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Total Synthesis of SS20846A via Intramolecular Pd(II)-Catalyzed Cyclization

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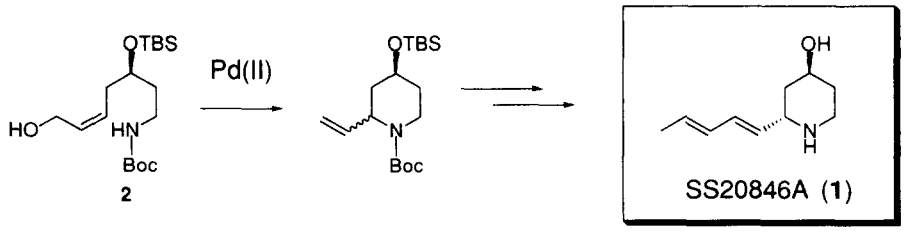
Abstract: A stereoselective total synthesis of SS20846A was efficiently accomplished by means of an intramolecular palladium(II)-catalyzed cyclization.

SS20846A(**1**) is a biologically active piperidine alkaloid isolated from *Streptomyces* sp. S20846[1,2]. It is also a biosynthetic intermediate of streptazolin[3,4]. For several years we have been investigating the stereoselective construction of nitrogen hetero-alicycles via the intramolecular palladium(II)-catalyzed cyclization[5,6,7], focusing on the challenging direct construction of *trans*-2,4-disubstituted piperidines such as **1** from acyclic precursors. We report here a novel stereoselective synthesis of SS20846A(**1**) by the intramolecular cyclization of the corresponding urethane using palladium(II) catalyst.



The substrate **2** for palladium(II)-catalyzed cyclization was prepared from (*S*)-glycidol (Scheme 1)[8]. Addition of [tetrahydro-2-(2-proynyloxy)-2*H*-pyran]-2-propyne to (*R*)-*O*-*t*-butyldimethylsilyl glycidol **3**, which was readily prepared from (*S*)-glycidol, in the presence of *n*-BuLi and TMEDA at -78°C gave the alcohol **4** in 34% yield. Deprotection of the alcohol **4** (TBAF, THF; 97% yield), mono-tosylation of the resulting diol **5** (TsCl, pyridine, CH_2Cl_2; 52% yield) and epoxidation of the tosylate **6** (K_2CO_3, MeOH; 86% yield) provided the epoxide **7** in 15% overall yield. The ring opening of the epoxide **7** by treatment with

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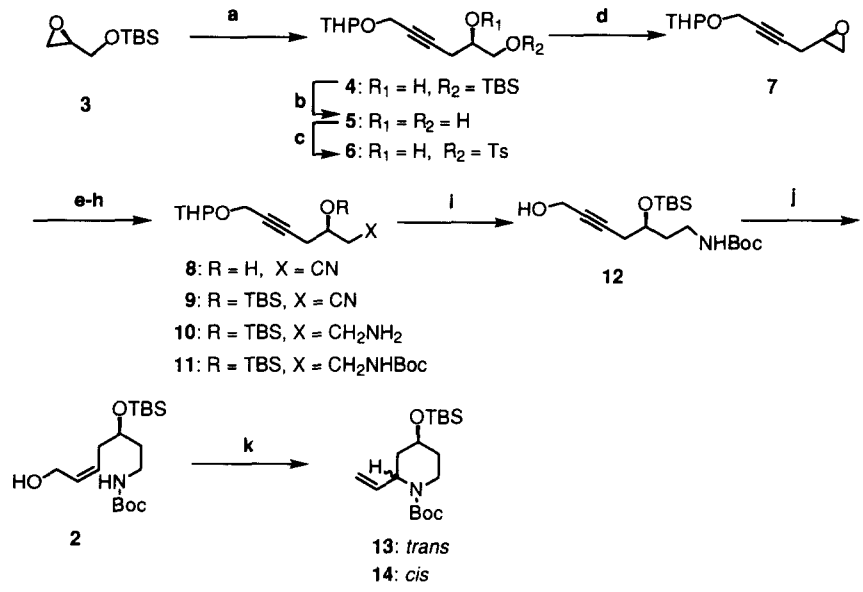
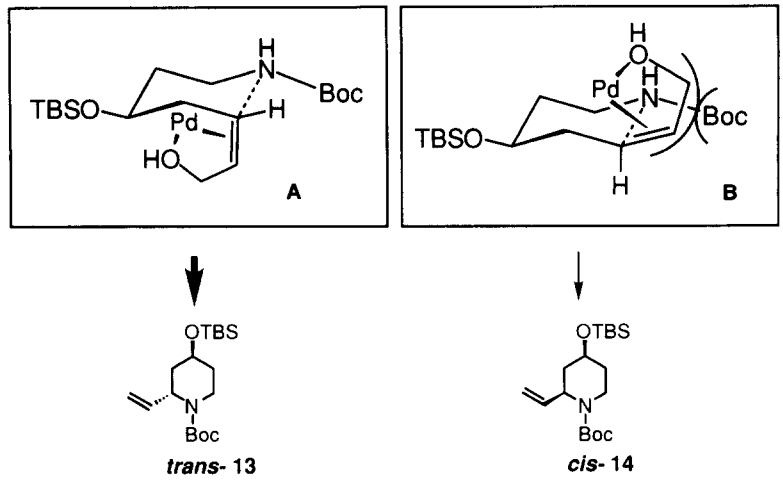
potassium cyanide (KCN, sat. $MgSO_4$ aq., MeOH, 99% yield) followed by protection of the resulting alcohol **8** (TBSCl, imidazole, DMF; 99% yield) gave the nitrile **9**. Reduction of the cyano group (LAH, THF) and the subsequent protection of the amine **10** ($(Boc)_2O$, Et_3N, CH_2Cl_2) gave the urethane **11** in 39% overall yield. The treatment of **11** with PPTS in MeOH at r.t. followed by hydrogenation of the resulting alcohol **12** afforded the desired substrate **2** in 47% yield[9].



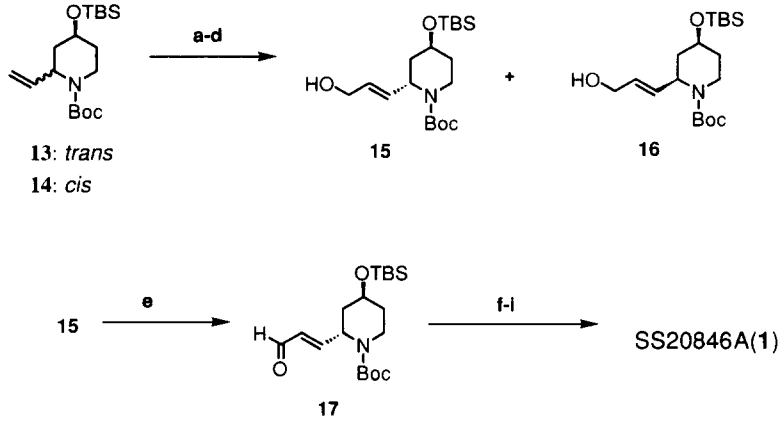
Scheme 1 a) $CH{\equiv}CCH_2OTHP$, *n*-BuLi, TMEDA, THF, -78 °C, 34%; b) TBAF, THF, 0 °C, 97%; c) TsCl, Pyridine, CH_2Cl_2, r.t., 52%; d) K_2CO_3, MeOH, 0 °C, 86%; e) KCN, MeOH, sat. $MgSO_4$aq., r.t., 99%; f) TBSCl, imidazole, DMF, r.t., 99%; g) $LiAlH_4$, Et_2O, 0 °C; h) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t., 2 steps = 39%; i) PPTS, MeOH, r.t., 49%; j) H_2, Lindlar cat., AcOEt, 0 °C, 95%; k) $PdCl_2(MeCN)_2$, THF, 0 °C., 89%(**13** : **14** = 85 : 15)

Pd-catalyzed cyclization of **2** was performed as follows. To a stirred solution of 10 mol% $PdCl_2(MeCN)_2$ in THF was added a solution of the substrate **2** in THF at 0 °C. The mixture was stirred for 1 h and usual workup gave a mixture of **13** and **14** (89% yield) in a ratio of 85:15[10]. A possible explanation for the stereoselective formation of **13** is as follows (Scheme 2). If the transition states are assumed to be **A** and **B**, the transition state **B**, which leads to **14**, would be disfavored because of non-bonding interaction between the carbamate moiety and the palladium complex.



Scheme 2

Next, the conversion of **13** to SS20846A was examined in the following way. The alcohol **15**[11] was prepared in 4 steps (dihydroxylation of olefin (OsO_4, NMO; 89% yield), reductive degradation ($NaIO_4$, CH_2Cl_2; 87% yield), Wittig reaction, and reduction (DIBAL, THF; 96% yield))[12]. Swern oxidation of **15** followed by Wittig reaction, olefin isomerization, and deprotection gave SS20846A in 22 % overall yield. The physical data for the synthetic product were in accordance with those reported for SS20846A[1a, 13].



Scheme 3 a) OsO_4, NMO, dioxane, r.t., 89%; b) $NaIO_4$, H_2O, CH_2Cl_2, 0 °C, 87%; c) $(EtO)_2POCH_2CO_2Et$, NaH, THF, -78 °C, 80%; d) DIBAL, THF, -78 °C, 96%; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 89%; f) $CH_3CH_2PPh_3Br$, *n*- BuLi, Et_2O, -78 °C, 84%; g) TBAF, THF, 0 °C, 97%; h) I_2, benzene, r.t., 30%; i) CF_3CO_2H, CH_2Cl_2, 0 °C,100%

In summary, a facile synthesis of SS20846A(**1**) was accomplished by using intramolecular palladium(II)-catalyzed *N*-alkylation as a key step. This catalytic *N*-alkylation is expected to be useful in the stereoselective synthesis of piperidine alkaloids.

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8. Yields were not optimised. All new compounds gave satisfactory spectral analyses. The details of these products will be reported elsewhere.
9. Data for **2** ; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.72 (dtt, J = 1.5, 6.8, 11.0 Hz, 1H), 5.52 (dtt, J = 1.2, 7.6, 11.0 Hz, 1H), 4.89 (br, 0.7H), 4.25-4.10 (m, 2H), 3.81 (quint, J = 5.6 Hz, 1H), 3.20-3.10 (m, 2H), 2.32-2.27 (m, 2H), 1.69-1.56 (m, 2H), 1.41 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H); IR (neat) 3355, 2931, 2859, 1695cm^{-1}, $[\alpha]^{28}_D$ -13.3° (c = 0.75, $CHCl_3$); Anal. Calcd for $C_{18}H_{37}O_4NSi$: C, 60.13; H, 10.37; N, 3.90. Found : C, 59.94; H, 10.57; N, 3.78.
10. The ratio was measured by ^{1}H-NMR analysis.
11. Data for **15** ; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.70-5.60 (m, 2H), 4.90 (brs, 1H), 4.16 (s, 2H), 4.00 (brd, J = 13.7 Hz, 1H), 3.80 (tt, J = 4.4, 11.2 Hz, 1H), 2.84 (td, J = 2.7, 13.7 Hz, 1H), 1.95-1.88 (m, 1H), 1.80-1.73 (m, 1H), 1.63 (ddd, J = 6.1, 11.2, 13.0 Hz, 1H), 1.48-1.38 (m, 10H), 0.87 (d, J = 0.5 Hz, 9H), 0.05 (s, 6H); IR (neat) 3445, 2931, 2859, 1696 cm^{-1}; $[\alpha]^{25}_D$ -17.4° (c = 0.30, $CHCl_3$)
12. The isomers **15** and **16** (85 : 15) could be separated by silica gel column chromatography.
13. $[\alpha]^{29}_D$ -15.2° (c = 0.34, $CHCl_3$) (lit. $[\alpha]^{20}_D$ -15° (c = 1.00, $CHCl_3$))[1a)]