ORGANIC LETTERS

2002
Vol. 4, No. 5
687−690

Enantiospecific, Stereospecific Total Synthesis of (+)-Majvinine, (+)-10-Methoxyaffinisine, and (+)-N_a-Methylsarpagine as Well as the Total Synthesis of the *Alstonia* Bisindole Macralstonidine

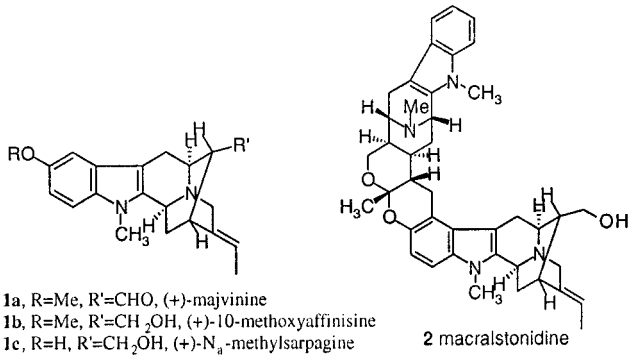
Shuo Zhao, Xuebin Liao, and James M. Cook*

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53211

capncook@csd.uwm.edu.

Received October 5, 2001

ABSTRACT



1a, R=Me, R'=CHO, (+)-majvinine
1b, R=Me, R'=CH_2OH, (+)-10-methoxyaffinisine
1c, R=H, R'=CH_2OH, (+)-N_a-methylsarpagine

2 macralstonidine

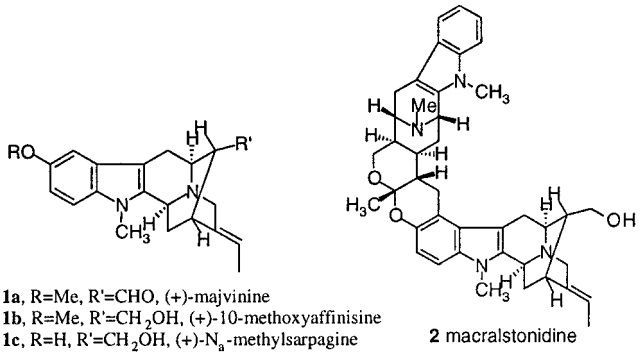
The enantiospecific stereospecific total synthesis of majvinine 1a, 10-methoxyaffinisine 1b, and N_a-methylsarpagine 1c are reported; this method has also resulted in the total synthesis of the *Alstonia* bisindole macralstonidine 2.

A number of bisindole alkaloids isolated from *Alstonia*[1,2] species have been shown to exhibit antimalarial activity[3] against a drug resistant (K-1) strain of *Plasmodia falciparum* including villalstonine, macrocarpamine, and macralstonine *O*-methyl ether.[4,5] Bisindoles are of special significance because they exhibit more potent biological activity than the monomeric units which comprise them,[3−5] which is reminiscent of the potent antitumor activity of the *Vinca* alkaloids vincristine and vinblastine. The biomimetic coupling of macroline with the obligatory monomeric alkaloid to provide the *Alstonia* bisindoles villalstonine[6,7] and macralstonine[8] as well as alstonisidine[6,9] was pioneered by Le Quesne. There are a number of other bisindoles in this series including

(1) Elderfield, R. C.; Gilman, R. E. *Phytochemistry*, **1972**, *11*, 339.
(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, p 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) Keawpradub, N.; Houghton, P. J.; Eno-Amooquaye, E.; Burke, P. J. *Planta Med.* **1997**, *63*, 97.
(5) Keawpradub, N.; Kirby, G. C.; Steele, J. C. P.; Houghton, P. J. *Planta Med.* **1999**, *65*, 690.
(6) Burke, D. E.; Cook, J. M.; Le Quesne, P. W. *J. Am. Chem. Soc.* **1973**, *95*, 546.
(7) Esmond, R. W.; Le Quesne, P. W. *J. Am. Chem. Soc.* **1980**, *102*, 7116.
(8) Burke, D. E.; Cook, G. A.; Cook, J. M.; Haller, K. G.; Lazar, H. A.; Le Quesne, P. W. *Phytochemistry* **1973**, *12*, 1467.

10.1021/ol010222h CCC: $22.00
Published on Web 02/08/2002

macrospegatrine,[10] alstomacrophylline,[5] dispegatrine,[10] and macralstonidine[11,12] which have not been evaluated for antimalarial activity due to the paucity of isolable material. These alkaloids are formed from the unique attack of a monomeric unit at C(9) of the sarpagine (**1a**−**1c**) ring system (Figure 1). The latter ring-A oxygenated indoles are not that



1a, R=Me, R'=CHO, (+)-majvinine
1b, R=Me, R'=CH_2OH, (+)-10-methoxyaffinisine
1c, R=H, R'=CH_2OH, (+)-N_a-methylsarpagine

2 macralstonidine

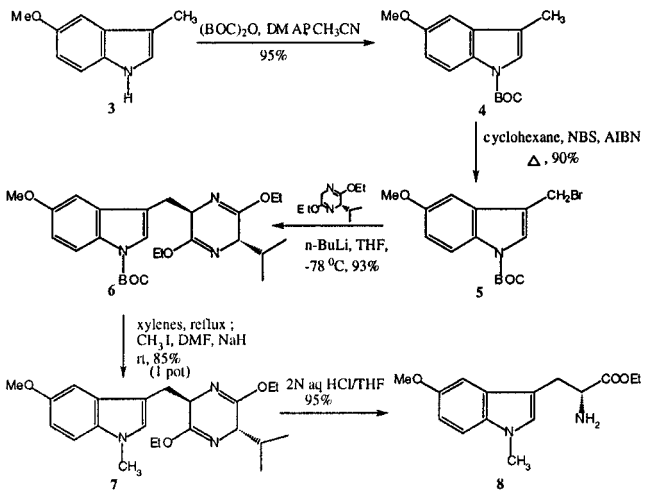
Figure 1.

stable; consequently only trace quantities of the bisindoles (see **2**, for example)[9,12] are obtained from plants.

We wish to report here an enantiospecific, stereospecific synthesis of (+)-majvinine (**1a**), (+)-10-methoxyaffinisine (**1b**), and (+)-N_a-methylsarpagine (**1c**) which has culminated in the total synthesis of the bisindole macralstonidine (**2**).[13] Since villalstonine-derived macroline[6] and plant-derived **1c** have been coupled by Le Quesne and Garnick[9] to provide **2**, the synthetic strategy rests on the total synthesis of **1c** with complete control of the stereocenters at C(3), C(5), C(15), and C(16) as well as the C(19)−C(20) *E* ethylidene function.

The synthesis began with the readily available 3-methyl-5-methoxyindole prepared on a 600 g scale[14a] via the Japp Kingemann/Fischer indole protocol developed by Abramovitch and Shapiro (Scheme 1).[14b] The indole N_a-H function of **3** was protected with a BOC group to facilitate the allylic bromination of the 3-methyl function[15] and to provide stable material with which to condense the anion of the Schöllkopf chiral auxiliary.[16] Since the asymmetric Pictet−Spengler

Scheme 1

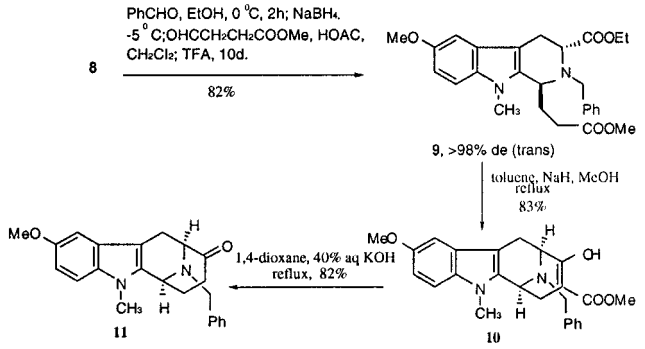


reaction would require D-tryptophans, the required Schöllkopf chiral auxiliary[16] was available on large scale from L-valine[17] via a trans transfer of chirality. The BOC-protected indole **4** was heated in refluxing cyclohexane or CCl_4 after which a mixture of NBS and AIBN(catalytic) were added. This provided allylic bromide **5** which was directly alkylated (100% de) with the anion of the Schöllkopf chiral auxiliary to provide the protected D-tryptophan analogue **6** in 93% yield. The BOC group was removed in refluxing xylenes after which the N_a-methylation (CH_3I/NaH/DMF) was carried out in this one-pot sequence. Hydrolysis under aqueous acidic conditions provided the desired optically pure N_a-methyl-5-methoxy-D-tryptophan ethyl ester **8** in 95% yield. This same ester **8** was also available via a three-step process,[13] although the Pd^0-mediated Larock heteroannulation reaction occurred in only 65% yield.[13,16,17]

A priori, the transformation of **8** into the desired trans diester **9** should follow the well-documented trans transfer of chirality in the asymmetric Pictet−Spengler reaction[18] in a straightforward fashion; however, this was not the case. The presence of the 5-methoxy group in **8** facilitated the Pictet−Spengler reaction (with benzaldehyde); moreover, this 5-methoxyindole system was not stable in TFA/CH_2Cl_2 for extended periods of time. Eventually, conditions were developed to execute the two-pot conversion of **8** into **10**, but they deserve mention here. If amine **8** were converted into the required N_b-benzyl imine with benzaldehyde/EtOH at room temperature,[18] significant amounts of the 1-phenyltetrahydro β-carbolines were formed.[13] However, if the imine were formed at 0 °C, followed by reduction at −5 °C, only the required N_b-benzyl analogue was observed. Second, since **8** was not stable in CH_2Cl_2/TFA for extended periods, the Pictet−Spengler reaction was carried out with the aldehyde (in place of the acetal[18]) in HOAc/CH_2Cl_2 (Scheme 2). Once the cyclization was completed (by TLC)

(9) Garnick, R. L.; Le Quesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213. See also Garnick, R. L., Ph.D. Thesis, Northeastern University, 1977.
(10) Lin, M.; Yang, B.; Yu, D.; Lin, X.; Zhang, Y. *Yaoxue Xuebao* **1987**, *22*, 833.
(11) Kishi, T.; Hesse, M.; Vetter, W.; Gemenden, C. W.; Taylor, W. I.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 946.
(12) Hesse, M.; Bodmer, F.; Gemenden, C. W.; Joshi, B. S.; Taylor, W. I.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 1173.
(13) Liao, X.; Zhao, S.; Cook, J. M. The Enantiospecific Total Synthesis of the Alstonia Bisindole Alkaloid, Macralstonidine, presented at the National Organic Symposium, Bozeman, MT, June 10−15, 2001, Abstract 239.
(14) (a) Heath-Brown, B.; Philpott, P. G. *J. Chem. Soc.* **1965**, 7185. Robinson, B. *The Fischer Indole Synthesis*; John Wiley & Sons: New York, 1982. (b) Abramovitch, R. A.; Shapiro, D. S. *J. Chem. Soc.* **1965**, 4589.
(15) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 3103.
(16) Ma, C.; Yu, S.; He, X.; Liu, X.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 2178. Ma, C.; He, X.; Liu, X.; Yu, S.; Zhao, S.; Cook, J. M.*Tetrahedron Lett.* **1999**, *40*, 2917.
(17) Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525.
(18) Cox, E.; Hamaker, L.; Li, J.; Yu, P.; Czerwinski, K.; Deng, L.; Bennett, D.; Cook, J. M.; Watson, W.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44.

Scheme 2

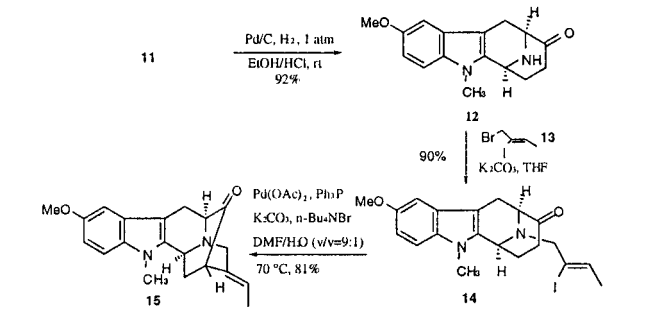


to provide a mixture of trans and cis diastereomers, a few drops of TFA were added[13,18] to facilitate epimerization (at C-1) of the cis isomer into the desired trans diastereomer (>98% de). The Dieckmann/hydrolysis protocols were uneventful under basic conditions and can now be carried out in one reaction vessel.

Recently, the enantiospecific, stereospecific total synthesis of (+)-vellosimine[19] was completed by Wang and Cook[19] in which an intramolecular palladium (enolate mediated)[20,21] cross coupling reaction[22−26] was employed. This Pd^0 process could presumably be employed for the synthesis of ring-A oxygenated systems; however, concern arose since these electron rich indoles might interact with the palladium catalyst and interfere with the palladium-mediated cross coupling process. For this reason the vinyl iodide **13**[22−24] was chosen to promote the oxidative addition reaction before other processes could take place.

As illustrated in Scheme 3, the N_b-benzyl ketone **11** was

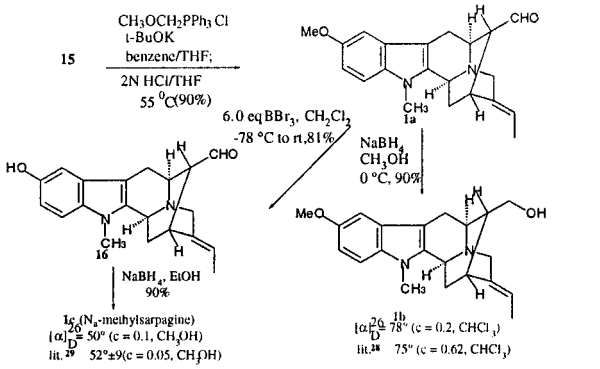
Scheme 3



stirred with Pd/C under an atmosphere of hydrogen to furnish the N_b-H ketone **12** in 92% yield, which was subsequently alkylated with (*Z*)-1-bromo-2-iodobutene[22−24] to provide the vinyl iodide **14**. Indeed, the enolate mediated Pd^0 cross coupling reaction took place (81% yield) in a stereospecific fashion to provide the 10-methoxysarpagine system present in **15**. If water was withheld from the reaction medium, the cyclization did not occur, nor did it take place with the vinyl bromide (see ref 19).

With the key *E*-ethylidene intermediate **15** in hand, conversion into the desired aldehyde present in (+)-majvinine could be accomplished by a Wittig/hydrolysis/epimerization sequence. When ketone **15** was stirred with $CH_3OCH_2PPh_3$-Cl/tBuOK, the enol ether was formed (Scheme 4). Since it

Scheme 4

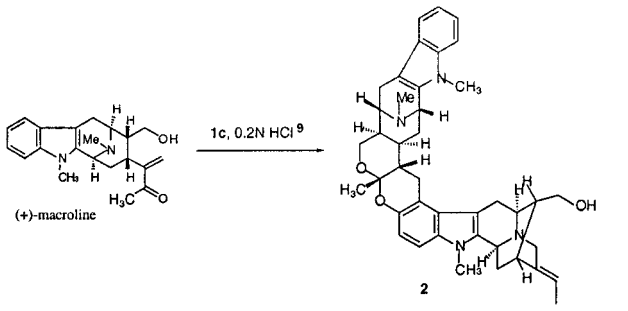


was known that the C(17) aldehyde in the sarpagine series occupied the thermodynamically more stable position,[19] the enol ether was simply stirred in aqueous HCl until only (+)-majvinine **1a** was observed (TLC). This one-pot process provided **1a** in 90% yield (in greater than 98% ee), the spectral data of which are identical to those of the natural product.[27] The structure of **1a** was also verified by single-crystal X-ray analysis (data not shown).[13] The aldehyde function of majvinine was reduced with sodium borohydride to provide the natural product 10-methoxyaffinisine **1b**, the spectral data and optical rotation of which are in complete agreement with the natural product.[28] The alkaloid (+)-majvinine **1a** was also employed for the total synthesis of (+)-N_a-methylsarpagine **1c**. As illustrated in Scheme 4, **1a** was stirred with 6 equiv of dry BBr_3 in CH_2Cl_2 (degassed) at −78 °C for 1 h, after which the solution was allowed to warm to room temperature and stirring continued for 2 h. After workup, the crude mixture was admixed with silica gel and employed in a wash column (silica gel) to provide the labile aldehyde **16**. This aldehyde was reduced without further purification with sodium borohydride to provide N_a-methylsarpagine in 90% yield. The spectral data and optical rotation of **1c** are in excellent agreement with those of the natural product.[29]

(19) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057.
(20) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454
(21) Piers, E.; Renand, J. *J. Org. Chem.* **1993**, *58*, 11.
(22) Rawal, V. H.; Michoud, C.; Monestel, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 3030.
(23) Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873. Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203.
(24) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1995**, *117*, 11017.
(25) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.
(26) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.
(27) Banerji, A.; Chakrabarty, M. *Phytochemistry* **1977**, *16*, 1124
(28) Kam, T. S.; Iek, I. H.; Choo, Y. M. *Phytochemistry* **1999**, *51*, 839.
(29) Waldner, E. E.; Hesse, M.; Taylor, W. I.; Schmid, H. *Helv. Chim. Acta* **1969**, *50*, 1926.

The enantiospecific total synthesis of (+)-macroline had originally been carried out by Bi[30] and has been improved in the enantiomeric series (11.2% overall yield) by Liu.[13] (+)-Macroline can be coupled with N_a-methylsarpagine **1c** under the biomimetic conditions of Garnick[9] to provide **2**; consequently this constitutes the first total synthesis of a bisindole alkaloid in the *Alstonia* series (Scheme 5). More importantly the recent synthesis of the enantiomer [(−)-macroline (from L-tryptophan)[13]] provides the first opportunity to prepare the mismatched pairs [(−)macroline + natural **1c**] in this series for biological screening. This stategy may be important in the search for drugs to treat chloroquine resistant strains (K-1) of *Plasmodia falciparum* malaria. The bisindole villalstonine was active against both the K-1 (chloroquine-resistant) and T9-96 (chloroquine-sensitive) strains of *P. falciparum*[4,5] while the close structural analogue macrocarpamine was active only against the K-1 strain.[4,5] Small alterations in structure have made a large difference in activity in these two bisindoles, and this effect may hold in the natural/unnatural pairs of dimers. Certainly, the ability to prepare (+)-macroline (from D-tryptophan) or (−)-macroline (from L-tryptophan)[13] in enantiospecific fashion (11.2% overall yield) provides the impetus for this suggestion. More importantly, the trans transfer of chirality with the Schöllkopf chiral auxiliary when coupled with the trans transfer which takes place in the asymmetric Pictet−Spengler reaction necessarily defines that natural ring-A alkoxylated indoles can be prepared from cheap L-valine while D-valine is required for the antipodal series.

Scheme 5



Outlined above is the first enantiospecific, stereospecific synthesis of ring-A alkoxylated indole alkaloids in the sarpagine series. The approach is unique since the natural series (**1a**, **1b**, **1c**) can be prepared from the cheap L-valine and the stereochemistry of the *E*-ethylidene function can be completely controlled by the enolate mediated Pd^0 cross coupling process. The strategy to prepare the bisindole **2** is doubly convergent since the same key stereochemical processes (asymmetric Pictet−Spengler reaction and enolate mediated Pd^0 process) have been employed[13] to prepare both monomeric units which can be coupled via the pioneering work of Le Quesne and Garnick.[9] The key optically active N_a-methyl-5-methoxy-D-tryptophan can be prepared on a large scale via the route described herein or in shorter fashion via a Pd^0 Larock heteroannulation sequence.[13] Because the synthesis of the Schöllkopf chiral auxiliary is available in both enantiomeric forms on multihundred gram scale,[16,17] the natural or unnatural (enantiomeric series) alkaloids can be readily prepared; moreover, the natural, enantiomeric, or mismatched bisindoles are available at will. (+)-Majvinine **1a** (from tryptophan ethyl ester **8**) was synthesized in gram quantities (eight reaction vessels) in 28% overall yield and serves as the key, stable intermediate for the preparation of other natural products in this series.

Acknowledgment. We wish to acknowledge the office of Naval Research, NIDA, and NIMH for support of this work.

OL010222H

(30) Bi, Y.; Cook, J. M. *Tetrahedron Lett.* **1993**, *34*, 4501. Bi, Y.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027.