ORGANIC LETTERS

2010
Vol. 12, No. 9
2140−2141

Racemization-Free Synthesis of (*S*)-(+)-Tylophorine from L-Proline by Radical Cyclization

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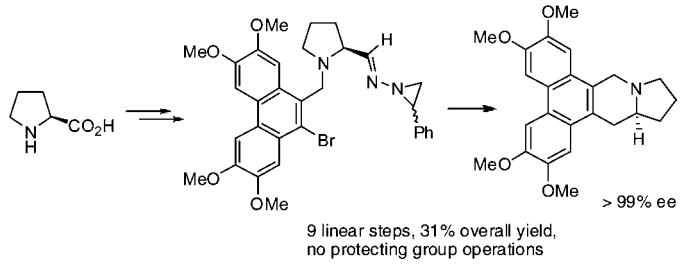
Received March 19, 2010

ABSTRACT



The phenanthroindolizidine alkaloid (*S*)-(+)-tylophorine was synthesized from L-proline in nine linear steps including a double bromination and a free-radical cyclization of an *N*-aziridinylimine as the key steps. The phenanthrene moiety was prepared from homoveratric acid and veratraldehyde and permits the variation of each oxygen-substituted ring.

Phenanthroindolizidine and phenanthroquinolizidine alkaloids represent a group of pentacyclic natural products isolated mainly from the *Cynanchum*, *Pergularia*, and *Tylophora* species.[1,2] Today, more than 60 members of this class are known. Because of their potent biological and pharmacological activities, they are of significant interest for medical research.[3,4] For example, some of these compounds suppress protein biosynthesis[5] and exhibit antiinflammatory effects.[6] Tylophorine (**1**) arrests carcinoma cells in the G1 phase by downregulation of cyclin A2 expression,[7] while (*R*)-antofine exerts its cytotoxic effects via cell cycle arrest in the G2/M phase.[8] The naturally occurring tylophorine is the levorotatory (*R*)-enantiomer, although its optical antipode surprisingly was found to be an even more potent inhibitor of cancer cell growth.[9] Consequently, numerous synthetic approaches to the phenanthroindolizidines and the phenanthroquinolizidines have been developed.[10]

Herein, we report a short racemization- and protecting-group-free synthesis of (*S*)-(+)-tylophorine from L-proline, veratraldehyde, and homoveratric acid (**2**). Condensation of the latter two starting materials in a mixture of triethylamine and acetic anhydride,[11] followed by esterification of the free acid with acetyl chloride in methanol, afforded methyl ester

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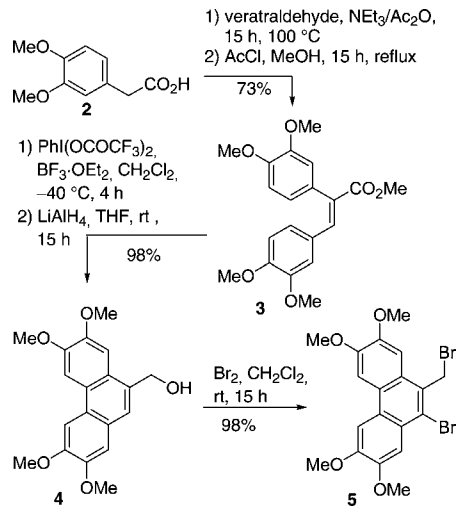
10.1021/ol100652b
Published on Web 04/08/2010

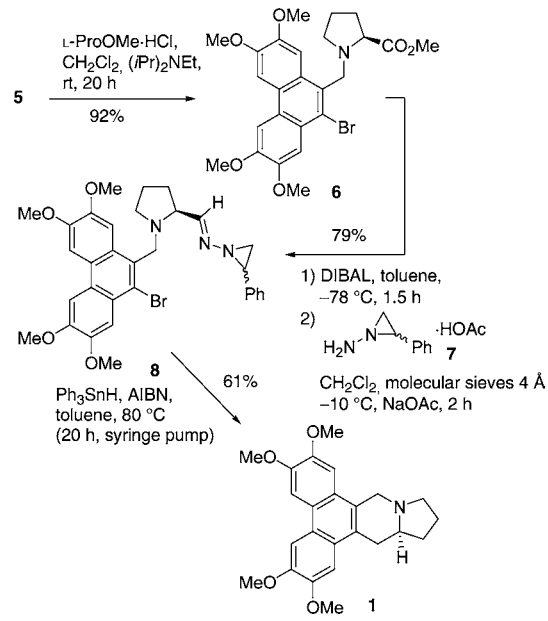
3.[12] This compound undergoes oxidative cyclization upon treatment with [bis(trifluoroacetoxy)iodo]benzene in combination with boron trifluoride etherate to furnish the phenanthrene carboxylate.[13] After treatment with lithium aluminum hydride in THF, the corresponding alcohol **4** was obtained (Scheme 1).[10c,e,g]

Scheme 1



Subsequently, alcohol **4** was treated with 1.1 equiv of bromine in dichloromethane, resulting in the formation of the double-brominated compound **5**,[14] which cleanly effects the N-alkylation of L-proline methyl ester in 92% yield (Scheme 2). Reduction of the obtained ester **6** with an excess of diisobutyl aluminum hydride in toluene at −78 °C turned out to be the method of choice for obtaining the unstable aminoaldehyde. Interestingly, reduction of **6** with $LiAlH_4$ in THF at room temperature resulted in quantitative debromination of the phenanthrene moiety. The crude aminoaldehyde was immediately transformed to the hydrazone **8** in 79% yield which was obtained as a mixture of diastereomers. The amino aziridine used as the nucleophile (**7**) was prepared in two steps from styrene glycol.[15] To achieve the 6-*exo*-*trig*[16] ring closure, the bromo-substituted *N*-aziridinylimine **8** was subjected to a free-radical reaction[17] according to the method of Kim,[18] leading to the direct formation of the pentacyclic alkaloid in 61% yield.

Scheme 2



The use of AIBN/Bu_3SnH in boiling benzene or in toluene at 90 °C led to significant debromination of the starting material, and the reactions furnished only small amounts (20% and 35%, respectively) of tylophorine while the use of the Et_3B/O_2 system in combination with Bu_3SnH or $(Me_3Si)_3SiH$ did not afford the desired product. The best results were obtained by using AIBN and Ph_3SnH in toluene at 80 °C, where (*S*)-(+)-tylophorine (**1**) was obtained in 61% yield with an enantiomeric excess of more than 99% (HPLC, ChiralPak AD-H, see the Supporting Information). The optical rotation ($[\alpha]^{22}_D = +78.9$ ($c = 0.5$, $CHCl_3$)) is slightly higher than the values reported in the literature.[10d,e]

In summary, a very short and efficient synthesis of (*S*)-(+)-tylophorine of high optical purity has been described. It requires only nine steps in the longest linear sequence, provides the target compound in an overall yield of 31% from readily available starting materials, and is devoid of any protecting group manipulations.

Supporting Information Available: Detailed experimental procedures and spectroscopic data as well as ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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