A formal synthesis of (±)-reserpine from methyl vanillate

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Cyclohexane 10, a key intermediate in the Stork's synthesis of reserpine, is prepared from methyl vanillate in 8 steps.

Reserpine **1**, a prominent member of yohimbine group of indole alkaloids, was originally isolated from Indian snake root, *Rauwolfia serpentina* Benth.[1] Owing to its complex architecture and high medicinal value, reserpine has been an attractive target for synthetic organic chemists for several years.[2–8] The first of its five total syntheses reported to date was achieved by R. B. Woodward.[3] The key feature of all the syntheses has been the construction of *E*-ring, a cyclohexane moiety substituted in all but one position. Here we report the synthesis of **10**, which was previously transformed into reserpine in two steps by Stork and co-workers.[4]

The synthetic sequence is shown in Scheme 1. Compound **2**, prepared by the intramolecular Diels–Alder reaction of the masked *o*-benzoquinone generated *in situ* from methyl vanillate and allyl alcohol,[9] was transformed into a separable 1 : 2 mixture of *endo*- and *exo*-**3** by reduction with $NaBH_4$. While the *exo*-**3** was subjected to K_2CO_3-catalysed Michael addition of methanol to obtain a 5 : 7 mixture of *trans* adducts **4**, *endo*-**3** was converted back into compound **2** by Swern oxidation. Michael addition of methanol on compounds **2** and *endo*-**3** was attempted under various conditions without success. No attempts were made to separate the Michael adducts, instead they were oxidized under Swern conditions to the corresponding ketones **5** and **6**. The ketones **5** and **6** were separated by column chromatography and their structures were determined by 1D and 2D NMR spectral analysis. Samarium iodide reduction of compound **6** afforded alcohol **7**, which upon treatment with tosyl chloride in the presence of pyridine followed by Baeyer–Villiger oxidation with *m*CPBA gave two isomeric lactones **8** and **9**. The lactone **9** upon reduction with DIBAL-H at −78 °C furnished the desired compound **10**.† The stereochemical assignments of cyclohexane **10** were based on 1D and 2D NMR spectral analysis. In addition, the ^1H NMR spectrum of **10** was found to be identical with that supplied by Professor Stork.

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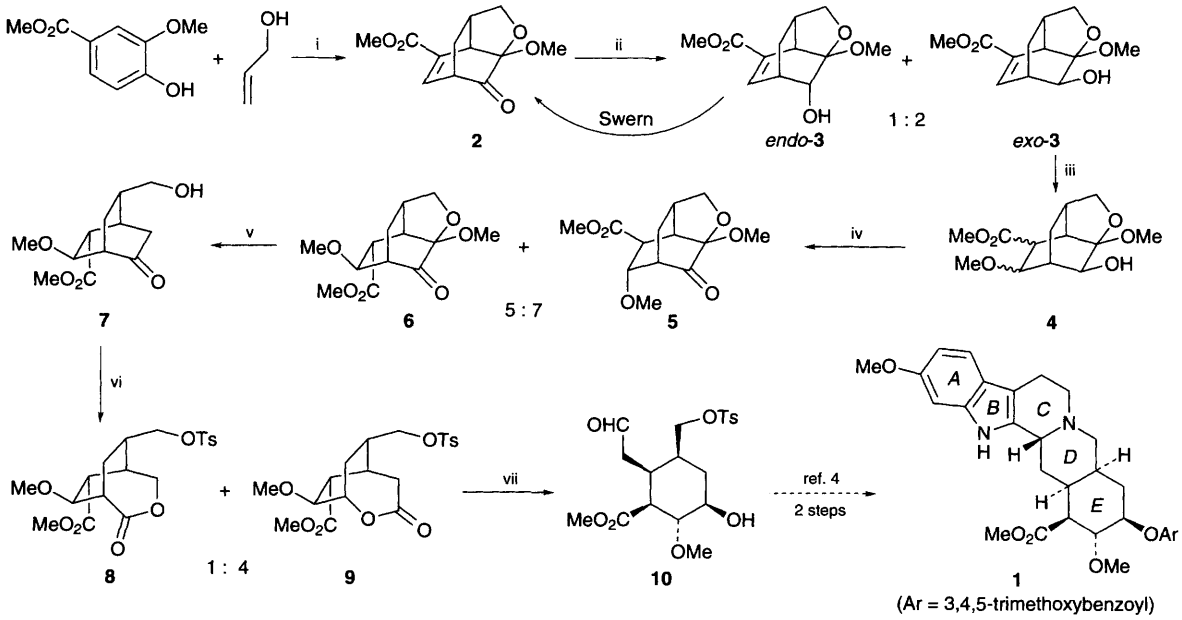
Footnote

† *Selected spectroscopic* data for **10**: IR ($CHCl_3$) ν/cm^{-1} 3468, 2937, 1733, 1597, 1450, 1359, 1179, 1094, 959, 825 and 665. ^1H NMR (600 MHz, $CDCl_3$): δ 9.56 (s, 1 H), 7.73 (d, *J* 8.3 Hz, 2 H), 7.34 (d, *J* 8.0 Hz, 2 H), 3.85–3.83 (m, 2 H and OH), 3.64 (s, 3 H), 3.53–3.51 (m, 1 H), 3.52 (s, 3 H), 3.31 (dd, *J* 8.9, 11.0 Hz, 1 H), 2.98 (m, 1 H), 2.75 (dd, *J* 6.8, 18.8 Hz, 1 H), 2.48 (dd, *J* 4.2, 11.1 Hz, 1 H), 2.45 (s, 3 H), 2.23 (dd, *J* 4.3, 18.7 Hz, 1 H), 2.07 (m, 1 H), 1.82 (m, 1 H) and 1.22 (m, 1 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 198.5 (d), 172.0 (s), 144.8 (s), 129.4 (d), 127.2 (d), 81.5 (d), 73.2 (d), 69.8 (t), 60.2 (q), 51.2 (q), 50.0 (d), 38.1 (t), 37.5 (d), 30.0 (d), 29.8 (t) and 20.8 (q). EI Mass (75 eV): *m/z* (relative intensity) 414 (M^+, 0.12%), 396 (9%), 241 (19%), 209 (15%), 198 (15%), 172 (19%), 166 (17%), 139 (22%), 121 (28%), 117 (52%) and 91 (100%). HRMS (FAB): Calcd. for $[M + H]^+$, $C_{19}H_{27}O_8S$: 415.1426; found: 415.1421. Calcd. for M^+, $C_{19}H_{26}O_8S$: 414.1348; found: 414.1345.



Scheme 1 *Reagents and conditions*: i, $PhI(OAc)_2$, CH_2Cl_2, 75%; ii, $NaBH_4$, MeOH, 93%; iii, MeOH, K_2CO_3, reflux, 3 h, 60%; iv, $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, −78 °C, 65%; v, SmI_2, MeOH, THF, 90%; vi, (*a*) TsCl, py, CH_2Cl_2, 12 h, 90%; (*b*) *m*-CPBA, CH_2Cl_2, 2 d, 80%; vii, DIBAL-H in hexanes, PhMe, −78 °C, 76%

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