Pergamon

Tetrahedron Letters 43 (2002) 9027–9029

TETRAHEDRON LETTERS

Stereoselective synthesis of D-*erythro*- and L-*threo*-sphinganines via palladium-catalyzed equilibration and Suzuki coupling

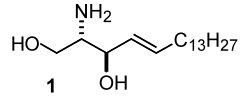
Gregory R. Cook* and Ketheeswaran Pararajasingham

Department of Chemistry, North Dakota State University, Fargo, ND, 58105-5516, USA

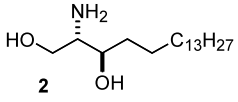
Received 2 October 2002; revised 14 October 2002; accepted 15 October 2002

Abstract—The Pd-catalyzed isomerization of 5-vinyloxazolines was utilized for the stereoselective synthesis of D-*erythro*- and L-*threo*-spinganine triacetate. A hydroboration/Suzuki coupling sequence was employed to elongate the hydrophobic chain.

Sphingolipids such as sphingosine **1** and the saturated derivative sphinganine **2** are important constituents of cellular membranes and play a critical role in many physiological processes including modulation of immune response, signaling and cell recognition.[1] As such, they have been the targets of intense interest for synthetic chemists due to the lack of readily available natural sources.[2,3] Key to the preparation of these compounds is the stereoselective construction of the aminodiol portion of the molecule. We have recently developed methodology for the synthesis of vicinal aminoalcohols via a palladium-catalyzed isomerization of 5-vinyloxazolines.[4] We thought application of this methodology to serine derivatives with the lipid chain attached would offer a concise route to sphingolipids. The results of our study and the preparation of D-*erythro*- and L-*threo*-sphinganine are presented in this letter.



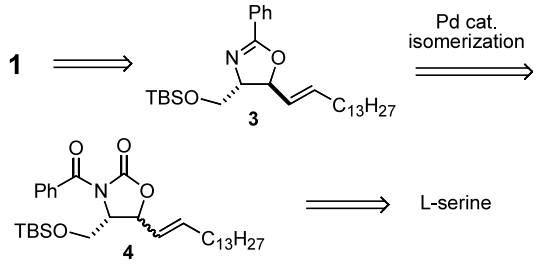
D-*erythro*-sphingosine



D-*erythro*-sphinganine

Our initial strategy for the synthesis of sphingolipids is outlined in Scheme 1. We envisioned a Pd-catalyzed ring-opening ring-closing sequence to afford the 5-vinyloxazoline **3** with high stereoselectivity. The oxazolidinone **4** would derive from L-serine. The metal-catalyzed diastereomeric equilibration of **3** would require the isomerization of the intermediate Pd-allyl complex from one face to the other. With unsubstituted vinyl derivatives, allyl isomerization occurs readily and efficiently via a π-σ-π equilibration of the intermediate palladium allyl complex, however, for the isomerization of more substituted derivatives the issues are more complex (Scheme 2). A π-σ-π isomerization of a disubstituted allyl complex would result in a change of olefin geometry concomitant with a change in the stereochemistry of the oxazoline ring. Thus, this mechanism would allow equilibration of **5** and **6** *or* **7** and **8**, but would not allow equilibration of all four stereoisomers. In order for all isomers to equilibrate an alternative mechanism, nucleophilic displacement by a second Pd atom, must occur. As both mechanisms have established precedence in Pd-catalyzed allylic substitution reactions,[5] we examined this route for the synthesis of **1** with the anticipation that all four stereoisomers would equilibrate to the favored *trans*, *E* isomer **7**.

Model compounds **5**, **6**, **7**, and **8**, (R = CH_2OTBS, R′ = *n*-Bu) were prepared from L-serine and independently subjected to the Pd-catalyzed equilibration conditions. To our disappointment, we found no evidence



Scheme 1.

* Corresponding author. Tel.: 701-231-7413; fax: 701-231-1057; e-mail: gregory.cook@ndsu.nodak.edu

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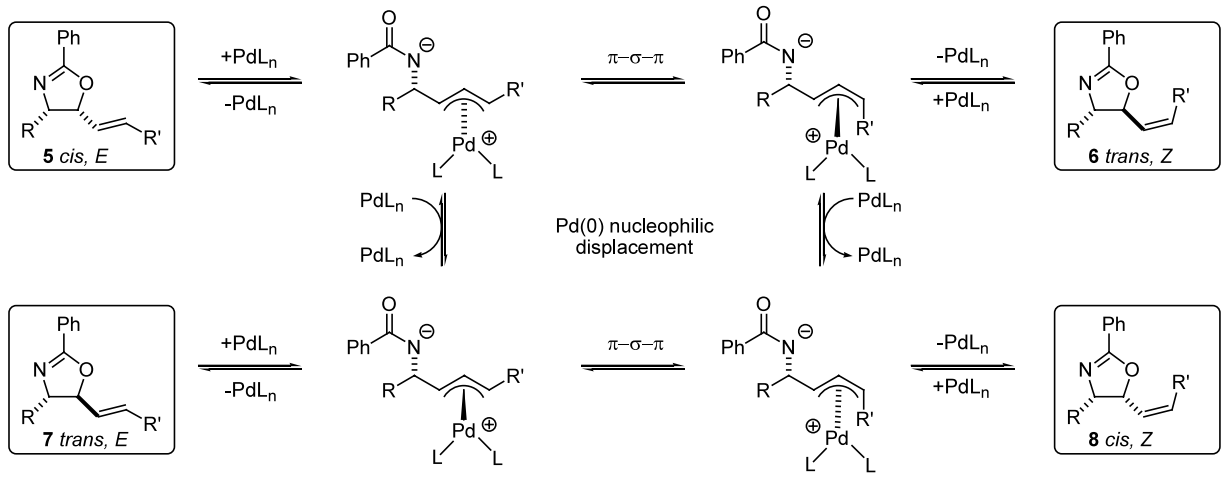
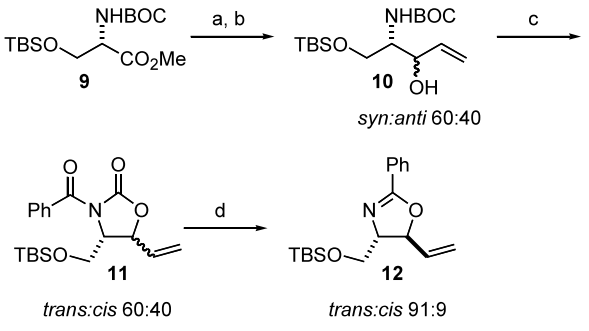
PII: S0040-4039(02)02309-2



Scheme 2.

for the Pd-displacement mechanism with these substrates after exploring a large variety of catalysts, ligands, and solvents. Oxazolines **5** or **6** were readily equilibrated to a near equal mixture (1.3:1), and **7** or **8** equilibrated to give the thermodynamically favored **7** (99:1), however, there was no equilibration of **5** or **6** with **7** or **8**. Thus, the direct preparation of sphingosines with the lipid chain attached was not attainable. We therefore focused our efforts toward utilizing an unsubstituted substrate that avoids the problem of olefin isomers, and explored methods to elongate the aliphatic chain after isomerization. We have previously shown that chain extension of 5-vinyloxazolines could be accomplished by a hydroboration/Suzuki coupling sequence[4c] and we pursued this avenue toward the synthesis of sphinganines.

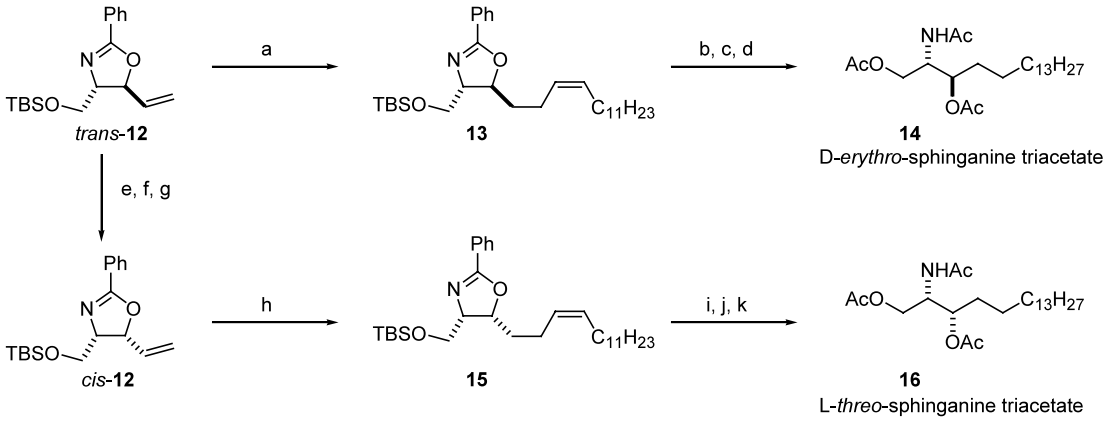
The synthesis of both D-*erythro*- and L-*threo*-sphinganine began with the protected L-serine derivative **9** (Scheme 3). Diisobutylaluminum hydride reduction followed by the addition of vinylmagnesium bromide afforded the aminoalcohol derivative **10**[6] as a mixture of diastereomers (*syn*:*anti*, 60:40).[7,8] Cyclization of the alcohol onto the BOC group with the assistance of sodium hydride followed by acylation gave **11** with the same isomer ratio. Treatment with a palladium(0) catalyst in acetonitrile provided predominantly the *trans*-oxazoline **12** in 90% isolated yield. Contrary to aminoalcohol **10**, the oxazoline diastereomers were readily separated by silica gel chromatography to afford the pure *trans* diastereomer. The minor diastereomer could be recycled simply by subjecting it once again to the conditions of the Pd-catalyzed isomerization to offer the same 91:9 mixture of *trans* to *cis* oxazolines. Accordingly, efficiency in the preparation of the *trans* isomer could be improved, particularly when carrying out the chemistry on larger scale.



Scheme 3. *Reagents and conditions*: (a) DIBAL-H, Tol, −78°C (82%); (b) vinylmagnesium bromide, THF (59%); (c) NaH, THF, PhCOCl (60%); (d) Pd(PPh$_3$)$_4$, CH$_3$CN (90%).

Completion of the synthesis is outlined in Scheme 4. Hydroboration of *trans*-**12** with 9-BBN was followed by Suzuki coupling with *Z*-1-bromo-1-tridecene[9] to afford the extended oxazoline **13**. Hydrogenation of the olefin and hydrolysis under acidic conditions afforded D-*erythro*-sphinganine, which was converted into the known triacetate derivative **14**[10] for ease of purification and characterization. The L-*threo*-isomer was readily obtained from *cis*-**12** by the analogous synthetic sequence. As *cis*-**12** was attained in only small amounts in the Pd-catalyzed isomerization reaction, a preparation from the *trans* isomer was developed. Partial hydrolysis of *trans*-**12** afforded the *N*-benzoylaminodiol derivative. The primary alcohol was reprotected with TBSCl and imidazole. Finally the *cis*-**12** oxazoline ring was formed in quantitative yield by activation of the secondary alcohol as the mesylate and S_N2 displacement by the amide carbonyl.

In conclusion, we have demonstrated the facile synthesis of both D-*erythro*- and L-*threo*-sphinganine from the same intermediate 5-vinyloxazoline prepared via a Pd-catalyzed isomerization and subsequent Suzuki coupling. Access to the L-*erythro*- and D-*threo*-isomers would be attainable in an analogous fashion starting from D-serine.



Scheme 4. *Reagents and conditions*: (a) 9-BBN, THF, $Pd(PPh_3)_4$, *Z*-1-bromo-tridecene, NaOH, THF (62%); (b) H_2, Pd/C, EtOAc (89%); (c) 2N HCl, THF, NaOH (59%); (d) Ac_2O, pyr. (58%); (e) 2N HCl, THF (77%); (f) TBSCl, imidazole (70%); (g) $MeSO_2Cl$, Et_3N (99%); (h) 9-BBN, THF, $Pd(PPh_3)_4$, *Z*-1-bromo-tridecene, NaOH, THF (52%); (i) H_2, Pd/C, EtOAc (86%); (j) 2N HCl, THF, NaOH (66%); (k) Ac_2O, pyr. (71%).

Acknowledgements

We are grateful to the National Science Foundation (CAREER Award 9875013) for financial support of this work.

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7. Diastereomer ratios were determined by careful analysis of the 400 MHz ^1H NMR spectra.
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10. Spectral characterization and optical rotation were consistent with that reported in the literature. See Ref. 3f and references cited therein.