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

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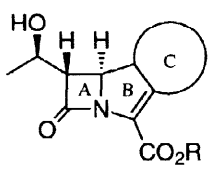
Abstract

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 α-methoxycarbonyl-α-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.

Keywords: antibiotics; insertion reactions; rhodium and compounds; enantioselection

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 β-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 β-lactamase producing strains and are currently in phase II clinical studies.[1] 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[2] or metal enolates of 2-methoxycyclohexanone,[3] 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.[4] Recently, we reported a highly enantioselective construction of 3-oxa-1-azabicyclo[4.2.0]octanes by intramolecular C-H insertion of α-



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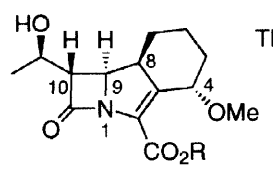
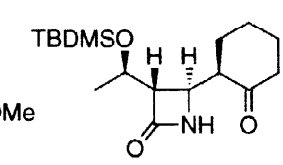


2a: R = Na (GV104326)
2b: R = $CH(Me)O_2COC_6H_{11}$



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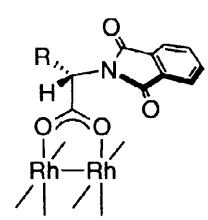

R = Bn: Rh_2(*S*-PTPA)$_4$
R = Me: Rh_2(*S*-PTA)$_4$
R = ^{i}Pr: Rh_2(*S*-PTV)$_4$
R = Ph: Rh_2(*S*-PTPG)$_4$
R = ^{t}Bu: Rh_2(*S*-PTTL)$_4$

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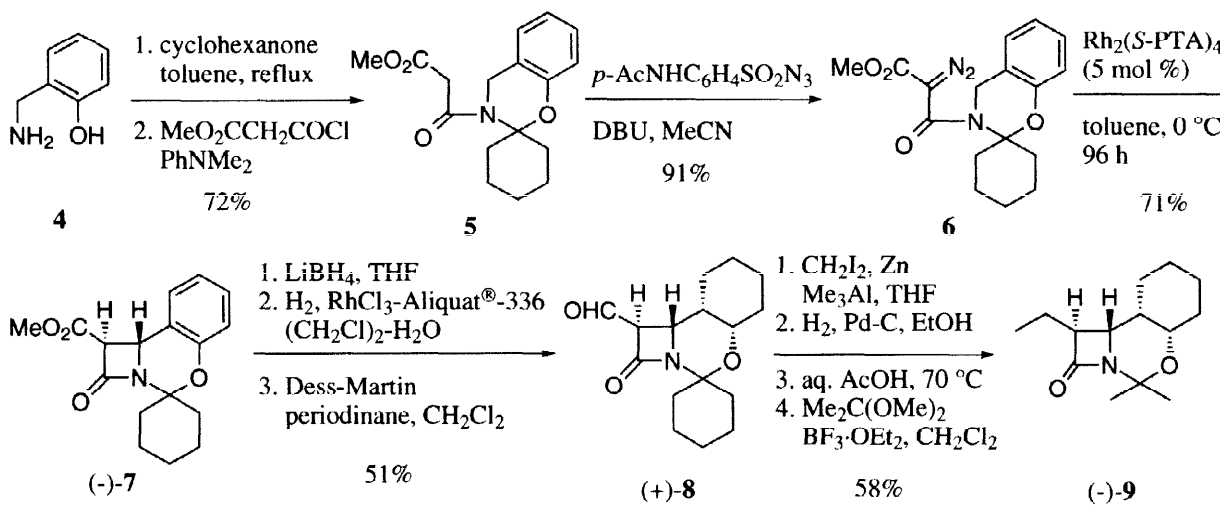
methoxycarbonyl-α-diazoacetamides catalyzed by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-alaninate], Rh_2(*S*-PTA)$_4$, which lead to the key azetidin-2-ones for the synthesis of 1-unsubstituted and 1β-methylcarbapenem antibiotics.[5] In continuation of our work on the enantioselective synthesis of nitrogen-containing heterocycles,[6] 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,[1,7] 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 α-methoxycarbonyl-α-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,[5] 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 α-methoxycarbonyl-α-diazoacetamide **6** was uneventfully prepared from salicylamine (**4**)[8] 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_2(*S*-PTA)$_4$ (Table 1, entries 1-3). The reaction in CH_2Cl_2 proceeded sluggishly to give the 3,4-*trans*-azetidin-2-one derivative (-)-**7**, $[\alpha]_D^{25}$ -12.3 (*c* 0.95, $CHCl_3$), in 62% yield. The enantioselectivity in this reaction was determined to be 41% ee by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ 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, $CHCl_3$), to the known azetidin-2-one **9**, a synthetic intermediate of 10-ethyl trinem,[4c] in order to determine the preferred absolute configuration at the



Scheme 1.

Table 1. Enantioselective Intramolecular C-H Insertion of α-Diazoacetamide **6** Catalyzed by Chiral Rh(II) Complexes[a]

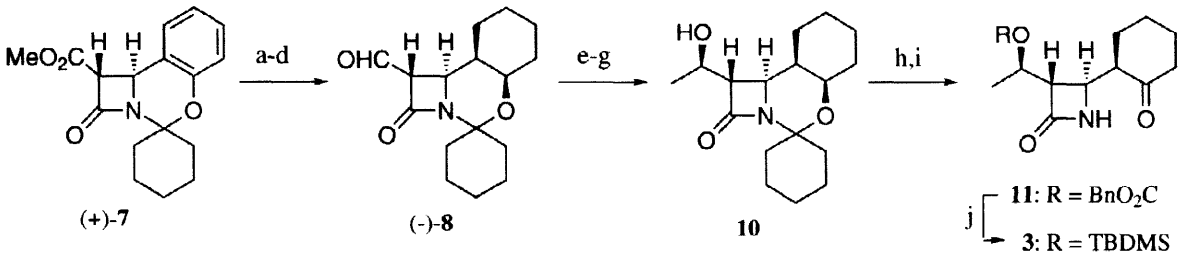
					Azetidin-2-one		
Entry	Rh(II) catalyst	Solvent	Temp, °C	Time, h		Yield, %	Ee, %[b]
1	Rh_2(*S*-PTA)$_4$	CH_2Cl_2	25	120	(-)-**7**	62	41
2	Rh_2(*S*-PTA)$_4$	toluene	25	72	(-)-**7**	60	70
3	Rh_2(*S*-PTA)$_4$	toluene	0	96	(-)-**7**	71	84
4	Rh_2(*S*-PTPA)$_4$	toluene	0	96	(-)-**7**	51	83
5	Rh_2(*S*-PTV)$_4$	toluene	0	96	(-)-**7**	56	45
6	Rh_2(*S*-PTPG)$_4$	toluene	0	72	(-)-**7**	78	10
7	Rh_2(*S*-PTTL)$_4$	toluene	0	96	(+)-**7**	66	84

[a] Reactions were carried out as follows: 5 mol % of the catalyst was added to a stirred solution of α-diazo amide **6** (1 mmol) in anhydrous solvent (5 mL) under argon. [b] Determined by ^{1}H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent.

insertion site. Reduction of (-)-**7** with $LiBH_4$ was followed by hydrogenation promoted by $RhCl_3$-methyltrioctylammonium chloride (Aliquat®-336)[9] and subsequent oxidation with the Dess-Martin periodinane to give aldehyde (+)-**8**, $[\alpha]_D^{25}$ +13.2 (*c* 1.01, $CHCl_3$), in 51% yield. Sequential methylenation[10] and hydrogenation followed by protective group interchange afforded (-)-**9**, $[\alpha]_D^{25}$ -13.2 (*c* 1.28, $CHCl_3$) [lit.,[4c] $[\alpha]_D^{25}$ +16 (*c* 0.49, $CHCl_3$) 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.[5] However, it should be noted that the crucial hydrogenation of the benzene ring catalyzed by the solvated ion pair $[(C_8H_{17})_3NCH_3]^+[RhCl_4]^-$ 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 (3*S*,4*R*)-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 ≃ benzyl < isopropyl < phenyl),[11] and that a dramatic reversal in enantioselection was observed with the exceptionally bulky *tert*-butyl group.[12]

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 ^{i}Pr$_2$O-hexane produced the optically pure sample, mp 96-97 °C, $[\alpha]_D^{25}$ +27.6 (*c* 1.53, $CHCl_3$), which was transformed to aldehyde (-)-**8**, $[\alpha]_D^{25}$ -15.0 (*c* 1.68, $CHCl_3$), under the foregoing conditions. Alkylation of (-)-**8** with Me_3Al[16] followed by oxidation with the Dess-Martin periodinane and stereocontrolled reduction with K-Selectride®[17] produced alcohol **10**, $[\alpha]_D^{25}$ +6.53 (*c* 1.73, $CHCl_3$), 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 ($^{i}Pr_2O$-hexane), 79%; (b) $LiBH_4$, THF, 0 °C, 2 h, 82%; (c) H_2, cat. $RhCl_3$-$(C_8H_{17})_3NMeCl$, $(CH_2Cl)_2$-H_2O, 25 °C, 38 h, 57%; (d) Dess-Martin periodinane, CH_2Cl_2, 0 °C, 4 h, 91%; (e) Me_3Al, CH_2Cl_2, 0 °C, 2 h, 83%; (f) Dess-Martin periodionane, CH_2Cl_2, 0 °C, 2 h, 96%; (g) K-Selectride®, THF, 0 °C, 1.5 h, 79%; (h) BnO_2CCl, DMAP, Et_3N, CH_2Cl_2, 3 h, 89%; (i) i. aq. AcOH, 70 °C, 6 h; ii. Dess-Martin periodinane, CH_2Cl_2, 0 °C, 2 h, 91%; (j) i. H_2, 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, $CHCl_3$), in 81% yield, which, upon protective group interchange, furnished the known intermediate **3**, $[\alpha]_D^{25}$ +33.9 (*c* 1.04, CH_2Cl_2) [lit.,[3d] $[\alpha]_D^{20}$ +33.9 (*c* 0.54, CH_2Cl_2)], 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_2(*S*-PTTL)$_4$ or Rh_2(*S*-PTA)$_4$ as a chiral catalyst. Mechanistic and stereochemical studies on the present C-H insertion reaction are currently in progress.[18]

References and Notes

1. For reviews on syntheses of trinem antibiotics, see: (a) Ngo, J.; Castañer, J. *Drugs of the Future* **1996**, *21*, 1238-1245. (b) Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333-2342. (c) Biondi, S. *Spec. Publ. -R. Soc. Chem.* **1997**, *198*, 86-100.
2. (a) Bismara, C.; Di Fabio, R.; Donati, D.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1995**, *36*, 4283-4286. (b) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604-9605.
3. (a) Ghiron, C.; Piga, E.; Rossi, T.; Tamburini, B.; Thomas, R. J. *Tetrahedron Lett.* **1996**, *37*, 3891-3894. (b) Hanessian, S.; Rozema, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 9884-9891. (c) Giacobbe, S. A.; Rossi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3079-3082. (d) Marchioro, C.; Pentassuglia, G.; Perboni, A.; Donati, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 463-468. (e) Rossi, T.; Marchioro, C.; Paio, A.; Thomas, R. J.; Zarantonello, P. *J. Org. Chem.* **1997**, *62*, 1653-1661.
4. (a) Camerini, R.; Panunzio, M.; Bonanomi, G.; Donati, D.; Perboni, A. *Tetrahedron Lett.* **1996**, *37*, 2467-2470. (b) Panunzio, M.; Camerini, R.; Pachera, R.; Donati, D.; Marchioro, C.; Perboni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2929-2938. (c) Panunzio, M.; Camerini, R.; Mazzoni, A.; Donati, D.; Marchioro, C.; Pachera, R. *Tetrahedron: Asymmetry* **1997**, *8*, 15-17.
5. Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun.* **1998**, 1517-1518.
6. (a) Watanabe, N.; Anada, M.; Hashimoto, S.; Ikegami, S. *Synlett* **1994**, 1031-1033. (b) Hashimoto, S.; Watanabe, N.; Anada, M.; Ikegami, S. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 988-999. (c) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79-82.
7. (a) Tranquillini, M. E.; Araldi, G. L.; Donati, D.; Pentassuglia, G.; Pezzoli, A.; Ursini, A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1683-1688. (b) Di Fabio, R.; Andreotti, D.; Biondi, S.; Gaviraghi, G.; Rossi, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2025-2030. (c) Di Fabio, R.; Rossi, T.; Thomas, R. J. *Tetrahedron Lett.* **1997**, *38*, 3587-3590.
8. Terent'ev, A. P.; Gusar, N. I. *Zh. Obshch. Khim.* **1965**, *35*, 125-129; *Chem. Abstr.* **1965**, *62*, 13068d.
9. Blum, J.; Amer, I.; Vollhardt, K. P. C.; Schwarz, H.; Höhne, G. *J. Org. Chem.* **1987**, *52*, 2804-2813.
10. Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698-1702.
11. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley, New York, 1994; Chapter 11.4.
12. While the enantioselectivity observed with Rh_2(*S*-TBSP)$_4$ developed by Davies[13] was 10% ee, decomposition of **6** under the influence of Rh_2(5*S*-MEPY)$_4$ devised by Doyle[14] occurred in 1,2-dichloroethane under reflux to give a complex mixture of products. These results suggest the unique ability of our dirhodium(II) complexes.[6b,15]
13. Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107-114.
14. Doyle, M. P. *Aldrichimica Acta* **1996**, *29*, 3-11.
15. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, 1998.
16. Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2514-2521.
17. Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208-2212.

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