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New Synthesis of Fused Tricyclic 2-Azetidinones Using Stereoselective Allylation of *cis*-4-Formyl-β-lactams and Intramolecular Diels-Alder Reaction

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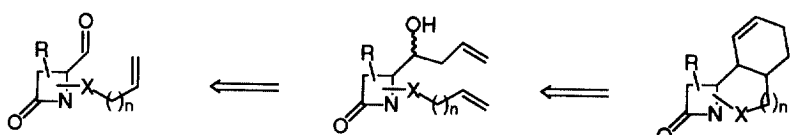
Abstract: Tin(IV) chloride promoted addition of allyltrimethylsilane to *cis*-4-formyl-2-azetidinones **1** gives 4-[(1'-hydroxy)homoallyl]-β-lactams **2** with excellent stereoselectivities. The mesylates of alcohols **2** are used for the diastereoselective preparation of both 4-butadienyl-2-azetidinones **6** and fused tricyclic β-lactams **3** through a tandem one-pot elimination-intramolecular Diels-Alder reaction.

The intramolecular Diels-Alder reaction (IMDA) is a powerful method for the construction of bicyclic and polycyclic systems.[1] On the other hand, the Lewis acid promoted addition of allylsilanes and allylstannanes to chiral aldehydes is now a well-established methodology and an important synthetic tool.[2] Recently, the trinem antibiotics have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidases.[3] As a result of their impressive biological activity, polycyclic β-lactams have become interesting targets for synthesis.[4] Continuing with our work on the synthesis and synthetic applications of chiral, functionalized 2-azetidinones,[4a,d,e, 5] we wish to report here a new, straightforward synthesis of different types of fused tricyclic β-lactams which involves the use of both stereoselective allylation of β-lactam aldehydes and its IMDA reaction (Scheme 1).



1 **2** **3**

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

Scheme 1

The starting substrates, *cis*-4-formyl-β-lactams **1**, were prepared both in the racemic form and in optically pure form using standard methodology. Racemic compounds **1a, 1b** and **1d** were obtained as single *cis*-diastereoisomers, following our one-pot method from *N,N*-di-(*p*-methoxyphenyl)glyoxal diimine.[6] Enantiopure 2-azetidinones **1c, 1e** and **1f** were obtained from imines of (*R*)-2,3-*O*-isopropylidenepropanal, through Staüdinger reactions with the corresponding acid chlorides in the presence of Et_3N as single *cis*-

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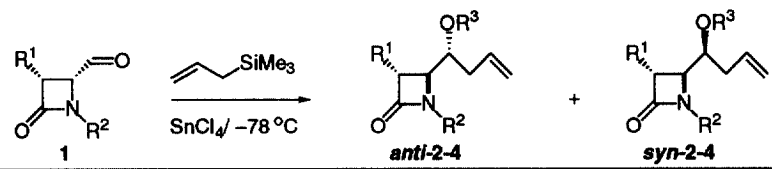
enantiomers.[7] First, we studied the tin(IV) chloride promoted reactions of *cis*-4-formyl-β-lactams **1** with some propenylmetal reagents. Reaction of *cis*-4-formyl-β-lactams **1** with allyltrimethylsilane at –78 °C for 45 minutes gave the homoallylic alcohols **2** with good to excellent *anti*-stereoselectivities (d.e. 80-100%, by ^{1}H NMR spectroscopy of the crude reaction mixtures). The configurations at the carbinolic stereocenters of the major products **(+)-2c** and **(+)-2e** were established by comparison of the ^{1}H NMR chemical shifts of acetylmandelates **(+)-3c**, **(+)-4c** and **(+)-3e**, **(+)-4e**,[8] and were assumed to be the same for the rest of the β-lactams **2**. The stereochemical result can be tentatively interpreted in terms of chelation of the tin(IV) chloride by the oxygen of the aldehyde, with participation of the carbonyl oxygen of the β-lactam ring, the allyl group being delivered from the less hindered face.

Table 1. Tin(IV) chloride mediated allylation of *cis*-4-formyl-β-lactams **1** with allyltrimethylsilane.



1 **anti-2-4** **syn-2-4**

Comp	R^1	R^2	R^3	*anti:syn* ratio	Yield(%)[a]
2a	CH_3	PMP[b]	H	92:8	79
2b	allyl	PMP	H	100:0	60
(+)-2c	*O*-allyl	PMP	H	95:5	71
(+)-3c	*O*-allyl	PMP	(*R*)-PhCH(OAc)		77
(+)-4c	*O*-allyl	PMP	(*S*)-PhCH(OAc)		68
2d	propargyl	PMP	H	95:5	66
(+)-2e	OCH_3	PMP	H	90:10	85
(+)-3e	OCH_3	PMP	(*R*)-PhCH(OAc)		88
(+)-4e	OCH_3	PMP	(*S*)-PhCH(OAc)		79
(+)-2f	OBn	homoallyl	H	100:0	54

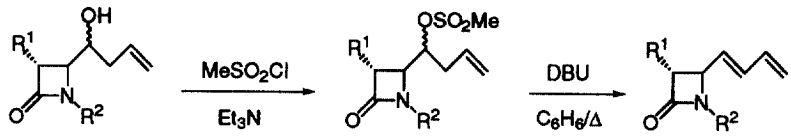
[a] Yield of pure, isolated product with correct analytical and spectral data. [b] PMP = 4-$MeOC_6H_4$.

In addition to the above allylation reaction, prop-2-enyl(tributyl)stannane is transmetallated by tin(IV) chloride to generate allyltin trichloride[9] which reacts with aldehydes **1** with modest levels of asymmetric induction (*ca.* 75 : 25) and similar overall yields.

Next, we investigated the dehydration of the hydroxy-β-lactams **2** to the 4-butadienyl derivatives **6**. Compounds **2** were transformed, in very good yields, into the mesylates **5** by treatment with mesyl chloride in the presence of Et_3N. Finally, mesylates **5** stereoselectively gave the novel conjugated dienes **6**[10] by gentle heating in benzene or toluene in the presence of DBU. The *trans*-geometry of the double bonds in these compounds was consistent with vinylic coupling constants of *ca.* 16.5 Hz in their ^{1}H NMR spectra (Table 2).

Interestingly, mesylates **5** having an extra alkene tether at positions 1 or 3 of the β-lactam ring, on heating in a sealed tube with equimolecular amounts of DBU in toluene, yielded the corresponding Diels-Alder cycloadducts **3**. These adducts were obtained in good to excellent yields (50-88%) with reasonable levels of

Table 2. Stereoselective preparation of mesylates **5** and conjugated dienes **6**.

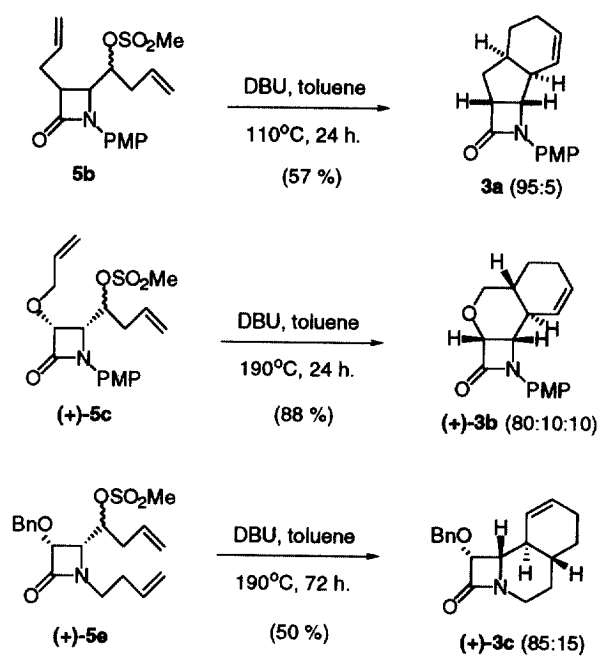


2 **5** **6**

Comp	R^1	R^2	Ratio *E*:*Z*	Yield(%) [a]
5a	CH_3	PMP[b]		97
5b	allyl	PMP		82
(+)-5c	*O*-allyl	PMP		92
5d	propargyl	PMP		83
(+)-5e	OBn	homoallyl		89
6a	CH_3	PMP	100:0	75
6b	allyl	PMP	75:25	74
(+)-6c	*O*-allyl	PMP	100:0	89
6d	propargyl	PMP	100:0	58
(+)-6e	OBn	homoallyl	95:5	66

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] PMP = 4-$MeOC_6H_4$.

stereoselectivity [88 (±7) : 12 (±7)] (Scheme 2; only major isomer for adducts **3** is represented). This stereoselectivity is not affected significantly by the nature of the substituents on the β-lactam ring. However, reactions at lower temperatures are more stereoselective. Thus, for example, the adduct **3a** accounted for an excellent (95%) yield of the products formed when the reaction was conducted in toluene at reflux. The stereochemistries of the compounds **3** were established by nOe experiments and the values of coupling constants in their ^1H NMR spectra. The cycloadducts were characterised as mixtures of diastereoisomers, except for **3a** that could be separated by flash chromatography. By contrast, treatment of some of dienes **6** with Lewis acids (Et_2AlCl and $SnCl_4$) failed to give the corresponding IMDA compounds, unreacted starting material being recovered in all cases.



Scheme 2

These results show that both the allylation of β-lactam aldehydes and tandem elimination/intramolecular Diels-Alder reaction are diastereoselective processes which can be used for the functionalisation of monocyclic 2-azetidinones and for the preparation of fused tricyclic 2-azetidinones from simple monocyclic precursors. Furthermore, as far as we know, these are the first examples of intramolecular Diels-Alder reactions of 2-azetidinone-tethered trienes, as well as the first stereoselective allylation of *cis*-4-formyl-2-azetidinones. Other aspects of this chemistry are under investigation, and full details will be reported in due course.

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