ORGANIC LETTERS

2000
Vol. 2, No. 23
3599−3601

Tandem Radical Cyclizations with Iodoaryl Azides: Formal Total Synthesis of (±)-Aspidospermidine

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Received August 17, 2000

ABSTRACT

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An iodoazide radical cascade cyclization strategy has been used as the key step in a formal synthesis of aspidospermidine. Specifically, this step generated the alkaloid's B- and E-rings in the ethylidene-functionalized tetracycle 5. In turn, this was converted into pentacycle 25, a known advanced synthetic precursor of aspidospermidine.

We recently announced a total synthesis[1] of (±)-aspidospermidine[2] **1** using the tetrathiafulvalene-mediated radical-polar crossover reaction[3] as the key step. In an effort to find alternative, efficient routes to complex alkaloids such as aspidospermidine, a second plan was devised, based on the relative reactivity toward attack by radicals of carbon−iodine bonds and azide groups. Kim et al. had performed[4] elegant experiments showing that alkyl iodides are selectively attacked by organosilyl radicals in the presence of alkyl azides. We extended this work[5] to show that *aryl* iodides are also selectively attacked in the presence of alkyl azides and used the resulting radical in a tandem cyclization reaction (**2** → **3**) to afford the ABCE tetracycle of *Aspidosperma* alkaloids. The key challenge was to find a route, using this tandem cyclization strategy, to allow the synthesis of aspidospermidine.

Diene **4** was selected as the crucial intermediate, since cyclization of this component would afford the tetracyclic intermediate **5**, functionalized with an ethylidene group. Our previous route to aspidospermidine[1] featured this intermediate (*E* isomer), and therefore its synthesis by the azide route

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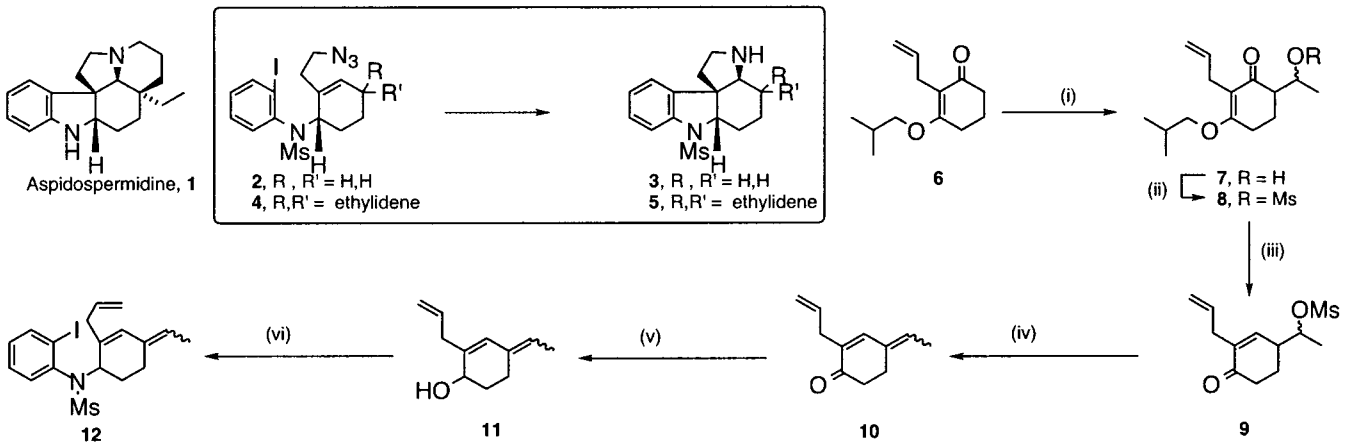
10.1021/ol006477x CCC: $19.00
Published on Web 10/13/2000

Scheme 1



Reagents and conditions : (i) LDA, CH_3CHO, 72%; (ii) Et_3N, MsCl, DMAP, DCM, 83%; (iii) DIBAL-H, DCM, 67%; (iv) DBU, C_6H_6, 53%; (v) $NaBH_4$, $CeCl_3.{}_7H_2O$, MeOH, 91%; (vi) DIAD, Me_3P, THF, 2-IC_6H_4NHMs, 60%

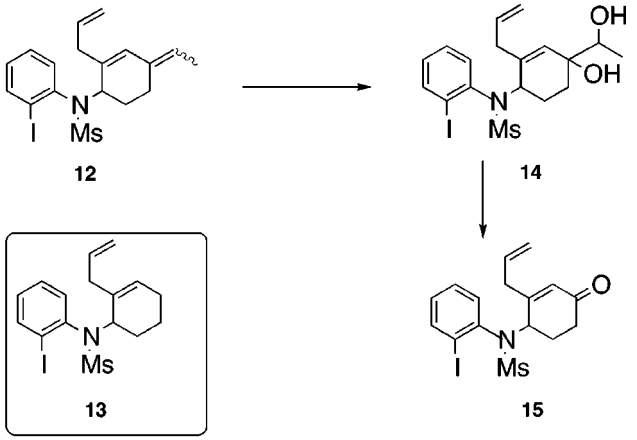
would constitute a formal total synthesis. The key questions were whether **4** could be prepared and whether it would undergo cyclization to the desired tetracycle.

The initial target became the potentially unstable ethylidene-containing trienone **10** (Scheme 1). Aldol reaction of the enolate of **6** with acetaldehyde afforded alcohol **7**, which was transformed into the corresponding mesylate **8**. This compound was reduced with DIBAL-H,[6] yielding the enone **9**, and we were pleased to see that the mesyloxy group had remained intact. Treatment with DBU then effected elimination of the mesylate selectively to give trienone **10** as an *E*/*Z* mixture.

Despite the basic conditions, aromatization of this compound was not observed. This ketone was reduced under Luche conditions,[7] and alcohol **11** was subjected to Mitsunobu[8] reaction with 2-iodophenylmethanesulfonamide. This reaction was not successful, and we reasoned that this was due to the use of the large phosphine, triphenylphosphine. However, tributylphosphine gave a mixture of starting alcohol and coupled product after 24 h, and trimethylphosphine gave clean conversion to coupled product **12**.

The side-chain allyl group needed to be oxidized[9] selectively in the presence of the other alkenes at this stage. Whereas the simpler product **13** had undergone selective osmium-triggered dihydroxylation at the side-chain allyl group, **12** produced a different result (Scheme 2). Dihydroxylation and subsequent separation from the osmium residues and oxidation with periodate gave ketone **15** as the major product, thus indicating that the regioselectivity of the dihydroxylation was not as desired and that the dihydroxylation had afforded **14** as the major intermediate.

Scheme 2



To overcome this problem, dihydroxylation of **9** and its Luche reduction product **16** was investigated (Scheme 3). In neither case was selective oxidation of the allylic group alkene observed. Accordingly, mesylate alcohol **16** was coupled with 2-iodophenylmethanesulfonamide to afford **17**. This was selectively oxidized to diol **18**, cleaved to aldehyde **19** and reduced to alcohol **20** without affecting the mesylate group.

Elimination afforded diene **21** selectively, which was then converted into the crucial azide **23** in two steps. This in turn

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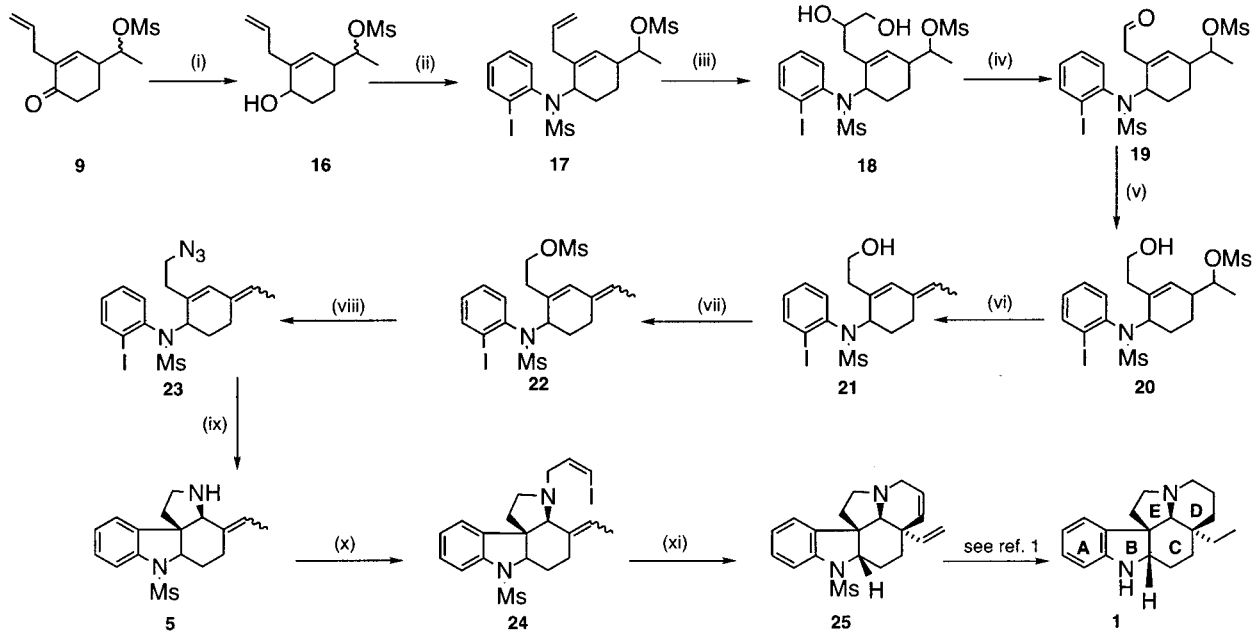
(10) All compounds had spectroscopic data in accord with the proposed structures and either high-resolution mass measurement or combustion analysis in support.

Scheme 3



Reagents and conditions: $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 67%; (ii) DIAD, Me_3P, THF, pyridine, 51%; (iii) OsO_4, NMO, acetone, water, tBuOH, 78%; (iv) $NaIO_4$, water, Et_2O, EtOH, 65%; (v) $NaBH_4$, MeOH, 20 min., 95%; (vi) DBU, toluene, reflux, 91%; (vii) MsCl, Et_3N, DMAP, DCM, 78%; (viii) NaN_3, DMF, 50°C, 72%; (ix) TTMSS/AIBN/C_6H_6/ reflux, 40%; (x) K_2CO_3, ICH=$CHCH_2Br$, THF, 63%; (xi) $Pd(OAc)_2$, Et_3N, PPh_3, MeCN, 32%.

was cyclized to the tetracycle **5**, as a mixture of *E* and *Z* isomers. Alkylation with (*Z*)-3-bromo-1-iodopropene afforded **24**, which was converted into the known[1] pentacycle **25**, thus completing the formal synthesis.[10] This synthesis complements our earlier radical-based synthesis of aspidospermidine, allowing the construction of the B- and E-rings in a single step. Application of the iodoazide cyclization method to other complex products is currently underway.

Acknowledgment. We thank the EPSRC for funding and the EPSRC National Mass Spectrometry Service, Swansea, for mass spectra.

OL006477X