Tetrahedron Letters,Vol.30,No.42,pp 5721-5724,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

DIVERGENT SYNTHESES OF STEREOISOMERS OF SWAINSONINE: (-)-8-*epi*-, (-)-8a-*epi*- AND (-)-8,8a-di*epi*-SWAINSONINE[1]

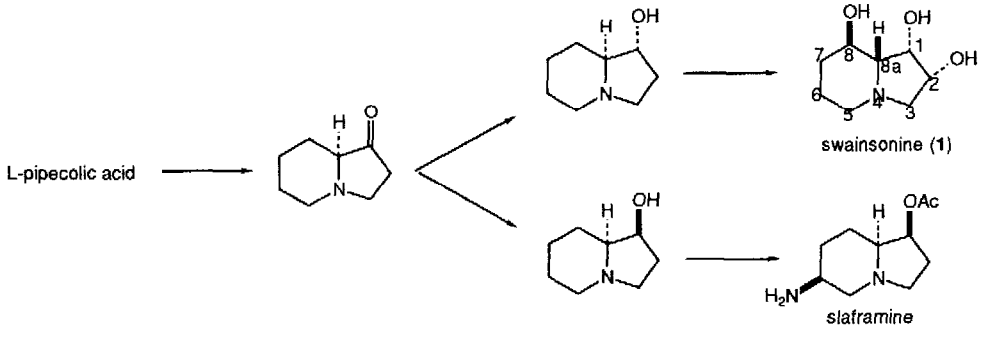
Young Gyu Kim and Jin K. Cha*
Department of Chemistry, Vanderbilt University, Nashville, TN 37235, U.S.A.

Abstract: Divergent stereoselective syntheses of three stereoisomers **2-4** of swainsonine (**1**) starting from the readily available common intermediates **5a,b** are described. A moderate to good stereoselectivity has been achieved by an allylic oxygen substituent.

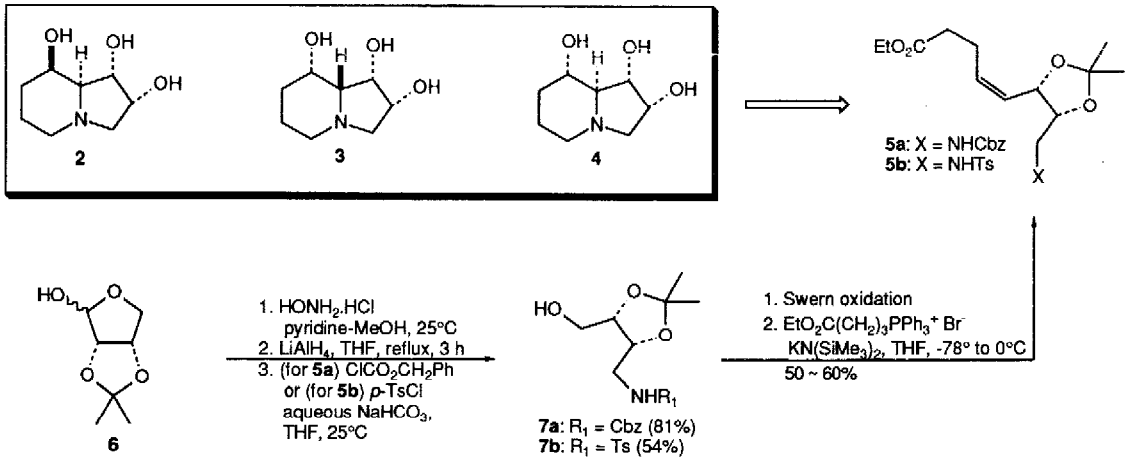
Concurrent with our studies which led to a short, stereoselective synthesis of (-)-swainsonine (**1**),[2,3] a potent immunomodulator, we have been interested in the preparation of its stereoisomers from a common intermediate. Preparation of 8a-*epi*-swainsonine (**2**), 8-*epi*-swainsonine (**3**), and 8,8a-di*epi*-swainsonine (**4**) would be valuable not only in investigating the timing of C-8 hydroxylation and iminium ion formation in biosynthetic studies of swainsonine (Scheme I), but also in locating their presence in the culture medium. It is likely that the isomer **2** is a biosynthetic precursor to **1**.[4] Furthermore, the preparation of stereoisomers and structural analogs of swainsonine is of current interest in the attempt to elucidate the correlation of structure and biological activity.[5,6] Herein we describe divergent syntheses of **2-4** from the readily available common intermediates **5a** and **5b**, with particular attention to the diastereoselection induced by an allylic oxygen substituent.[7]

We anticipated that various modes of electrophile-mediated cyclization of olefins **5a** and **5b** would provide an easy entry to swainsonine and its stereoisomers.[6] As illustrated in Scheme II, the requisite starting materials were most conveniently prepared in good yield starting from the known 2,3-O-isopropylidene-L-erythrose (**6**).[8] Thus, treatment of **6** with hydroxylamine, followed by LAH reduction and protection (with benzyl chloroformate or *p*-TsCl) gave alcohols **7a** and **7b**, respectively. Swern oxidation[9] and subsequent Wittig reaction with (3-carbethoxypropyl)triphenylphosphonium bromide gave the desired Z olefins **5a** and **5b** in 50~60% overall yield .[10]

Scheme I: The postulated biosynthetic pathway of swainsonine (**1**) and slaframine in *Rhizoctonia leguminicola*.[4]

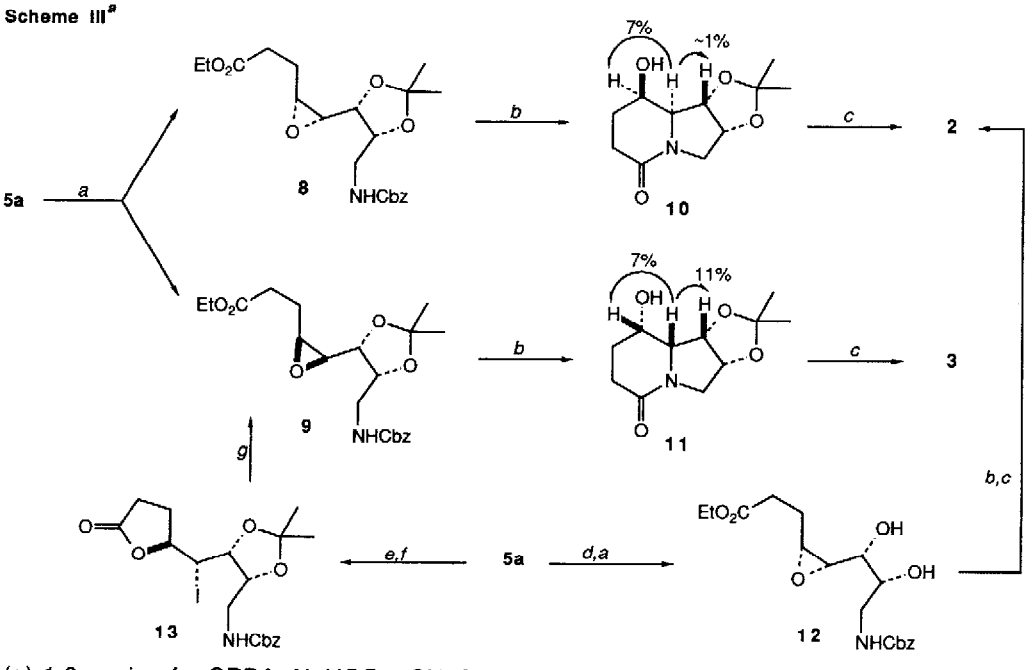


Scheme II



Not surprisingly, epoxidation of **5a** with mCPBA gave an equal mixture of epoxides **8** and **9** in 86% yield. After ready separation by SiO_2 column chromatography, each epoxide was then converted to the desired alkaloids **2** and **3** in three steps (50~60% overall yield): 1. H_2, 10% Pd/C, EtOH ; 2. reflux, EtOH; 3. BH_3, THF, followed by 6N HCl. Assignment of the structures for indolizidine lactams **10** and **11** was made from the determination of nuclear

Scheme III[a]



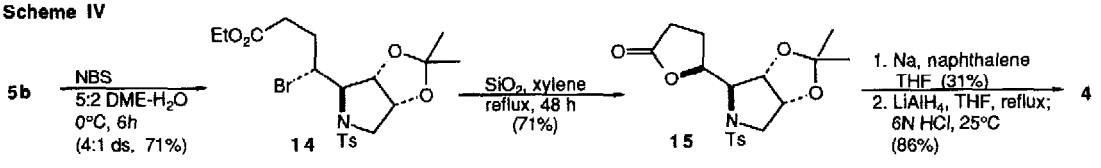
[a] (a) 1.2 equiv of mCPBA, $NaHCO_3$, CH_2Cl_2, 25°C, 24 h; (b) 10% Pd-C, 1 atm of H_2, EtOH, 25°C, followed by EtOH, reflux, 80~90%; (c) 10 equiv of BH_3·THF, reflux, 4 h, followed by 6N HCl, THF, 25°C, 83%; (d) 5 equiv of PPTS, MeOH, 25°C, 72h, 90%; (e) 5 equiv of K_2CO_3, MeOH/H_2O (2:1), 25°C, 24 h, 84~90%; (f) 3 equiv of I_2, 5 equiv of $NaHCO_3$, CH_3CN, 0°C, 24 h, 60~90%; (g) 5 equiv of K_2CO_3, EtOH, 25°C, 24 h, 88%.

Overhauser effects: the percentage NOE observed are shown in Scheme III. Also, the swainsonine stereoisomers **2** and **3** were found to exhibit physical and spectroscopic data identical with published results.[c] The one-pot tandem cyclization approach to indolizidines **10** and **11** from epoxy amino esters **8** and **9**, respectively, is reminiscent of previous syntheses of **1** by Sharpless[3e] and Fujisawa chemists.[3f]

Stereoselective routes for **2** and **3** were then investigated. Deprotection of acetonide **5a** and subsequent hydroxyl-directed epoxidation of the resulting diol gave the *threo* epoxide **12** in *ca.* 5:1 selectivity. The sense and extent of the epoxidation is in accord with similar literature examples,[11] and was confirmed by the straightforward conversion of **12** to **2**. On the other hand, the basic hydrolysis of ester **5a**, followed by halolactonization of the resulting acid gave lactone **13** in *ca.* 5:1 diastereoselectivity, which was found to be dependent on the reaction conditions. Treatment of the latter with K_2CO_3-EtOH then gave epoxide **9** in 55% overall yield. It is noteworthy that the kinetic lactonization of a somewhat similar E olefin has been reported to give nearly equal proportions of the two diastereomeric lactones.[7b]

Finally, haloamidation of sulfonamide **5b** proceeded with moderate (4:1) selectivity to afford (71% yield) the chromatographically inseparable mixture of pyrrolidine **14** and its diastereomer (Scheme IV). When the latter mixture was subjected to the lactonization procedure of Takeda,[12] a considerable difference in reactivity was observed, resulting in their kinetic (≥10:1) separation. Thus, the major product **14** cyclized preferentially to give lactone **15**, whereas the minor diastereomer remained virtually unchanged. Subsequent deprotection (sodium naphthalenide) of the tosyl group of **15** yielded the corresponding indolizidine lactam, which was then converted uneventfully to **4**. It should also be pointed out that the haloamidation of **5b** proceeded with *trans* stereoselectivity due to the buttressing effect of the Z-alkyl group.[7d]

Scheme IV



Forthcoming are biosynthetic studies utilizing d_2-**2** [HRMS (M^+) 175.1177 calcd for $C_8H_{13}D_2O_3N$, found 175.1167], which was readily prepared from **10** by $LiAlD_4$ reduction.

Acknowledgment Financial support from the National Institutes of Health (GM 35956) is gratefully acknowledged. We thank Professors Thomas and Constance Harris (Vanderbilt University), and Kenneth Olden (Howard University) for their interest. We are also indebted to Dr. Brian Sweetman (NIH RR01688) for obtaining the mass spectral data.

References and Footnotes

1. Presented in part at the 40th ACS Regional Meeting, Atlanta, GA, November 9~11, 1988: ORGN 493 & 534.

2. Bennett, R. B. III; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580.
3. (a) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853. (b) Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447; *Carbohydrate Res.* **1985**, *136*, 225. (c) Suami, T.; Tadano, K.-I.; Iimura, Y. *Chem. Lett.* **1984**, 513; *Carbohydrate Res.* **1985**, *135*, 67. (d) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1984**, 1201. (e) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420. (f) Setoi, H.; Takeno, H.; Hashimoto, M. *ibid.*, **1985**, *50*, 3948. (g) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140. (h) Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022.
4. For an elegant biosynthetic investigation of **1** in the fungus *Rhizoctonia leguminicola*, see Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 940 and references cited therein.
5. Cenci di Bello, I.; Fleet, G.; Namgoong, S. K.; Tadano, K.-I.; Winchester, B. *Biochem. J.* **1989**, *259*, 855.
6. (a) Synthesis of **2**: Tadano, K.-I.; Hotta, Y.; Morita, M.; Suami, T.; Winchester, B.; Cenci di Bello, I. *Chem. Lett.* **1986**, 2105; Bull. Chem. Soc. Jpn. **1987**, *60*, 3667. (b) syntheses of **3**: Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1985**, 31. Iimura, Y.; Hotta, Y.; Fukabori, C.; Tadano, K.-I.; Suami, T. *J. Carbohydr. Chem.* **1986**, *5*, 147; *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3885. Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140. Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095. (c) synthesis of **4**: Tadano, K.-I.; Morita, M.; Hotta, Y.; Ogawa, S.; Winchester, B.; Cenci di Bello, I. *J. Org. Chem.* 1988, 53, 5209.
7. For related electrophilic cyclizations, see (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. Chamberlin, A. R.; Mulholland, R. L. Jr.; Kahn, S. D.; Hehre, W. J. *Ibid.* **1987**, *109*, 672. (c) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063. Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4062. (d) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. III *J. Org. Chem.* **1987**, *52*, 4191. (e) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 2011, and references cited therein.
8. (a) Baxter, J. N.; Perlin, A. S. *Can. J. Chem.* **1960**, *38*, 2217. (b) Lerner, L. M. *Carbohydrate Res.* **1969**, *9*, 1.
9. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
10. Satisfactory spectroscopic data were obtained for all new compounds. Listed below are some selected spectroscopic data:

    (a) **2**: mp 116~118 °C [lit.[6a] mp 122~124 °C]; $[\alpha]^{25}_D$ = -64° (c 0.84, MeOH) [lit.[6a] $[\alpha]^{19}_D$ = -64.5° (c 0.95, MeOH)]; ^{1}H NMR (D_2O, 300 MHz) δ 1.43~1.57 (m, 2H), 1.62~1.73 (m, 1H), 1.80~1.89 (m, 1H), 2.03~2.13 (m, 3H), 2.90 (m, 1H), 3.35 (dd, 1H, J = 6.8 and 10.5 Hz), 3.83 (dd, 1H, J = 7.1 and 8.9 Hz), 4.05~4.12 (m, 2H); ^{13}C NMR (D_2O, ref CH_3OH, 100 MHz) δ 19.10, 29.85, 52.33, 60.37, 63.39, 66,69, 69.41, 69.65; HRMS (M^+) 173.1052 calcd for $C_8H_{15}O_3N$, found 173.1052.

    (b) **3**: $[\alpha]^{25}_D$ = -20° (c 0.30, MeOH) [lit.[6b] $[\alpha]^{21}_D$ = -24.8° (c 0.67, MeOH)]; ^{1}H NMR (D_2O, 300 MHz) δ 1.38~1.52 (m, 2H), 1.72~1.88 (m, 2H), 2.02 (m, 1H), 2.08 (dd, 1H, J = 1.2 and 4.3 Hz), 2.40 (dd, 1H, J = 7.3 and 11.1 Hz), 2.86 (dd, 1H, J = 2.0 and 11.1 Hz), 2.99 (m, 1H), 4.25 (ddd, 1H, J = 2.0, 6.2 and 7.3 Hz), 4.33 (m, 2H); ^{13}C NMR (D_2O, ref CH_3OH, 100 MHz) δ 18.94, 30.08, 52.58, 60.40, 66.36, 66,97, 68.65, 72.62; HRMS (M^+) 173.1052 calcd for $C_8H_{15}O_3N$, found 173.1049.

    (c) **4**: $[\alpha]^{25}_D$ = -14° (c 0.51, MeOH) [lit.[6c] $[\alpha]^{22}_D$ = -21.2° (c 0.78, MeOH)]; ^{1}H NMR (D_2O, 300 MHz) δ 1.19~1.33 (m, 1H), 1.37~1.55 (m, 1H), 1.67~1.77 (m, 1H), 1.91 (t, 1H, J = 8.6 Hz), 1.94~2.10 (m, 2H), 2.20 (dd, 1H, J = 6.3 and 10.3 Hz), 2.85 (m, 1H), 3.34 (dd, 1H, J = 6.9 and 10.3 Hz), 3.48 (m, 1H), 3.87 (t, 1H, J = 7.6 Hz), 4.13 (m, 1H); ^{13}C NMR (D_2O, ref CH_3OH, 100 MHz) δ 23.12, 32.73, 51.09, 59.44, 67.16, 71.28, 72.10, 73.72; HRMS (M^+) 173.1052 calcd for $C_8H_{15}O_3N$, found 173.1055.

    (d) **5a**: $[\alpha]^{25}_D$ = +58° (c 2.30, $CHCl_3$); IR ($CHCl_3$) 3450, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, 3H, J = 7.2 Hz), 1.37 (s, 3H), 1.46 (s, 3H), 2.39 (m, 4H), 3.10 (ddd, 1H, J = 4.2, 8.6 and 13.1 Hz), 3.35 (ddd, 1H, J = 4.2, 7.4 and 13.1 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.24 (m, 1H), 5.01 (m, 1H), 5.10 (br s, 3H), 5.46 (dd, 1H, J = 8.8 and 11.0 Hz), 5.61 (m, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.10, 23.16, 25.32, 27.95, 33.63, 41.70, 60.43, 66.64, 72.95, 76.70, 108.61, 125.68, 127.98, 128.38, 133.02, 136.49, 156.25, 172.58.
11. (a) Pierre, J.-L.; Chautemps, P.; Arnaud, P. *Bull. Soc. chim. Fr.* **1969**, 1317. (b) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549.
12. Tsuboi, S.; Fujita, H.; Muranaka, K.; Seko, K.; Takeda, A. *Chem. Lett.* **1982**, 1909.

(Received in USA 10 July 1989)