## AN ASYMMETRIC SYNTHESIS OF A 3-HYDROXY-β-LACTAM BY KETENE-IMINE CYCLOADDITION: UTILIZATION OF CHIRAL KETENES FROM CARBOHYDRATES

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**Abstract:** The Staudinger reaction of a chiral carbohydrate-based ketene and an imine proceeds to give, after removal of the sugar, cis-3-hydroxy- $\beta$ -lactam 7 in moderate yield with good asymmetric induction (70% e.e.).

A recent publication of a  $\beta$ -lactam synthesis utilizing a sugar-based chiral auxilliary in a vinyl ether-isocyanate reaction<sup>2</sup> has prompted us to disclose our initial work on asymmetric  $\beta$ -lactam formation using the Staudinger reaction. As we had a need for chiral *trans*-3-amino- $\beta$ -lactams, we thought that a suitable precursor would be the *cis*-3-hydroxy- $\beta$ -lactams, as the Staudinger reaction provides easy access to the *cis* compounds. The 3-hydroxy- $\beta$ -lactams could then be elaborated *via* tosylation and displacement with the azide ion.<sup>3</sup> Evans and Sjogren have demonstrated<sup>4</sup> that  $\beta$ lactams can be formed with excellent asymmetric induction through the use of chiral oxazolidinonesubstituted ketenes. Therefore, carbohydrates with the appropriate substitution at the anomeric carbon seemed to be ideal chiral ketenes for the formation of 3-hydroxy- $\beta$ -lactams. We chose the substituted Dglucose derivative 1 as a model chiral ketene precursor. This could be prepared easily from tri-Oacetyl-D-glucal according to Scheme 1.



The reaction of tri-O-acetyl-D-glucal 2 with the protected glycolic acid 3 and  $BF_3 \bullet Et_2O$  gave a 7:3 anomeric mixture of 4 with the  $\alpha$  form predominating.<sup>5</sup> The anomers were easily separated by column chromatography to give pure 4 (30%).<sup>6</sup> Subsequent hydrogenolysis of the benzyl ester and reduction of the double bond gave the required chiral ketene precursor 1 in 99% yield. The carboxylic acid 1 was converted to the acid chloride [(COCl)<sub>2</sub>/cat. DMF]. Addition of 1.5 eq. triethylamine, followed by the imine 5 (Scheme 2), gave the crude  $\beta$ -lactam 6.<sup>7</sup>



Deprotection of the chiral auxilliary using 4:1:1 THF/H<sub>2</sub>O/HOAc gave, after chromatography, the 3hydroxy- $\beta$ -lactam 7 as a mixture of enantiomers in 52% yield.<sup>8</sup> The enantiomeric excess was determined to be 70% by chiral HPLC of the 3,5-dinitrobenzoate.<sup>9</sup> The absolute configuration was proved to be *cis*- $\alpha$ , $\alpha$  {[ $\alpha$ ]<sub>D</sub>=+163° (c 0.01, MeOH)} by comparison of optical rotations with an authentic sample of the *cis*- $\beta$ , $\beta$  enantiomer {[ $\alpha$ ]<sub>D</sub>=-237° (c 0.01, MeOH)}.<sup>10</sup>

This result indicates the potential of carbohydrate-based chiral auxilliaries for the asymmetric synthesis of 3-hydroxy- $\beta$ -lactams.

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References and Notes:

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- 6. All new compounds gave consistent spectral and analytical/mass spectrometric data.
- 7. See reference 4 for reaction conditions.
- m.p. 157-160°C.; [α]<sub>D</sub> +163° (c 0.01, MeOH); Rf 0.36 (petrol-EtOAc, 1:1); IR (CHCl<sub>3</sub>) 3334, 1734 cm<sup>-1</sup>; <sup>δ</sup>H (400 MHz, CDCl<sub>3</sub>) 3.74 (4 H, s, OCH<sub>3</sub> and OH), 4.80 (1 H, dd, J 5.2, 7.9 Hz), 5.13 (1 H, d, J 5.2 Hz), 6.39 (1 H, dd, J 7.9, 16.0 Hz), 6.79 (3 H, m), 7.33 (7 H, m); <sup>δ</sup>C (100 MHz, CDCl<sub>3</sub>) 55.45, 61.67, 77.23, 114.37, 118.87, 123.13, 126.83, 128.36, 128.66, 130.92, 135.88, 136.56, 156.51, 166.37; (Found: C, 72.81; H, 5.85; N, 4.72. C<sub>18</sub>H<sub>17</sub>NO<sub>3</sub> requires C, 73.20; H, 5.80; N, 4.74%).
- Pirkle D-naphthylalanine column using 20% 2-propanol in n-hexane as eluent; see Pirkle, W. H.; Pochapsky, T. C. J. Am. Chem. Soc. 1986, 352.
- 10. The authentic cis- $\beta$ , $\beta$  enantiomer was prepared via a compound derived from the method of Evans and Sjogren.<sup>4</sup>

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