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The First Regiospecific, Enantiospecific Total Synthesis of 6-Oxoalstophylline and an Improved Total Synthesis of Alstonerine and Alstophylline as Well as the Bisindole Alkaloid Macralstonine

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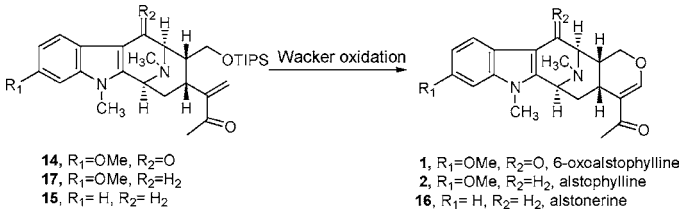
ABSTRACT



A Wacker sequence has been modified to rapidly generate ring E of (–)-alstonerine, (+)-6-oxoalstophylline, and (–)-alstophylline via a domino process. This one-pot sequence provides facile entry into the dihydropyranyl enone unit of many *Alstonia* alkaloids.

Indole alkaloids of the macroline/sarpagine type comprise one of the largest groups of structurally related indole natural products.[1−3] It has been reported that a number of bisindole alkaloids isolated from *Alstonia*[2,4] species have been shown to exhibit antimalarial activity[5,6] against the drug-resistant K1 strains of *Plasmodia falciparum* including macralstonine acetate **4** and its *O*-methyl ether **5**.[6] Macralstonine **3**[7] was synthesized via the biomimetic coupling of (+)-macroline and alstophylline **2** under acidic conditions by Le Quesne et al.[8,9] (+)-Macroline has been synthesized in enantiospecific fashion by Bi[10] and could be obtained via an improved process of Liu et al.[11] in gram quantities. However, alstophylline **2**, originally synthesized by Liu,[12] was not available in large quantities due to the difficulty in forming the dihydropyranyl enone system in ring E. This cis-fused dihydropyranyl enone unit is present in many other indole alkaloids including alstonerine,[13] alstonisine,[13] N_a-demethylalstonisine,[14,15] alstofoline,[15] isoalstonisine,[15] 16-hydroxyalstonisine,[16] and N_b-demethylalstophylline oxindole.[17] It is

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well-known that the design of natural product based libraries has become an important tool in the development of drugs.[18] In the present case, this required development of an efficient route to synthesize these alkaloids and their hybrids. Furthermore, (+)-6-oxoalstophylline **1** (Figure 1), isolated from

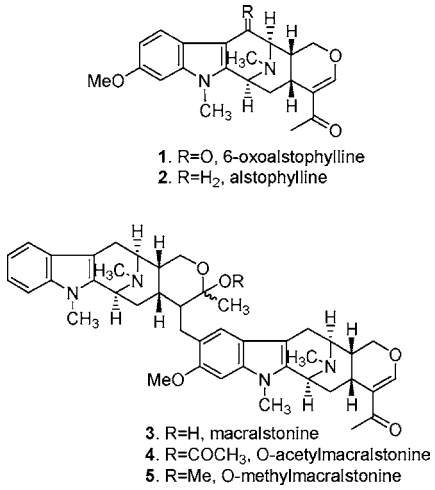


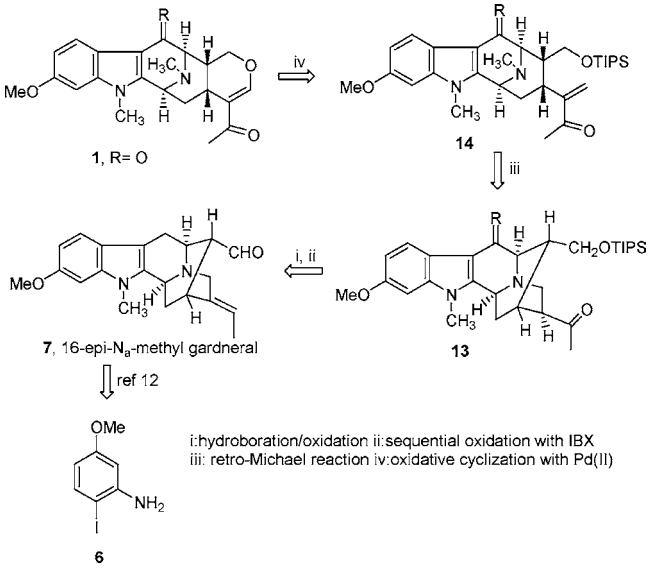
Figure 1.

Alstonia species in 2004,[16] represents the first example of a natural product with oxygenation at carbon-6 of the macroline skeleton. Because of its unique structure, it was decided to design a synthesis of this alkaloid in enantiospecific fashion via a method amenable to construct ring E of other alkaloids. Herein, we report the first total synthesis of 6-oxoalstophylline **1** as well as a much-improved total synthesis of (−)-alstonerine and (−)-alstophylline **2**. Establishment of the double bond in ring-E was accomplished by a key palladium(II) (Wacker oxidation) mediated carbon−oxygen bond formation in domino fashion.

As illustrated in Scheme 1 (retrosynthetic analysis), the strategy here rested on the use of the palladium π-olefin[19] (or Wacker oxidation) process, an IBX-mediated conversion, a base-induced retro-Michael reaction, and a chemospecific hydroboration. The stereocenters at C(3), C(5), C(15), and C(16) were controlled in stereospecific fashion.

The synthesis began with the 6-*epi*-N_a-methylgardneral **7**, which had been prepared in eight reaction vessels from iodoaniline **6** (300 g scale) in a regiospecific, stereospecific fashion.[12] The aldehydic group of **7** was reduced with sodium borohydride to afford 11-methoxyaffinisine **8** in 95% yield. As illustrated in Scheme 2, the hydroxyl group of **8** was then protected as a triisopropylsilyl ether **9**, and this was followed by a hydroboration−oxidation[11,12] sequence at 25 °C. The desired C(19) secondary alcohol **10** could be obtained in 90% yield, accompanied by 6% of the tertiary alcohol. This mixture was then stirred in the presence of 5

Scheme 1



equiv of Na_2CO_3 in refluxing MeOH overnight, after which time the desired secondary alcohol **11**, which contained the

Scheme 2

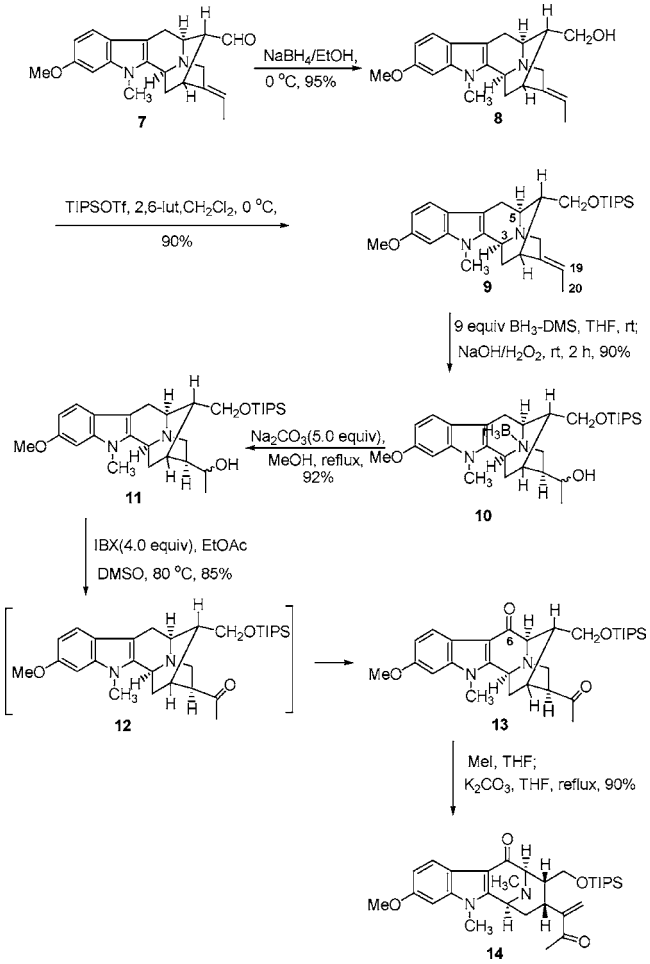


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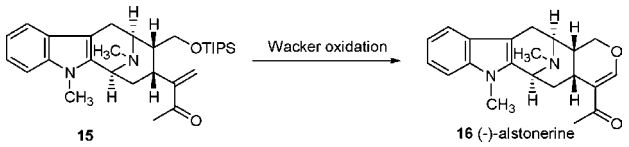
Table 1. Synthesis of (−)-Alstonerine via Intramolecular Wacker Oxidation

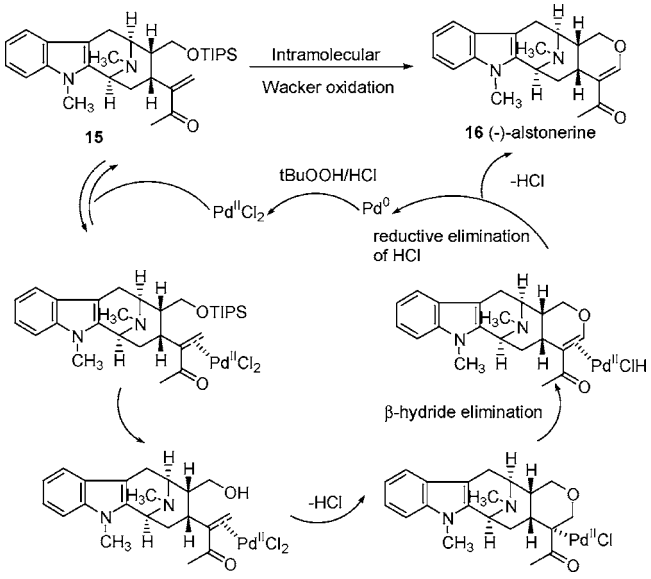


entry	Pd source (mol %)	co-oxidant (equiv)	solvent	T (°C)	yield (%)
1	Na_2PdCl_4 (40%)	t-BuOOH (1.5)	HOAc/H_2O	55	20
2	Na_2PdCl_4 (40%)	t-BuOOH (1.5)	HOAc/t-BuOH/H_2O	55	37
3	Na_2PdCl_4 (40%)	t-BuOOH (1.5)	HOAc/t-BuOH/H_2O	80	45
4	$Pd(TFA)_2$ (40%)	t-BuOOH (1.5)	HOAc/dioxane/H_2O	80	40
5	Na_2PdCl_4 (40%)	t-BuOOH (1.5)	HOAc/dioxane/H_2O	80	50
6[a]	Na_2PdCl_4 (40%)	t-BuOOH (1.5)	HOAc/dioxane/H_2O	80	60

[a] With 1 equiv of NaOAc.

free N_b-nitrogen function, was obtained in 92% yield. With the secondary alcohol **11** in hand, attempts to convert it into the ketone **12** accompanied by oxygenation at C(6) returned a promising result. Recently, a process for the oxidation of benzylic positions effected by IBX has been developed by Nicolaou.[20] Consequently, oxidation of the secondary alcohol of **11** into the ketone **12** with the first equivalent of IBX could be accomplished in 1 h, after which time an additional 3 equiv of IBX could be added to oxidize the C(6) position of **12** to afford the desired oxygenated system in **13** (85% overall yield). Simple alteration of the number of equivalents of IBX could provide either the ketone **12** or the 6-oxo ketone **13**. The 6-oxo ketone **13** was then stirred with methyl iodide in THF at 0 °C to furnish the N_b-methiodide salt to undergo a retro-Michael reaction analogous to the earlier biomimetic work of Le Quesne and Garnick.[21] This salt was stirred under modified conditions with K_2CO_3 in refluxing THF to provide the ring-opened enone **14** via the retro-Michael reaction in greater than 90% yield. With this stable 6-oxo enone **14** in hand, attention next turned to conversion into the corresponding dihydropyranyl enone system present in the natural 6-oxoalstophylline **1**. Liu[12,22] and Le Quesne[21] both previously reported different strategies to approach the synthesis of alkaloids related to 6-oxoalstophylline **1**, which were not practical in the present case. To accomplish the synthesis, an efficient and general transformation to form enones in indole systems in the presence of methoxyl substitutents must be developed. A domino process which permitted deprotection of the TIPS protecting group followed by carbon−oxygen bond formation would be efficient, if successful. In 1980, Tsuji et al.[23] reported that under acidic conditions α,β-unsaturated carbonyl compounds could regioselectively be converted into 1,3-dicarbonyl compounds. This modified acidic Wacker-related process seemed promising. In the model system, the macroline equivalent **15** was employed as the substrate (Table 1). Successful transformation to (−)-alstonerine **16** (four operations here) was accomplished in 20% yield under the original conditions of Tsuji et al.[23] This was significant because under normal Wacker conditions the presence of a substituent on the vinylic carbon atom adjacent to the carbonyl group resulted in no reaction or a very poor yield.[24,25] To the best of our knowledge, this is the first example of a Wacker oxidation involving an α-substituted α,β-unsaturated ketone. When t-BuOH or dioxane was employed as cosolvent to provide a homogeneous solution (entries 2 and 4, Table 1) or the reaction temperature was increased (entry 3, Table 1), yields were improved. Replacement of Na_2PdCl_4 with $Pd(TFA)_2$ decreased the yield, presumably, because the choloride ions stabilized the Pd(0) and prevented formation of Pd black. This had facilitated the oxidation of Pd(0) to Pd(II) in the catalytic cycle. Surprisingly, on addition of 1 equiv of NaOAc (entry 6) to the mixture, (−) alstonerine **16** could be obtained in 60% yield (includes four transformations, each in greater than 85%

Scheme 3



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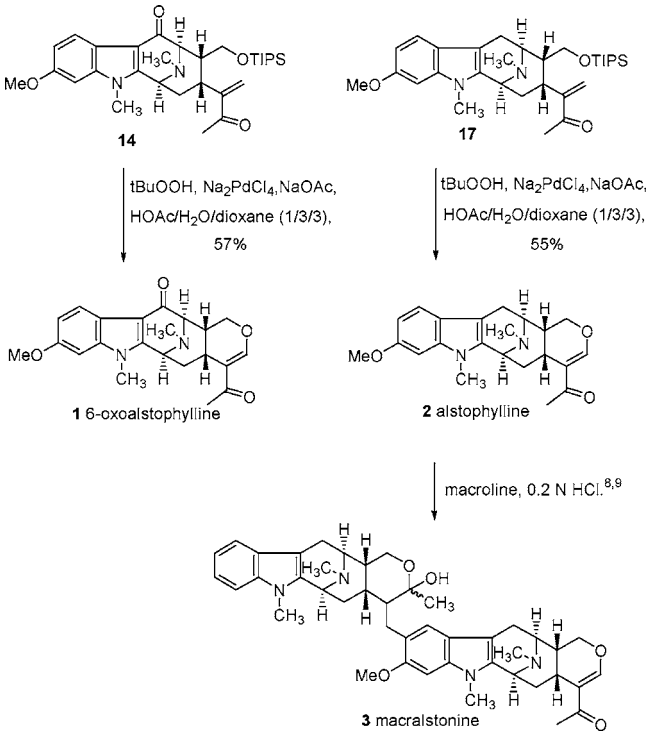
yield). Further optimization and generalization of this process are under investigation.

Although the detailed mechanism is not clear, a proposed one is illustrated in Scheme 3. The process is believed to originally involve the fast and reversible coordination of the alkene by the Pd(II) salt. Under acidic conditions, in the presence of chloride ions the silyl group was cleaved to afford nucleophilic oxygen which attacked the Pd(II) olefin complex. β-Hydride elimination, followed by reductive elimination (see Scheme 3), provided the desired **16**, while the Pd(0) was reoxidized to Pd(II) by *t*-BuOOH.

Once the optimized conditions were in hand, the process was carried out with 6-oxo enone **14** to provide 6-oxoalstophylline **1** in 57% yield. The spectral properties of **1** were in excellent agreement with the natural product.[16] It must be pointed out that four transformations were also executed in this one-pot process, each of which took place in over 85% yield. This represents the first synthesis of **1** and was completed in regiospecific, enantiospecific fashion. In addition, extension of this Wacker process to the 11-methoxymacroline substrate **17** provided a much improved total synthesis of alstophylline **2** (four transformations, 55% overall yield). Because a more efficient and practical synthesis of alstophylline **2** was accomplished, this can be coupled with (+)-macroline (gram quantities have been prepared[11]) to provide an improved total synthesis of the bisindole alkaloid, macralstonine **3**.

In conclusion, a Wacker-related process was utilized in the first total synthesis of 6-oxoalstophylline **1**, which also provided much improved routes to (−)-alstonerine, (−)-alstophylline, and macralstonine (Scheme 4). Because alstonerine, alstophylline, 6-oxoalstophylline, alstonisine, and N_b-demethylalstophylline oxindole contain the dihydropyranyl enone system in ring E, this Wacker process provides a rapid entry into this enone system for the synthesis of a number of indole alkaloids including bisindole alkaloids. The one-pot domino Wacker process is efficient and practical.

Scheme 4



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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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