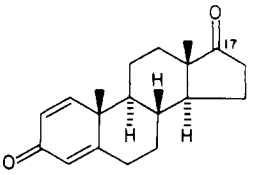
4 h generated two ketals. The ratio of (conversion of **11** to **11**-ethylene ketal)/(conversion of **12** to **12**-ethylene ketal) was 1:7.3. This example indicates that, in the absence of steric bias, nonconjugated carbonyl groups are ketalized much faster than α,β-unsaturated ketones by the reagents Me_3SiOTf/BTSE. Also, Me_3SiOTf is generally regarded as a strong aprotic acid.[4b] Therefore, selective ketalization of the enone moiety in **5** must not be due to the acidity of the catalyst but to the other factor—steric hindrance.

The trimethylsilyl cationic species can also bias a less congested enone moiety vs. a more hindered acetyl functionality. Thus, reaction of progesterone (**8**) and BTSE (1.2 equiv) with a catalytic amount (0.03 equiv) of Me_3SiOTf afforded the isomeric ketals **9**[11] and **10**,[11] plus a small amount of diketal. The ratio of **9**:**10** obtained with the Me_3SiOTf/BTSE system (2.7:1) was remarkably different from that obtained with an H^+/ethylene glycol system (1:3.5).[11] However, this Me_3Si^+-catalyzed reaction proceeded very slowly at −78 °C. Raising the temperature to −60 °C in an attempt to accelerate the reaction gave lower selectivity (1:1). Addition of more Me_3SiOTf (0.10 equiv) did not change the reaction rate significantly.

Excellent selectivity was observed with two additional dicarbonyl substrates. Thus, when 7,7-dimethyl-6-oxo-2-octenal (**13**) was stirred with BTSE (1.05 equiv) and Me_3SiOTf (0.02 equiv) at −78 °C for 5 h, acetal **14** was obtained as the only major product (91%). The corresponding ketal could not be detected.[12] To our knowledge, this is the first example of acetalization of an α,β-unsaturated aldehyde with BTSE and Me_3SiOTf.

Selective protection of a benzylic ketone function in the presence of a nonconjugated ketone group was also achieved. Treatment of **15** with BTSE (1.15 equiv) and Me_3SiOTf (0.25 equiv) in CH_2Cl_2 at ~−45 °C for 31 h gave **16**[13] in 82% yield. The monodioxolane that would have resulted from reaction of BTSE with the nonconjugated carbonyl group in **15** could not be detected in the reaction mixture.[14] Substrate **15** did not react with BTSE and Me_3SiOTf at −78 °C in CH_2Cl_2.

We have also found that the cross-conjugated dienone moiety is inactive toward Me_3SiOTf/BTSE. Under the same conditions used for the other substrates, no reaction occurred with 1,4-androstadiene-3,17-dione (**17**) at −78 °C



17

in 26 h. Comparing this result with that obtained for substrate **3**, it surprises us that the C-17 carbonyl group in **17** is inert. This may be due to a conformational transmission effect. Such effects are well-known to occur in steroids.[15]

In conclusion, the role of Me_3Si^+ in dioxolanation is similar to that of H^+. However, the bulkiness of Me_3Si^+ allows it to differentiate between carbonyl groups on the basis of steric hindrance. Our evidence confirms that Me_3Si^+ can be regarded as a bulky proton. Its unique properties with regard to chemoselectivity possess synthetic value.

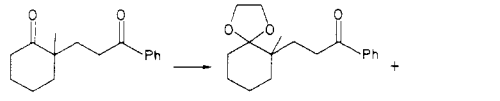
Acknowledgment. This research was supported by grants from Research Corporation, the Petroleum Research Fund, administered by the donors of the American Chemical Society, and BRSG Grant S07 RR7041, awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health. We are grateful to Professor Alex Nickon for valuable suggestions and discussion. Support from NSF (PCM83-03176) and NIH (1 S10 RR01934) for the purchase of a Varian XL-400 NMR spectrometer is acknowledged.

(11) Brown, J. J.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1964**, *86*, 2183. ^1H NMR ($CDCl_3$) of **9**: δ 5.23 (br s, 1 H), 3.97 (m, 4 H), 2.11 (s, 3 H), 2.67–0.74 (m, 20 H), 1.03 (s, 3 H), 0.63 (s, 3 H).

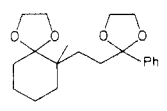
(12) In the absence of significant steric bias, a nonconjugated ketone is dioxolanated more rapidly than an α,β-unsaturated aldehyde with BTSE and Me_3SiOTf; see: Leu, L.-C.; Robl, J. A.; Wetzel, J. M.; Hwu, J. R., submitted for publication. ^1H NMR ($CDCl_3$) of **14**: δ 5.96 (dt, *J* = 15.3, 6.0 Hz, 1 H), 5.49 (dd, *J* = 15.3, 6.0 Hz, 1 H), 5.17 (d, *J* = 6.0 Hz, 1 H), 3.93 (m, 4 H), 2.70–2.10 (m, 4 H), 1.13 (s, 9 H).

(13) ^1H NMR of **16** ($CDCl_3$): δ 7.40–7.23 (m, 5 H), 4.10–3.63 (m, 4 H), 2.35–1.02 (m, 10 H), 0.88 (s, 3 H), 0.85 (s, 3 H), 0.76 (s, 3 H).

(14) As in the case of α,β-unsaturated aldehydes, significant steric bias is required in order to selectively dioxolanize a benzylic ketone moiety in the presence of a nonconjugated ketone group with bulky proton containing reagents. E.g., **18** with BTSE (0.98 equiv) and Me_3SiOTf (0.09 equiv) in CH_2Cl_2 at −78 °C for 78 h gave **19** as the only monodioxolane product (68%), along with diketal **20** (30%).



18 **19**



20

(15) (a) Barton, D. H. R.; Head, A. J.; May, P. J. *J. Chem. Soc.* **1957**, 935. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis;" Interscience; reprinted by the American Chemical Society: Washington, DC, 1981; p 345.

Jih Ru Hwu,* John M. Wetzel
Department of Chemistry
The Johns Hopkins University
Baltimore, Maryland 21218
Received December 20, 1984

Enantiospecific Total Synthesis of (−)-Swainsonine: New Applications of Sodium Borohydride Reduction

Summary: A short, enantiospecific synthesis of (−)-swainsonine (**1**) from D-mannose has been achieved by a route involving, as a key step, a double cyclization of **4c**. The synthesis takes advantage of new features of sodium borohydride for reducing conjugated esters and lactams.

Sir: Swainsonine (**1**) is a representative of the class of polyhydroxylated indolizidine alkaloids which inhibit the biosynthesis of oligosaccharides through their glycosidase inhibitory activities.[1-3] It has recently been found that

(1) Isolation: (a) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. (b) Malyneux, R. J.; James, L. F. *Science (Washington, D.C.)* **1982**, *216*, 190. (c) Schneider, M. J.; Ungermach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1982**, *39*, 29.

(2) Activity: (a) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 7393. (b) Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936. (c) Chotai, K.; Jennings, C.; Winchester, B.; Dorling, P. R. *J. Cell Biochem.* **1983**, *21*, 107. (d) Greenaway, V. A.; Jessup, W.; Dean, R. T.; Dorling, P. R. *Biochem. Biophys. Acta* **1983**, *762*, 569. (e) Winkler, J. R.; Segal, H. L. *J. Biol. Chem.* **1984**, *259*, 1958.

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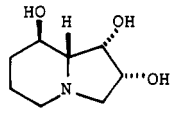
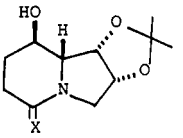
swainsonine, isolated from the cultured broth of *Metarhizium anisopliae* F-3622 in our laboratories, has an ability to restore, in mouse spleen cells, mitogenic responses depressed by immunosuppressive factors in the tumor-bearing mouse serum.[4] This biological result of swainsonine aroused our interest in establishing a practical total synthesis of this alkaloid for providing the amounts necessary for detailed biological evaluations.

The success of this synthesis entirely depends upon how efficiently the indolizidine ring of swainsonine can be constructed. We envisioned that this ring could be constructed by a one-step double cyclization of the epoxy amine ester **4c** to the lactam **3** (as shown in **4**),[5] followed

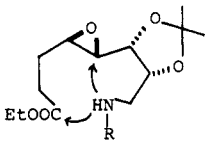


1

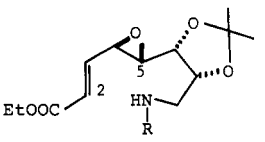


2 X= H_2

3 X= O



4



5

a R= $CO_2CH_2C_6H_5$ (Cbz)

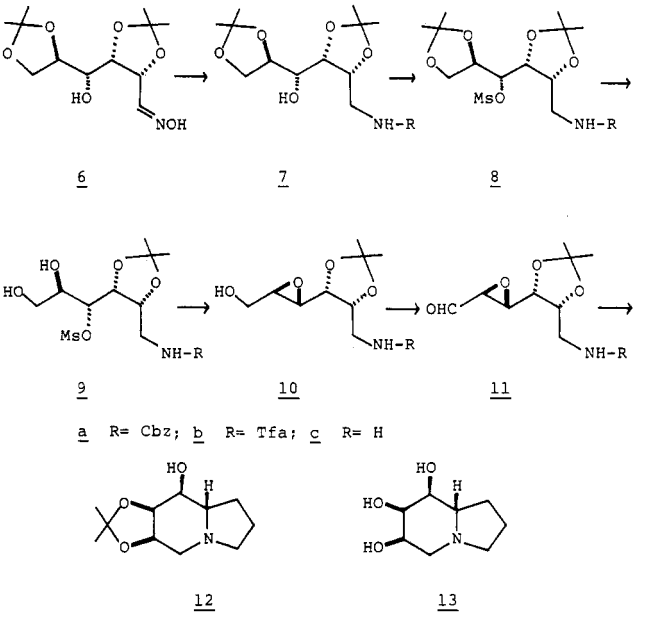
b R= $COCF_3$ (Tfa)

c R= H

by reduction of the lactam carbonyl in **3** to the protected swainsonine **2**. We have found in this investigation that sodium borohydride reduces, in the presence of trifluoroethanol (TFE), the conjugated ester **5a** to the key intermediate **4a** and, further, the lactam **3** to **2**. Therefore, we further envisioned that, when the amino group in **5c** would be appropriately protected so as to be regenerated by a $NaBH_4$ treatment (e.g., trifluoroacetyl, Tfa), a direct conversion of **5b** to **2** could result through a synchronous occurrence of a sequence of reactions: reduction and deprotection of **5b** to **4c**, double cyclization of **4c** to **3**, and reduction of **3** to **2**. Herein we report an extremely short, enantiospecific total synthesis of (−)-swainsonine (**1**) from D-mannose by a route involving, as a key step, the above conversion of **5b** to **2**.

The requisite intermediate **5a** (Cbz series) for our initial investigation was prepared in a straightforward manner from the oxime **6**,[6] readily accessible from D-mannose (Scheme I). Reduction of the oxime group in **6** with $LiAlH_4$ (THF, room temperature), followed by acylation of the resulting amine **7c** with $C_6H_5CH_2OCOCl$ (THF–H_2O, 0 °C), gave the compound **7a** (100% yield from **6**), which was then treated with MsCl (pyridine, 0 °C) to provide the mesylate **8a** (95%). Partial hydrolysis of the acetonide groups in **8a** was performed by treatment with TsOH (0.1 equiv, MeOH–H_2O, room temperature, 3 days) and followed by neutralization with Amberlite IRA-400 (OH^- type) to directly produce, via **9a**, the epoxide **10a** in 43% yield with a 33% recovery of **8a**. Oxidation of **10a** with Collins reagent (CH_2Cl_2, 5 °C) gave the aldehyde **11a** (unstable), which, without purification, was subjected to the Wittig reaction with $Ph_3P{=}CHCO_2Et$ (THF, 0 °C), yielding the desired trans-α,β-unsaturated ester **5a** in 43% yield from **10a**.

Scheme I



6 7 8

9 10 11

a R= Cbz; b R= Tfa; c R= H

12 13

We examined, at this stage, reduction of **5a** with $NaBH_4$ after several other attempts[7] and found that the reaction proceeded smoothly to give **4a**. Thus, **5a** was treated with $NaBH_4$ (10 equiv) in EtOH–TFE (10:1) at reflux for 1 h to afford **4a** in 58% yield.[8] After removal of the Cbz group in **4a** by catalytic reduction [H_2 (30 psi)/10% Pd–C/EtOH], the product **4c** (not isolated) was refluxed in EtOH for 4 h to provide the lactam **3** [mp 125–127 °C, 60%], which clearly arose via a spontaneous double cyclization as shown in **4**. Reduction of the lactam carbonyl in **3** was also effected by using $NaBH_4$ in the same manner as described above, giving swainsonine acetonide **2** in 60% yield.[9] Removal of the acetonide group in **2** (6 N HCl/THF, room temperature) provided **1** [mp 141–142 °C, $[\alpha]^{25}_D$ −79.8° (*c* 0.55, MeOH), 75%], identical with an authentic sample. The application of $NaBH_4$ to the reduction of **5a** and **3** is remarkable and this may be generally applicable to other conjugated esters and lactams (or amides).[8]

With these results in hand, we next focused on the direct one-step conversion of **5** to **2**. For this purpose, we prepared **5b** (Tfa series), after protection of the amine **7c** by acylation with $(Tfa)_2O$ (CH_2Cl_2, 0 °C), in an exactly parallel

(3) Synthesis: (a) Fleet, G. W. J.; Grough, 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. (c) Suami, T.; Tadano, K.; Iimura, Y. *Chem. Lett.* **1984**, 513. (d) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Ibid.* **1984**, 1201. (e) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 422.

(4) (a) Isolation: Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926. (b) Activity: Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 936.

(5) A stepwise cyclization approach using an intermediate similar to **4** was adopted by Sharpless et al.: see ref 3e.

(6) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273.

(7) For the reduction of **5a** to **4a**, several conditions (e.g., catalytic hydrogenations, $NaBH_4$ reductions) were examined and the use of $NaBH_4$ in the presence of TFE in EtOH gave the best result.

(8) The $NaBH_4$ reduction of **5a** to **4a** required the presence of an appropriately acidic proton source and TFE met this requirement. More acidic proton sources (e.g., AcOH or TFA) gave complex mixtures. Details will be reported elsewhere.

(9) Reduction of **3** was also effected by using $LiAlH_4$ in THF (room temperature, 2 h) to give **2** in 59% yield.

way to that for **5a**: **6** → **7b**, 95%; **7b** → **8b**, 81%; **8b** → **10b**, 35% with 25% recovery of **8b**; **10b** → **5b**, 44%. Differently from **5a**, however, the compound **5b** was obtained as a mixture of *E* and *Z* isomers (ca. 3:1).

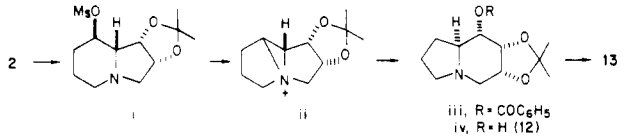
On treatment of **5b** using 10 equiv of $NaBH_4$ in the same way as described for the preparation of **4a** and **2**, the desired product **2** was obtained as expected in 32% total yield[10] and identified with the sample described above. This reaction, however, was found to coproduce the compound **12** (mp 85–86 °C, 23%), which was formed probably by attack of the amino group to the active allyl carbon (e.g., in **5c**) prior to the reduction of the conjugated ester group. These products were easily separated by simple silica gel chromatography in the yields described, respectively. The compounds **2** and **12** obtained here could be derived to **1** and its isomer **13** [mp 166–168 °C, $[\alpha]^{25}_D$ −36.3° (*c* 0.49, H_2O), 58%],[11,12] respectively.

The present synthesis of swainsonine constitutes a strategically new approach for the construction of the indolizidine ring system of the swainsonine type and also proves useful in the total synthesis of this class of alkaloids.[13] Moreover, this synthesis involves the attractive features of utilizing sodium borohydride for reducing the conjugated esters and the lactams, claiming new utility values of this reagent.

Supplementary Material Available: Experimental details of compounds prepared (10 pages). Ordering information is given on any current masthead page.

(10) Attempts for improving the yield of **2** and the ratio of **2** to **13** were not carried out at this stage.

(11) The structure of **13** was assigned on the basis of its spectral data and further confirmed by identification with the sample derived from **2** (1. mesylation of **2** to i; 2. conversion of i by treatment with $C_6H_5CO_2Na$ to iii via ii; 3. alkaline hydrolysis of iii to iv; 4. acid treatment of iv to **13**). Details will be reported separately.



(12) The mitogenic activity and the mannosidase inhibitory activity of **13** were somewhat weaker than those of **1**.

(13) Very recently, we have completed the synthesis of (+)-castanospermine, which will be reported in due course.

Hiroyuki Setoi, Hidekazu Takeno
Masashi Hashimoto*

Exploratory Research Laboratories
Fujisawa Pharmaceutical Co., Ltd.
2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan

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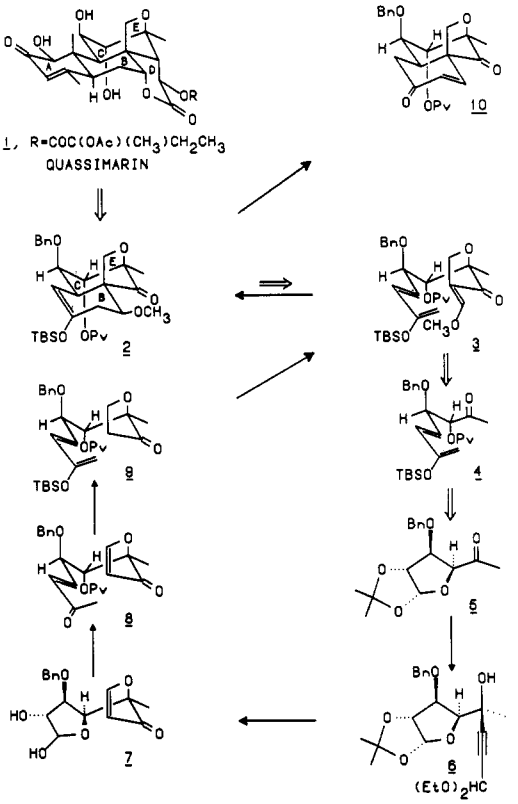
An Approach to Quassimarin Based on an Exo-Selective Intramolecular Diels–Alder Reaction

Summary: A novel exo-selective intramolecular Diels–Alder reaction is used to secure the preparation of the tricyclic adduct **2**, a material that contains three of the rings and five of the stereogenic centers present in the bitter principal quassimarin.

Sir: Quassimarin (**1**)[2] is a pentacyclic bitter principle which has elicited considerable synthetic activity.[3] Certainly, the most beguiling quality of **1** resides in the ring C ensemble, which serves not only as a linchpin for rings B, D, and E but also carries on the remaining nonannulated positions two hydroxyl groups, trans and diaxial to one another.

Our response to the issues presented by ring C led us to recast **1** in terms of the tricyclic species **2**. **2** possesses all but one of the stereogenic centers found on ring C and in addition carries a suitable ring B along with ring E. Via an exo-cyclic retro [4 + 2] cycloaddition,[4] **2** simplifies to the monocycle **3** which we hoped to secure by addition of an appropriate nucleophile to an equivalent of the methyl ketone **4**. The synthesis of **2** together with an X-ray structure of a product derived from **2** are given below.



The methyl ketone **5**[5] served as our synthetic equivalent of **4**. We required for the successful use of **5** in this synthetic scheme a nucleophilic reagent able to undergo Felkin addition onto the methyl ketone and to undergo ready reformulation into a 3-furanone residue. As might be imagined, a number of methods were examined before 1-lithio-3,3-diethoxypropyne[6] (3.1 equiv in Et_2O at −78 °C) was found to react with **5** (1 equiv) in the Felkin mode (17:1)[7] to give **6**, $[\alpha]_D$ −43.11° (*c* 2.35, CH_2Cl_2), in 87%

(1) Hooker Corp. Fellow, Sherman Clarke Fellow, ACS Graduate Fellow in Organic Chemistry.

(2) Kupchan, S. M.; Streelman, D. R. *J. Org. Chem.* **1976**, *41*, 3497. Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

(3) (a) Grieco, P. A.; Kanai, K.; Zelle, R. E.; Sham, H.-L.; Callant, P. *J. Org. Chem.* **1984**, *49*, 3867. (b) Batt, D. G.; Taramura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (c) Grieco, P. A.; Sham, H.-L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345. (d) Doyle, M.; Dunlap, N. K.; Watt, D. S.; Anderson, O. P. *J. Org. Chem.* **1983**, *48*, 3242. (e) Kraus, G. A.; Taschner, M.; Shimagaki, M. *Ibid.* **1982**, *47*, 4271.

(4) Schlessinger, R. H.; Wood, J. L.; Poss. A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146.

(5) Kiely, D. E.; Wall, H., Jr.; Black, R. L. *Carbohydr. Res.* **1973**, *31*, 387. Also see, Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535. Schmidy, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318. Schaffer, R.; Isbell, H. S. *J. Res. Nat. Bur. Stand. (U.S.)* **1956**, *56*, 191.

(6) LeCoq, A.; Gorgues, A. *Org. Synth.* **1980**, *59*, 10.

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