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Asymmetric Synthesis of the Balanol Heterocycle via a Palladium-Mediated Epimerization and Olefin Metathesis

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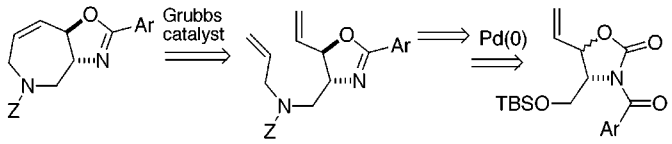
ABSTRACT



The enantioselective formal synthesis of balanol, a potent protein kinase C inhibitor, was accomplished from D-serine utilizing a Pd-catalyzed equilibration of diastereomeric 5-vinyloxazolines to set the stereochemistry of the vicinal amino and hydroxyl groups. A ruthenium-catalyzed ring-closing metathesis was employed to form the seven-membered nitrogen heterocycle.

Balanol (**1**, Figure 1) was first isolated in 1993 from the fungus *Verticillium balanoides*[1] and again in 1994 from a species of *Fusarium*.[2] It is a potent inhibitor of human protein kinase C displaying IC_{50} values of 4−9 nM.[3] Due to its high inhibitory activity, balanol has been the target of a number of synthetic efforts. Most recently, a samarium-mediated radical cyclization of an oxime ether afforded the nitrogen heterocycle in racemic form as a 6.6:1 mixture of diastereomers, and the major isomer was subsequently resolved at a later stage.[4] The Nicolaou group has reported an asymmetric synthesis of balanol beginning with D-serine. Key to the synthesis was a chiral allylation of a protected serinal with $(Ipc)_2$B-allyl to afford a 12:1 mixture of diastereomers.[5] The Tanner group utilized regio- and stereoselective opening of chiral epoxides and aziridines to control the vicinal amino alcohol stereochemistry.[6] Preparation of (2*S*,3*R*)-3-hydroxylysine in enantiomerically pure form[7] was key to the total synthesis of balanol reported by Lampe and Hughes.[8] Other total syntheses relying on chiral resolution of racemates have

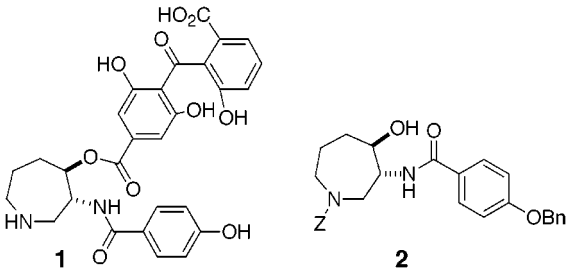


Figure 1.

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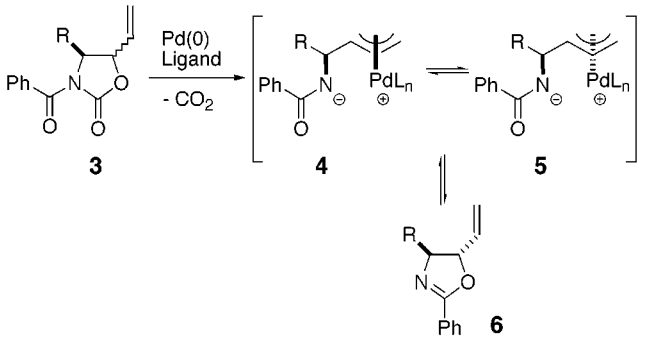
appeared.[8a,9] The hexahydroazepine **2** (Figure 1) has been targeted in several formal syntheses of balanol.[10]

We have recently shown[11] that chiral 5-vinyloxazolidinones (**3**) derived from α-amino acids react with palladium(0) catalysts to afford 5-vinyloxazolines (**6**) via oxidative insertion, loss of CO_2, and subsequent cyclization of the amide oxygen (Scheme 1). The oxazoline products were obtained

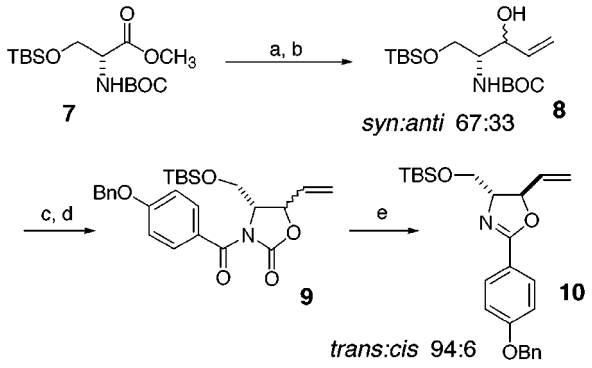
Scheme 1



with enhanced diastereomeric ratios, which suggested that the intermediate π-allyl palladium complexes **4** and **5** were undergoing equilibration. Oxazolines **6** were also ionized by the palladium catalyst and were in equilibrium with **4** and **5**, thus giving rise to thermodynamic product ratios.[12] We envisioned that this equilibration could be utilized to set the vicinal amino alcohol stereochemistry of the balanol heterocycle. The pendant vinyl group could be employed in a transition metal catalyzed ring-closing metathesis to generate the hexahydroazepine ring. This approach to the synthesis of **2** is presented in this Letter.

The synthesis of **2** began with the protected D-serine derivative **7** as shown in Scheme 2. Diisobutylaluminum hydride reduction of the ester and addition of vinylmagnesium bromide to the crude aldehyde afforded the allylic

Scheme 2[a]

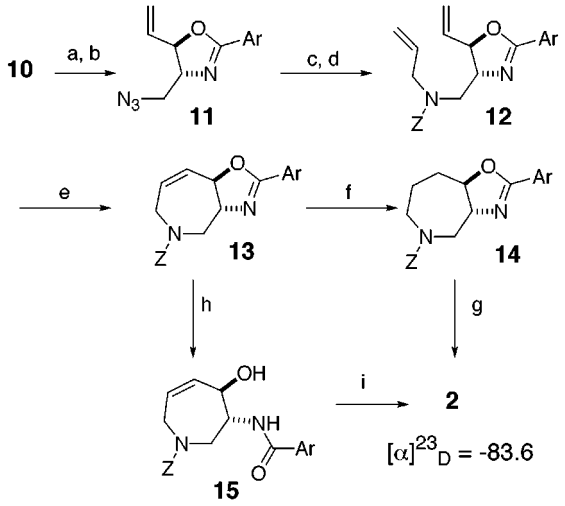


[a] (a) DIBAL-H, Tol, −78 °C; (b) vinylmagnesium bromide, THF, 58% for two steps; (c) NaH, THF, 91%; (d) 4-BnO-C_6H_4COCl, NaH, 90%; (e) $Pd_2(dba)_3CHCl_3$ (1 mol %), dppp (4 mol %), THF, 35 °C, 79% isolated pure *trans* diastereomer.

alcohol **8**[13,14] in 58% yield (two steps) as a 67:33 mixture of *syn* and *anti* diastereomers, respectively.[15,16] Oxazolidinone formation was achieved by treatment with sodium hydride in THF, and acylation gave the required 5-vinyloxazolidinone **9** in high yield. The palladium-catalyzed oxazoline formation/epimerization provided **10** as a 94:6 (*trans:cis*) mixture of diastereomers.[15] The isolated yield of the purified major diastereomer was 79% (*cis* isomer, 3%). The optimal epimerization conditions were 35 °C in THF. When toluene was employed as the solvent, a slightly lower selectivity was obtained. Higher temperatures resulted in the formation of trace amounts of elimination products with no improvement in the diastereomer ratio.

Removal of the *tert*-butyldimethylsilyl protecting group from **10** with tetrabutylammonium fluoride afforded the free alcohol in 83% yield (Scheme 3). Mitsunobu reaction with

Scheme 3[a]



[a] (a) TBAF, THF, 83%; (b) DPPA, Ph_3P, DEAD, 88%; (c) Ph_3P, THF−H_2O; then BnOCOCl, Et_3N, 70%; (d) NaH, allyl bromide, 87% (11% recovered starting material); (e) $Cl_2(PCy_3)_2Ru$=CHPh (2 × 5 mol %), 45 °C, CH_2Cl_2, 77%; (f) KO_2CNNCO_2K, AcOH, 50%; g) 1 N HCl, EtOH, 60 °C; then excess Et_3N, MeOH, rt, 63%; (h) 2 N HCl, THF, rt; then excess Et_3N, MeOH, rt, 72%; (i) $(Ph_3P)_3RhCl$ (5 mol %) H_2 (25 psi), benzene, 94%.

diphenylphosphoryl azide[17] was employed to introduce the nitrogen in 88% yield (**11**). Reduction with triphenylphos-

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(11) Cook, G. R.; Shanker, P. S. *Tetrahedron Lett.* **1998**, *39*, 3405.

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phine and water, protection with benzyl chloroformate, and allylation with allyl bromide gave the diene **12**. The olefin metathesis reaction with 10 mol % of the Grubbs ruthenium alkylidene catalyst[18] provided the desired seven-membered nitrogen heterocycle **13** in a respectable yield (77%). The experimental conditions for the olefin metathesis reaction are worthy of comment. Optimal results were obtained when 5 mol % of the catalyst was used followed by the addition of another 5 mol % after 4 h. The reaction would not proceed to completion with a single loading of the catalyst, even up to 20 mol %. Presumably, the catalyst decomposed and an additional loading was required to obtain complete conversion.

Diimide reduction of the olefin was accomplished with potassium azodicarboxylate in acetic acid to afford the saturated nitrogen heterocycle **14** in a moderate yield. Hydrolysis of the oxazoline was carried out with 1 N HCl in ethanol at 60 °C. The formation of **2** required subsequent treatment with base. Under simple aqueous workup conditions, the benzoate derivative was isolated as the amine hydrochloride salt. Stirring with triethylamine in methanol for 36 h was necessary to effect the benzoyl transfer to the amine. A higher overall yield from **13** to **2** was realized by reversing the hydrolysis and reduction steps. Acidic hydrolysis and base treatment afforded **15** in 72% yield, and hydrogenation with Wilkinson's catalyst gave **2** with no observed cleavage of the protecting groups.

We have described an asymmetric synthesis of the balanol heterocycle from D-serine which incorporated a palladium-mediated equilibration to set the relative stereochemistry. Seven-membered ring formation was accomplished with a ruthenium-catalyzed olefin metathesis reaction in high yield. The utility of intermediate **13** for the synthesis of balanol analogues[19] and novel azasugar derivatives is currently under investigation and will be reported in due course.

Acknowledgment. We thank NSF (OSR-9452892, CHE-9875013), NIH (GM58470-01), and North Dakota State University for support of our programs. We are grateful to Boulder Scientific, Inc. for a generous gift of Grubbs' catalyst. We thank Dr. Peter Wuts for helpful discussions.

Supporting Information Available: Experimental procedures and characterization data for compounds **2** and **9**−**15** and unnumbered intermediates isolated. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The alcohol **8** is a known compound. See ref 12a and references therein.

(14) All compounds displayed satisfactory spectroscopic (NMR, IR) data consistent with their structures.

(15) Diastereomer ratios were determined by ^{1}H NMR (400 MHz).

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