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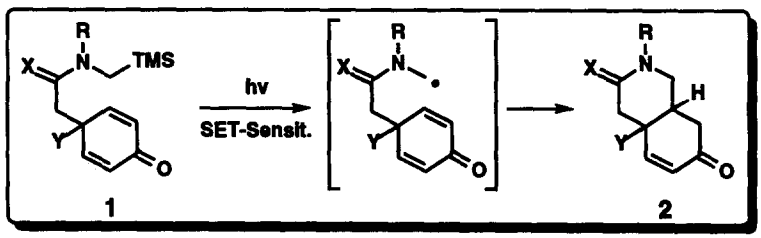
A New Strategy for Yohimbane Synthesis Based On A Silylamido-Cyclohexadienone Photoinduced Radical Cyclization Process

Young Shik Jung and Patrick S. Mariano*
Department of Chemistry and Biochemistry
University of Maryland, College Park, MD 20742, USA

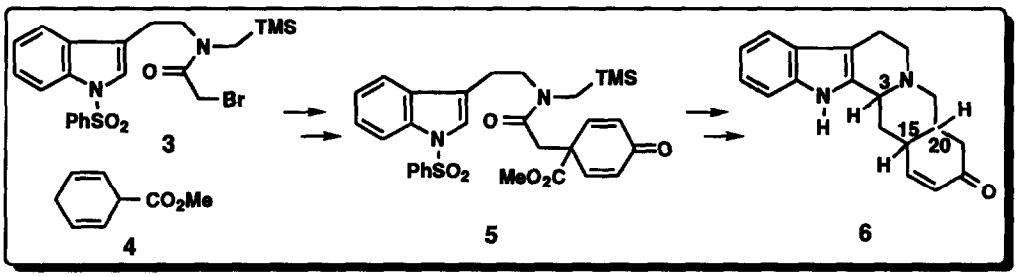
Abstract. A new strategy for highly E-ring functionalized yohimbane synthesis is presented. This scheme developed takes advantage of an SET-photoinduced, radical cyclization reaction of a key α-silylamido-cyclohexadienone intermediate.

We recently reported the results of a study probing the direct and SET-sensitized photocyclization reactions of α-silylamido- and α-silylamino-2,5-cyclohexadienones.[1] In that effort we demonstrated that cyclohexadienones **1** are converted with modest efficiency to hydroisoquinolines **2** by use of 9,10-dicyanoanthracene (DCA) sensitized irradiation conditions. This cyclization process appeared to possess several unique features that would make it suited to a novel route for yohimbane alkaloid synthesis[2] following the plan shown in Scheme 1. The strategy is based upon (1) Schultz's[3] cyclohexadienone synthesis methods to deliver the intermediate **5** from bromoamide **3** and dihydrobenzoate **4**, (2) photocyclization to install the functionalized DE-hydroisoquinoline unit, and (3) Bischler-Napieralski cyclization to complete yohimbane pentacyclic ring construction. The results of efforts to develop this plan are described below in the context of a synthesis of the yohimbenones **6**, substances which contain functionality which we have previously shown[4] to be useful for introducing E-ring substituents present in even the most functionally complex yohimbanes (*e.g.* deserpidine).

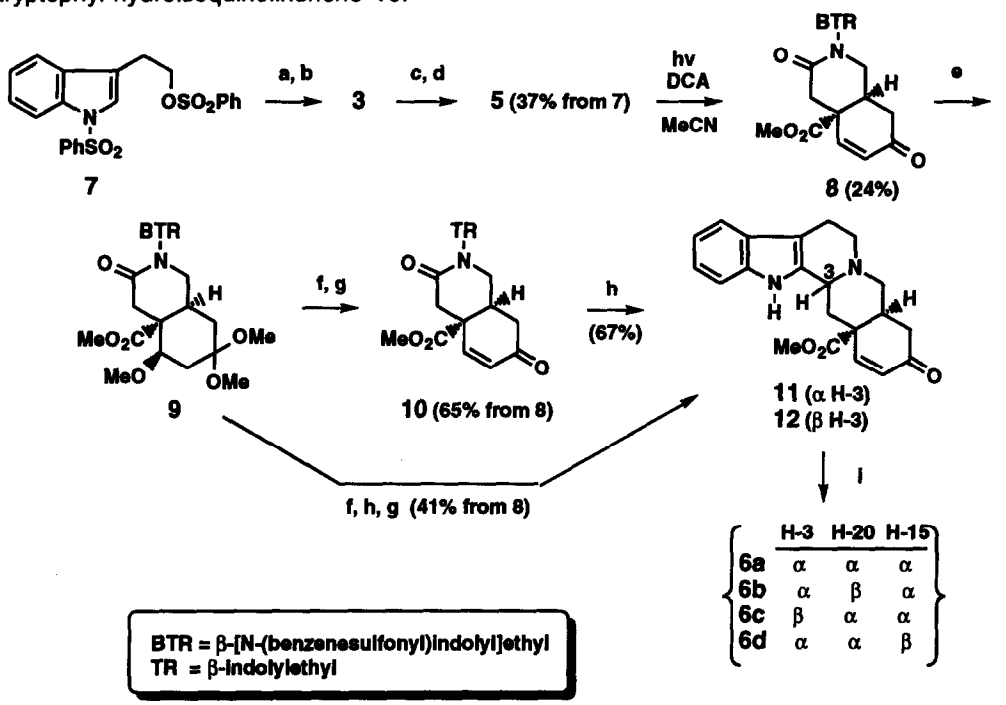


The N-tryptophyl-bromoamide **3** used in the sequence derives from the known[4b] tryptophol derivative **7** by sequential reaction with $TMSCH_2NH_2$ and $BrCH_2COBr$. Alkylation of the enolate of dihydrobenzoate **4**[5] with **3** gives a cyclohexadiene which is transformed to the cyclohexadienone **5** by PDC/$tBuO_2H$ oxidation.[3] The key photocyclization step is promoted by irradiation of an MeCN solution containing DCA[1] and **5**. This process furnishes the N-tryptophyl-hdroisoquinoline **8** with the expected1 cis-stereochemistry. Attempts to remove the indole-sulfon-

Scheme 1.

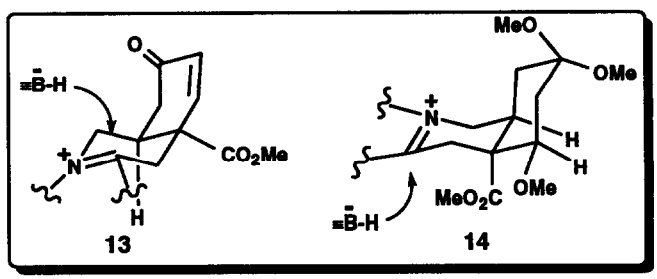


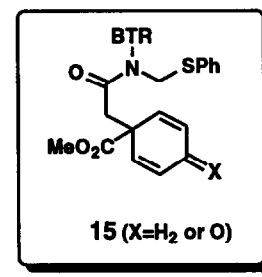
amide protecting group from **8** by standard reduction conditions[6] were unsuccessful owing to concomitant enone reduction. This problem is circumvented by first protecting the enone, *via* its trimethoxy-derivative **9**, followed by sulfonamide reductive cleavage[6] and hydrolysis to give the N-tryptophyl-hydroisoquinolinenone **10**.



(a) $TMSCH_2NH_2$, Et_3N, MeCN; (b) $BrCH_2COBr$, Et_3N, CH_2Cl_2; (c) 4, nBuLi, THF; (d) PDC, BuO_2H Et_3N; (e) H_2SO_4, MeOH; (f) 6% Na-Hg, MeOH; (g) HCl, THF; (h) $POCl_3$; aq NaOAc; $NaBH_3CN$, MeOH; (i) 3-quinuclidinol, o-xylene, refl.

The two-step ($POCl_3/NaCNBH_3$) Bischler-Napieralski cyclization process with **10** leads to efficient generation of separable C-3 epimeric yohimbenones **11** and **12** in an *ca.* 1:2 ratio. Interestingly, when the indole deblocked derivative of **9** is subjected to the cyclization/reduction condition and then the E-ring enone function is liberated by hydrolysis, yohimbenone epimers **11** and **12** are obtained in an *ca.* 7:1 ratio. The difference between the stereochemical outcome of the two sequences appears to be due to factors influencing conformer preferences (*e.g.* **14** to a greater extent than **13**) in the iminium ions which serve as intermediates in the reaction coupled with the facial selectivities in the stereoelectronically controlled borohydride reduction steps. Finally, removal of the C-15 CO_2Me group, which is part of a vinylogous β-keto ester function, is performed by treatment with quinuclidinol.[7] In this way, **11** is converted cleanly (50%) to the allo-yohimbenone stereoisomer **6a**. This substance possesses identical spectroscopic properties with material we have prepared previously by a more lengthly amino-Claisen rearrangement based route.[4b] In contrast, decarboxylation of **12** under these conditions gives a complex mixture of yohimbenone stereoisomers **6a-6d** in 9, 19, 6 and 13% respective yields. The structural and stereochemical assignments to **6b** and **6c** were made by comparison of their properties to those of previously prepared materials.[4a] While the high stereoselectivity for reaction of **11** is understandable on the basis of steric preferences for intermediate dienolate protonation, the near stereorandom nature (especially C-3 epimerization) of the analogous reaction of **12** is less clear.





Although the yield (24% isolated) of the photocyclization step in this sequence is lower than anticipated,[1] it does not detract greatly from the concise nature of the strategy developed for assembly of relevantly E-ring functionalized yohimbanes. Parallel efforts[8] attempting to find procedures to circumvent the photocyclization step, have shown that nBuSnH induced radical cyclizations of the α-thioamides **15** occur with very low (<14%) yields. The inefficiencies of these radical cyclization processes appear to be due to competitive α-amido radical addition to the blocked indole nucleus in the case of the diene (**15**, X=H2), and fragmentation to produce methyl *p*-hydroxybenzoate in the case of the dienone (**15**, X=O).

Several questions remain unanswered about the above strategy, especially concerning the yields of key steps and the control of absolute stereochemistry. These issue are being addressed in our ongoing efforts.

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References

(1) Jung, Y.S.; Swartz, W.H.; Xu, W.; Mariano, P.S.; Green, N.J.; Schultz, A. G. *J. Org. Chem.*, **1992**, *57*, 6037.
(2) Baxter, E.W.; Mariano, P.S. *Alkaloids Chemical and Biological Perspectives*, Ed. Pelletier, S.W., Vol. 8, Springer Verlag, New York, 1992.
(3) Schultz, A.G. *Acc. Chem. Res.*, **1990**, *23*, 207.
(4) (a) Baxter, E.W.; Labaree, D.; Chao, S.; Mariano, P.S. *J. Org. Chem.*, **1989**, *54*, 2893; (b) Baxter, E. W.; Labaree, D.; Ammon, H.L.; Mariano, P.S. *J. Am. Chem. Soc.*, **1990**, *112*, 7682.
(5) Kuehne, M.E.; Lambert, B.F. *Org. Syn.*, Collect Vol. 5, Wiley, New York, 1972.
(6) Sundberg, R.J.; Bloan, J.D. *J. Org. Chem.*, **1981**, *46*, 4836.
(7) Parish, E.J.; Huang, B.S.; Miles, D.H. *Synth. Commun.*, **1975**, *5(5)*, 341.
(8) Jung, Y.S.; Mariano, P.S. unpublished results.

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