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A new approach to the synthesis of the carbon framework of SC-84536, an inducible nitric oxide synthase inhibitor

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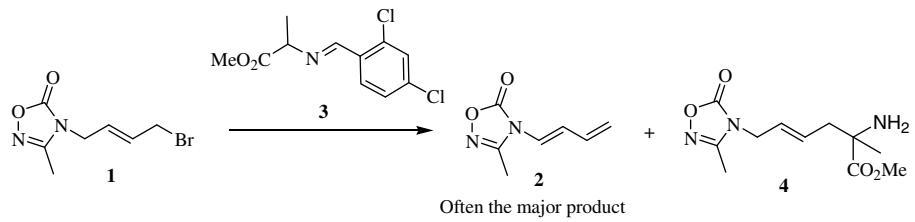
Abstract

SC-84536, a selective inhibitor of inducible nitric oxide synthase (iNOS), is targeted for the treatment of osteoarthritis, neuropathic pain, and asthma. The initial technology for constructing this molecule was acceptable only for the preparation of small quantities of material, but was not practical for larger scale work. This Letter describes our effort toward developing an alternative synthetic route for the carbon framework of SC-84536.

Given that osteoarthritis, neuropathic pain, and asthma remain as clinical issues and that inducible nitric oxide synthase (iNOS) is implicated in these conditions, a program was initiated that targeted the inhibition of iNOS.[1] From this program, SC-84536 was identified as a useful inhibitor to this enzyme. The chemistry used for the initial preparation of SC-84536 was deemed impractical for larger scale work and thus an alternative approach was sought.[2]

The primary issue associated with the original synthesis was that the alkylation reaction to produce **1** was messy and proceeded in only 30% yield, largely due to the elimination of HBr to form **2**. Elimination was also an issue during the course of the coupling of **1** and **3** to produce **4** making reproducibility a major concern. Secondarily, the 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one in **1** is unstable, expensive, and posed a safety risk for scaling this chemistry. These issues led us to devise a more robust alternative for building the carbon framework that would be more predictably scaled (Scheme 1).

For the sake of convergency, we explored a synthon that contained the nitrogen in a stable form and was not prone to elimination as was **1**. In light of this, we felt that the oxazolidinone would be ideal and that palladium-catalyzed alkylation could be used for the construction of the key CC bond. A US Patent described the synthesis of a mixture of isomeric oxazolidinones **6** and **7** that were difficult to



Scheme 1. Original approach to SC-84536.

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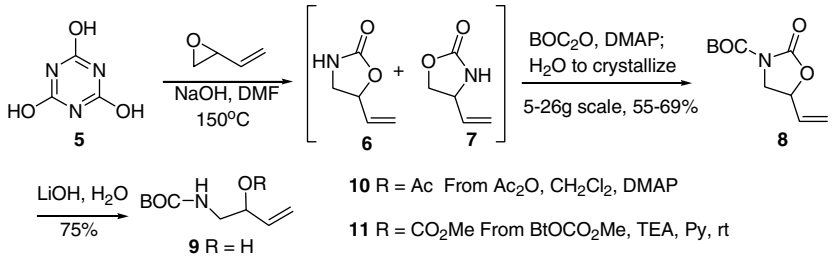
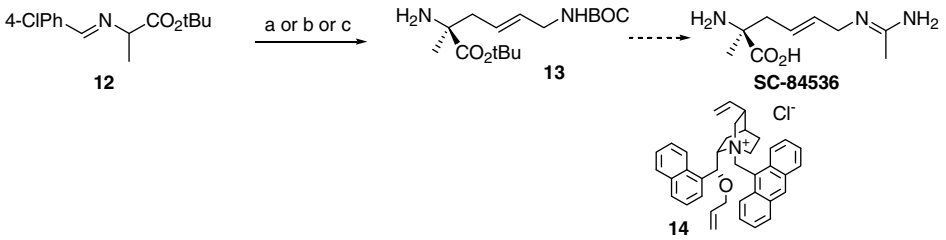


Scheme 2. Oxazolidinone preparation.



Scheme 3. Phase transfer alkylation. Reagents and conditions: (a) LDA, [π-allylPdCl]$_2$, THF, (*S*)-BINAP, **8**, −78 °C to rt, 90% yield, racemic; (b) CsOH–H_2O, THF, [π-allylPdCl]$_2$, (*S*)-BINAP, **8**, PTC **14**, low ee; (c) KOH, toluene, [π-allylPdCl]$_2$, $(PhO)_3P$, PTC **14**, **10**, 95.5% yield, 75% ee.

separate.[3] Through the modification of the described procedure, we were able to prepare the BOC-protected oxazolidinone in 55–69% yield as an easily isolated crystalline solid. The key simplification was to react the crude reaction mixture containing both isomers directly with DMAP and $(BOC)_2O$ to form the BOC derivative which was consistently crystallized from the reaction mixture by slowly adding water to the DMF solution in 55–69% yield (Scheme 2).

The oxazolidinone proved to be a competent electrophile in the palladium-catalyzed coupling with the Schiff base **12** giving the desired carbon framework in 90% yield after imine hydrolysis with citric acid, although in racemic form. (*S*)-BINAP failed to induce any chirality. Using a combination of both a chiral phase transfer catalyst and a chiral Pd ligand [$Pd_2(dba)_3$, (*S*)-BINAP, $CsOH{\cdot}H_2O$, **14**] gave the desired product **13**.[4] Studies of this system showed that the chiral inductions were not where we would have liked them to be, that the chirality of the BINAP was not influential, and that the chirality of the oxazolidine[5] also did not affect the outcome of the reaction (Scheme 3).

Inspired by a report describing improvements in the palladium-catalyzed allylic alkylation reaction, we decided to investigate linear allylating reagents such as **10** and **11**.[6] The linear analogs were prepared by hydrolysis of oxazolidinone **8** to form the amino alcohol **9** in 75% yield. Acetate **10** was formed in 93% yield from the crude amino alcohol under standard conditions (Ac_2O, DMAP, TEA, CH_2Cl_2, 0 °C). The related carbonate **11** was prepared using $BtOCO_2Me$.[7] Both the acetate and the carbonate were tested in the reaction with acetate giving a much cleaner product than the carbonate. We were able to achieve the key bond construction in 94.5% yield with 75% ee.[8] These results indicate that the nature of the π-allylpalladium precursor, cyclic or acyclic, makes a significant difference to the induction of chirality. No other catalysts such as the elegant and effective Maruoka catalysts were examined in this work largely for cost considerations and availability on scale. Preliminary experiments were done to examine upgrading the ee by crystallization with some success using the Naproxen® salt, but at this point the project was cancelled based on preliminary clinical work and so no further work was done on either the alkylation or the crystallization.

In this work, we have developed a useful new route to a 4-carbon synthon[9] and demonstrated its utility in the preparation of a tertiary chiral center using π-allylpalladium chemistry in the phase transfer mode. The new preparation of the SC-84536 carbon framework represents a substantial improvement to the initial route.[10]

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References and notes

1. Alderton, W. K.; Cooper, C. E.; Knowles, R. G. *Biochem. J.* **2001**, *357*, 593.
2. Durley, R. C.; Sikorski, J.; Hansen, D., Jr.; Promo, M. A.; Webber, R. K.; Pitzele, B. S.; Awasthi, A. K.; Moorman, A. E. Preparation of 2-amino-2-alkyl-4-hexenoic and -hexynoic acid derivatives useful as nitric oxide synthase inhibitors. PCT Int. Appl. WO 2002022559, 2002, 117 pp; Manning, P. T.; Misko, T. P. PCT Int. Appl. WO 2005025620, 2005.
3. Little, E. D.; Donald, P. 5-Vinyl-2-oxazolidone. U.S. Patent 3,157,668, 1964; 3 pp.

4. The ee was not determined because we did not have an assay at the time.
5. Both enantiomers were prepared from the chiral epoxides obtained from Eastman chemical.
6. Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329–3331; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 1515–1517.
7. Wuts, P. G. M.; Ashford, S. W.; Anderson, A. M.; Atkins, J. R. *Org. Lett.* **2003**, *5*, 1483.
8. For a reviews on chiral PTC reactions: Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222; Maruoka, K.; Ooi, T.; Kano, T. *Chem. Commun.* **2007**, 1487; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222; Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506; Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.
9. *Oxazolidinone synthesis*: In a Mettler-Toledo Multimax autoclave a mixture of cyanuric acid (5.18 g), butadiene monoepoxide (10 mL), 200 mg of NaOH in 30 mL of DMF was heated to 80 °C over 20 min and then held there for 2 h. The mixture was then heated to 150 °C over 1 h and held for 6 h. The solution was cooled to 20 °C and treated with 25 g of BOC_2O and 500 mg of DMAP and heated to 40 °C for 45 min. One hundred milliliters of water was then slowly added to crystallize the product. The solids were filtered, washed with water and dried to give 17.5 g (68.5% yield) of oxazolidinone **8**. ^{1}H NMR (DMSO): 5.95 (m, vinyl H), 5.40 (d, $J = 17.2$ Hz, 1H), 5.31 (d, $J = 10.4$ Hz, 1H), 5.0 (q, $J = 7.76$ Hz, 1H), 4.05 (t, $J = 9.4$ Hz, 1H), 3.59 (dd, $J = 9.76$, 9.76, 1H), 1.45 (s, 9H) ppm. ^{13}C NMR (DMSO): 151.3, 149.0, 134.7, 119.4, 82.5, 73.2, 48.1, 27.8 ppm.
10. *Experimental for coupling*: In a Mettler-Toledo Multimax autoclave were combined **12** (1.0 g, 3.735 mmol), **14** (226 mg, 0.3735 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (106 mg, 0.187 mmol) and $(PhO)_3P$ (97 μL, 0.373 mmol). Toluene (15 mL) and **10** (868 mg, 7.022 mmol) were added and the reaction was stirred at 0 °C for 18 h. After the reaction was complete, the product was extracted into EtOAc. The organic was washed with satd $NaHCO_3$ and concentrated to an oil. The Schiff base was hydrolyzed in THF with aqueous citric acid. The reaction solution was washed with EtOAc and then basified (pH 9) with concentrated NaOH. The product was extracted into EtOAc, dried over $MgSO_4$, filtered, and concentrated to an oil (1.11 g, 94.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 2H), 4.71 (m, 1H), 3.66 (m, 2H), 2.3 (m, 2H), 1.68 (s, 2H), 1.42 (s, 9H), 1.40 (s, 9H), 1.24 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.29, 155.63, 131.14, 126.55, 80.89, 79.16, 57.67, 43.48, 42.26, 28.34, 27.94, 26.27 ppm.