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Enantiospecific Synthesis of (+)-N_a-Methylpericyclivine and (−)-N_a-Methylakuammidine as Well as the Ring-A Oxygenated Natural Products, (+)-10-Methoxy N_a-Methylpericyclivine and 10-Hydroxy N_a-Methylpericyclivine

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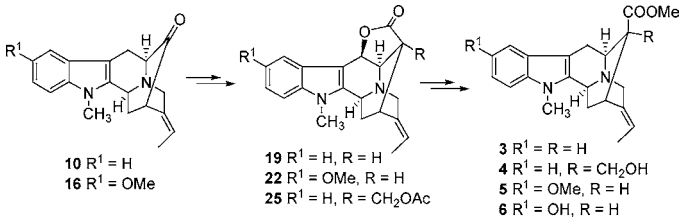
ABSTRACT



The first enantiospecific, regiospecific total synthesis of the enantiomers of N_a-methylpericyclivine and N_a-methylakuammidine as well as the ring-A oxygenated natural products (+)-10-methoxy N_a-methylpericyclivine and 10-hydroxy N_a-methylpericyclivine was achieved. The lactones (see 19, 22, and 25) are key to the formation of the β-axial methyl ester moiety.

The sarpagine-related indole alkaloids comprise one of the largest groups of structurally related indole natural products. Interest in these indole alkaloids derives from both the structural diversity and the complexity of its members and the important medicinal properties of some of these natural bases.[1] Many sarpagine alkaloids comprise a key component of bioactive bisindole alkaloids;[1,3,5] the structures of a few of these are illustrated in Figure 1.

Undulatine **1**[2] and deformoundulatine **2**[2] are two dimeric bisindole alkaloids isolated from *Alstonia undulata* and *Alstonia sphaerocapitata*.[2] They are expected to originate through bond formation between C-10 of cabucraline and the C-6 position of the N_a-methylpericyclivine alkaloids.[2,3] Because of the structures of bisindoles **1** and **2**, interest has arisen in the series of bases, which contain an exo methyl ester function at C-16 (*S*) with the β-axial stereochemistry, examples of which are illustrated in Figure 1. Because it is well-known that the aldehyde function at C-16 prefers the α-equatorial stereochemistry,[4] the more stable stereochemistry for the ester at C-16 is assigned as α-equatorial as well. No total synthesis of these indole alkaloids **1**−**7** has appeared to date. Execution of the enantiospecific total synthesis of **3**

(1) Lounasmaa, M.; Hanhinen, P.; Westersund, M. The Sarpagine Group of Indole Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1999; Vol. 52.

(2) Nuzillard, J.-M.; Pinchon, T. M.; Caron, C.; Massiot, G.; Le Men-Olivier, L. *C. R. Acad. Sci. Ser. II* **1989**, *309*, 195.

(3) Massiot, G.; Nuzillard, J.-M.; Le Men-Olivier, L. *Tetrahedron Lett.* **1990**, *31*, 2883.

(4) Bartlett, M. F.; Sklar, R.; Taylor, W. I.; Schlittler, E.; Amai, R. L. S.; Beak, P.; Bringi, N. V.; Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 622.

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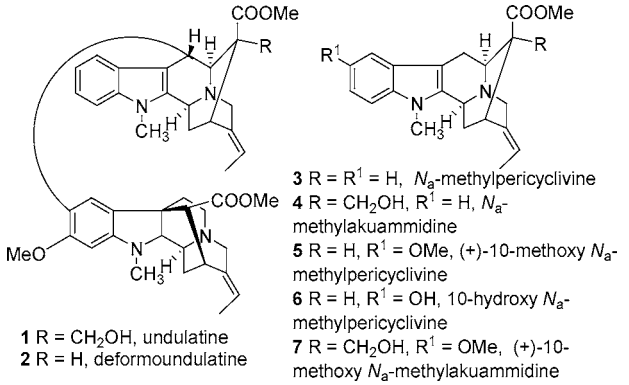
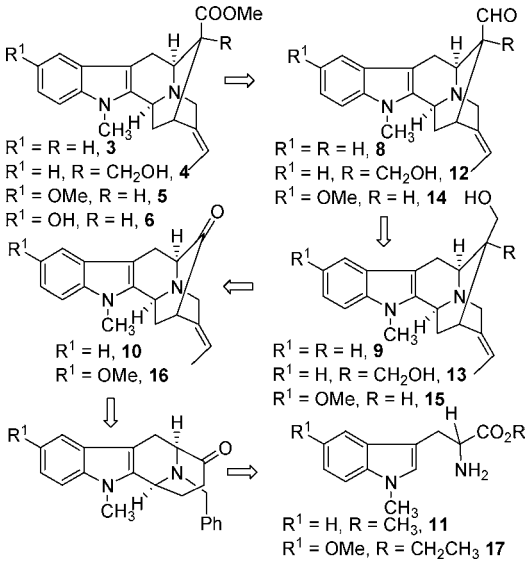


Figure 1. Sarpagine indole alkaloids.

and **4** which comprise the northern units of bisindoles **1** and **2**, respectively, as well as the 10-methoxy pericyclivine related alkaloids **5** and **6** forms the basis of this letter.

In the 1990s, N_a-methylpericyclivine **3** was isolated from the stem, bark, and leaves of *Peschiera buchtieni*, a medicinal plant from the tropical regions of Bolivia, used locally as a treatment for leishmaniasis.[5] The structure of **3** was established by comparison of the proton spectrum with that of natural pericyclivine and 10-methoxy pericyclivine.[5] In a retrosynthetic sense (Scheme 1), N_a-methylpericyclivine **3**

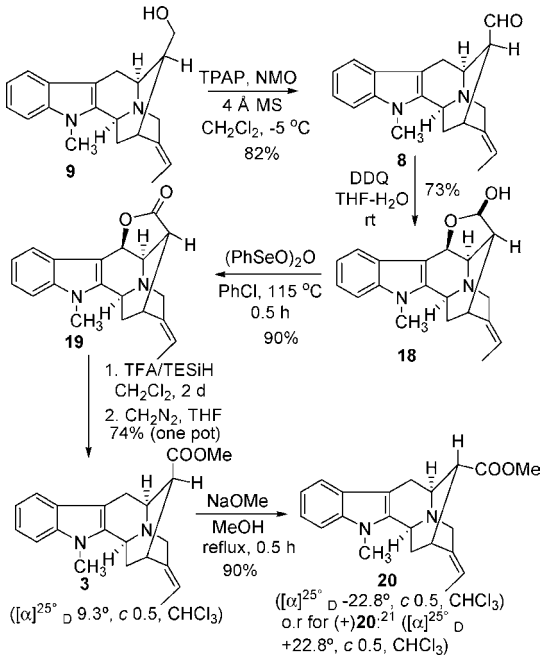
Scheme 1. Retrosynthetic Analysis



was envisaged to arise from aldehyde **8** via oxidation, the latter of which might be accessed by the controlled oxidation of (−)-(*E*)-16-epiaffinisine **9** at C-16 to avoid epimerization. The synthesis of **9** had been achieved recently from a D-(+)-tryptophan methyl ester derivative in seven reaction vessels in 25% overall yield.[6] In the present synthesis, the more readily available L-(−)-tryptophan methyl ester derivative **11** was employed and was converted into (+)-(*E*)-16-epiaffinisine **9** by following the published procedure.[6] This material was enantiomeric with the natural product. Once the exo (β-axial) alcohol **9** was obtained, various oxidative conditions (i.e., Dess−Martin periodinate,[7] IBX,[8] PDC,[9] Swern conditions,[10] and benzeneseleninic anhydride[11]) were originally attempted to furnish the thermodynamically less stable aldehyde **8**.

However, most of these efforts resulted in the formation of the more stable endo aldehyde or in decomposition of the starting material. Gratifyingly, it was found that a catalytic amount of TPAP[12] in the presence of NMO in CH_2Cl_2 converted the exo alcohol **9** into the aldehyde function of **8** in a 3:2 ratio in favor of the exo isomer **8**. Modification of the reaction conditions by lowering the reaction temperature, increasing the amount of catalyst, and decreasing the amount of base provided the less stable exo aldehyde **8** as the exclusive product (Scheme 2). With the exo aldehyde in

Scheme 2. Synthesis of (+)-N_a-Methylpericyclivine



hand, attention turned to the conversion of the carbonyl group into the methyl ester of **3** to complete the synthesis. It was

(5) (a) Muñoz, V.; Moretti, C.; Sauvain, M.; Caron, C.; Porzel, A.; Massiot, G.; Richard, B.; Le Men-Olivier, L. *Planta Med.* **1994**, *60*, 455. (b) Azoug, M.; Loukaci, A.; Richard, B.; Nuzillard, J.-M.; Moreti, C.; Zeches-Hanrot, M.; Le Men-Olivier, L. *Phytochemistry* **1995**, *39*, 1223.

(6) Yu, J.; Wang, T.; Wearing, X. Z.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 5852.

(7) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(8) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3183.

(9) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

(10) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

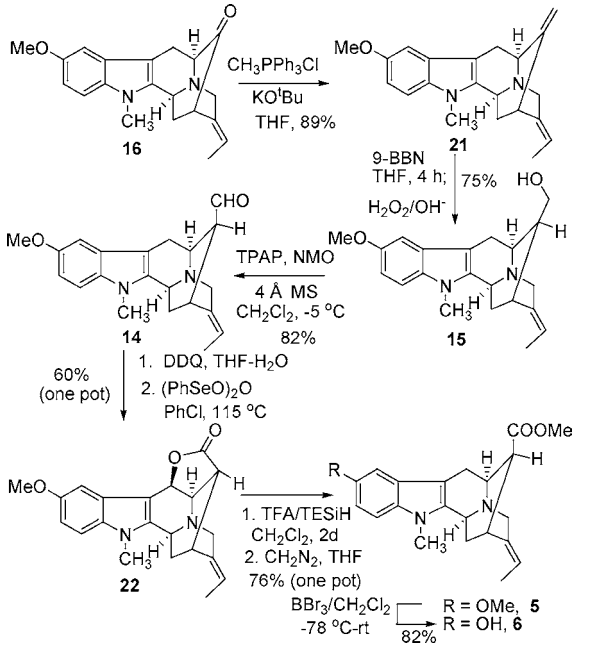
(11) Barton, D. H. R.; Brewster, A. G.; Hui, R.; Lester, D.; Ley, S. V.; Back, T. *J. Chem. Soc., Chem. Commun.* **1978**, *11*, 952.

(12) For a review on TPAP/NMO oxidations, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *23*, 639.

imperative to prevent epimerization of the aldehyde moiety in **8** during formation of the methyl ester in **3**. However, all of the conditions which were attempted[13−18] resulted either in an epimerized aldehyde/ester or in decomposition of the starting material. At this stage, to prevent the epimerization of the aldehyde, it was decided to fix the stereochemistry of the aldehyde at C-16 using an oxidative cyclization with DDQ at C-6, a reaction successfully employed to form 6-oxygen substituted tetrahydro β-carbolines several years ago,[19] following the earlier work of Oikawa and Yonemitsu.[20] Accordingly, the exo aldehyde **8** was cyclized using DDQ in aq THF[19] to obtain the lactol **18**. This intermediate was further oxidized to the corresponding lactone **19** on heating with benzeneseleninic anhydride in 54% overall yield for the three-step process. To the best of our knowledge, this is the first report of oxidation of a lactol to a lactone using benzeneseleninic anhydride. This intramolecular oxidation was key for DDQ or CrO_3 oxidations would cleave the ether function at C-6, which resulted in byproducts of oxidation. This lactone was the key intermediate for the synthesis of many sarpagine natural products with an ester function in the β-axial position. The novel acid-catalyzed reductive ring opening of the lactone **19** was effected using TFA/TESiH in CH_2Cl_2 to yield the exo acid with no epimerization. The acid function was methylated with diazomethane to complete the synthesis of the enantiomer of natural N_a-methylpericyclivine **3** in 74% yield (one pot). The mass spectral data of **3** were in complete agreement with the literature values (MS *m*/*z* 336 $[M]^+$);[5] however, the ^1H NMR spectral data did not completely match the reported values[5] for N_a-methylpericyclivine. Disappointed with this outcome, we further established the structure of **3** using 2D NMR spectroscopy (COSY, NOESY, HMBC, HSQC). To confirm that the structure of synthetic **3** was correct unequivocally, the ester funtion was epimerized with NaOMe in refluxing methanol into the more stable (−)-N_a-methylepipericyclivine **20**. This was the enantiomer of the natural product which had been synthesized by a different route.[21] The spectral data and the optical rotation of synthetic (−)-**20** were in excellent agreement with those of (+)-**20** prepared earlier from the D-tryptophan methyl ester derivative,[21] except for the sign of the optical rotation. This confirmed the structure of the enantiomer of N_a-methylpericyclivine **3** (from L-tryptophan) and established a simple and concise route for the synthesis of pericyclivine related natural products.

Because the preparation of the parent compound **3** in the pericyclivine series had been realized, it was decided to expand this strategy to the synthesis of the 10-methoxy N_a-substituted indole alkaloids **5** and **6**. These two alkaloids, (+)-N_a-methyl 10-methoxypericyclivine **5**[22b] and N_a-methyl 10-hydroxypericyclivine **6**, had been isolated from the leaves of *A. undulata* found in New Caledonia.[2,22] Retrosynthetic analysis (Scheme 1) of **5** and **6** identified the aldehyde intermediate **14** as a potential precursor, which could be synthesized by controlled oxidation of the exo alcohol in **15**. The alcohol **15** could be synthesized from the pentacyclic ketone **16** by following the route reported for the synthesis of the natural (−)-(*E*)-16-epiaffinisine **9**.[6] The pentacyclic ketone **16** had been synthesized recently from the chiral auxiliary, 5-methoxy tryptophan ethyl ester derivative **17**, in enantiospecific fashion.[23] Wittig olefination of the ketone **16** with methyltriphenyl phosphonium bromide in benzene in the presence of potassium *tert*-butoxide provided the exocyclic olefin **21** in 89% yield (Scheme 3). Regiospecific

Scheme 3. Synthesis of (+)-10-Methoxy N_a-Methylpericyclivine and 10-Hydroxy N_a-Methylpericyclivine



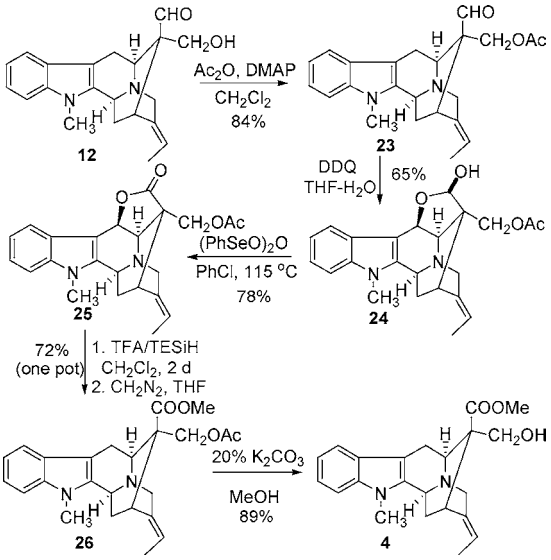
hydroboration/oxidation of the olefin **21** with 9-BBN and H_2O_2/OH^- yielded the required exo alcohol **15** in 75% yield. This alcohol **15** was oxidized to the exo aldehyde **14** (exclusive product) using the TPAP/NMO conditions developed in the parent system (Schemes 2 and 3). The aldehyde was immediately converted into the lactol with DDQ in aq THF and was then further oxidized (benzene selenenic anhydride) to the lactone **22** in 50% overall yield for the three steps. Acid-catalyzed reductive ring opening of **22** followed by methylation with diazomethane yielded the methyl ester **5** in 76% yield. The optical rotation ($[\alpha]^{25}_D$

(13) Yamada, S.; Morizano, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329.
(14) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213.
(15) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647.
(16) McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741.
(17) Wuts, P. G. M.; Bergh, C. L. *Tetrahedron Lett.* **1986**, *27*, 3995.
(18) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235.
(19) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933.
(20) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.
(21) Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543.
(22) (a) Pinchon, T.-M.; Nuzillard, J.-M.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Sevenet, T. *Phytochemistry* **1990**, *29*, 3341. (b) Mroue, M. A.; Euler, K. L.; Ghuman, M. A.; Alam, M. *J. Nat. Prod.* **1996**, *59*, 890.
(23) Zhao, S.; Liao, X.; Wang, T.; Flippen-Anderson, J.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 6279.

22.0°) and spectroscopic properties of synthetic **5** were in excellent agreement with those of natural (+)-N_a-methyl 10-methoxypericyclivine ($[\alpha]^{25}_D$ +23.0°).[22] Demethylation of the methoxy function in **5** using BBr_3 delivered the N_a-methyl 10-hydroxypericyclivine **6** in 82% yield.

Because a synthetic route to pericyclivine related alkaloids had been developed, attention turned toward the synthesis of akuammidine related natural products. N_a-Methylakuammidine **4**, a material which had not yet been isolated as a natural product, represented the northern unit of the bisindole of undulatine **1**[2] and was, therefore, chosen as a target. In a retrosynthetic sense (Scheme 1), **4** was envisaged to arise from the oxidation of the aldehyde **12**. The aldehyde **12** can be obtained from N_a-methylvellosimine which had been prepared recently from the D-(+)-tryptophan methyl ester derivative in 11 reaction vessels in 32% overall yield via a combination of the asymmetric Pictet Spengler reaction, Dieckmann cyclization, a stereocontrolled intramolecular enolate driven palladium-mediated cross-coupling process, and a Wittig olefination.[24] The synthesis again began with the cheaper and readily available L-(−)-tryptophan methyl ester derivative **11** to provide the aldehyde **12**. This material had been obtained earlier via a Tollens reaction on N_a-methylvellosimine with formaldehyde followed by selective oxidation of the diol **13**, to provide the exo aldehyde **12** (see **9**).[25] When aldehyde **12** was subjected to various conditions of oxidation[13−18] to obtain the corresponding acid or the methyl ester, the presence of strong base (KOH or NaOH) resulted in a retroaldol reaction and yielded N_a-methylvellosimine.[26] In most cases, these conditions resulted in recovered starting material or in decomposition of the starting aldehyde **12**. The sterically congested quarternary position of the aldehyde moiety was responsible, in part, for the limited success in these oxidations. At this stage, the approach employed for the synthesis of pericyclivine related natural products was revisited. The alcohol moiety in **12** was protected as its acetate **23** (Scheme 4). Oxidative cyclization of **23** with DDQ in aq THF[19] gave the epimeric mixture of alcohols represented by **24**, and this material was converted into lactone **25** by oxidation with benzeneseleninic anhydride in hot chlorobenzene in 43% yield for the three steps. After the key lactone **25** was obtained in good yield, the acid-catalyzed reductive ring opening was effected using TFA/TESiH in CH_2Cl_2. This was followed by treatment of the acid with diazomethane to yield the ester **26**. The acetate moiety in ester **26** was removed by hydrolysis with 20% aq K_2CO_3 in MeOH to yield N_a-methylakuammidine **4** in 89% yield. The structure of **4** was established by extensive analysis

Scheme 4. Synthesis of (−)-N_a-Methylakuammidine



of the 2D NMR (COSY, NOESY, HMBC, HSQC) and mass spectral data. Consequently, a simple route was developed for the synthesis of the akuammidine related natural products, some of which are found in bisindole alkaloids.

In conclusion, the first total synthesis of the enantiomer of N_a-methylpericyclivine **3** has been achieved via a simple and convergent route from the L-(−)-tryptophan methyl ester derivative in 10% overall yield. The structure of **3** was established through extensive 2D NMR and also by conversion into (−)-N_a-methylepipericyclivine, the enantiomer of the known (+)-N_a-methylepipericyclivine. This latter alkaloid had been synthesized via a different route.[21] This strategy has also been successfully employed for the regiospecific synthesis of the 10-methoxy containing indole bases **5** and **6**. In addition, the total synthesis of (−)-N_a-methylakuammidine **4**, which is the enantiomer of the natural product, was achieved via a short route from the L-(−)-tryptophan methyl ester derivative in 12% overall yield. Simply, replacement of L-(−)-tryptophan with D-(+)-tryptophan in the asymmetric Pictet−Spengler reaction will provide the natural products **3** and **4**. This strategy can be employed to synthesize a wide variety of pericyclivine and akuammidine related natural products as well as their enantiomers for natural product libraries.[27]

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(24) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057.
(25) Yu, J.; Wearing, X. Z.; Cook, J. M. *J. Org. Chem.* **2005**, *70*, 3963.
(26) For a report of a retroaldol process in akuammidine related systems, see: Banerji, J.; Das, B.; Chakrabarti, R.; Shoolery, J. N. *Indian J. Chem.* **1987**, *26B*, 709.
(27) Liu, X.; Zhang, C.; Liao, X.; Cook, J. M. *Tetrahedron Lett.* **2002**, *43*, 7373.