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Total synthesis of (±)-desoxycodeine-D: a novel route to the morphine skeleton

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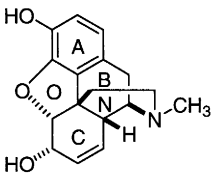
Abstract

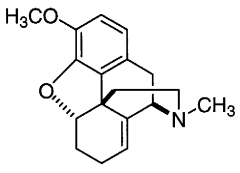
A novel approach towards the construction of the morphine skeleton was demonstrated by a total synthesis of (±)-desoxycodeine-D (**11**) from 5,6,7,8-tetrahydroisoquinoline and isovanillin. The key steps are two consecutive Pd-catalyzed cyclizations and a Stevens rearrangement for the formation of ring B.

Keywords: analgesics; alkaloids; palladium; palladium compounds; rearrangements.

Morphine is a potent analgesic alkaloid with a rigid pentacyclic (ABCNO) structure. A number of total syntheses of morphine have been published since the first one achieved by Gates and Tschudi in 1952.[1] However, a more practical and stereoselective synthetic route for morphine alkaloids remains an attractive research goal for synthetic organic chemists.[2] In a previous publication,[3] we have demonstrated an efficient synthesis of morphine ANO and ACNO fragments, namely spiro[benzofuran-3(2*H*),4′-piperidine] and octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline, by intramolecular Heck reaction. We have now developed a novel approach for the construction of ring B in morphine, based on a Pd-catalyzed intramolecular *N*-benzylation followed by a Stevens rearrangement. The current strategy coupled with our previous method for the construction of the ACNO ring system has provided us an efficient access to the complete pentacyclic skeleton of morphine. Described here is a total synthesis of (±)-desoxycodeine-D (**11**),[4] which serves to exemplify the applicability of the above methodology.



Morphine



Desoxycodeine-D (11)

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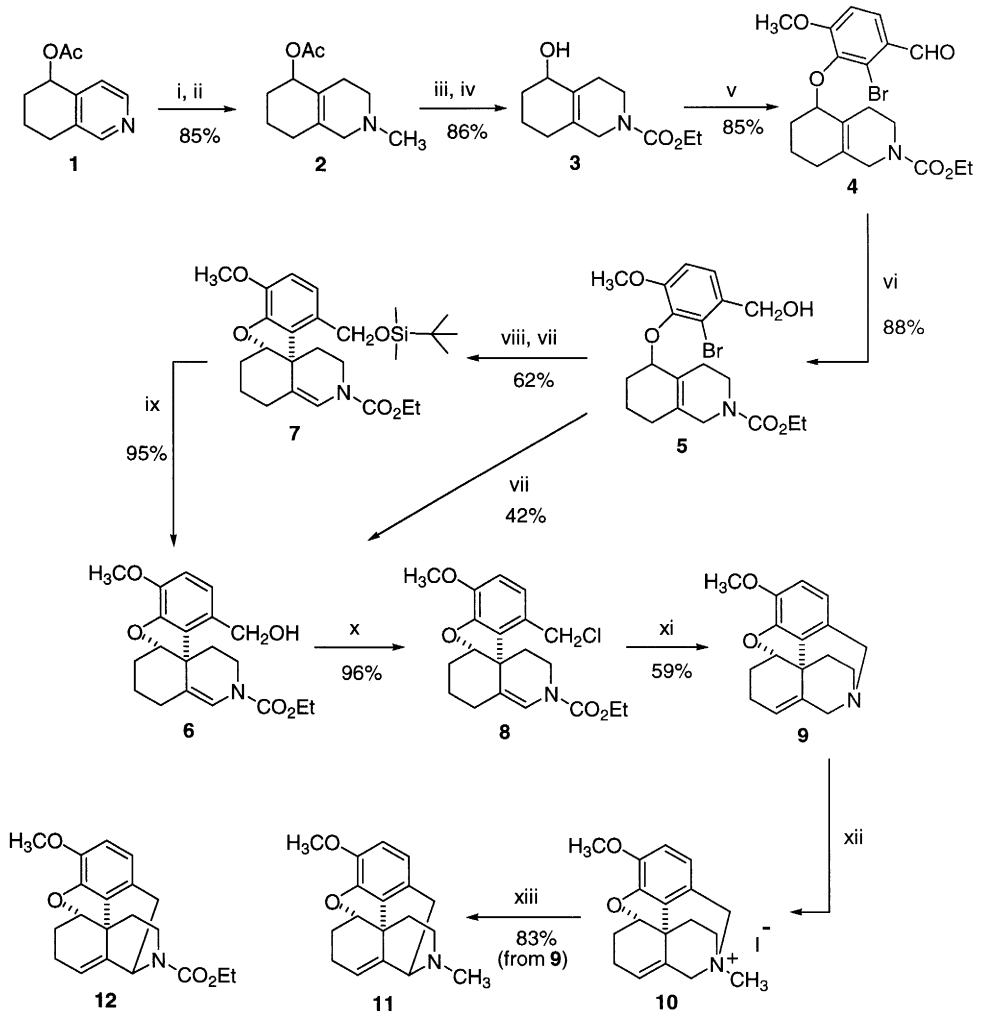
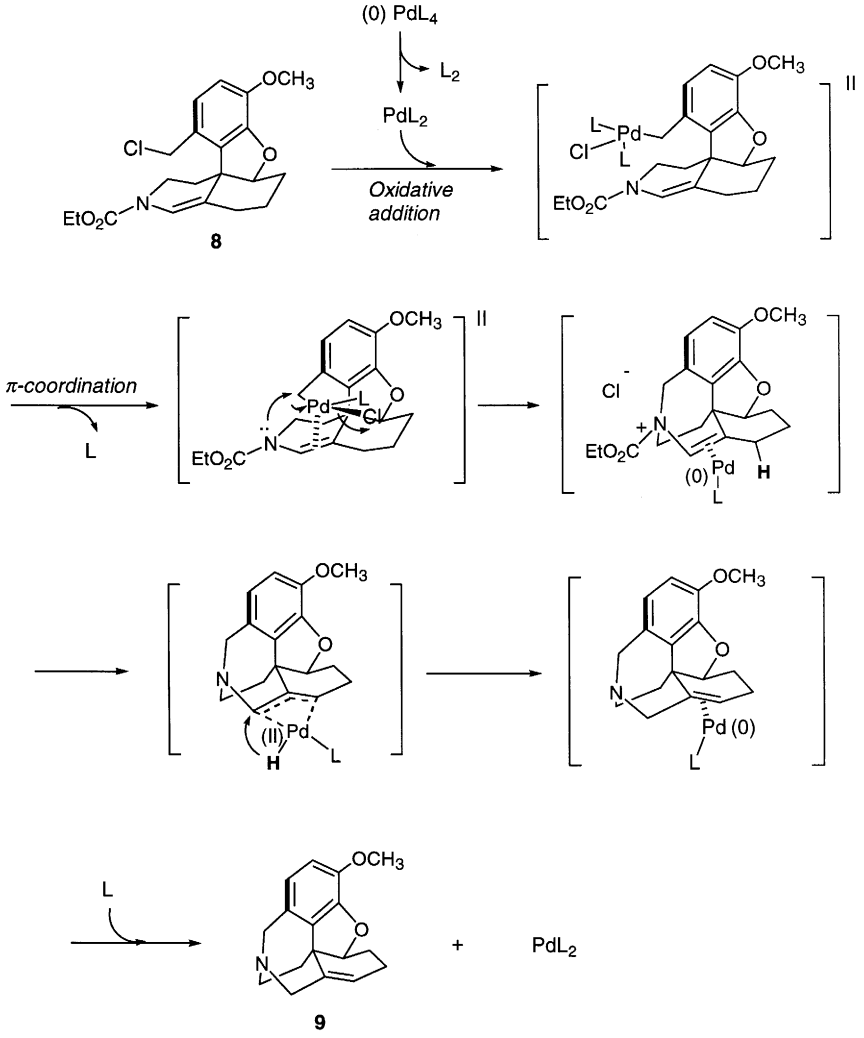


Scheme 1. Reagents and conditions: i. CH_3I, CH_2Cl_2, room temp.; ii. $NaBH_4$, MeOH, 0°C; iii. EtOOCCl, $KHCO_3$, $ClCH_2CH_2Cl$, reflux; iv. NaOH, MeOH, 0°C; v. 2-bromoisovanillin, DEAD, $(n\text{-}C_4H_9)_3P$, THF.; vi. $NaBH_4$, MeOH, 0°C; vii. $Pd(OAc)_2$, PPh_3, Et_3N, CH_3CN, 120–130°C; viii. TBDMSCl, imidazole, THF; ix. $(n\text{-}C_4H_9)_4N^+F^-$, THF, room temp.; x. NCS, PPh_3, THF, room temp.; xi. $Pd(PPh_3)_4$, Et_3N, CH_3CN, 120–130°C; xii. CH_3I, CH_2Cl_2, room temp.; xiii. PhLi, ether, 0°C

As outlined in Scheme 1, the synthesis of **11** starts from readily available 5,6,7,8-tetrahydroisoquinoline and isovanillin. Thus, 5-acetoxy-5,6,7,8-tetrahydroisoquinoline (**1**)[5,6] derived from 5,6,7,8-tetrahydroisoquinoline was treated with iodomethane, followed by $NaBH_4$ reduction, to give the octahydroisoquinoline **2**.[7] Compound **2** was treated with ethyl chloroformate followed by hydrolysis of the acetate group to give carbamate **3**. The condensation of compound **3** with 2-bromoisovanillin[8] under Mitsunobu conditions[9] provided compound **4**, which was reduced with $NaBH_4$ to give the benzyl alcohol intermediate **5**. The formation of the O-ring was achieved when compound **5** was subjected to Heck reaction conditions, and the tetracyclic (ACNO) compound **6**[10] was obtained in 42% yield. The yield of the above intramolecular cyclization was significantly increased via prior protection of the alcohol function in **5** as a silyl ether. Compound **6** was then converted to the benzyl chloride **8** via treatment with *N*-chlorosuccinimide and triphenylphosphine. Our original plan for the construction of ring B was to utilize the documented Pd-catalyzed cyclization of benzyl

halides containing alkenes.[11] However, when compound **8** was subjected to Heck reaction conditions ($Pd(PPh_3)_4$, Et_3N, CH_3CN, 120°C), instead of giving the anticipated compound **12**, an intramolecular *N*-benzylation occurred and provided the tertiary amine **9**.[10] A likely mechanism for the formation of compound **9** from **8** is given in Scheme 2. Prompted by literature reports[12] of Stevens rearrangement of quaternary tetrahydroisoquinoline alkaloids, compound **9** was first converted into the corresponding *N*-methylammonium iodide **10**, which was then treated with PhLi in ether. To our gratification, compound **10** underwent the anticipated Stevens rearrangement, and provided (±)-desoxycodeine-D (**11**) in 83% yield.[13]



Scheme 2.

In summary, we have demonstrated a novel synthetic route to the morphine skeleton, starting from 5,6,7,8-tetrahydroisoquinoline and isovanillin. Notable features of the synthesis include an unexpected Pd-catalyzed intramolecular *N*-benzylation and the efficient formation of ring B via a Stevens rearrangement. Further work towards a total synthesis of (−)-morphine is currently underway in our laboratory.

Acknowledgements

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