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A NEW APPROACH TO GEPHYROTOXIN

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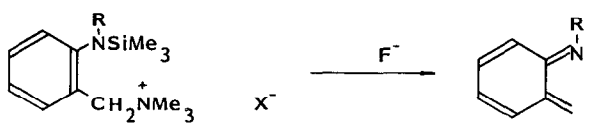
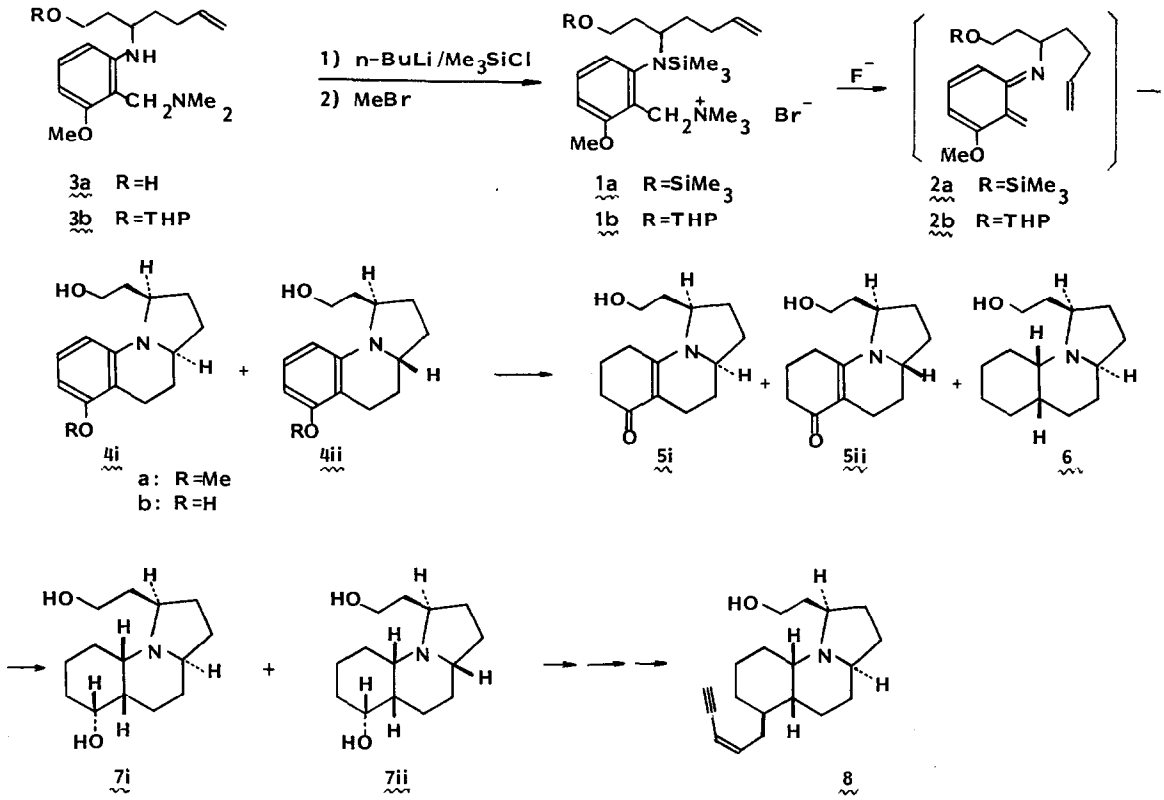
Summary: CsF induced 1,4-elimination of ammonium bromide 1a and the subsequent intramolecular cyclization of the resulting o-quinone methide N-alkenylimine 2a afforded benzo[e]-indolizidine 4a as a 4~5 : 1 stereoisomeric mixture. Hydrogenation of 4a with 5% Rh on alumina gave tricyclic enaminoketones 5i and 5ii, of which stereoselective elaboration to gephyrotoxin 8 has already been established.

Diels-Alder cycloaddition of o-quinone methide N-substituted imine intermediate (2)[1] provides a convenient method for the synthesis of nitrogen-containing polycycles, which, however, has scarcely been exploited, because the general methodology for the generation of 2 is lacking. Recently, the fluoride-anion induced 1,4-elimination, which offered a mild and efficient generation of o-quinodimethanes[2], has successfully been extended to o-[N-(trimethylsilyl)-N-alkylamino]benzyltrimethylammonium halides (1) to generate in situ o-quinone methide N-alkylimines (2)[3].



1 2

In this paper, we describe a new approach to the synthesis of biologically active alkaloid, gephyrotoxin (8)[4] which has been performed on the basis of an intramolecular cycloaddition of the o-quinone methide N-alkenylimine (2a) and the subsequent reductive elaboration of the resulting benzo[e]indolizidine framework.



Preparation of a starting ammonium salt 1a requisite for the generation of o-quinone methide N-alkenylimine (2a) was carried out by N- and O-silylations of 3a[5], followed by quaternization with methyl bromide. Thus, n-BuLi (4.4 mmol, hexane solution) was added to a solution of 3a[5] (2 mmol) in THF (6 mL) and stirred for 6 hr. The stirring solution was treated with trimethylchlorosilane (4.4 mmol) and a catalytic amount of 4-dimethylaminopyridine (25 mg in THF) at 0°C for 3 hr and then at room temperature overnight. The N-trimethylsilylation in the presence of 4-dimethylaminopyridine remarkably improved a yield of the final cyclization product (4) (24%→71%). The reaction mixture was diluted with ether and filtered to remove insoluble materials under nitrogen atmosphere followed by evaporation in vacuo. The residue was dissolved in acetonitrile and stirred with a large excess of methyl bromide (30 mmol) at 0°C to room temperature overnight, and then evaporated in vacuo.

Viscous ammonium bromide 1a thus prepared was used without purification for the following generation and cyclization of 2a. A solution of the crude 1a in acetonitrile (10 mL) was added dropwise into a stirring mixture of CsF (6 mmol) and acetonitrile (10 mL) at ca. 65°C over

1.5 hr and then gently refluxed for 2.5 hr. After the reaction mixture was diluted with ether, filtered and evaporated in vacuo, the residue was subjected to preparative thin layer chromatography on silica gel with 1 : 2 acetone-hexane to give benzo[e]indolizidine derivative (4a) (71% based on 3a) [TLC on silica gel R_f=0.45 (1 : 2 acetone-hexane)]. ^{13}C NMR spectrum[6] of 4a produced exhibited two set of signals in a relative ratio of 4~5 : 1, suggesting that 4a consists of a mixture of cis and trans isomers 4a-i and 4a-ii. Attempts to separate the two stereoisomers have failed.

Similarly, cycloaddition of an ammonium bromide 1b, in which the hydroxy group has been protected with tetrahydropyran instead of trimethylchlorosilane, afforded a mixture of 4a-i and 4a-ii in a ratio of 4~5 : 1 (ca. 60% yield) after deprotection.

Next, 4a was transformed to a tricyclic enaminoketone 5, which has already been converted to gephyrotoxin (8) by Kishi[4a,b]. Initial attempts to reduce 4a by the Birch reaction were not satisfactory. Reduction of 4a with metallic lithium in liquid ammonia containing THF and tert-amyl alcohol did not give any products, resulting in the recovery of 4a. Use of n-propylamine instead of ammonia in the reduction produced the desired 5 but only in a low yield (~10%). High-yielding reduction to 5 has been effected by hydrogenation (70 atm., 70°C, 1.5 hr) of 4b[7] using 5% Rh on alumina in anhydrous ethanol to afford 5 (75%) [TLC on silica gel R_f=0.50(4 : 1 acetone-methanol)] together with a small amount of 7 and the hydrogenolysis product 6 (6+7 < 10%) after chromatography on silica gel with a 4 : 1 acetone-methanol. ^1H NMR and IR spectra of 5 produced were almost consistent with those of 5-i, not 5-ii, reported by Kishi[4a]. But ^{13}C NMR exhibited two set of signals for the product 5 in a ratio of 5 : 1[8], which may be assignable to cis-5i and trans-5ii, respectively. Separation of the two stereoisomers of 5 was difficult. The desired stereoisomer is most conveniently isolated at the stage of 7[4a], which is obtained by stereoselective hydrogenation of 5 with 5% Pt on alumina in anhydrous ethyl acetate.

Transformation of the tricyclic enaminoketone 5 to gephyrotoxin 8 via 7 has already been established by Kishi [4a,b]. Consequently, a sequence of reactions mentioned above presents a formal total synthesis of gephyrotoxin.

References and Notes

1) a) E. M. Burgess and L. McCullagh, J. Am. Chem. Soc., 88, 1580 (1966).

b) M. Fisher and F. Wagner, Chem. Ber., 102, 3486 (1969).

c) Y.-I. Mao and V. Boekelheide, J. Org. Chem., 45, 1547 (1980).

d) M. Lancaster and D. J. H. Smith, J. Chem. Soc., Chem. Commun., 471 (1980).

2) a) Y. Ito, M. Nakatsuka and T. Saegusa, J. Am. Chem. Soc., 104, 7609 (1982).

b) Y. Ito, Y. Amino, M. Nakatsuka and T. Saegusa, J. Am. Chem. Soc., in press.

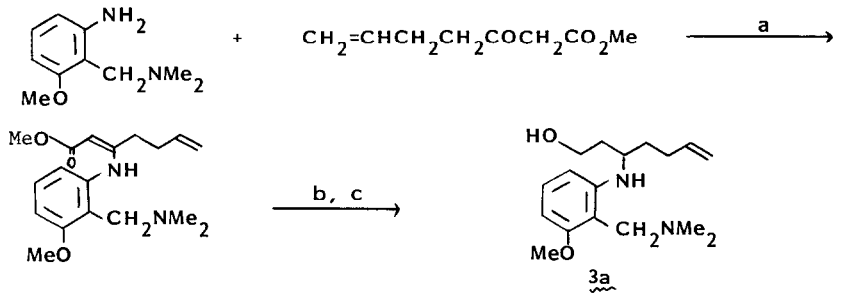
3) Y. Ito, S. Miyata, M. Nakatsuka and T. Saegusa, J. Am. Chem. Soc., 103, 5250 (1981).

4) a) R. Fujimoto, Y. Kishi and J.F. Blount, J. Am. Chem. Soc., 102, 7156 (1980).

b) R. Fujimoto and Y. Kishi, Tetrahedron Letts, 4197 (1981).

c) L.E. Overman and C. Fukaya, J. Am. Chem. Soc., 102, 1454 (1980).

5) Compound 3a (bp 130-132°C/0.1 mm Hg) was prepared in 69% overall yield according to the following scheme.



a: refluxed in benzene containing AcOH b: $NaBH_3CN$ in CH_3OH, pH 4 c: $LiAlH_4$ in Et_2O

6) 4a-i: ^{13}C NMR ($CDCl_3$) δ19.97, 26.13, 28.91, 30.71, 35.25, 54.45, 55.79, 59.39, 97.15, 103.49, 108.70, 126.05, 143.94, 156.35. 4a-ii: ^{13}C NMR ($CDCl_3$) δ21.00, 27.48, 28.56, 29.77, 35.03, 53.82, 57.32, 59.71, 97.33, 103.85, 109.15, 144.12, 156.97. 4a: Anal. Calcd for $C_{15}H_{21}NO_2$ C, 72.84; H, 8.56; H, 5.66. Found C, 72.55; H, 8.83; N, 5.72.

7) Compound 4b [TLC on silica gel R_f=0.45 (10:7 acetone-hexane)] was prepared in 75% yield by treating 4a with BBr_3 in methylene chloride at 0° to room temperature for 2 hr.

8) 5i: ^{13}C NMR ($CDCl_3$) δ18.85, 20.69, 25.99, 26.35, 27.74, 29.36, 34.35, 37.01, 55.66, 56.34, 57.50, 103.80, 159.27, 191.50. 5ii: ^{13}C NMR ($CDCl_3$) δ19.08, 20.19, 26.17, 27.02, 28.42, 29.19, 34.76, 37.50, 55.08, 58.08, 58.35, 105.33, 159.45, 192.22.

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