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Synthesis of (±)-Conduramines from Pyrrole[1]

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Abstract: The Diels-Alder product **1b**, of tosylacetylene and N-*tert*-Boc-pyrrole, was converted into (±)-conduramine C-1 (**22**) and the tetraacetates of (±)-conduramine A-1 (**9b**) and F-1 (**15b**).

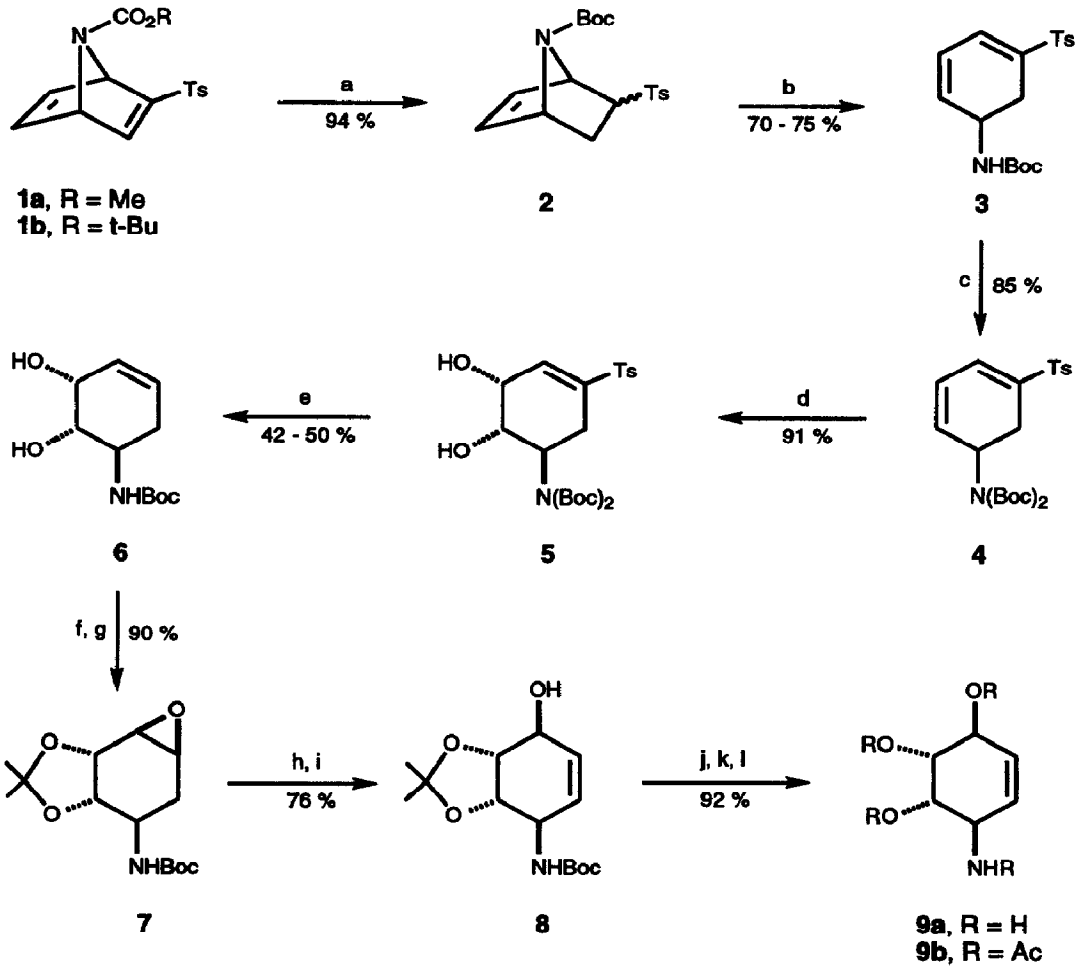
Conduramines[2] are aminocyclohexenetriols which are of interest as precursors of other aminocyclitols[3-5] and as inhibitors of some glycosidases.[6] The synthesis of several members of this class of compounds has recently been described in both the racemic[3a,5] and optically pure[4,7-10] forms.

It seemed to us that the Diels-Alder products **1** (Scheme 1) of tosylacetylene and N-alkoxycarbonylpyrroles, first described by Vogel, et al.,[11] would be particularly attractive precursors of conduramines. The nitrogen atom bridge would serve as the eventual amino group and the tosyl moiety would be used to initiate anionic fragmentation[12] of the bicyclic system to a cyclohexene derivative, either before or after hydroxyl group installation. This paper describes some of our preliminary studies in the utilization of **1b** as a conduramine progenitor.

Compound **1b** (mp 96-7 °C)[13,14] was prepared in 80-85% yield by heating a 2:1 molar mixture of N-Boc-pyrrole[15] and tosylacetylene at 85 °C for 24 h. Reaction of **1b** with sodium borohydride gave the product **2** of conjugate reduction as an 8:1 mixture of endo (mp 101-2 °C) and exo (mp 95-6 °C) isomers which, without separation, was converted into the stable diene **3** (mp 130-32 °C) with lithium bis(trimethylsilyl)amide.[12b] Whereas osmium tetroxide catalyzed hydroxylation of **3** gave a 1:1 mixture of cis diols, the bis-Boc derivative **4** (mp 121-22 °C) produced a single diol **5** (mp 156-58 °C) which was reductively desulfonylated with sodium amalgam in buffered methanol[16] to the mono-Boc diol **6**. Acetonide formation on **6** followed by buffered peracid oxidation generated the epoxide **7** (mp 67-8 °C) which on regioselective cleavage with phenylselenide and subsequent hydrogen peroxide oxidation[17] was converted into the conduramine A-1 derivative **8** (mp 93-5 °C). This substance was transformed into (±)-conduramine A-1 (**9a**, not purified) and its tetraacetate **9b** (mp 156-59 °C; lit.[3a] mp 156-57 °C)[18] by the reaction sequence shown in Scheme 1.

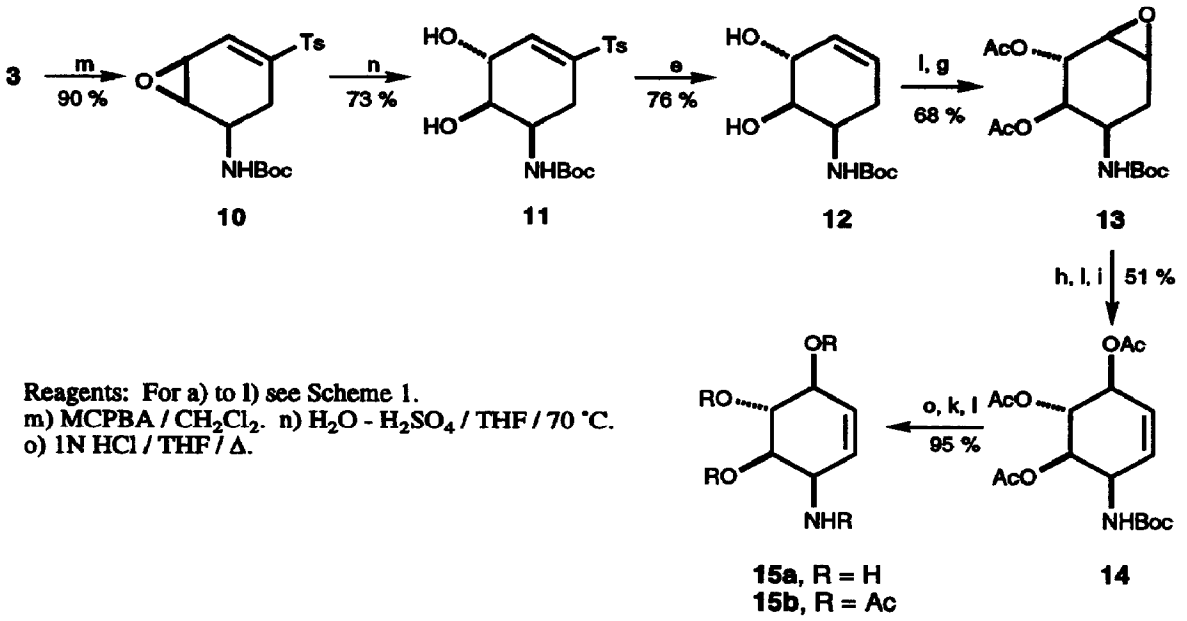
The diene **3** was also used to prepare a member of the conduramine F series. Thus, peracid oxidation of **3** gave the cis epoxy compound **10** (mp 73-5 °C, Scheme 2) exclusively, which was converted into the trans diol **11** (mp 172-73 °C) by sulfuric acid catalyzed hydrolysis at 70 °C. Desulfonylation of **11** gave **12** (mp 41-3 °C) from which the conduramine F-1 derivative **14** (mp 110-12 °C) was generated by a process similar to that which had been utilized for the conduramine A-1 synthesis. Compound **14** was transformed into (±)-conduramine F-1 (**15a**, not purified) and its tetraacetate **15b** (mp 139-41 °C, lit.[5] mp 142 °C).

An approach to conduramines based on hydroxylation before fragmentation of the bicyclic system is illustrated in Scheme 3. Osmium tetroxide catalyzed hydroxylation of **1b** and subsequent protection provided the exo acetonide **16** (mp 121-22 °C) exclusively. Reduction of **16** occurred predominantly from the endo face to



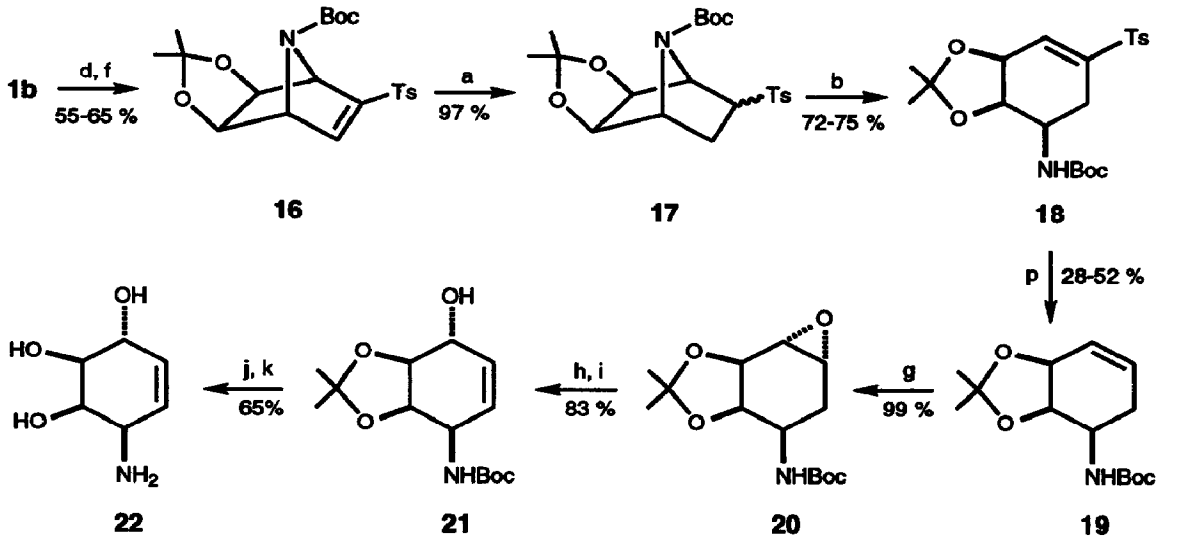
Reagents: a) $NaBH_4$ / MeOH. b) LHMDS / THF / -78°C - R.T.
c) $(Boc)_2O$ / cat. 4-DMAP / MeCN. d) OsO_4 - NMO / $NaHCO_3$ - t-BuOH - H_2O - THF. e) 6 % Na-Hg / Na_2HPO_4 / MeOH - THF.
f) $Me_2C(OMe)_2$ - Me_2CO / TsOH. g) MCPBA / $NaHCO_3$ / CH_2Cl_2.
h) $(PhSe)_2$ / BuLi / THF. i) H_2O_2 / CH_2Cl_2 then i-Pr_2NEt - THF / Δ.
j) TFA - H_2O / CH_2Cl_2. k) NH_3 / MeOH. l) Ac_2O / Py - cat. 4-DMAP.

Scheme 1



Reagents: For a) to l) see Scheme 1.
m) MCPBA / CH_2Cl_2. n) H_2O - H_2SO_4 / THF / 70 °C.
o) 1N HCl / THF / Δ.

Scheme 2



Reagents: For a) to n) see Schemes 1 and 2. p) SmI_2 / THF - HMPA / -23 °C.

Scheme 3

give a 5.5:1 mixture of the exo (mp 169-71 °C) and endo (mp 134-36 °C) isomers of **17**. Reaction of this mixture with lithium bis(trimethylsilyl)amide produced the cyclohexene derivative **18** (mp 181-82 °C) containing three contiguous cis substituents. Reductive desulfonylation of **18**, which required the use of samarium (II) iodide,[19] gave compound **19** (mp 72-4 °C) and a small amount (ca 5%) of 1-*tert*-butoxycarbonyl-aminocyclohexa-2,4-diene. Compound **19** was converted by a three-step process into the conduramine C-1 derivative **21** (mp 104-6 °C) and the latter after deprotection gave (±)-conduramine C-1 (**22**) itself (mp 147-49 °C, lit.[10] mp 148-50 °C).

We are currently engaged in devising syntheses of **1b** in both optically pure forms.

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