Enantiospecific Total Synthesis of (−)-Anhydromacrosalhine-methine and Partial Synthesis of the Antiamoebic Bisindole Alkaloid (−)-Macrocarpamine[1]

Tong Gan and James M. Cook*

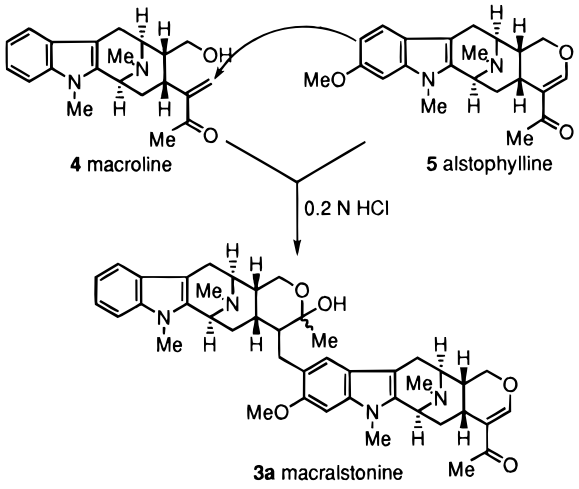
Department of Chemistry, University of Wisconsin−Milwaukee, Milwaukee, Wisconsin 53201

Received August 22, 1997

An enantiospecific total synthesis of (−)-anhydromacrosalhine-methine (**7a**) was completed from D-(+)-tryptophan via the asymmetric Pictet−Spengler reaction. In addition, a partial synthesis of (−)-anhydromacrosalhine-methine (**7a**) was carried out from the natural product (+)-ajmaline (**10**). The coupling reaction of plant-derived (+)-pleiocarpamine (**8**) with synthetic diene **7a** provided the antiamoebic bisindole alkaloid (−)-macrocarpamine (**1**) in 75% yield. This sequence serves as the first example of the action of a nucleophile at [at C(2)] on a protonated form [C(3)] of pleiocarpamine **8** in the *Alstonia* series to provide a bisindole alkaloid.

During the last several decades, more than 80 macroline/sarpagine-related indole alkaloids have been isolated from *Alstonia macrophylla* Wall, *Alstonia muelleriana* Domin, and other *Alstonia* species.[2,3] Among these alkaloids, at least 18 are bisindoles including (−)-macrocarpamine (**1**), villalstonine (**2**), and macralstonine (**3a**). Interest in macroline/sarpagine alkaloids isolated from *Alstonia* species originated as a result of folk tales that described the medicinal properties of these plants.[4,5] For example, the hypotensive base macralstonine **3a**, isolated from *A. macrophylla* Wall,[6,7] is a member of this family. The biomimetic interconversions of *Alstonia* alkaloids and the coupling reactions of monomeric indoles into bisindoles were pioneered by LeQuesne.[8−11] Recently, the total synthesis of macroline **4**[12] has resulted in the partial synthesis of macralstonine **3a** (Scheme 1); the addition of **4** to natural alstophylline **5**[11] was carried out under the same conditions employed for the partial synthesis of the antimalarial alkaloid villastonine (**2**).[13]

Scheme 1



The bisindole (−)-macrocarpamine (**1**) was first isolated from the bark of *A. macrophylla* Wall by Hesse et al. in 1978.[14] Moreover, in 1988, Ghedira et al. reported the isolation of the related bisindoles 10-methoxymacrocarpamine (**6**) and 10-methoxymacrocarpamine *N*-4′-oxide from the leaves of *Alstonia angustifolia*.[15] Macrocarpamine is comprised of a unit of anhydromacrosalhine-methine (**7a**) and pleiocarpamine (**8**). Anhydromacrosalhine-methine (**7a**) was first reported as a dehydration product of macrosalhine,[16] a quaternary salt related to macroline. In 1978, Hesse and Mayerl reported the fragmentation of (−)-macrocarpamine (**1**) into anhydromacrosalhine-methine (**7a**) and pleiocarpamine (**8**) under pyrolytic conditions. It was proposed by Hesse et al. that under biomimetic conditions the coupling reaction of **7a** and **8** would provide **1**. It is important to note that diene **7a** also comprises the northern portion of pandicine (**9**), a bisindole isolated from the leaves of *Pandacastrum saccharatum* Pichon.[17,18]

There is a need for new therapeutic agents in the tropics where diseases caused by protozoa and/or resis-

(1) A portion of this study was reported in preliminary form in: (a) Gan, T.; Cook, J. M. *Tetrahedron Lett.* **1996**, *37*, 5033. (b) Gan, T.; Cook, J. M. *Tetrahedron Lett.* **1996**, *37*, 5037.

(2) Bi, Y.; Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Alkaloids. In *Studies in Natural Products Chemistry, Bioactive Natural Products, Part A*; Basha, F. Z., Rahman, A., Ed.; Elsevier Science: Amsterdam, 1993; Vol. 13; p 383.

(3) 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.

(4) Cook, J. M.; LeQuesne, P. W. *Phytochemistry* **1971**, *10*, 437.

(5) Chatterjee, A.; Banerji, J.; Banerji, A. *J. Indian Chem. Soc.* **1949**, *51*, 156.

(6) Isidro, N.; Manalo, G. D. *J. Phillipine Pharm. Assoc.* **1967**, *53*, 8.

(7) Talapatra, S. K.; Adityachaudhury, N. *Sci. Cult.* **1958**, *24*, 243.

(8) Garnick, R. L. Ph.D. Thesis, Northeastern University, 1977.

(9) Garnick, R. L.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213.

(10) Esmond, R. W.; LeQuesne, P. W. *J. Am. Chem. Soc.* **1980**, *102*, 7116.

(11) Burke, D. E.; DeMarkey, C. A.; LeQuesne, P. W.; Cook, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 1346.

(12) Bi, Y.; Cook, J. M. *Tetrahedron Lett.* **1993**, *34*, 4501.

(13) Bi, Y.; Cook, J. M.; LeQuesne, P. W. *Tetrahedron Lett.* **1994**, *35*, 3877.

(14) Mayerl, F.; Hesse, M. *Helv. Chim. Acta* **1978**, *61*, 337.

(15) Ghedira, K.; Zeches-Hanrot, M.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Sevenet, T.; Goh, S. H. *Phytochemistry* **1988**, *27*, 3955.

(16) Khan, Z. M.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 1002.

(17) Kan-Fan, C.; Massiot, G.; Das, B. C.; Potier, P. *J. Org. Chem.* **1981**, *46*, 1481.

S0022-3263(97)01570-3 CCC: $15.00
Published on Web 02/10/1998

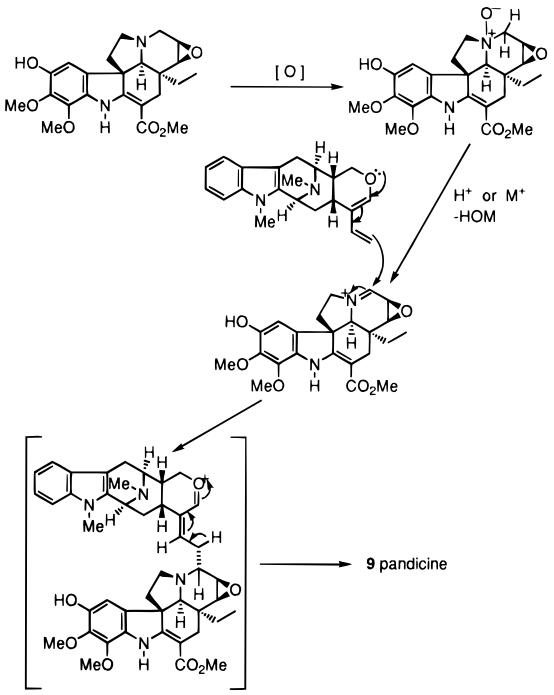
tant strains of parasites are responsible for many deaths. With respect to the macroline/sarpagine alkaloids, Wright et al.[19] reported on the antiprotozoal activity of nine alkaloids from *A. angustifolia* against *Entamoeba histolytica* and *Plasmodium falciparum* in vitro. Of the nine alkaloids tested, macrocarpamine (**1**), villalstonine (**2**), and macralstonine acetate (**3b**) were found to possess significant activity against both protozoa. Macrocarpamine (**1**) was found to the most active antiamoebic compound against *E. histolytica* of the series [ED_{50} (95% C.I.) = 8.12 (7.76−8.48) μM], although it was only one-fourth as potent as the standard drug emetine. Villalstonine (**2**) was found to be the most potent alkaloid against *P. falciparum* [ED_{50} (95% C.I.) = 2.92 (1.11−3.14) μM] of the alkaloids tested. The results of these in vitro studies provide some basis for the traditional use of *A. angustifolia* for the treatment of amoebic dysentery and malaria by the people of the Malaya peninsula.[19] It was also reported that the monomeric alkaloids possessed virtually no antiprotozoal activity. This suggests that at least part of both of the ring systems present in the dimeric alkaloids are essential for activity. The structures and studies via molecular modeling of the standard antiamoebic drug emetine and the base usambarensine also support this suggestion.[20] The cytotoxic activity of villalstonine (**2**) against KB cells was also tested and found to be similar to its antiamoebic activity.[19] However, the standard antiamoebic drug emetine is highly toxic to KB cells and is three times less toxic to amoebas than to KB cells. Therefore, villalstonine (**2**) appears to have a more favorable antiamoebic/cytotoxic ratio as compared with emetine. Consequently, the synthesis of bisindole alkaloids has become more important since these studies may lead to more selective antiprotozoal agents in the future. In 1993, a partial synthesis of the antimalarial alkaloid (+)-villalstonine (**2**) was completed by coupling synthetic macroline (**4**) with plant-derived pleiocarpamine (**8**).[13] This provided additional stimulus for the synthesis of macrocarpamine.

Since a number of ring-A alkoxylated macroline/sarpagine indole alkaloids have been isolated from *Alstonia* species,[2,3] a route to **1** was chosen that could later be extended to **6** and to other ring-A alkoxylated alkaloids. This approach was based on the proposed coupling reaction of (−)-anhydromacrosalhine-methine (**7a**) with (+)-pleiocarpamine (**8**) to provide (−)-macrocarpamine (**1**) analogous to the biogenetic proposal of Mayerl and Hesse.[14] In keeping with this interest in the total synthesis of *Alstonia* bisindoles,[21−23] we wish to describe an enantiospecific total synthesis of (−)-anhydromacrosalhine-methine (**7a**) and a partial synthesis of (−)-macrocarpamine (**1**). To our knowledge,[21−23] this is the first example of the addition of a vinylogous enol ether (diene **7a**) to an iminium ion to provide a bisindole alkaloid and serves as a potential route to pandicine[17] and other bisindole alkaloids.

To obtain an authentic sample of **7a**, a partial synthesis from (+)-ajmaline (**10**) was first carried out. Ajmaline (**10**) exhibits important antiarrhythmic activity and is stereochemically identical to the macroline/sarpagine alkaloids at C(3), C(5), and C(15). Degradation of ajmaline (**10**) to provide hemiacetal **11** was accomplished following the improved procedure of Sakai.[24] As illustrated in Scheme 3, dehydration of **11** to provide deoxyalstonerine **12**[25] was executed in 95% yield by stirring **11** with 1.1 equiv of *p*-toluenesulfonic acid in refluxing benzene. Initial attempts to introduce a functional group into the C-19 position of enol ether **12** were carried out via allylic bromination with NBS, which resulted in an inseparable mixture of alkaloidal material. Allylic oxidation with various reagents including SeO_2 was also employed to introduce a hydroxyl group at the C-19 position of **12**. These reactions failed or gave mixtures of inseparable material. Consequently, the regioselective oxyselenation of the olefin **12** was carried out with *N*-(phenylseleno)phthalimide[26] in CH_2Cl_2 in the presence of 2−3 equiv of water and 1.3 equiv of *p*-toluenesulfonic acid to afford **13** in 90% yield. Allylic alcohol **14** was obtained in 90% yield by selenoxide elimination of **13** on treatment with $NaIO_4$. Although treatment of **14** with 2,4-dinitrobenzenesulfonyl chloride[27] in the presence of triethylamine produced diene **7a** in 55% yield, the 1,4-elimination in **14** was improved by simply stirring this olefin with 1.1 equiv of *p*-toluenesulfonic acid in dry THF to provide anhydromacrosalhine-methine (**7a**) in 85% yield (Scheme 3). The spectral properties of this material were identical to those reported by Mayerl and Hesse.[14] This synthesis confirms for the first time the absolute configuration of **7a** at stereogenic centers C(3), C(5), C(15), and C(16).

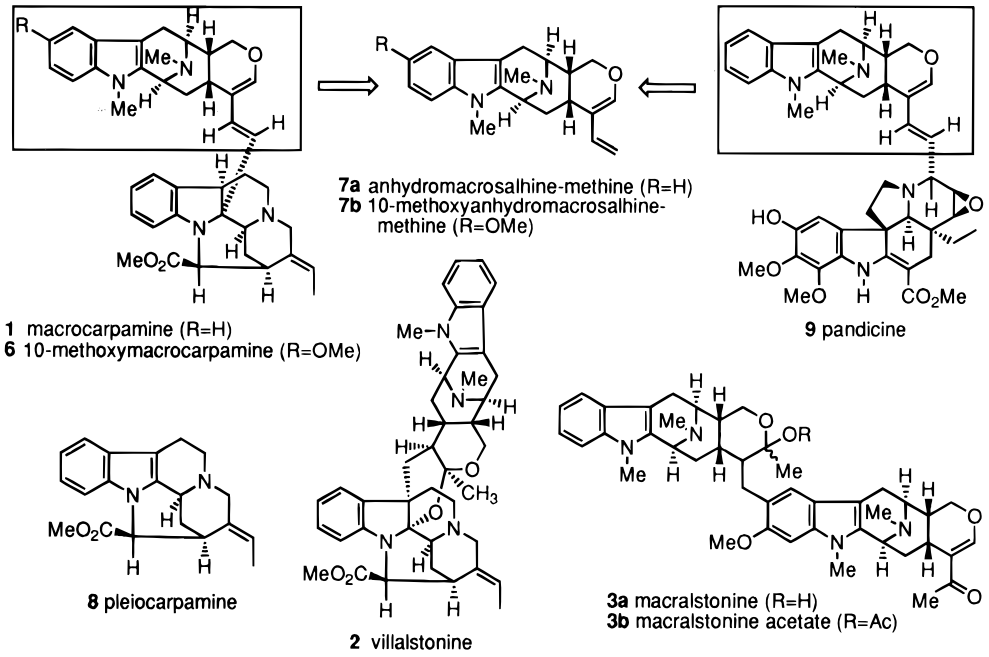
Since a sample of **7a** was now in hand, the enantiospecific total synthesis of **7a** was initiated via the 1,3 chiral

(18) A potential biomimetic route to pandicine **9** is illustrated below. Other pathways are also possible.

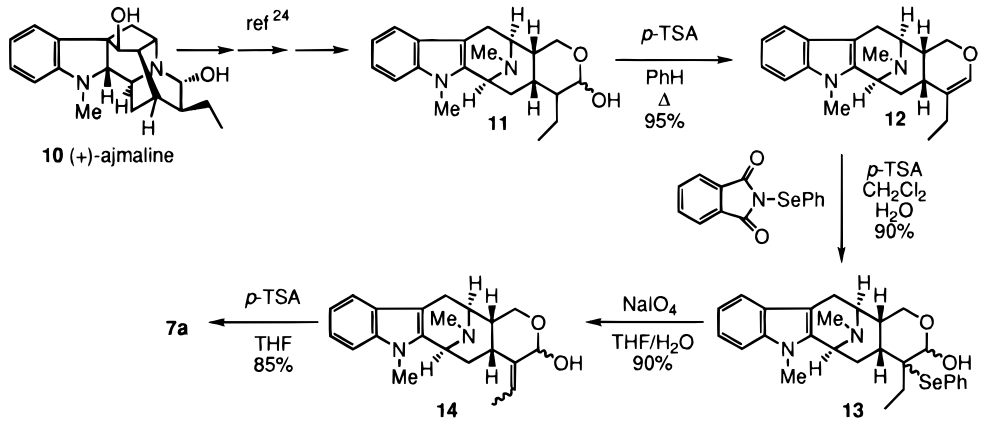


(19) Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1992**, *6*, 121.
(20) Quetin-Leclercq, J.; Dupont, L.; Wright, C. W.; Philipson, J. D.; Warhurst, D. C.; Angenot, L. *J. Pharm. Belg.* **1991**, *46*, 82.
(21) Zhang, L. H.; Cook, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 4088.
(22) Fu, X.; Cook, J. M. *J. Am. Chem. Soc.* **1992**, *114*, 6910.
(23) Bi, Y.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027.
(24) Takayama, H.; Phisalaphong, C.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1991**, *47*, 1383.
(25) Kishi, T.; Hesse, M.; Gemenden, C. W.; Taylor, W. I.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 1349.
(26) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
(27) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051.

Scheme 2



Scheme 3



transfer[28,29] developed in the enantiospecific Pictet–Spengler reaction [from D-(+)-tryptophan].[2,3] The optically active tetracyclic ketone **15** (>98% ee) was prepared from D-(+)-tryptophan by a stereospecific regiospecific method developed in our laboratory and is now readily available.[29] This ketone was enantiospecifically converted into alstonerine **16**, as previously reported.[23] The reduction of alstonerine with sodium borohydride provided the allylic alcohol **17** in 90% yield. Dehydration of **17** with *p*-toluenesulfonic acid gave (−)-anhydromacrosalhine-methine (**7a**) in 92% yield identical in all respects with material prepared from **10**. The chemical shifts and coupling constants of the ^{1}H NMR of (−)-anhydromacrosalhine-methine **7a** (from alstonerine) as well as the literature values from the report of Hesse[14] are depicted in Table 1.

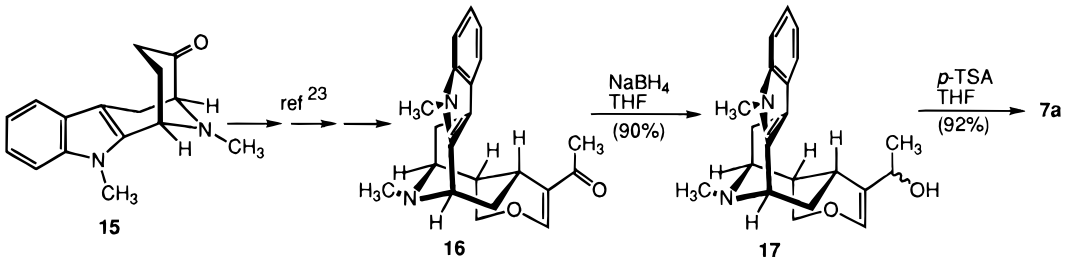
When anhydromacrosalhine-methine **7a** was coupled with natural pleiocarpamine (**8**) under aqueous acidic conditions (0.2 N aqueous HCl), the enol ether **7a** was converted into byproducts of hydration. It was determined that diene **7a** was unstable when maintained under aqueous acidic conditions for extended periods of time. However, addition of 6 equiv of **7a** (portionwise) to **8** in 0.2 N anhydrous HCl/THF provided (−)-macrocarpamine (**1**) in 75% yield (Scheme 5). Nucleophilic attack of the diene **7a** did occur on the cup-shaped

Table 1. ^{1}H NMR Data for (−)-Anhydromacrosalhine-methine (7a)

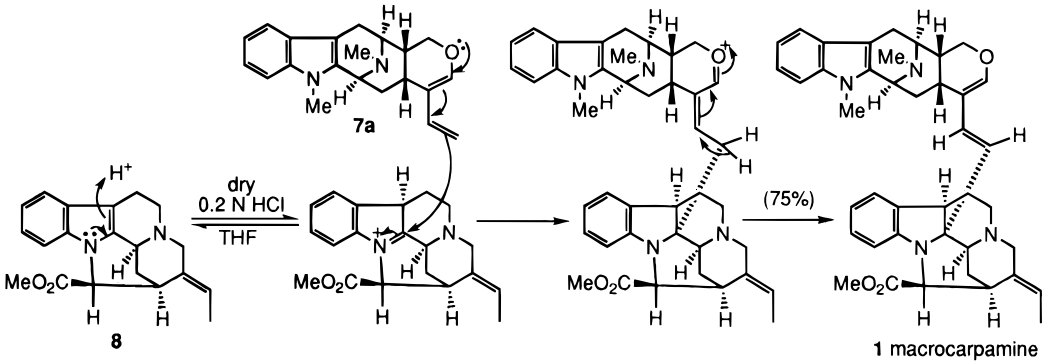
proton	lit.[14] δ (*J*, Hz)	synthetic material δ (*J*, Hz)
2H	1.95−2.05 (m)	1.96−2.03 (m)
1H	2.13 (dt, 13, 4 Hz)	2.12 (dt, 13.1, 3.8 Hz)
N_bCH_3	2.36 (s)	2.34 (s)
1H	2.33−2.43 (m)	2.30−2.40 (m)
H (6)	2.54 (d, 16 Hz)	2.52 (d, 16.5 Hz)
H (5)	3.12 (d, 7 Hz)	3.10 (d, 6.7 Hz)
H (6)	3.34 (dd, 16, 7 Hz)	3.33 (dd, 16.5, 6.9 Hz)
N_aCH_3	3.65 (s)	3.64 (s)
H (3)	3.92 (br, s)	3.91 (br, s)
H (17)	4.04 (dd, 11, 3 Hz)	4.02 (dd, 10.9, 3.2 Hz)
H (18)	4.40 (d, 17 Hz)	4.38 (d, 17.4 Hz)
H (17)	4.40 (t, 11 Hz)	4.39 (t, 11.3 Hz)
H (18)	4.55 (d, 11 Hz)	4.54 (d, 10.8 Hz)
H (19)	6.00 (dd, 17, 11 Hz)	5.99 (dd, 17.5, 10.9 Hz)
H (21)	6.46 (s)	6.45 (s)
H (10)	7.11 (t, 8 Hz)	7.10 (t, 7.4 Hz)
H (11)	7.21 (t, 8 Hz)	7.20 (t, 7.5 Hz)
H (12)	7.32 (d, 8 Hz)	7.31 (d, 8.2 Hz)
H (9)	7.51(d, 8 Hz)	7.50 (d, 7.7 Hz)

(28) Zhang, L. H.; Cook, J. M. *Heterocycles* **1988**, *27*, 2795.
(29) Zhang, L. H.; Bi, Y.; Yu, F.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, *34*, 517.

Scheme 4



Scheme 5



alkaloid, pleiocarpamine (**8**), from the bottom face of the 2,3-indole double bond as planned.[30] The spectroscopic properties (MS, NMR) of **1** were virtually identical to those reported by Mayerl and Hesse.[14] The chemical shifts and coupling constants of the ^{1}H NMR of (−)-macrocarpamine (**1**) as well as the literature values from the report of Hesse[14] are depicted in Table 2.

This sequence serves as the first example of a proton-mediated coupling reaction between two monomeric units in the *Alstonia* series to provide a bisindole alkaloid. In the biomimetic syntheses of LeQuesne,[8−11] the Michael acceptor (macroline) served as the electrophile and its addition to pleiocarpamine was not readily reversible in acidic solution. In contrast, in the condensation between pleiocarpamine (**8**) and the diene **7a** the electrophile is a proton. Since protonation of the indole double bond of **8** is a readily reversible process, the sequence illustrated here is unique. The diene **7a** must be added to an acidic solution of **8** in small portions to immediately quench the iminium ion intermediate; otherwise, only products of diene decomposition are obtained. Although at least four bisindoles[21−23] have been isolated which could presumably be formed by condensation of a diene such as **7a** with another monomeric indole unit, to our knowledge this is the first example of a coupling reaction between a vinylogous enol ether (diene **7a**) of this type and an iminium ion. In addition to alkaloids in the macrocarpamine series, there is at least one other bisindole, plumocraline (**18**), (Figure 1) whose biogenesis can be rationalized by the action of a nucleophile on a protonated form of pleiocarpamine **8**.[31]

Further work is in progress to extend this approach to the preparation of 10-methoxymacrocarpamine (**6**) via D-(+)-5-methoxytryptophan, recently synthesized in optically pure form from 3-methyl-5-methoxyindole in our laboratory.[32−35] In summary, the work described above constitutes the first partial synthesis of the antiamoebic alkaloid (−)-macrocarpamine (**1**) as well as the enantiospecific total synthesis of **7a** and supports the earlier

Table 2. ^{1}H NMR Data for (−)-Macrocarpamine (1)

proton	lit.[14] δ (*J*, Hz)	synthetic material δ (*J*, Hz)
CH_3(18)	1.55 (dd, 7, 2 Hz)	1.58 (dd, 6.8, 2.0 Hz)
8H	not able to interpret	1.75−2.20 (m)
N'_bCH_3	2.33 (s)	2.31 (s)
H (6′)	2.46 (d, 16 Hz)	2.44 (d, 16.8 Hz)
H (7)	2.60 (dd, 11, 7 Hz)	2.64 (br, dd, 11.2, 7.8 Hz)
4H	2.89−2.97 (m)	2.90−3.10 (m)
H (5′)	3.05 (d, 7 Hz)	3.03 (d, 6.7 Hz)
H (15)	3.15 (qa, 4 Hz)	3.15 (m)
H (6′)	3.28 (dd, 16, 7 Hz)	3.26 (dd, 16.7, 6.3 Hz)
N'_aCH_3	3.68 (s)	3.65 (s)
CO_2CH_3	3.70 (s)	3.71 (s)
H (3′)	3.86 (br, s)	3.84 (br, s)
H (17′)	3.95 (dd, 11, 4 Hz)	3.94 (dd, 11.1, 3.2 Hz)
H (16)	4.18 (d, 4 Hz)	4.13 (d, 3.5 Hz)
H (17′)	4.26 (t, 11 Hz)	4.26 (t, 11.3 Hz)
H (21)	4.32 (br, d, 13 Hz)	4.43 (br, d, 12.7 Hz)
H (18′)	4.85 (d, 16 Hz)[a]	4.52 (d, 16.3 Hz)
H (19)	5.37 (qa, 6 Hz)	5.43 (m)
H (19′)	5.44 (d, 16 Hz)	5.48 (d, 15.8 Hz)
H (12)	5.84 (d, 8 Hz)	5.83 (d, 8.1 Hz)
H (21′)	6.27 (s)	6.27 (s)
H (10)	6.51 (t, 7 Hz)	6.53 (t, 7.4 Hz)
H (11)	6.74 (t, 8 Hz)	6.79 (t, 7.7 Hz)
H (9)	6.91 (d, 7 Hz)	6.90 (d, 7.2 Hz)
H (10′)	7.10 (t, 8 Hz)	7.08 (t, 7.4 Hz)
H (11′)	7.23 (t, 8 Hz)	7.22 (t, 8.1 Hz)
H (12′)	7.36 (d, 8 Hz)	7.35 (d, 7.8 Hz)
H (9′)	7.44(d, 8 Hz)	7.42 (d, 7.9 Hz)

[a] The literature value for H (18′) for **1** is 4.85 ppm.[14] We believe this is a typographical error since the literature values for H (18) of anhydromacrosalhine-methine (**7a**),[14] 10-methoxymacrocarpamine (**6**),[15] and 10-methoxymacrocarpamine *N*-4′ oxide[15] are 4.55, 4.56, and 4.49 ppm, respectively.

(30) Burke, D. E.; Cook, G. A.; Cook, J. M.; Haller, K. G.; Lazar, H. A.; LeQuesne, P. W. *Phytochemistry* **1973**, *12*, 1467.

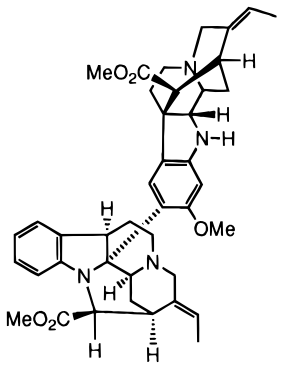
(31) Jaquier, M. J.; Vercauteren, J.; Massiot, G.; Le Men-Olivier, L.; Pussett, J.; Sevenett, T. *Phytochemistry* **1982**, *21*, 2973.

(32) Zhang, P.; Cook, J. M. *Synth. Commun.* **1995**, *25*, 3883.

(33) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 3103.

(34) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 7411.

(35) Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 9133.



18 plumocraline

Figure 1.

biogenetic proposal of Hesse in regard to the origin of bisindole **1**.[14] In addition, the enantiospecific synthesis of diene **7a** provides a route to the northern portion of pandicine (**9**),[17] a bisindole with a structure very different from that of **1** and **6** in keeping with the synthetic potential of the asymmetric Pictet−Spengler reaction.[2,3,36]

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus or an Electrothermal model IA8100 digital melting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240C carbon, hydrogen, and nitrogen analyzer. All samples submitted for CHN analyses were first dried under high vacuum for a minimum of 6 h using a drying pistol with methylene chloride or isopropyl alcohol as the solvent with phosphorus pentoxide in the drying bulb. Proton and carbon high-resolution nuclear magnetic resonance spectra were obtained on a Bruker 250-MHz multiple probe NMR instrument or a GE 500-MHz NMR spectrometer. The low-resolution mass spectra (EI/CI) were obtained on a Hewlett-Packard 5985B gas chromatography−mass spectrometer, while high-resolution spectra were recorded on a Finnigan HR mass spectrometer. Infrared spectra were recorded on a Nicolet MX-1 FT-IR or a Perkin-Elmer 1600 Series FT-IR spectrometer.

Analytical thin-layer chromatography plates used were E. Merck Brinkmann UV-active silica gel (Kieselgel 60 F254) on plastic. Silica gel 60A, grade 60 for flash and gravity chromatography, was purchased from E. M. Laboratories.

Alkaloids were visualized with Dragendorf's reagent or a saturated solution of ceric ammonium sulfate in 50% sulfuric acid, or with an aqueous solution of 2,4-dinitrophenylhydrazine in 30% sulfuric acid. Methanol (MeOH) and ethanol (EtOH) were dried by distillation over magnesium metal and iodine. Tetrahydrofuran (THF), benzene, toluene, dioxane, and diethyl ether were dried by distillation from sodium−benzophenone ketyl. Methylene chloride was dried over $MgSO_4$ and then distilled over P_2O_5. *N*-(Phenylseleno)phthalimide was prepared following the procedure of Nicolaou[26] while all other chemicals were purchased from Aldrich Chemical Co.

Dehydration of Hemiacetal (11) with *p*-TSA To Provide Enol Ether (12). A solution of hemiacetal **11** (300 mg, 0.88 mmol), prepared by the method of Sakai,[24] and *p*-toluenesulfonic acid (185 mg, 0.97 mmol) in dry benzene (10 mL) was heated to reflux under an N_2 atmosphere for 3 h. The reaction mixture was allowed to cool and was then diluted with EtOAc and brought to alkaline pH with 15% aqueous NH_4OH at 0 °C. The aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc−hexane, 2:3), and the solid that resulted was recrystallized from ether to afford enol ether **12** as colorless prisms (270 mg, 95%). **12**: mp 166−167 °C (from ether); IR (KBr) 2900 (br), 1670, 1470, 1380, 1130, 760 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (t, J = 7.5 Hz, 3 H), 1.65−2.04 (m, 8 H), 2.33 (s, 3 H), 2.49 (d, J = 16.5 Hz, 1 H), 3.08 (d, J = 6.9 Hz, 1 H), 3.30 (dd, J = 16.5 and 6.9 Hz, 1 H), 3.64 (s, 3 H), 3.90−3.95 (m, 2 H), 4.19 (t, J = 10.9 Hz, 1 H), 6.14 (s, 1 H), 7.11 (t, J = 7.8 Hz, 1 H), 7.20 (td, J = 7.8 and 0.9 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ: 12.9, 23.0, 23.5, 27.1, 29.0, 33.1, 40.6, 41.9, 53.8, 55.3, 66.3, 106.5, 108.8, 117.4, 118.0, 118.8, 120.8, 126.7, 133.6, 137.2, 138.1; CIMS (CH_4) *m/e* (relative intensity) 323 (M + 1, 100); EIMS (70 eV) *m/e* (relative intensity) 322 (M^+, 100), 307 (12.5) 279 (33.0), 253 (45.1), 224 (26.9), 212 (21.3), 197 (69.7), 182 (29.7), 170 (67.8), 149 (47.9). Anal. Calcd for $C_{21}H_{26}N_2O \cdot 1/3H_2O$: C, 76.79; H, 8.18; N, 8.53; Found: C, 76.73; H, 7.95; N, 8.47.

Oxyselenation of Enol Ether (12) with *N*-(Phenylseleno)phthalimide To Provide a Mixture of Hydroxy Selenides 13a,b. To a solution of enol ether **12** (200 mg, 0.62 mmol) in CH_2Cl_2 (10 mL) were added *N*-(phenylseleno)phthalimide[26] (244 mg, 0.81 mmol), *p*-toluenesulfonic acid (130 mg, 0.68 mmol), and 1 drop of H_2O. The reaction mixture was stirred at rt for 5 h, diluted with CH_2Cl_2, and brought to alkaline pH with 15% aqueous NH_4OH at 0 °C. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc) to afford **13a** as an amorphous powder (76 mg, 24.7%) and **13b** as a crystalline solid (210 mg, 68.2%, from EtOAc). Hydroxy selenide **13a** was composed of a mixture of diastereomers that could not readily be separated. It was used directly in the next step. **13a**: EIMS (70 eV) *m/e* (relative intensity) 496 (M^+, 13.3), 339 (27.5), 321 (20.1), 252 (13.6), 197 (100), 182 (37.7), 170 (35.6), 157 (66.8), 144 (29.8). **13b**: colorless crystals; mp 208−211 °C; IR (KBr) 3450 (br), 2940, 2890, 1470, 1435, 1380, 1070, 1020, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3 H), 0.97 (m, 1 H), 1.47 (m, 1 H), 1.55 (s, 1 H), 1.81 (m, 1 H), 2.35 (s, 3 H), 2.42 (d, J = 3.0 Hz, 1 H), 2.49 (d, J = 16.0 Hz, 1 H), 2.72 (td, J = 13 and 4 Hz, 1 H), 2.90 (m, 1 H), 3.00 (d, J = 7.0 Hz, 1 H), 3.28 (dd, J = 7.0 and 16.5 Hz, 1H), 3.53 (s, 3 H), 3.61 (dd, J = 4.5 and 11.5 Hz, 1 H), 3.89 (s, br, 1 H), 4.52 (t, J = 11.5 Hz, 1 H), 5.00 (s, 1 H), 6.74 (t, J = 7.5 Hz, 2 H), 7.04 (t, J = 7.5 Hz, 1 H), 7.14 (t, J = 7.5 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.21−7.25 (m, 3 H), 7.54 (d, J = 7.5 Hz, 1 H); EIMS (70 e/V) *m/e* (relative intensity) 496 (M^+, 12.5), 339 (79.6), 321 (63.1), 252 (25.8), 197 (100), 182 (37.1), 158 (32.0), 144 (26.0). This material was employed directly in the next step.

Selenoxide Elimination of 13a,b with $NaIO_4$ To Provide the Mixture of Allylic Alcohols 14a,b. To a stirred solution of **13a** or **13b** (130 mg, 0.262 mmol) in THF (11 mL) at 0 °C was added a solution of $NaIO_4$ (82 mg, 0.384 mmol) in H_2O (2.4 mL). The reaction mixture was allowed to stir at rt for 5 h. The precipitate that formed was removed by filtration, and the reaction mixture was concentrated, after which it was brought to alkaline pH with 15% aqueous NH_4OH at 0 °C. The aqueous layer was extracted with $CHCl_3$. The organic extracts were washed with brine, dried (K_2CO_3), and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH−$CHCl_3$, 1:9) to provide a mixture of allylic alcohols **14a,b** as an amorphous powder (80 mg, 90%). **14a,b**: IR (KBr) 3350 (br), 2900, 1450, 1000, 750 cm^{-1}; CIMS (CH_4) *m/e* (relative intensity) 339 (M + 1, 100), 321 (57.9); EIMS (70 eV) *m/e* (relative intensity) 338 (M^+, 23.2), 320 (5.0), 197 (100), 181 (43.7), 170 (50.1), 154 (20.9), 144 (17.5). This material was employed in the next step without further purification.

The 1,4-Elimination of Water from Allylic Alcohols 14a,b with *p*-TSA To Provide Diene 7a. A solution of allylic alcohols represented by **14** (14 mg, 0.041 mmol) and *p*-toluenesulfonic acid (13 mg, 0.068 mmol) in dry THF (2 mL) was stirred at rt for 5 h. The reaction mixture was brought to alkaline pH with 10% aqueous NH_4OH solution and

(36) Cox, E. D.; Cook, J. M. *Chem. Rev. (Washington, D.C.)* **1995**, *95*, 1797.

extracted with $CHCl_3$. The combined organic extracts were dried (K_2CO_3). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc−hexane, 3:2) to afford anhydromacrosalhine-methine **7a** (11.3 mg, 85%). The solid was recrystallized from EtOAc to provide **7a** as colorless crystals: mp 146−150 °C (from EtOAc); IR (KBr) 3420, 2890, 1630, 1470, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.03−1.96 (m, 2 H), 2.12 (dt, J = 13.1, 3.8 Hz, 1 H), 2.34 (s, 3 H), 2.40−2.30 (m, 1 H), 2.52 (d, J = 16.5 Hz, 1 H), 3.10 (d, J = 6.7 Hz, 1 H), 3.33 (dd, J = 16.5, 6.9 Hz, 1 H), 3.64 (s, 3 H), 3.91 (s, br, 1 H), 4.02 (dd, J = 10.9, 3.2 Hz, 1 H), 4.38 (d, J = 17.4 Hz, 1 H), 4.39 (t, J = 11.3 Hz, 1 H), 4.54 (d, J = 10.8 Hz, 1 H), 5.99 (dd, J = 17.5, 10.9 Hz, 1 H), 6.45 (s, 1 H), 7.10 (t, J = 7.4 Hz, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 1 H), 7.50 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.9, 23.6, 29.0, 32.4, 39.3, 41.9, 54.0, 55.1, 87.1, 106.4, 106.7, 108.8, 116.9, 118.1, 119.0, 120.9, 126.8, 133.5, 134.3, 137.3, 145.5; CIMS (CH_4) *m/e* (relative intensity) 321 (M^+, 100); EIMS (70 eV) *m/e* (relative intensity) 320 (M + 1, 100), 251 (38.0), 222 (15.9), 197 (64.6), 181 (34.8), 170 (64.1). Anal. Calcd for $C_{21}H_{24}N_2O \cdot 1/2H_2O$: C, 76.56; H, 7.65; N, 8.50; Found: C, 76.60; H, 7.64; N, 8.30. The spectral data for **7a** were identical to those reported by Hesse in ref 14.

Reduction of Alstonerine (16) with $NaBH_4$ To Provide a Mixture of Allylic Alcohols Represented by 17a,b. To a solution of alstonerine (**16**)[21] (28 mg, 0.0833 mmol) in dry MeOH (2 mL) at 0 °C was added sodium borohydride (70 mg) in one portion, and the mixture was allowed to stir at 0 °C for 20 min, after which time it was stirred at rt for 9 h. Additional sodium borohydride (60 mg) was added, and the reaction mixture was allowed to stir at rt for 1.5 h. The mixture was diluted with water and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were combined, washed with water, and dried (K_2CO_3). The solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 5% MeOH/$CHCl_3$) to afford 25.4 mg (90%) of a diastereomeric mixture of allylic alcohols represented by **17a,b**. **17a,b**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.13 and 1.05 (d, J = 6.4 Hz, 3 H), 2.30 (s, 3 H), 2.49 (dd, J = 16.4, 5.4 Hz, 1 H), 3.08 (d, J = 6.0 Hz, 1 H), 3.30 (dd, J = 16.4, 6.5 Hz, 1 H), 3.62 (s, 3 H), 3.88 (br s, 1 H), 4.25 (t, J = 11.3 Hz, 1 H), 6.47 and 6.43 (s, 1 H), 7.09 (t, J = 7.3 Hz, 1 H), 7.19 (t, J = 7.4 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 7.6 Hz, 1 H); CIMS (CH_4) *m/e* (relative intensity) 339 (M + 1, 19), 321 (100), 197 (7). The alcohols were employed directly in the next step without further purification.

Dehydration of the Mixture of Allylic Alcohols 17a,b To Provide the Diene 7a. A solution of the allylic alcohols **17a,b** (14 mg, 0.041 mmol) and *p*-toluenesulfonic acid (16 mg, 0.084 mmol) in dry THF (8 mL) was stirred at rt for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 and brought to alkaline pH with a solution of 15% aqueous NH_4OH at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc−hexane, 3:2) to afford 12.2 mg (92%) of anhydromacrosalhine-methine **7a** as colorless crystals. The spectral data for **7a** prepared here were identical to those for **7a** prepared above.

The Partial Synthesis of Macrocarpamine (1). To a solution of plant-derived pleiocarpamine **8** (5 mg, 0.0155 mmol) in 0.2 N HCl (anhydrous) in dry THF (1 mL) was added anhydromacrosalhine-methine **7a** (7.5 mg, 0.0234 mmol). After the reaction mixture was allowed to stir at rt for 6 h, an additional 5 mg (0.0156 mmol) of **7a** was added. The reaction mixture was allowed to stir at rt overnight, after which another 6 mg (0.0187 mmol) of **7a** was added. After the mixture was stirred for 10 h, another 6.5 mg (0.0203 mmol) of **7a** was added. After the mixture was stirred for 14 h, 5 mg (0.0156 mmol) more of **7a** was added. In essence, the diene **7a** was added until all of the pleiocarpamine (**8**) had been used up as indicated by TLC (total of 6 equiv of **7a** was added). The reaction mixture was stirred at rt for an additional 6 h and then poured into a solution of 15% aqueous NH_4OH at 0 °C. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, 4% MeOH/$CHCl_3$ to 8% MeOH/$CHCl_3$) to provide 7.5 mg (75%) of macrocarpamine (**1**) as an amorphous powder. **1**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.58 (dd, J = 6.8, 2.0 Hz, 3 H), 1.75−2.20 (m, 8 H), 2.31 (s, 3 H), 2.44 (d, J = 16.8 Hz, 1 H), 2.64 (t, J = 9.4 Hz, 1 H), 2.90−3.10 (m, 4 H), 3.03 (d, J = 6.7 Hz, 1 H), 3.15 (m, 1 H), 3.26 (dd, J = 16.7, 6.3 Hz, 1 H), 3.65 (s, 3 H), 3.71 (s, 3 H), 3.84 (s, br, 1 H), 3.94 (dd, J = 11.1, 3.2 Hz, 1 H), 4.13 (d, J = 3.5 Hz, 1 H), 4.26 (t, J = 11.3 Hz, 1 H), 4.43 (d, br, J = 12.7 Hz, 1 H), 4.52 (d, J = 16.3 Hz, 1 H), 5.43 (m, 1 H), 5.48 (d, J = 15.8 Hz, 1 H), 5.83 (d, J = 8.1 Hz, 1 H), 6.27 (s, 1 H), 6.53 (t, J = 7.4 Hz, 1 H), 6.79 (t, J = 7.7 Hz, 1 H), 6.90 (d, J = 7.2 Hz, 1 H), 7.08 (t, J = 7.4 Hz, 1 H), 7.22 (t, J = 8.1 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 7.42 (d, J = 7.9 Hz, 1 H); EIMS (70 eV) *m/e* (relative intensity) 642 (M^+, 39), 583 (18), 321 (14), 320 (11), 263 (15), 197 (100), 170 (67), 135 (59), 107 (49); exact mass calcd for $C_{41}H_{46}N_4O_3$ 642.3609, found 642.3570. The spectral data for **1** were virtually identical to those reported by Hesse in ref 14 (see Table 2).

JO971570T