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General Approach for the Synthesis of Macroline/Sarpagine Related Indole Alkaloids *via* the Asymmetric Pictet-Spengler Reaction: The Enantiospecific Synthesis of (-)-Anhydromacrosalhine-methine.

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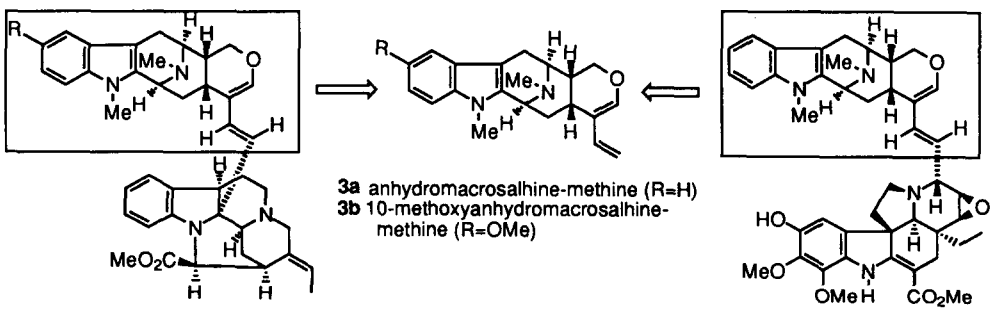
Abstract: *An enantiospecific total synthesis of (-)-anhydromacrosalhine-methine **3a** has been accomplished from D-(+)-tryptophan via the asymmetric Pictet-Spengler reaction. A partial synthesis of **3a** from the natural product (+)-ajmaline has also been completed.* Copyright © 1996 Elsevier Science Ltd

During the last several decades more than eighty indole alkaloids have been isolated from *Alstonia macrophylla* Wall, *Alstonia muelleriana* Domin, and other *Alstonia* species.[1,2] Among these alkaloids, at least eighteen are bisindoles including macrocarpamine **1** and villalstonine. Recently Wright *et al.*[3] isolated **1** from *Alstonia angustifolia* and reported it was active against *Entamoeba histolytica*. Macrocarpamine **1** apparently is the most potent of the bisindoles responsible for the use of *Alstonia angustifolia* against amoebic dysentery by the people of Malaya.[3] Furthermore, in 1988 Ghedira *et al.* reported the isolation of the related bisindoles 10-methoxymacrocarpamine **2** and 10-methoxymacrocarpamine-N-4'-oxide from the leaves of *Alstonia angustifolia*.[4]

Scheme 1



3a anhydromacrosalhine-methine (R=H)
3b 10-methoxyanhydromacrosalhine-methine (R=OMe)

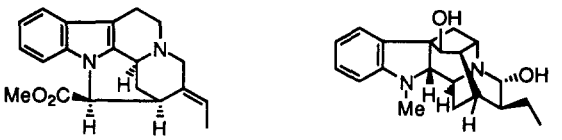
1 macrocarpamine (R=H)
2 10-methoxymacrocarpamine (R=OMe)

4 pandicine

(-)-Anhydromacrosalhine-methine **3a** was first obtained from the dehydration of macrosalhine.[5] In addition, under pyrolytic conditions **1**[6] was degraded into (-)-anhydromacrosalhine-methine **3a** and the other known base (+)-pleiocarpamine **5**. It is important to note that diene **3a** also comprises the northern portion of

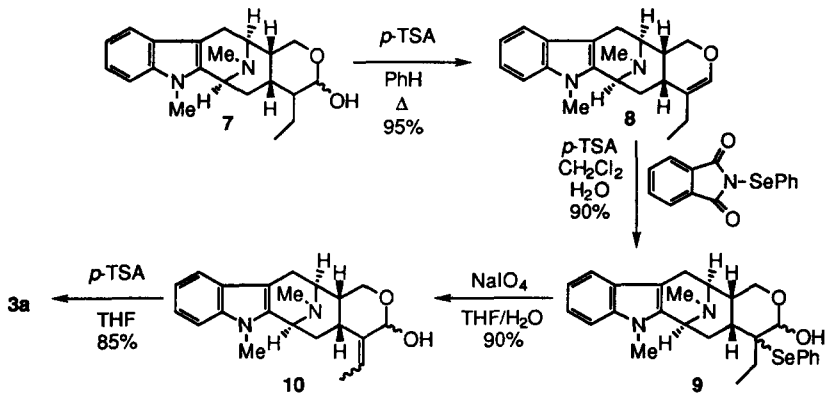
pandicine, a bisindole isolated from the leaves of *Pandacastrum saccharatum* Pichon.[7] The biogenetic origin of bisindole **1** has been proposed by Mayerl and Hesse[6] to arise by condensation of **3a** with pleiocarpamine **5**. In keeping with our interest in the synthesis of *Alstonia* bisindole alkaloids including **1**,[8-10] we wish to report an enantiospecific total synthesis of anhydromacrosalhine-methine **3a** from D-(+)-tryptophan *via* the asymmetric Pictet-Spengler reaction.[1,2] This route was chosen because it could presumably be extended to **3b** and to other ring-A alkoxylated indole alkaloids.

Figure 1



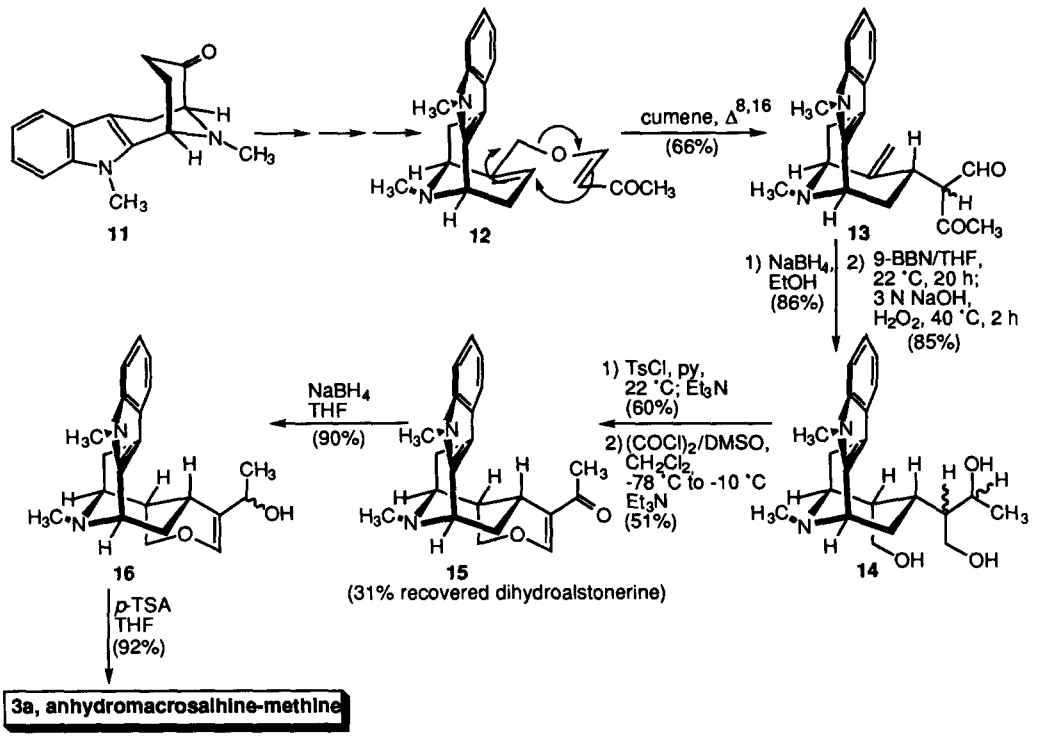
5 pleiocarpamine **6** (+)-ajmaline

Scheme 2



In order to obtain an authentic sample of **3a**, a partial synthesis from (+)-ajmaline **6** was first carried out. Degradation of ajmaline **6** to provide hemiacetal **7** was accomplished following the improved procedure of Sakai.[11] Dehydration of **7** to provide enol ether **8** was executed in 95% yield by stirring **7** with 1.1 equivalents of *p*-toluenesulfonic acid in refluxing benzene (Scheme 2). Attempts to introduce a functional group into the C-19 position of deoxyalstonerine **8**[12] by allylic bromination with NBS or allylic oxidation with various reagents failed. Consequently, the regioselective oxyselenation of the olefin **8** was carried out with N-phenylselenophthalimide[13] in CH_2Cl_2 in the presence of 2-3 equivalents of water and 1.3 equivalents of *p*-toluenesulfonic acid to afford **9** in 90% yield. Allylic alcohol **10** was obtained in 90% yield by selenoxide elimination of **9** on treatment with $NaIO_4$. Although treatment of **10** with 2,4-dinitrobenzenesulfonyl chloride[14] in the presence of triethylamine produced diene **3a** in 55% yield, the 1,4-elimination in **10** was improved by simply stirring this olefin with 1.1 equivalents of *p*-toluenesulfonic acid in dry THF to provide anhydromacrosalhine-methine **3a** in 85% yield (Scheme 2).

Scheme 3



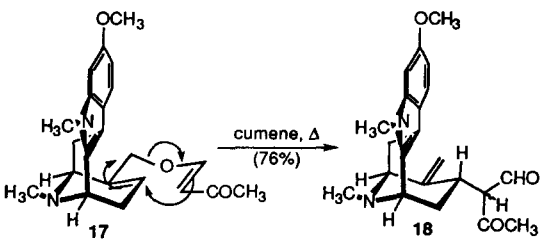
Since a sample of **3a** was now in hand, the enantiospecific total synthesis of **3a** was initiated from D-(+)-tryptophan.[1,2] The optically active tetracyclic ketone **11** (>98% ee) was prepared from D-(+)-tryptophan by a stereospecific regiospecific method developed in our laboratory and is now readily available.[15] The desired enone ether **12** required for the synthesis of **3a** was prepared from **11** in four steps by reported procedures.[8] The Claisen rearrangement (145°C) took place stereoselectively, as illustrated in Scheme 3, from the desired α face of **12** in 66% yield.[8] The diastereoselectivity of this process was at least 4:1 and maybe as high as 10:1 (see reference 16). The β-dicarbonyl compound **13** was reduced to a diol with sodium borohydride and this was followed by a stereospecific hydroboration-oxidation to furnish triol **14**.[8] The triol **14** was then regioselectively cyclized to tetrahydroalstonerine and the tetrahydropyran which resulted was oxidized to the desired enone **15** under modified Swern conditions.[8] (-)-Alstonerine **15** was isolated in 51% yield, accompanied by dihydroalstonerine (31%).[8] The dihydroalstonerine could be reduced and then converted into **15** to provide additional material. A possible mechanism for the unique formation of the enone **15** under the modified Swern conditions has been proposed.[1] The reduction of alstonerine with sodium borohydride provided the allylic alcohol **16** in 90% yield. Dehydration of **16** with *p*-toluenesulfonic acid gave (-)-anhydromacrosalhine-methine **3a** in 92% yield identical in all respects with material prepared from **6**.

In summary, (-)-anhydromacrosalhine-methine **3a** has been synthesized enantiospecifically from **11** *via* D-(+)-tryptophan. The partial synthesis from (+)-ajmaline **6** provided authentic material for comparison

purposes. Further work is in progress to extend this approach to the preparation of 10-methoxy anhydromacrosalhine-methine **3b** *via* 5-methoxy-D-(+)-tryptophan, recently synthesized in our laboratory.[17] In addition, diene **3a** can be employed in the biomimetic synthesis of macrocarpamine **1** (see the following paper) and would also provide a route to the northern portion of pandicine,[7] a bisindole with a structure very different from that of **1** and **2** in keeping with the synthetic potential of the asymmetric Pictet-Spengler reaction.[8]

References and Notes:

1. Bi, Y.; Hamaker, L. K.; Cook, J. M. *The Synthesis of Macroline Related Alkaloids*. In *Bioactive Natural Products, Part A*; Basha, F. Z. and Rahman, A., Ed.; Elsevier Science: Amsterdam, 1993; Vol. 13; 383.
2. Hamaker, L. K.; Cook, J. M. *The Synthesis of Macroline Related Sarpagine Alkaloids*. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science: New York, 1995; Vol. 9; 23.
3. Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1992**, *6*, 121.
4. Ghedira, K.; Zeches-Hanrot, M.; Richard, B.; Massiot, G.; LeMen-Oliver, L.; Sevenet, T.; Goh, S. H. *Phytochemistry* **1988**, *27*, 3955.
5. Khan, Z. M.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 1002.
6. Mayerl, F.; Hesse, M. *Helv. Chim. Acta* **1978**, *61*, 337.
7. Kan-Fan, C.; Massiot, G.; Das, B. C.; Potier, P. *J. Org. Chem.* **1981**, *46*, 1481.
8. Zhang, L. H.; Cook, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 4088.
9. Fu, X.; Cook, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6910.
10. Bi, Y.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027.
11. Takayama, H.; Phisalaphong, C.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1991**, *47*, 1383.
12. Kishi, T.; Hesse, M.; Gemenden, C. W.; Taylor, W. I.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 1349.
13. Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
14. Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051.
15. Zhang, L. H.; Bi, Y.; Yu, F.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, *34*, 517.
16. The Claisen rearrangement in the 11-methoxy series **17** provided the desired β-dicarbonyl compound **18** in 76% yield. See Hamaker, L. K. Ph.D. Thesis, University of Wisconsin-Milwaukee, 1995.



17. Zhang, P.; Cook, J. M. *Syn. Comm.* **1995**, *25*, 3883.

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