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## Enantioselective Intramolecular C-H Insertion Route to a Key Intermediate for the Synthesis of Trinem Antibiotics

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## Abstract

A new route to the enantiomerically pure azetidin-2-one 3, a key intermediate for the synthesis of trinems, has been developed, incorporating enantioselective intramolecular C-H insertion of  $\alpha$ -methoxycarbonyl- $\alpha$ -diazoacetamide catalyzed by chiral Rh(II) complexes and diastereoselective arene hydrogenation as the key steps. The use of dirhodium(II) tetrakis[N-phthaloyl-(S)-tert-leucinate] as a catalyst produced the desired azetidinone in 84% ee, whereas catalysis with dirhodium(II) tetrakis[N-phthaloyl-(S)-alaninate] afforded its enantiomer in 84% ee.  $\bigcirc$  1998 Elsevier Science Ltd. All rights reserved.

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The ongoing challenge of bacterial resistance to existing chemotherapeutic drugs provides a constant driving force for the discovery and development of novel antibacterial compounds. In this respect, the discovery of a new family of synthetic  $\beta$ -lactam antibiotics, the trinems of general structure 1, by scientists at Glaxo Wellcome Laboratories is a notable recent landmark. Sanfetrinem (GV104326) **2a** and its metabolically labile ester **2b** in this class have shown excellent activity against a wide range of bacteria including  $\beta$ -lactamase producing strains and are currently in phase II clinical studies.<sup>1</sup> Due to their particular structure bearing five stereogenic centers as well as the large amount of final drug material required to support development studies, they have also presented a considerable synthetic challenge. While most of the reported syntheses rely on condensation of commercially available (1'*R*,3*R*,4*R*)-4-acetoxy-3-[1'-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one with properly designed cyclohexenylmetals<sup>2</sup> or metal enolates of 2-methoxycyclohexanone,<sup>3</sup> an alternative route to **2** involving the [2+2] cycloaddition between *N*-trimethylsilylimine derived from (1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-ethoxycarbonylcyclohexane and the lithium enolate of *tert*-butyl acetate has recently been developed.<sup>4</sup> Recently, we reported a highly enantioselective construction of 3-oxa-1-azabicyclo[4.2.0]octanes by intramolecular C-H insertion of  $\alpha$ -



methoxycarbonyl- $\alpha$ -diazoacetamides catalyzed by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-alaninate], Rh<sub>2</sub>(*S*-PTA)<sub>4</sub>, which lead to the key azetidin-2-ones for the synthesis of 1-unsubstituted and 1 $\beta$ -methylcarbapenem antibiotics.<sup>5</sup> In continuation of our work on the enantioselective synthesis of nitrogen-containing heterocycles,<sup>6</sup> we now report a new route to the key intermediate **3** for the synthesis of **2**, wherein the key steps involve enantioselective intramolecular C-H insertion and diastereoselective arene hydrogenation.

The azetidinone 3 has been well demonstrated to serve as a key synthetic intermediate to 2 and their analogues,<sup>1,7</sup> since a regiocontrolled formation of olefin or enol phosphate from 3 could be followed by an amide-directed stereocontrolled epoxidation and subsequent regiocontrolled epoxide ring-opening with nucleophiles to produce the advanced intermediate for the elaboration of the target molecule. On the basis of our recent finding that a tetrahydro-1,3-oxazine ring tethered to  $\alpha$ -methoxycarbonyl- $\alpha$ -diazoacetamides plays a role not only as a protecting group for amine and alcohol groups but also as a rigid template for controlling enantioselectivity during the Rh(II)-catalyzed intramolecular C-H insertion,<sup>5</sup> we selected *N*,*O*-cyclohexylidene acetal **6** as an ideal carbene precursor (Scheme 1). Consequently, enantiocontrol in the C-H insertion as well as diastereocontrol in hydrogenation of the benzene ring to create a stereogenic center at C8 (trinems numbering) was crucial to the success of our scenario.

The requisite  $\alpha$ -methoxycarbonyl- $\alpha$ -diazoacetamide **6** was uneventfully prepared from salicylamine (4)<sup>8</sup> by condensation with cyclohexanone followed by *N*-acylation with methyl malonyl chloride and subsequent diazo transfer. We initially explored cyclization of **6** with the aid of 5 mol % of Rh<sub>2</sub>(S-PTA)<sub>4</sub> (Table 1, entries 1-3). The reaction in CH<sub>2</sub>Cl<sub>2</sub> proceeded sluggishly to give the 3,4-*trans*-azetidin-2-one derivative (-)-7,  $[\alpha]_D^{25}$ -12.3 (*c* 0.95, CHCl<sub>3</sub>), in 62% yield. The enantioselectivity in this reaction was determined to be 41% ee by <sup>1</sup>H NMR spectroscopy using Eu(hfc)<sub>3</sub> as a chiral shift reagent. After screening of solvents, toluene was found to enhance the cyclization rate to give (-)-7 in 60% yield and 70% ee. Furthermore, lowering the reaction temperature to 0 °C enhanced the enantioselectivity to 84% ee. At this stage, we attempted to transform (-)-7 of 84% ee,  $[\alpha]_D^{25}$ -23.4 (*c* 1.10, CHCl<sub>3</sub>), to the known azetidin-2-one **9**, a synthetic intermediate of 10-ethyl trinem,<sup>4</sup>c in order to determine the preferred absolute configuration at the



Scheme 1.

Entry	Rh(II) catalyst	Solvent	Temp, °C	Time, h	Azetidin-2-one		
						Yield, %	Ee, % <sup>b</sup>
1	Rh <sub>2</sub> (S-PTA) <sub>4</sub>	CH <sub>2</sub> Cl <sub>2</sub>	25	120	(-)-7	62	41
2	Rh <sub>2</sub> (S-PTA) <sub>4</sub>	toluene	25	72	(-) <b>-7</b>	60	70
3	Rh <sub>2</sub> (S-PTA) <sub>4</sub>	toluene	0	96	(-)-7	71	84
4	Rh <sub>2</sub> (S-PTPA) <sub>4</sub>	toluene	0	96	(-)- <b>7</b>	51	83
5	Rh <sub>2</sub> (S-PTV) <sub>4</sub>	toluene	0	96	(~)-7	56	45
6	Rh <sub>2</sub> (S-PTPG) <sub>4</sub>	toluene	0	72	(-)-7	78	10
7	Rh <sub>2</sub> (S-PTTL) <sub>4</sub>	toluene	0	96	(+)-7	66	84

Table 1. Enantioselective Intramolecular C-H Insertion of α-Diazoacetamide 6 Catalyzed by Chiral Rh(II) Complexes<sup>a</sup>

<sup>*a*</sup> Reactions were carried out as follows: 5 mol % of the catalyst was added to a stirred solution of  $\alpha$ -diazo amide 6 (1 mmol) in anhydrous solvent (5 mL) under argon. <sup>*b*</sup> Determined by <sup>1</sup>H NMR analysis using Eu(hfc)<sub>3</sub> as a chiral shift reagent.

insertion site. Reduction of (-)-7 with LiBH<sub>4</sub> was followed by hydrogenation promoted by RhCl<sub>3</sub>methyltrioctylammonium chloride (Aliquat<sup>®</sup>-336)<sup>9</sup> and subsequent oxidation with the Dess-Martin periodinane to give aldehyde (+)-8,  $[\alpha]_D^{25}$  +13.2 (*c* 1.01, CHCl<sub>3</sub>), in 51% yield. Sequential methylenation<sup>10</sup> and hydrogenation followed by protective group interchange afforded (-)-9,  $[\alpha]_D^{25}$ -13.2 (*c* 1.28, CHCl<sub>3</sub>) [lit.,<sup>4c</sup>  $[\alpha]_D^{25}$  +16 (*c* 0.49, CHCl<sub>3</sub>) for the known intermediate], in 58% yield. Thus, the chemical correlation disclosed that the present insertion reaction occurred predominantly at the C-H bond enantiomeric to that we expected from the previous result.<sup>5</sup> However, it should be noted that the crucial hydrogenation of the benzene ring catalyzed by the solvated ion pair [(C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>NCH<sub>3</sub>]<sup>+</sup>[RhCl<sub>4</sub>]<sup>-</sup> proceeded stereoselectively from the same side as the hydroxymethyl group, suggesting the chelation effect of the hydroxy group.

Thus, we next screened other chiral dirhodium(II) carboxylates,  $Rh_2(S-PTPA)_4$ ,  $Rh_2(S-PTV)_4$ ,  $Rh_2(S-PTPG)_4$ , and  $Rh_2(S-PTTL)_4$ , derived from N-phthaloyl-(S)-phenylalanine, valine, phenylglycine, and *tert*-leucine, respectively (Table 1, entries 4-7). To our great surprise,  $Rh_2(S-PTTL)_4$  proved to be the only catalyst for achieving the desired sense of enantioselection as well as the highest enantioselectivity (84% ee), whereas catalysis of **6** with the aid of the other dirhodium(II) complexes provided the undesired (3S,4R)-azetidinone (-)-**7** as with the case of  $Rh_2(S-PTA)_4$ . While the effects of bridging ligands on the sense and magnitude of enantioselection have yet to be elucidated, it is worthy of note that a decrease in enantioselectivity was observed on increasing the steric bulk of the substituent (methyl  $\simeq$  benzyl < isopropyl < phenyl),<sup>11</sup> and that a dramatic reversal in enantioselection was observed with the exceptionally bulky *tert*-butyl group.<sup>12</sup>

With a facile access to (+)-7 of 84% ee secured, we proceeded to the elaboration of the target intermediate (Scheme 2). Fortunately, it was found that this amorphous material crystallized by a laborious trituration. One recrystallization from  $iPr_2O$ -hexane produced the optically pure sample, mp 96-97 °C,  $[\alpha]_D^{25}$  +27.6 (*c* 1.53, CHCl<sub>3</sub>), which was transformed to aldehyde (-)-8,  $[\alpha]_D^{25}$  -15.0 (*c* 1.68, CHCl<sub>3</sub>), under the foregoing conditions. Alkylation of (-)-8 with Me<sub>3</sub>Al<sup>16</sup> followed by oxidation with the Dess-Martin periodinane and stereocontrolled reduction with K-Selectride<sup>®17</sup> produced alcohol **10**,  $[\alpha]_D^{25}$  +6.53 (*c* 1.73, CHCl<sub>3</sub>), in 63% yield. Protection of the hydroxy group with benzyl chloroformate and subsequent deblocking of the cyclohexylidene group was followed



Scheme 2. Reagents and conditions: (a) Trituration and recrystallization (Pr<sub>2</sub>O-hexane), 79%; (b) LiBH<sub>4</sub>, Scheme 2. Reagents and conditions: (a) Infutation and recrystatilization ( $Pr_{12}O$ -nexane), 79%; (b) L1BH<sub>4</sub>, THF, 0 °C, 2 h, 82%; (c) H<sub>2</sub>, cat. RhCl<sub>3</sub>-(C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>NMeCl, (CH<sub>2</sub>Cl)<sub>2</sub>-H<sub>2</sub>O, 25 °C, 38 h, 57%; (d) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 4 h, 91%; (e) Me<sub>3</sub>Al, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 83%; (f) Dess-Martin periodionane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 96%; (g) K-Selectride<sup>(a)</sup>, THF, 0 °C, 1.5 h, 79%; (h) BnO<sub>2</sub>CCl, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 3 %, 89%; (i) i. aq. AcOH, 70 °C, 6 h; ii. Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 91%; (j) i. H<sub>2</sub>, cat. Pd-C, EtOH, 0 °C, 1.5 h; ii. TBDMSCl, imidazole, DMF, 0 °C, 3 h, 91%.

by Dess-Martin oxidation to afford ketone 11,  $[\alpha]_D^{25}$  -32.2 (c 1.58, CHCl<sub>3</sub>), in 81% yield, which, upon protective group interchange, furnished the known intermediate 3,  $[\alpha]_D^{25}$  +33.9 (c 1.04, CH<sub>2</sub>Cl<sub>2</sub>) [lit., <sup>3d</sup>  $[\alpha]_D^{20}$  +33.9 (c 0.54, CH<sub>2</sub>Cl<sub>2</sub>)], in 91% yield.

In conclusion, we have developed a new, efficient and general method for the catalytic enantioselective synthesis of trinems. It is also worthy of note that either of the (+) and (-) enantiomers could be obtained by choosing Rh<sub>2</sub>(S-PTTL)<sub>4</sub> or Rh<sub>2</sub>(S-PTA)<sub>4</sub> as a chiral catalyst. Mechanistic and stereochemical studies on the present C-H insertion reaction are currently in progress.<sup>18</sup>

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