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The Stereocontrolled Total Synthesis of (−)-*O*-Methylpallidinine

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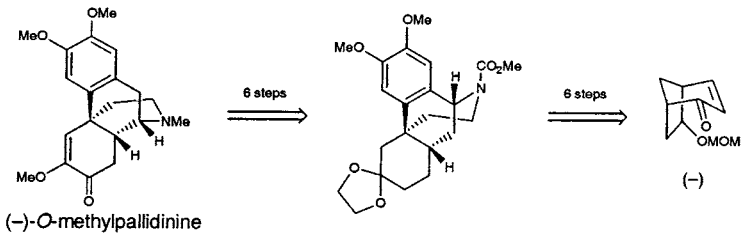
ABSTRACT



The stereocontrolled total synthesis of (−)-*O*-methylpallidinine, a naturally occurring Morphinan alkaloid with a B/C-*trans*-hydrophenanthrene framework, has been achieved starting from the chiral bicyclo[3.2.1]octenone building block by employing a single-step dihydrophenanthrene formation reaction as the key step.

(−)-*O*-Methylpallidinine **1**,[1] isolated from the leaves of the South American plant *Ochotea acutangula*, is a Morphinan alkaloid the B/C-*trans*-hydrophenanthrene stereochemistry of which is diastereoisomeric with that of (−)-morphine **2**[2] having a B/C-*cis*-hydrophenanthrene stereochemistry (Figure 1). We recently developed a concise enantio- and diastereo-

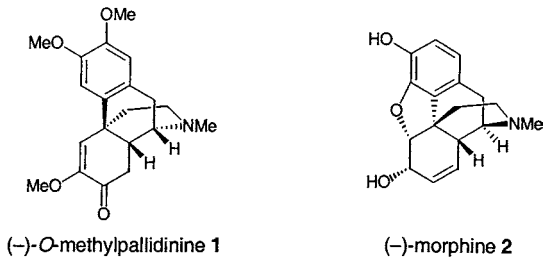


Figure 1.

controlled route[3] to (−)-morphine **2** starting from the enantiopure bicyclo[3.2.1]octenone (−)-**3** accessible either by an enzymatic[4] or a chemical[5] resolution method. We have now investigated the enantio- and diastereocontrolled synthesis[6] of (−)-*O*-methylpallidinine **1** applying the same methodology to extend the versatility of the enantiopure enone **3** as a chiral building block and to widen the applicability of our tandem hydrophenanthrene formation reaction to the construction of Morphinan alkaloids having a B/C-*trans* stereochemistry. Because of its inherent stereochemical and chemical nature with a sterically biased structure, the enone (−)-**3** exhibits convex-face selectivity to allow diastereoselective construction of the benzylic quaternary stereogenic center and facile retro-aldolization leading to the tandem single-step formation of the B/C-*cis*-hydrophenanthrene required for (−)-morphine **2** in the previous synthesis.[3] In the present investigation, we employed the same methodology to synthesize (−)-*O*-methylpallidinine **1** having the *trans*-morphinan stereochemistry from the same

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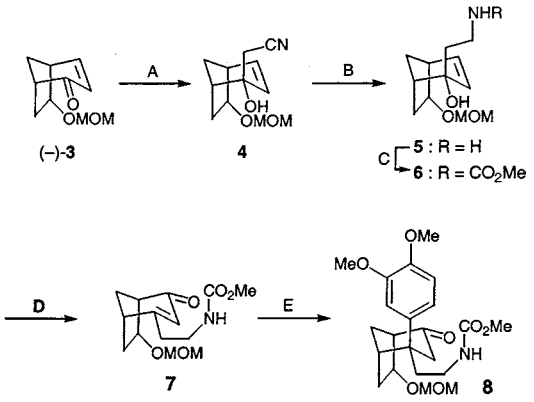
chiral building block (−)-**3** by control of the stereochemistry at the benzylic quaternary stereogenic center. This was accomplished by simply inverting the order of introduction of the aliphatic and aromatic nucleophiles on the chiral building block to lead to the key intermediate with the requisite benzylic quaternary center that is opposite in configuration to that of (−)-morphine **2**. We report here the first diastereo- and enantiocontrolled synthesis of (−)-*O*-methylpallidinine **1**, which required a 12-step sequence of reactions starting from the enantiopure bicyclo[3.2.1]-octenone (−)-**3**.

Thus, the reaction of the enone (−)-**3** with lithioacetonitrile generated in situ from acetonitrile and butyllithium gave the single 1,2-addition product **4**, $[\alpha]_D^{21}$ −191.1 (*c* 1.5, $CHCl_3$), which was sequentially reduced with lithium aluminum hydride and acylated with methyl chlorocarbonate to give the carbamate **6**, $[\alpha]_D^{22}$ −139.4 (*c* 1.2, $CHCl_3$), via the primary amine **5**. Oxidation of **6** with pyridinium chlorochromate (PCC) afforded the enone **7**, $[\alpha]_D^{24}$ +87.5 (*c* 1.1, $CHCl_3$), with rearrangement of the double bond. Upon reaction with the cuprate, prepared in situ from veratrylmagnesium bromide and copper(I) bromide, in the presence of trimethylsilyl chloride,[7] the ketone **8**, $[\alpha]_D^{25}$ +108.4 (*c* 1.2, $CHCl_3$), was obtained with a *β*-benzylic quaternary center and a *β′*-alkoxyl functionality as the single product after treatment of the intermediate crude silyl enol ether with tetrabutylammonium fluoride (TBAF). During the conversion both the 1,2- and 1,4-additions occurred diastereoselectively from the convex-face, respectively, owing to the sterically biased molecular structure of the chiral building block (Scheme 1).

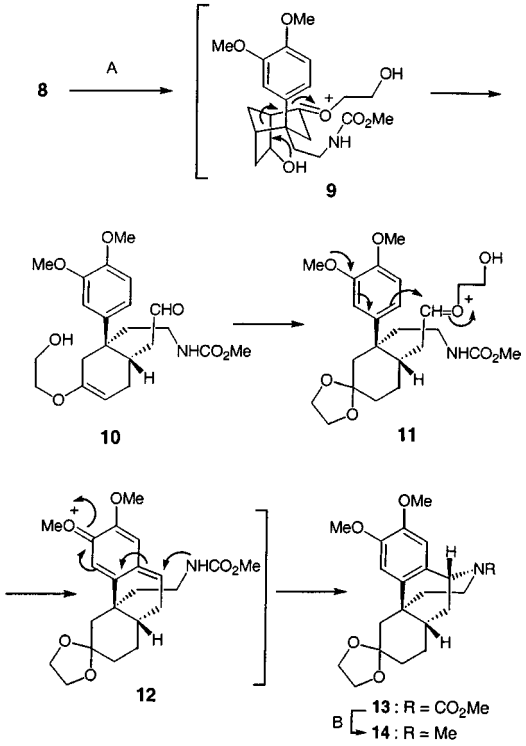
Scheme 1[a]



[a] Reagents and conditions: (A) MeCN, BuLi, THF, −78 °C (92%). (B) $LiAlH_4$, THF. (C) $ClCO_2Me$, Et_3N, CH_2Cl_2 (75%, 2 steps). (D) PCC, CH_2Cl_2 (89%). (E) 3,4-$(MeO)_2C_6H_3MgBr$, CuBr-Me_2S, TMS-Cl, HMPA, THF, −78 °C then TBAF (82%).

When the ketone **8** was refluxed with ethylene glycol in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid, a facile reaction occurred to give a single product that was found to be not the expected tricyclic secondary carbamate but the tetracyclic tertiary carbamate **13**, $[\alpha]_D^{26}$ +155.8 (*c* 1.1, $CHCl_3$), having a B/C-*trans*-hydrophenanthrene moiety. The reaction may be triggered by the *β′*-alkoxy functionality which induced a hydrophenanthrene formation involving the following tandem sequence of reactions: (i) deprotection of the MOM ether and ketoxonium formation (**8**−**9**), (ii) retro-aldolization forming the aldehyde (**9**−**10**), (iii) aldoxonium ion formation (**11**−**12**), (iv) cyclization to form the quinone methide intermediate, and (v) *C*-*N* cyclization (**12**−**13**). In the synthesis of (−)-morphine **2** previously reported,[3] the tricyclic 9,10-dehydro derivative having a B/C-*cis* stereochemistry was directly generated since the secondary carbamate nitrogen was absent. In the present reaction, the cyclization by the secondary nitrogen occurred to give the tetracyclic product **13** instead of forming the 9,10-double bond. The tetracyclic carbamate **13** generated was reduced with lithium aluminum hydride to afford the tertiary amine **14**, $[\alpha]_D^{22}$ +98.0 (*c* 1.4, $CHCl_3$), without affecting the tetracyclic ring system (Scheme 2).

Scheme 2[a]

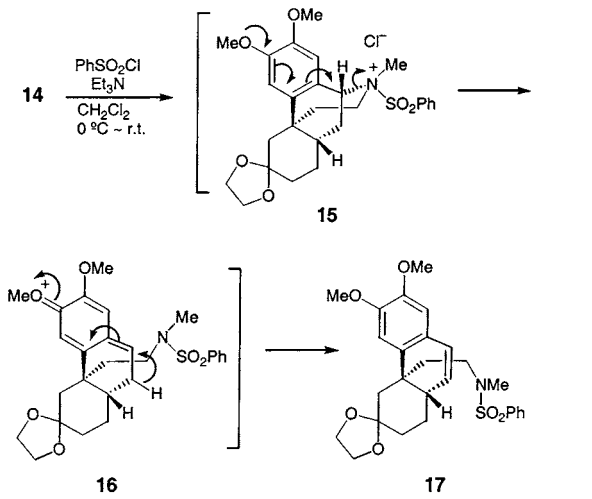


[a] Reagents and conditions: (A) $(CH_2OH)_2$, *p*-TsOH (cat.), toluene, reflux (77%). (B) $LiAlH_4$, THF, reflux (95%).

To introduce the 9,10-olefin functionality required for the construction of the morphinan framework,[3,8] the amine **14** was treated with phenylsulfonyl chloride in the presence of triethylamine. As expected, a facile sulfonylative elimination took place to furnish the tricyclic compound **17**, $[\alpha]_D^{20}$ +81.1 (*c* 1.2, $CHCl_3$), having a 9,10-double bond in 82% yield, presumably through transient intermediates such as **15** and **16** (Scheme 3).

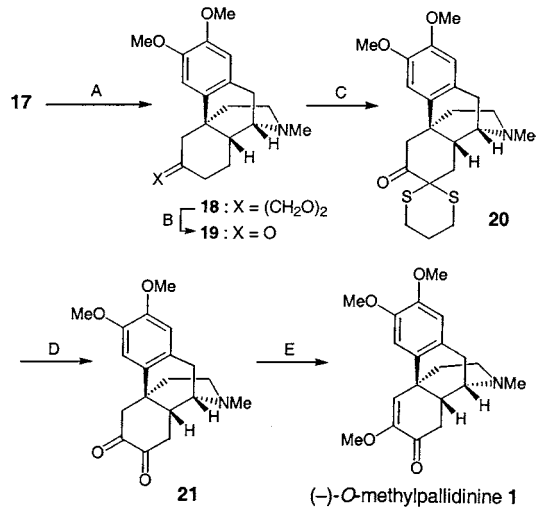
As in the morphine synthesis,[3,8] exposure of the sulfonamide **17** to lithium in liquid ammonia resulted in reductive

Scheme 3



cyclization to furnish the morphinan **18**, $[\alpha]_D^{29}$ +47.1 (*c* 0.8, $CHCl_3$), in good yield. Cyclization of **17** also occurred with sodium naphthalenide in THF[9] to give the same cyclization product **18** in moderate yield. Acid hydrolysis of the ketal functionality of **18** afforded the ketone **19**, $[\alpha]_D^{27}$ +61.3 (*c* 1.0, $CHCl_3$), whose spectroscopic data were identical with those reported for the racemate (±)-**18** synthesized using completely different procedures.[6b,c] Since the racemic ketone **19** has been transformed into racemic *O*-methylpallidinine (±)-**1**,[6] the present synthesis of the optically active ketone (+)-**19** constitutes a formal enantiocontrolled synthesis of (−)-*O*-methylpallidinine **1**. To complete the total synthesis, the optically active ketone (+)-**19** thus obtained was first transformed into the α-diketone monothioketal[6a,b] **20**, $[\alpha]_D^{25}$ −81.0 (*c* 1.0, $CHCl_3$), on treatment with trimethylene dithiotosylate[10,11] via the pyrrolidine enamine intermediate. The dithiane functionality was then removed by following the McMurry procedure[6a,b] to give the α-diketone **21**, $[\alpha]_D^{28}$ +21.9 (*c* 0.4, $CHCl_3$). Finally, the diketone **21** was then refluxed in methanol[6a,b] containing a catalytic amount of *p*-toluenesulfonic acid to give (−)-*O*-methylpallidinine **1**, $[\alpha]_D^{28}$ −33.8 (*c* 0.4, $CHCl_3$), hydrochloride (mp 195−197 °C, $[\alpha]_D^{27}$ −21.3 (*c* 0.4, MeOH) {natural[1] hydrochloride; mp 195−200 °C, $[\alpha]_D^{20}$ −50 (MeOH)}), in 20% yield with 55% recovery of starting **21**, to complete the first enantiocontrolled total synthesis. The spectroscopic data of the synthetic material were identical with those reported for the natural and synthetic products.[1,6a,b] The overall yield of (−)-*O*-methylpallidinine **1** from the bicyclo[3.2.1]octenone chiral building block (−)-**3** was 5% in 12 steps after correction for recovered starting material in the final step (Scheme 4).

Scheme 4[a]



[a] Reagents and conditions: (A) Li, NH_3. *t*-BuOH, THF, −78 °C (76%) or sodium naphthalenide, THF, −30 °C (35%). (B) *p*-TsOH (cat.), aq. acetone, reflux (90%). (C) pyrrolidine, $CH_2(CH_2STs)_2$ (76%). (D) *m*-CPBA (1.2 equiv), −30 °C, then dil. HCl, reflux (69%). (E) *p*-TsOH, MeOH, reflux (20%, 44% based on recovered **21**).

In conclusion, we have achieved the enantio- and diastereocontrolled synthesis of (−)-*O*-methylpallidinine **1**, a morphinan alkaloid with B/C-*trans* stereochemistry, from our bicyclo[3.2.1]octenone chiral building block (−)-**3** on the basis of its inherent stereochemical and chemical nature.[12] The same methodology developed in the synthesis of (−)-morphine **2** with B/C-*cis* stereochemistry utilizing the same chiral building block was applied to this synthesis.

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