Concise total synthesis of (±)-aspidospermidine *via* an oxidative Hosomi–Sakurai process†

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A concise total synthesis of (±)-aspidospermidine has been achieved in twelve steps from inexpensive 4-ethylphenol, based on an oxidative Hosomi–Sakurai reaction *via* the concept of "aromatic ring umpolung".

Electron-rich aromatic compounds such as phenols, anilines, and their derivatives normally express nucleophilic reactivity. However, oxidative activation[1–3] can convert these aromatics into reactive electrophilic intermediates, which may be intercepted with appropriate nucleophiles in synthetically useful yields. Thus, oxidative attack of a phenol[4] with iodobenzene diacetate (DIB), an environmentally benign and inexpensive reagent, in the presence of allyltrimethylsilane promotes an oxidative Hosomi–Sakurai process[5] that produces products **3** in 37–84% yield.[5d] The erstwhile electron-rich aromatic substrate expresses electrophilic character in this reaction. The overall transformation may thus be thought of as involving "aromatic ring umpolung",[6] Fig. 1.

This concept provides new strategic opportunities in synthetic chemistry. Indeed, this method has already allowed us to develop an innovative method directly applicable to the expeditious total syntheses of natural products.[7] In this communication, we illustrate a new use of the concept by a direct application of a bimolecular oxidative Hosomi–Sakurai condition in connection with a fully stereocontrolled total synthesis of (±)-aspidospermidine, **4**. Compound **4** belongs to the family of aspidosperma alkaloids (Fig. 2).[8] The complex architecture and biological activities of these products[9] have elicited substantial interest in the synthetic arena. Aspidospermidine and aspidospermine contain a pentacyclic ring system and five asymmetric centers. The usual strategy used to produce these compounds is generally based on the formation of a key intermediate **6**, first described by Stork and Dolfini.[10] Since then, many other syntheses or formal syntheses have been reported.[11]

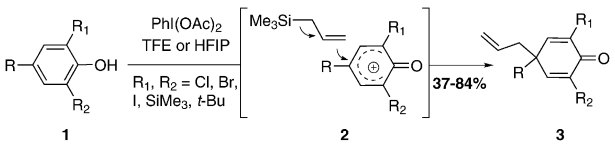


Fig. 1 Aromatic ring umpolung.

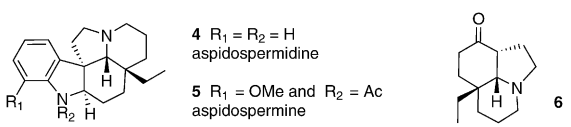
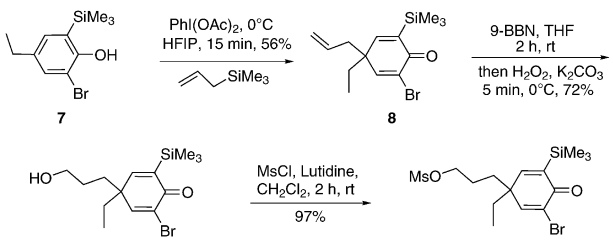


Fig. 2 Aspidosperma alkaloid family.

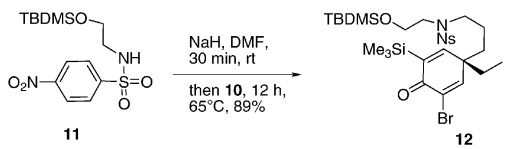
Our approach, based on aromatic ring umpolung, starts with a polysubstituted phenol **7**.[12] This compound can be rapidly converted into the corresponding dienone **8** *via* a bimolecular oxidative Hosomi–Sakurai process in 56% yield by DIB oxidation in the presence of allyltrimethysilane and a perfluorinated solvent such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP). The use of a polysubstituted phenol such as **7**, containing removable directing groups, is very important in order to force the subsequent allyltrimethylsilane to locate exclusively at position 4. The corresponding dienone **8** is treated under hydroboration conditions to produce alcohol **9** in 72% yield. The latter is activated with mesyl chloride to generate compound **10** in 97% yield, Scheme 1.

Compound **10** is thus produced rapidly from **7** *via* the oxidative allylation strategy. At this point the nitrogen moiety is efficiently introduced by an S_N2 reaction between **10** and the corresponding anion of **11**[13] to afford the sulfonamide **12** in 89% yield. This product contains protected secondary amine and alcohol groups which represents a good precursor of the main tricyclic core of aspidospermidine. The nosylamide or Fukuyama's sulfonamide[14] was chosen because it is known to be easily cleaved under mild reaction conditions, Scheme 2.

Indeed, the elaboration of aspidospermidine required a method for the stereoselective construction of the main



Scheme 1 Oxidative Hosomi–Sakurai reaction.



Scheme 2 Alkylation of sulfonamide **11**.

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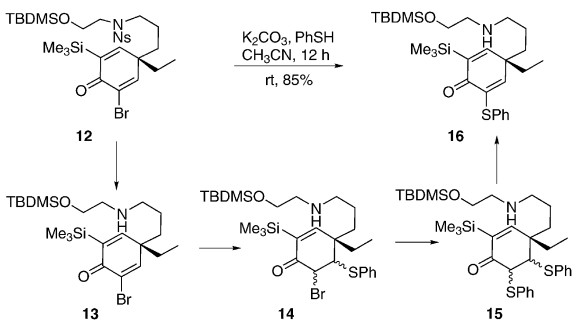
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds along with copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b903530c

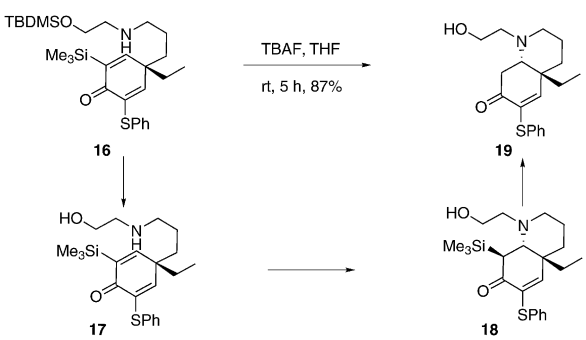
tricyclic core. We envisaged, by means of Fukuyama's deprotection, generating the free secondary amine, which could cyclize (6-exo-trig), to produce the first heterocycle. Intriguingly, addition of thiophenolate, under these conditions, leads to compound **16** *via* a substitution of the bromide by a thioether. This transformation, occurring in 85% yield, takes place *via* four successive distinct steps: (1) nucleophilic aromatic substitution (S_NAr) deprotection leads to the corresponding free amine **13**; (2) addition of thiophenol leads to compound **14**; (3) substitution of the bromide by an S_N2 process generates **15**; and (4) a final retro-Michael reaction produces **16**. At this point, the addition of the free amine on the dienone is not observed, Scheme 3.

Treatment of compound **16** with TBAF produces the free alcohol and bicyclic ring **19** in 87% yield. Once again, different transformations occurred in the same pot: (1) desilylation of the TBDMS moiety produces **17**; (2) the free amine reacts *via* a Michael process to afford the bicyclic compound **18**; (3) desilylation of the TMS group occurs to produce **19**, Scheme 4.

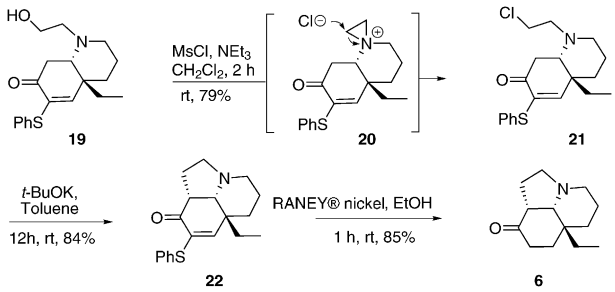
The action of mesyl chloride on compound **19** results in the formation of the corresponding chloride **21** in 79% yield. Compound **21** is obtained probably due to the formation of the corresponding aziridinium **20** in the medium, which is opened by nucleophilic attack by the released chloride. Treatment of **21** with a base such as potassium *tert*-butoxide leads to the desired tricyclic compound **22** in 84% yield. At this point, treatment of compound **22** with RANEY® nickel in ethanol produces **6** in 85% yield. This sequence of reactions, including a Fukuyama and Michael–retro-Michael tandem process, offers an efficient access to key intermediate **6**, known as formal synthesis of aspidospermine, aspidospermidine and quebrachamine,[11m] Scheme 5.



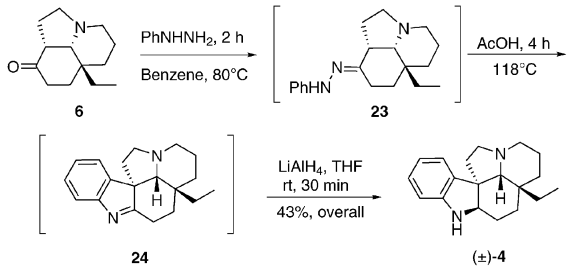
Scheme 3 Fukuyama and Michael–retro-Michael tandem process.



Scheme 4 Formation of the bicyclic core **19**.



Scheme 5 Formal total syntheses of (±)-aspidospermine, (±)-aspidospermidine and (±)-quebrachamine.



Scheme 6 Synthesis of (±)-aspidospermidine.

To complete the total synthesis, the known tricycle **6** is converted to (±)-aspidospermidine *via* a Fischer indole synthesis,[15] as demonstrated first by Stork and Dolfini.[10] Indeed, treatment of compound **6** with phenylhydrazine at reflux leads to the hydrazone **23**, which is converted to imine **24** in acetic acid. The latter is reduced in the same pot by $LiAlH_4$ to produce (±)-aspidospermidine, **4**, in 43% yield overall, Scheme 6.

In summary, a concise and fully diastereoselective synthesis of (±)-aspidospermidine is accomplished in ten steps from phenol **7** in 5.4% yield overall. This novel synthesis is based on a first application of a bimolecular oxidative Hosomi–Sakurai reaction. In addition, an efficient method to produce the bicyclic ring of this compound *via* a Fukuyama–Michael tandem process has been developed. Formal total syntheses of (±)-aspidospermine and (±)-quebrachamine have also been presented. This work demonstrates the potential of "aromatic ring umpolung", further applications of which are under study in our laboratories.

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12 Details of the preparation of **7** are provided as ESI†. This compound has been prepared in two steps from inexpensive 4-ethyl phenol in 86% overall yield.

13 Details of the preparation of **11** are provided as ESI†. This compound has been prepared in two steps from inexpensive 2-aminoethanol in 89% overall yield.

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