SYNTHESIS OF THE *SEDUM* ALKALOID SEDININE

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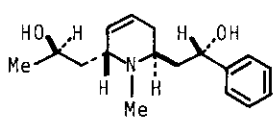
Abstract —— The *Sedum* alkaloid sedinine (1) was synthesized in the racemic form from 1-methoxycarbonyl-2-(1-propynyl)-1,2-dihydropyridine (4) by way of tetrahydropyridine derivatives (5, 10a, 20, and 24b).

In a previous communication, we reported a facile synthesis of sedacryptine (2),[1] a minor alkaloid isolated from *Sedum acre*.[2] This plant also contains sedinine,[3] whose structure was finally established to be 1 with the absolute stereochemistry,[4] resembling closely the representative of *Lobelia* alkaloids, lobeline (3).[5] Here we report our investigation leading to a synthesis of (±)-sedinine (1), which opens a way to synthesize a variety of alkaloids having similar structures.[6] This study implies at the same time a formal synthesis of (±)-dihydrosedinine.[7]



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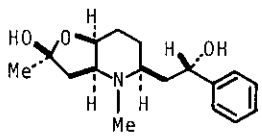

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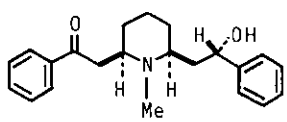

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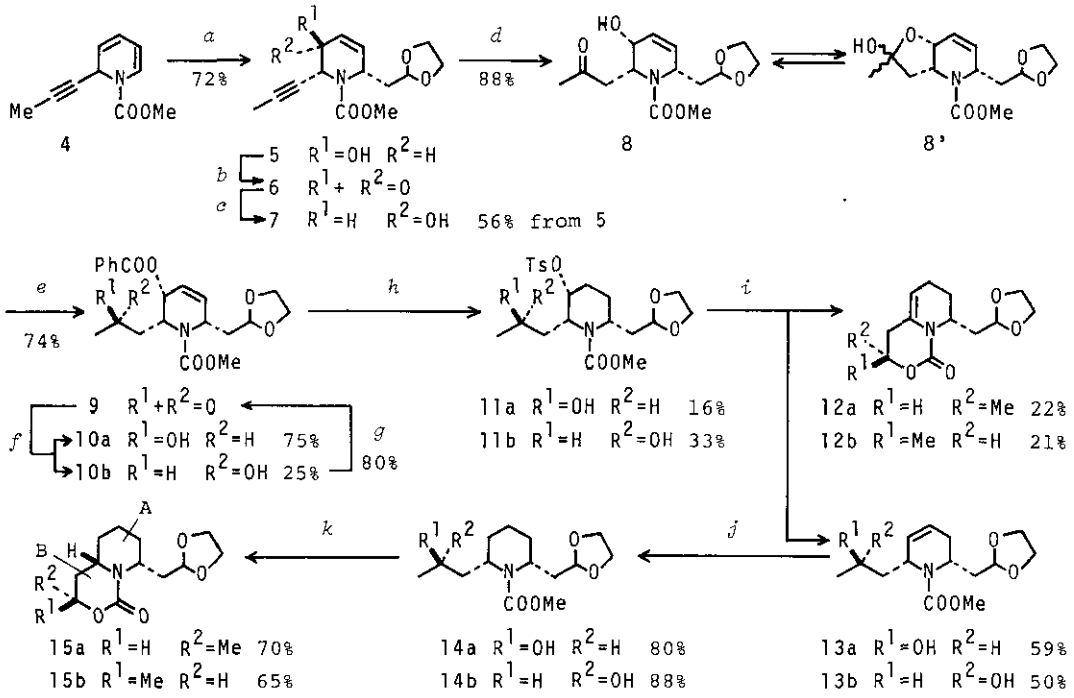
A dihydropyridine derivative (4), readily prepared from pyridine, MeC≡CMgBr, and ClCOOMe, was submitted to the reaction reported previously,[1] *i.e.*, sensitized photooxygenation and addition of a nucleophile in the presence of $SnCl_2$, followed by acetalization to produce an important starting material (5) in 72% yield. As the previous finding suggested that the hydration of the triple bond was successful only with the intramolecular participation of a hydroxyl group,[1] the configuration of the hydroxyl function in 5 was isomerized to the desired orientation as in 7 by way of an unstable α,β-unsaturated ketone derivative (6). Brief exposure of 7 to $HgSO_4$ in a diluted acidic solution afforded *ca.* a 1:1 mixture of ketone (8) and hemiacetal (8') compounds, their ratio being estimated by inspection of the

singlet signals of the methyl protons at 2.18 and 1.50 ppm in the ^1H NMR spectrum. Benzoylation of the mixture afforded 9 in good yield, and a key intermediate (10a) possessing the necessary stereochemistry of the hydroxyl group at the side chain was best obtained by reduction of 9 with $Li(t\text{-}BuO)_3AlH$ in THF in 75% yield, accompanied by the formation of an unwanted compound (10b) in 25% yield.[8] As 10b was converted back to 9 by Swern oxidation[9] in 80% yield, 10a was produced almost stereoselectively.

In order to determine the configuration of the side chain hydroxyl group, compounds (10a and 10b) were transformed into 15a and 15b, respectively, by the sequence of reaction steps described in Chart 1. It can be emphasized in step *h* that the hydroxyl group at the piperidine ring is sterically less hindered than

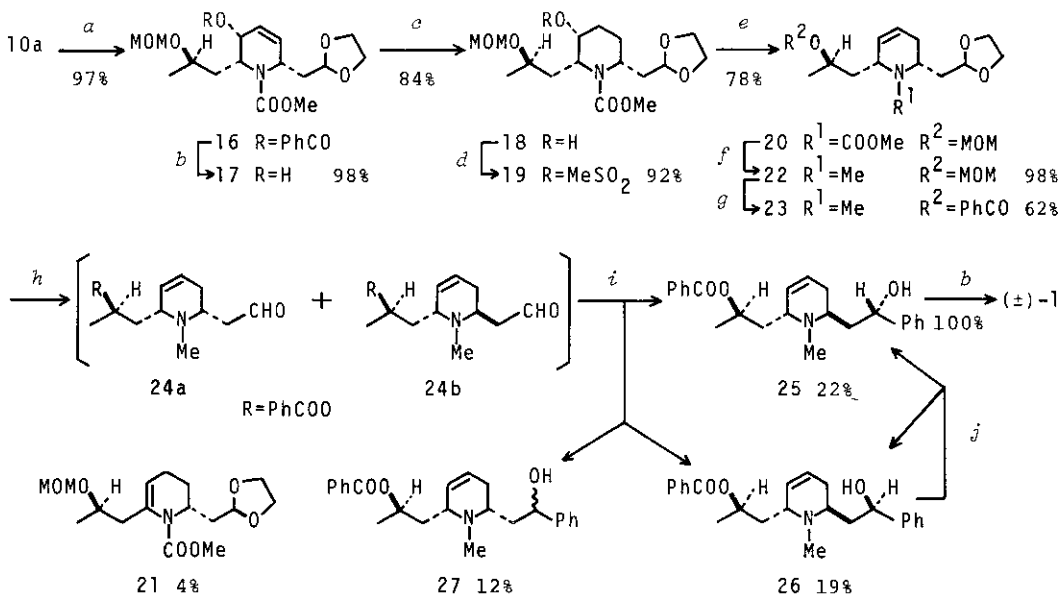


a: i) $^1O_2$; ii) ethyl vinyl ether, $SnCl_2$; iii) ethylene glycol. *b*: Jones reagent, acetone, 0 °C, 15 min. *c*: $LiBH_4$, MeOH, -20– -15 °C, 15 min. *d*: $HgSO_4$, 1% H_2SO_4 in DME-H_2O (5:2), 0 °C, 3 min. *e*: PhCOCl, Py, 0 °C, 5 min and then r.t., 3 h. *f*: $Li(t\text{-}BuO)_3AlH$,THF, 0 °C, 30 min. *g*: DMSO, $(CF_3CO)_2O$, CH_2Cl_2, -70 °C, 30 min and then Et_3N, -70 °C → r.t., 30 min. *h*: i) K_2CO_3, MeOH, r.t., 30 min; ii) H_2, Pt, DME, r.t., 1 h; iii) NaH, THF-DMF (4:1), 0 °C, 5 min and then *p*-TsCl, -20– -15 °C, 30 min. *i*: DBU, 70-80 °C, 21 h. *j*: H_2, 10% Pd-C, MeOH, r.t., 1h. *k*: NaH, DMF, r.t., 2.5 h for a series and 5.5 h for b series.

Chart 1

that of the side chain, and therefore, monotosylates (11a and 11b) were obtained predominantly.[10] Analysis of the coupling pattern of the protons adjacent to the lactonic oxygen atoms in ^{1}H NMR spectra of 15a [a doublet of double quartet at 4.33 ppm (J=11.5, 2.5, 6 Hz)] and 15b [a doublet of double quartet at 4.46 ppm (J=6, 6, 6 Hz)] suggested the stereochemistry of the hydroxyl groups as shown, assuming that both A and B rings are situated in the chair form and joined together so as to occupy the trans nature of the bridge-head hydrogen with respect to the nitrogen lone pair.[11]

For the goal of the synthesis, a double bond was next introduced at the desired location (Chart 2). This was carried out by protecting the side chain hydroxyl function of 10a by the methoxymethyl (MOM) group and then converting 16 to a methanesulfonate (19) using the conventional procedures. Base treatment of 19 required a very careful selection of a reaction condition in order to minimize the production of a by-product (21) and the best result was obtained by heating 19 in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at about 70 °C for 4 days to afford 20 in



a: $MeOCH_2Cl$, i-Pr_2NEt, 1,2-dichloroethane, 80 °C, 1h. b: K_2CO_3, MeOH, r.t. c: H_2, Pt, DME, r.t., 1 h. d: $MeSO_2Cl$, Py, 0 °C, 5 min and then r.t., 40 min. e: DBU, 68-72 °C, 4 d. f: $LiAlH_4$, THF, reflux, 10 min. g: i) p-TsOH·H_2O, acetone, r.t., 10.5 h; ii) PhCOCl, Py, 0 °C, 5 min and then r.t., 1 h. h: i) conc. HCl-DME (2:3), r.t., 20 h; ii) i-Pr_2NEt, MeOH, r.t., 1 h. i: PhMgBr, CuI·Bu_3P, THF, 0 °C, 15 min. j: i) Jones reagent, acetone, 0 °C; ii) Li(t-BuO)$_3$AlH, THF, 0 °C.

Chart 2

78% yield, accompanied by the formation of 21 in only 4% yield. The N-COOMe function of 20 was reduced to N-Me, the oxygen protecting group was changed from MOM to the benzoyl group, as in 23, to readily separate the isomers at the later stage, and an aldehyde (24a) obtained from 23 was submitted to the epimerization reaction of the side chain, based on the retro-Michael reaction followed by recyclization. This was achieved by treatment with *N*,*N*-diisopropylethylamine in MeOH at room temperature for one hour,[12] and the resulting equilibrated mixture of 24a and 24b was treated directly with $PhMgBr\text{-}Bu_3P\cdot CuI$[13] to form 25, 26, and 27 in 22%, 19%, and 12% yields, respectively. The unwanted product (26) was converted to 25 by Jones oxidation, followed by the reduction with $Li(t\text{-}BuO)_3AlH$ in 50% yield, accompanied by a recovery of 26 in 36% yield. Removal of the protecting group of 25 furnished (±)-sedinine (1), mp 106-107 °C (Et_2O-hexane), which was identified with a natural specimen by comparison of TLC [Al_2O_3, CH_2Cl_2-Et_2O (4:1); benzene-AcOEt (2:1)] as well as MS, IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and ^{13}C NMR ($CDCl_3$) spectra.

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11. This assumption is proved to be valid in the case of sedacryptine synthesis.[1]
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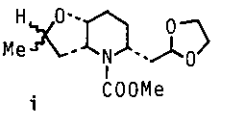
13. Use of a limited amount of PhMgBr alone even at low temperature afforded only an intractable mixture, whose ^1H NMR spectrum still showed aldehyde signals, suggesting that PhMgBr behaved partly as a base to produce a Mg enolate.



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