solvent system in order to achieve the cycloaddition process. Thus, reaction of **1e** (1 mmol) with MeHNOH.HCl (3 mmol) and Na_2CO_3 (3 mmol) in methanol, at room temperature under argon for 24 h, gave a quantitative yield of an isomeric mixture of fused adduct **2b** and bridged isoxazolidine **3d** in a 1.5:1 ratio, respectively (Scheme 2). The ring size (by DEPT,

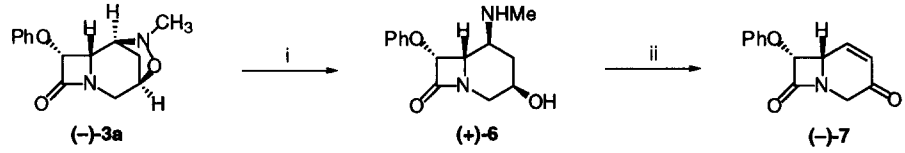
HETCOR, and COSY) and the stereochemistry (by vicinal proton couplings and NOE experiments) of compounds **2-4** were established by NMR mono- and two-dimensional techniques.[14]



Key: i) MeNHOH-HCl (1 equiv.), Et_3N, C_6H_6, rt. ii) MeNHOH-HCl (1 equiv.), Na_2CO_3, MeOH, rt.

Scheme 2

The above results clearly show that intramolecular nitrone-alkene cycloaddition is an effective process for rapid access to polycyclic β-lactams starting from 2-azetidinone-tethered alkenylaldehydes. Finally, some simple transformations were carried out on selected bridged tricyclic β-lactams **3** (Scheme 3) to test their viability as intermediates in the synthesis of other highly functionalized bicyclic systems. Thus, reductive cleavage of the N-O bond in compound **3a** with Zn (10 equiv.) in 50% aqueous HOAc[15] gave, after heating for 24 h, the 1-amino-3-hydroxy-carbacepham **6** (80%, pure product), not affecting the configuration of the different stereocenters. In addition, treatment of compound **6** with Swern reagent[16] afforded 3-oxo-carbacephem **7** in an almost quantitative yield, through a tandem oxidation-elimination process.[17]



Key: i) Zn (10 equiv.), 50% aqueous HOAc, Δ, 24h. ii) $COCl_2$, DMSO, Et_3N, –78°C.

Scheme 3

The above transformations demonstrate the utility of the reported methodology for the elaboration of highly functionalised enantiopure bicyclic β-lactam systems relevant to the synthesis of antibiotics. Further aspects of this chemistry will be reported in due course.

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6. INAC reactions of aliphatic 2-substituted 5-hexenyl and 5-heptenyl nitrones have been successfully used for the synthesis of key monocyclic intermediates of 1β-methylthienamycin. A notable feature of such processes is their propensity for the predominant formation of the fused bicyclic systems as opposed to the bridged systems. See, for example: a) Kang, S. H.; Kim, W. J. *Synlett.* **1991**, 520. b) Kang, S. H.; Lee, H. S. *Tetrahedron Lett.* **1995**, *36*, 6713. b) Junk, M. E.;Vu, B. T. *J. Org. Chem.* **1996**, *61*, 4427.
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10. Crystal data: **(–)-3a**, C14H16N2O3, M = 260.29, orthorhombic, space group $P2_12_12_1$, a = 11.2110 (10); b = 16.881 (2); c = 6.7730 (10) A; a = b = g = 90°; V = 1281.8 93) A^3; Z = 4; cd = 1.349 Mg/m^{-3}; ac = 0.79 mm^{-1}; F(000) = 552. A colourless crystal of 0.66x0.16x0.16 mm was used. 1210 independent reflections were collected on four circle Seifert XRD 3000S difractometer. The structure was solved by direct methods (SIR92 and difference Fourier techniques; not absorption correction was applied (m = 0.79 mm-1); all calculations were done with the program SHELX97 on a VAX 6410 computer. The structure was refined using full matrix least-squares procedures. Coordinates have been deposited at the Cambridge Crystallographic Data Centre.

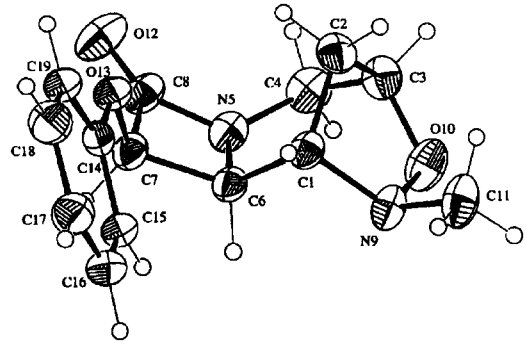

Figure. Crystal structure of **(–)-3a**

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13. See, for example: a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.*, **1976**, *41*, 855. b) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.;Petrzilka, M. *Tetrahedron Lett.* **1979**, 4391. c) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. d) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929. e) Ciganek, E.; Read, J. M.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795. f) Davison, E. C.; Forbes, I. T.; Holmes, A. B.; Warner, J. A. *Tetrahedron* **1996**, *52*, 11601.Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8549 and other references cited therein.
14. The salient features which distinguished between the two regioisomers (**2a** and **3a**, for example) was the presence, in the NMR spectrum of compound **2a**, of a highfield one proton multiplet at δ(H) 2.78 coupled to five other protons and a methine carbon signal at δ(C) 37.8 (DEPT), which would be expected for the C-8 methine in the fused structure **2a**. Also, this compound showed two methylene carbon resonances at δ(C) 60.8 and 68.6 (DEPT) attributable to two oxygen substituted methylene carbons. Compound **3a** displayed a highfield geminally coupled (12.7 Hz) proton signals at δ(H) 2.40 (m) and 1.92 (d), and a methylene carbon resonance at δ(C)28.5 (DEPT), and was consistent with its bridged structure.
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