Pergamon

Tetrahedron Letters 39 (1998) 5971–5974

TETRAHEDRON LETTERS

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

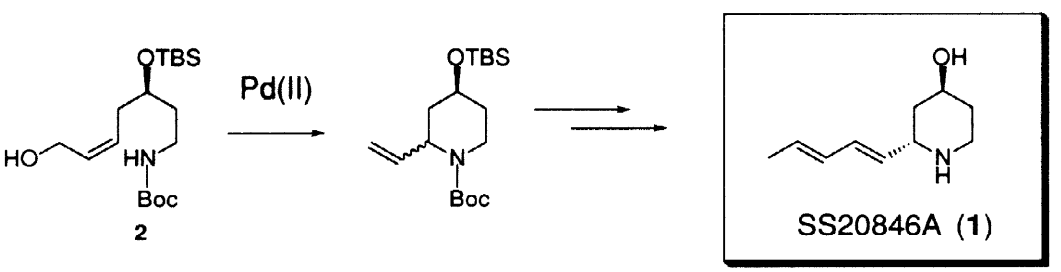
Hajime Yokoyama, Kumiko Otaya, Seiji Yamaguchi and Yoshiro Hirai*

Department of Chemistry, Toyama University, Gofuku 3190, Toyama 930, Japan

Received 22 April 1998; revised 8 June 1998; accepted 12 June 1998

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

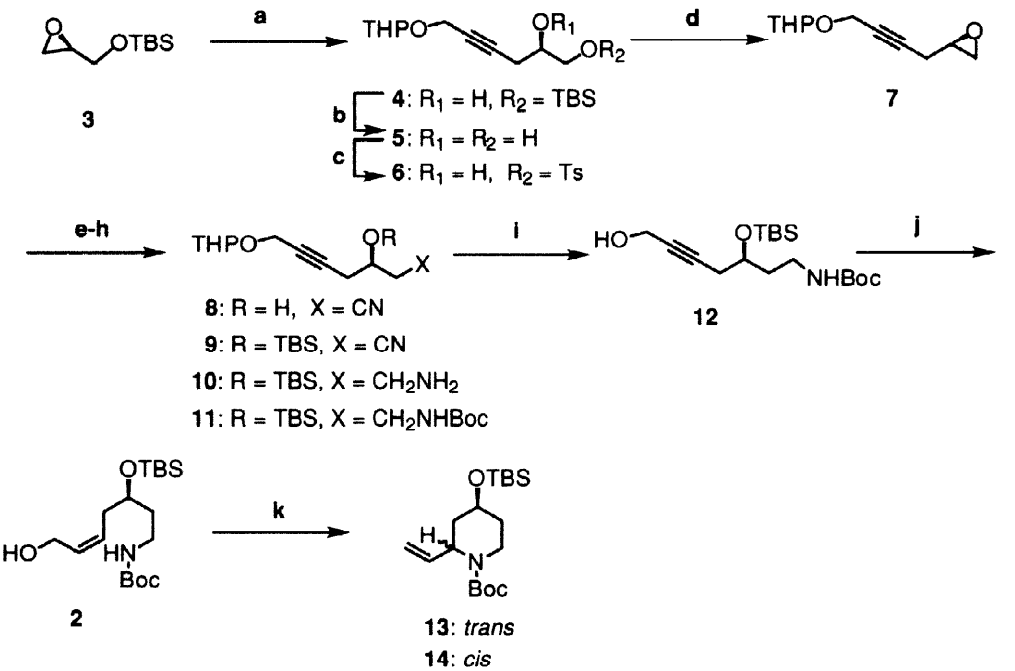
SS20846A(**1**) is a biologically active piperidine alkaloid isolated from *Streptomyces* sp. S20846[1,2]. It is also a biosynthetic intermediate of streptazolin[3,4]. For several years we have been investigating the stereoselective construction of nitrogen hetero-alicycles via the intramolecular palladium(II)-catalyzed 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

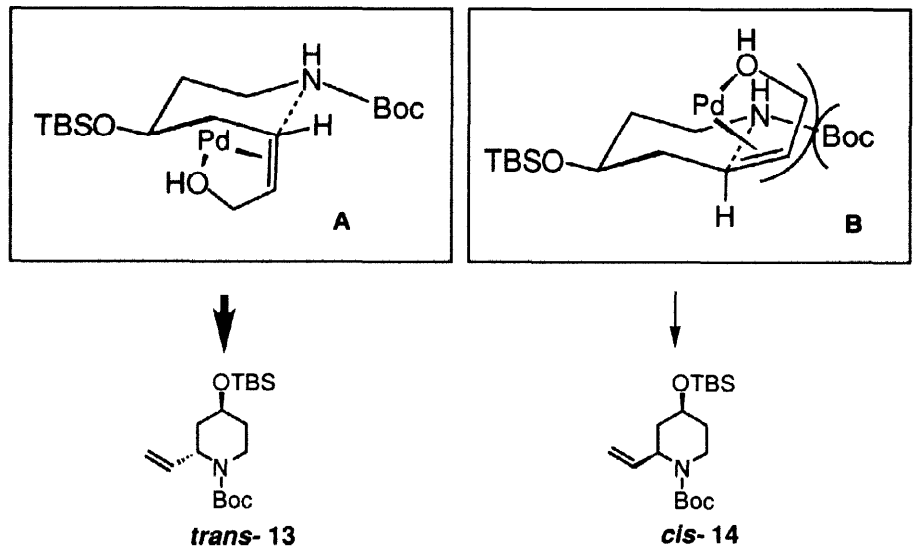
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01225-8

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].



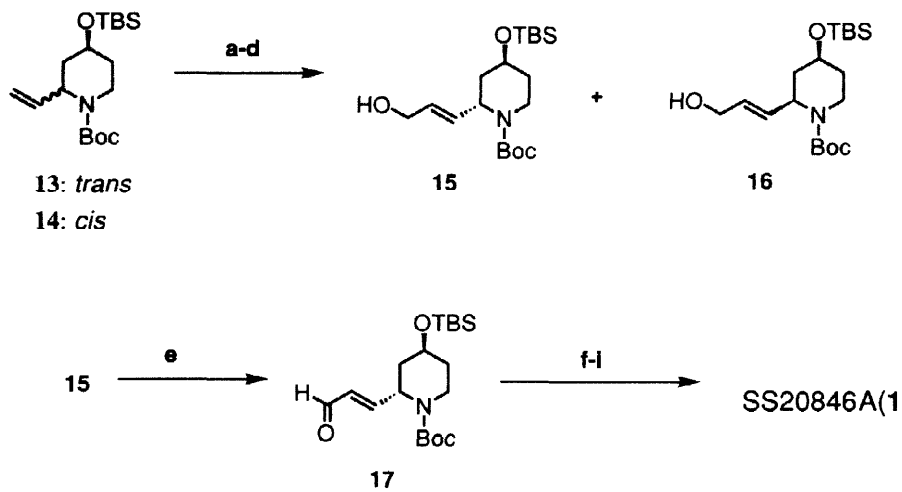
Scheme 1 a) $CH{\equiv}CCH_2OTHP$, *n*-BuLi, TMEDA, THF, -78 °C, 34%; b) TBAF, THF, 0 °C, 97%; c) TsCl, Pyridine, CH_2Cl_2, r.t., 52%; d) K_2CO_3, MeOH, 0 °C, 86%; e) KCN, MeOH, sat. $MgSO_4$aq., r.t., 99%; f) TBSCl, imidazole, DMF, r.t., 99%; g) $LiAlH_4$, Et_2O, 0 °C; h) $(Boc)_2O$, Et_3N, CH_2Cl_2, 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.

Acknowledgment. We are grateful for Dr. Yoshiji Takemoto, Kyoto University, for his kind gift of the spectral data for SS20846A. This work financially supported by the Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

References and Notes

1. (a) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. *J. Antibiot.* **1991**, *44*, 797. (b) Komoto, T.; Yano, K.; Ono, J.; Okawa, J.; Nakajima, T. *Jpn. Kokai 35788 ('86)*, Feb. 20, 1986.
2. Takemoto, Y.; Ueda, S.; Takeuchi, J.; Nakamoto, T.; Iwata, C. *Tetrahedron Lett.* **1994**, *35*, 8821.
3. Isolation; Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chem. Acta.* **1981**, *64*, 1752.
4. Synthesis; (a) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054. (b) Kozikowski, A. P.; Park, P. *J. Org. Chem.* **1990**, *55*, 4668. (c) Flann, C. J.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109* , 6115. (d) Kozikowski, A. P.; Park, P. *J. Am. Chem. Soc.* **1985**, *107* , 1763.
5. (a) Hirai, Y.; Yokoyama, H. *Yugouka* , **1998**, *56*, 34. (b) Hirai, Y.; Shibuya, K.; Fukuda, Y.; Yokoyama, H.;Yamaguchi, S. *Chem. Lett.* **1997**, 221. (c) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776. (d) Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21. (e) Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893.
6. For palladium(0)-promoted cyclization, see; (a) Tamaru, Y.; Tanigawa, H.; Itoh, S.; Kimura, M.; Tanaka, S.; Fugami, K.; Sekiyama, T.; Yoshida, Z. *Tetrahedron Lett.* **1992**, *33*, 631. (b) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731. (c) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994. (d) Tamaru, Y.; Hojo, M.; Kawamura, S.; Yoshida, Z. *J. Org. Chem.* **1986**, *51*, 4089.
7. (a) Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681. (b) Tadano, K.; Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Ogawa, S. *SYNLETT*, **1993**, 565.
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)]