

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

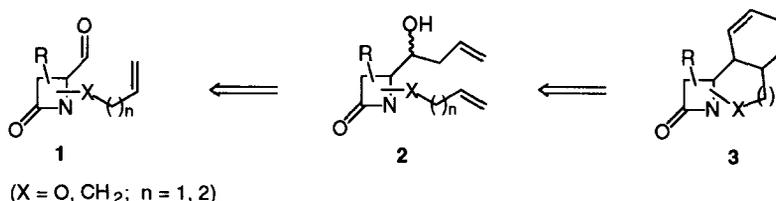
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**Abstract:** Tin(IV) chloride promoted addition of allyltrimethylsilane to *cis*-4-formyl-2-azetidiones **1** gives 4-[(1'-hydroxy)homoallyl]- $\beta$ -lactams **2** with excellent stereoselectivities. The mesylates of alcohols **2** are used for the diastereoselective preparation of both 4-butadienyl-2-azetidiones **6** and fused tricyclic  $\beta$ -lactams **3** through a tandem one-pot elimination-intramolecular Diels-Alder reaction. © 1999 Elsevier Science Ltd. All rights reserved.

The intramolecular Diels-Alder reaction (IMDA) is a powerful method for the construction of bicyclic and polycyclic systems.<sup>1</sup> 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.<sup>2</sup> Recently, the trinem antibiotics have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to  $\beta$ -lactamases and stability to renal dehydropeptidases.<sup>3</sup> As a result of their impressive biological activity, polycyclic  $\beta$ -lactams have become interesting targets for synthesis.<sup>4</sup> Continuing with our work on the synthesis and synthetic applications of chiral, functionalized 2-azetidiones,<sup>4a,d,e, 5</sup> we wish to report here a new, straightforward synthesis of different types of fused tricyclic  $\beta$ -lactams which involves the use of both stereoselective allylation of  $\beta$ -lactam aldehydes and its IMDA reaction (Scheme 1).



Scheme 1

The starting substrates, *cis*-4-formyl- $\beta$ -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.<sup>6</sup> Enantiopure 2-azetidiones **1c**, **1e** and **1f** were obtained from imines of (*R*)-2,3-*O*-isopropylidenepronal, through Staudinger reactions with the corresponding acid chlorides in the presence of Et<sub>3</sub>N as single *cis*-

enantiomers.<sup>7</sup> First, we studied the tin(IV) chloride promoted reactions of *cis*-4-formyl- $\beta$ -lactams **1** with some propenylmetal reagents. Reaction of *cis*-4-formyl- $\beta$ -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  $^1\text{H}$  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  $^1\text{H}$  NMR chemical shifts of acetylmandelates (+)-**3c**, (+)-**4c** and (+)-**3e**, (+)-**4e**,<sup>8</sup> and were assumed to be the same for the rest of the  $\beta$ -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  $\beta$ -lactam ring, the allyl group being delivered from the less hindered face.

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

Comp	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	<i>anti</i> : <i>syn</i> ratio	Yield(%) <sup>a</sup>
<b>2a</b>	CH <sub>3</sub>	PMP <sup>b</sup>	H	92:8	79
<b>2b</b>	allyl	PMP	H	100:0	60
(+)- <b>2c</b>	<i>O</i> -allyl	PMP	H	95:5	71
(+)- <b>3c</b>	<i>O</i> -allyl	PMP	( <i>R</i> )-PhCH(OAc)		77
(+)- <b>4c</b>	<i>O</i> -allyl	PMP	( <i>S</i> )-PhCH(OAc)		68
<b>2d</b>	propargyl	PMP	H	95:5	66
(+)- <b>2e</b>	OCH <sub>3</sub>	PMP	H	90:10	85
(+)- <b>3e</b>	OCH <sub>3</sub>	PMP	( <i>R</i> )-PhCH(OAc)		88
(+)- <b>4e</b>	OCH <sub>3</sub>	PMP	( <i>S</i> )-PhCH(OAc)		79
(+)- <b>2f</b>	OBn	homoallyl	H	100:0	54

<sup>a</sup> Yield of pure, isolated product with correct analytical and spectral data. <sup>b</sup> PMP = 4-MeOC<sub>6</sub>H<sub>4</sub>.

In addition to the above allylation reaction, prop-2-enyl(tributyl)stannane is transmetallated by tin(IV) chloride to generate allyltin trichloride<sup>9</sup> 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- $\beta$ -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<sub>3</sub>N. Finally, mesylates **5** stereoselectively gave the novel conjugated dienes **6**<sup>10</sup> 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  $^1\text{H}$  NMR spectra (Table 2).

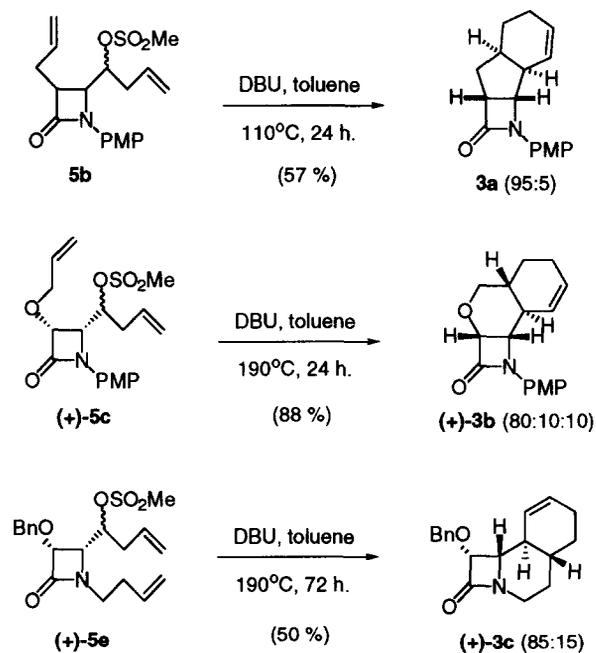
Interestingly, mesylates **5** having an extra alkene tether at positions 1 or 3 of the  $\beta$ -lactam ring, on heating in a sealed tube with equimolecular amounts of DBU in toluene, yielded the corresponding Diels-Alder cycloadducts **3**. These adducts were obtained in good to excellent yields (50-88%)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

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

Comp	R <sup>1</sup>	R <sup>2</sup>	Ratio <i>E</i> : <i>Z</i>	Yield(%) <sup>a</sup>
<b>5a</b>	CH <sub>3</sub>	PMP <sup>b</sup>		97
<b>5b</b>	allyl	PMP		82
(+)- <b>5c</b>	<i>O</i> -allyl	PMP		92
<b>5d</b>	propargyl	PMP		83
(+)- <b>5e</b>	OBn	homoallyl		89
<b>6a</b>	CH <sub>3</sub>	PMP	100:0	75
<b>6b</b>	allyl	PMP	75:25	74
(+)- <b>6c</b>	<i>O</i> -allyl	PMP	100:0	89
<b>6d</b>	propargyl	PMP	100:0	58
(+)- <b>6e</b>	OBn	homoallyl	95:5	66

<sup>a</sup> Yield of pure, isolated product with correct analytical and spectral data. <sup>b</sup> PMP = 4-MeOC<sub>6</sub>H<sub>4</sub>.

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 <sup>1</sup>H 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<sub>2</sub>AlCl and SnCl<sub>4</sub>) 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  $\beta$ -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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## References and Notes

- For reviews of the IMDA reaction, see for example: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991, Vol. 5, p 513. (d) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187 (d) Ciganek, E. *Org. React.* **1984**, *32*, 1. (e) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.
- (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991, Vol. 2, p 1. (c) Fleming, I., in *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991, Vol. 2, p 595.
- Recent examples on the application of cyclization reactions to trinem and trinem derivatives synthesis: (a) Camerini, R.; Donati, D.; Marchioro, C.; Mazzoni, A.; Pachera, R.; Panunzio, M. *Tetrahedron: Asymmetry*, **1997**, *8*, 15. (b) Di Fabio, R.; Rossi, T.; Thomas, R.J. *Tetrahedron Lett.* **1997**, *38*, 3587. (c) Marchioro, C.; Pentassuglia, G.; Perboni, A.; Donati, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 463. (d) Rossi, T.; Marchiro, C.; Paio, A.; Thomas, R.J.; Zarantonello, P. *J. Org. Chem.* **1997**, *62*, 1653. (e) Hanessian, S.; Griffin, A.M.; Rozema, M.J. *BioMed. Chem. Lett.* **1997**, *7*, 1857. (f) Guiron, C.; Rossi, T.; Thomas, R.J. *Tetrahedron Lett.* **1997**, *20*, 3569. (g) Hanessian, S.; Rozema, M.J. *J. Am. Chem. Soc.* **1996**, *118*, 9884.
- For recent references, see: (a) Alcaide, B.; Rodríguez-Vicente, *Tetrahedron Lett.* **1998**, *39*, 6589. (b) A. Sakya, S.M.; Strohmeyer, T.W.; Lang, S.A.; Lin, Y-I *Tetrahedron Lett.* **1997**, *38*, 5913. (c) Annibal, A.D.; Pesce, A.; Resta, S.; Irogolo, C.T.; *Tetrahedron* **1997**, *53*, 13129. (d) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125. (e) Alcaide, B.; Polanco, C.; Sáez, E.; Sierra, M. A. *Tetrahedron Lett.* **1996**, *38*, 6901. (f) Banik, B. K.; Gottumukkala, V.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1996**, *37*, 1363. (g) Chuansheng, N.; Pettersson, T.; Miller, M.J. *J. Org. Chem.* **1996**, *61*, 1014. (h) Gilchrist, T.L.; Graham, K. *Tetrahedron Lett.* **1995**, *47*, 8693.
- See, for instance: (a) Alcaide, B.; Rodríguez-Vicente, A.; Sierra, M. A. *Tetrahedron Lett.* **1998**, *39*, 163. (b) Alcaide, B.; Aly, M. F.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 8819. (c) Alcaide, B.; Martín-Cantalejo, Y.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 9156.
- (a) Alcaide, B.; Martín-Cantalejo, Y.; Plumet, J.; Rodríguez-López, J.; Sierra, M. A. *Tetrahedron Lett.*, **1991**, *32*, 803. (b) Alcaide, B.; Martín-Cantalejo, Y.; Pérez-Castells, J.; Rodríguez-López, J.; Sierra, M. A.; Monge, A.; Pérez-García, V. *J. Org. Chem.*, **1992**, *57*, 5921.
- See, for instance: (a) Palomo, C.; Aizpurua, J. M.; Mielgo, A.; Linden, A. *J. Org. Chem.* **1996**, *61*, 9186. (b) Welch, J. T.; Araki, K.; Kaweck, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454. (c) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227. (d) Hubschwerelen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206.
- See, for example: (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovic, J. M.; Balwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (b) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.*, **1998**, *120*, 877.
- (a) McNeill, A. H.; Thomas, E. J. *Synthesis*, **1994**, 322. (b) Almendros, P.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2561.
- For a different synthesis of related 3-butadienyl- $\beta$ -lactams, see: Sharma, A. K.; Mazumdar, S. N.; Mahajan, M. P. *J. Org. Chem.* **1996**, *61*, 5506.