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TRANSFORMATION OF PROTOBERBERINES INTO BENZO[*c*]PHENANTHRIDINES A NOVEL AND EFFICIENT SYNTHESIS OF ANTITUMOR BENZO[*c*]PHENANTHRIDINE ALKALOIDS, FAGARONINE AND NITIDINE

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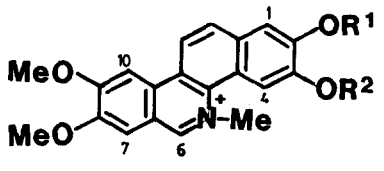
Summary: Antileukemic benzo[*c*]phenanthridine alkaloids, fagaronine (1a) and nitidine (1c) were synthesized from the corresponding protoberberines through C_6-N bond fission and subsequent cyclization between C_6 and C_{13} position of the protoberberines.

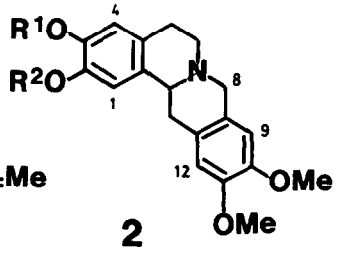
Fully aromatized 2,3,8,9-tetraoxygenated benzo[*c*]phenanthridine alkaloids, fagaronine (1a) and nitidine (1c), isolated from *Zanthoxylum* and *Fagara* species (Rutaceae),[1,2] were found to exhibit considerably strong antileukemic activities[1,3] in L-1210 and P-388 systems in mice. Because of these potential pharmacological activities, much attention have so far been paid on the synthesis of fagaronine (1a)[4] and nitidine (1c).[5]

Recently we have achieved[6] the first biomimetic transformation of protoberberine alkaloid, berberine into benzo[*c*]phenanthridine alkaloid, chelerythrine. Our endeavor is now focused on the development of the general



1

a : R^1=H, R^2=Me
b : R^1=benzyl, R^2=Me
c : R^1+R^2=CH_2



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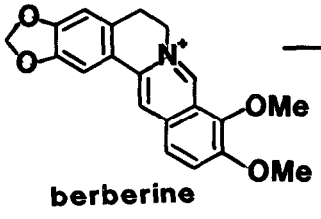
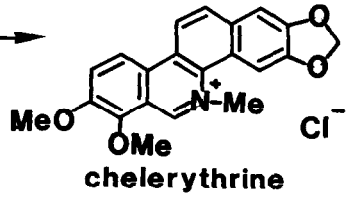


berberine

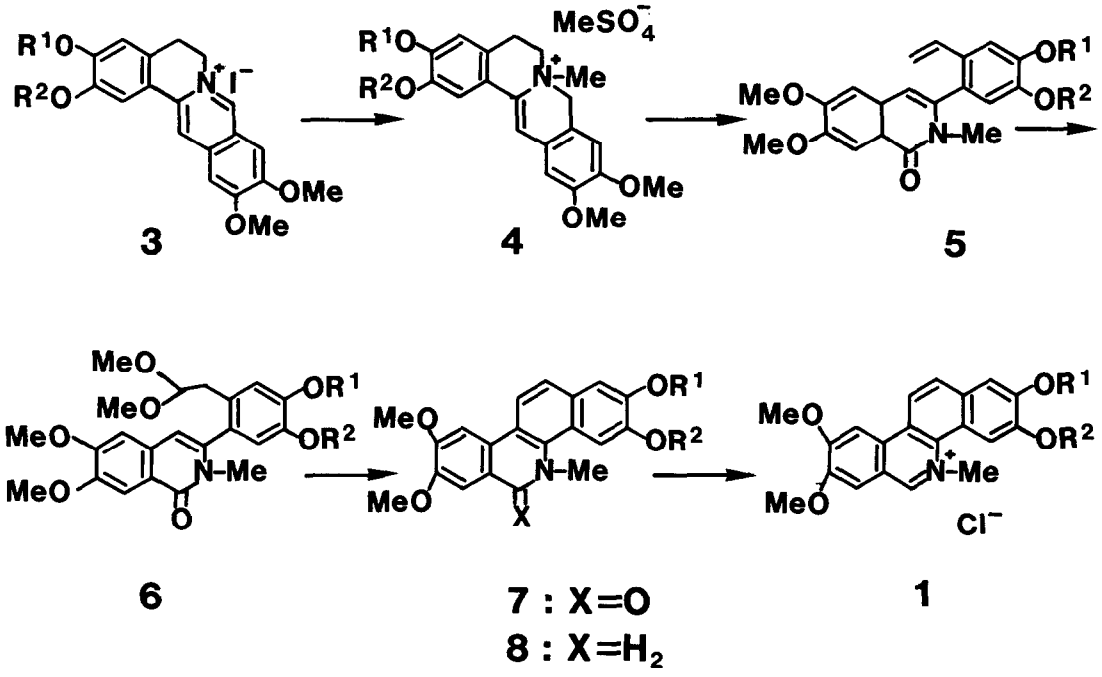


chelerythrine

and efficient method for the preparation of antileukemic benzo[*c*]phenanthridine alkaloids. This communication deals with a novel and efficient synthesis of fagaronine (1a) and nitidine (1c) from the corresponding protoberberines, *O*-benzyldiscretine (2b)[7] and tetrahydropseudoberberine (2c),[8] respectively.

O-Benzyldiscretine (2b) was dehydrogenated with iodine in refluxing ethanol to give *O*-benzyldehydrodiscretine (3b) [84%; mp 277-280°], which was reduced with lithium aluminum hydride ($LiAlH_4$) in dry tetrahydrofuran (THF), followed by treatment with dimethyl sulfate to afford the methosulfate (4b) [81%; mp 275-280°]. Hofmann degradation of 4b with 25% methanolic potassium hydroxide effected C_6-N bond fission to provide a labile enamine, which was then subjected to successive oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and potassium ferricyanide producing the stable enamide (5b) [46%; mp 205-206°; *m/z* 457 (M^+); ν 1640; δ 6.42 (1H, dd, *J*=17 and 11), 6.37 (1H, s), 5.49 (1H, dd, *J*=17 and 1), 5.09 (1H, dd, *J*=11 and 1)]. Upon treatment with thallium trinitrate (TTN) in methanol[9] at room temperature, the styrene derivative (5b) gave the acetal (6b) [*m/z* 519 (M^+); ν 1640; δ 4.31 (1H, dd, *J*=6 and 5), 3.14, 3.12 (each 3H, each s), 2.79 (1H, dd, *J*=14 and 6), 2.60 (1H, dd, *J*=14 and 5)]. Treatment of the acetal (6b) with 10% hydrochloric acid effected hydrolysis, cyclization, and dehydration to afford directly a benzo[*c*]phenanthridine, *O*-benzyl-oxyfagaronine (7b) [mp 227-229°; *m/z* 455 (M^+); ν 1620; δ 7.98 (1H, d, *J*=9), 7.93 (1H, s)] in a quantitative overall yield from 5b. Compound (7b) was reduced with $LiAlH_4$ in dry THF followed by sodium borohydride in methanol to afford *O*-benzyldihydrofagaronine (8b) [95%; mp 205-206°; *m/z* 441 (M^+); δ 4.15 (2H, s)], DDQ oxidation of which gave *O*-benzylfagaronine (1b) [93%; mp 242-244°; *m/z* 425, 334 (base peak); δ 9.93 (1H, s), 8.77 (1H, brs)]. Finally fagaronine (1a) [mp 266-269° (186-190°)[10] (lit.[1a] 255°(202°); lit.[4a] 260-261°(198-200°); lit.[4b] 276°(193-195°)); *m/z* 349, 335 (base peak); ν 3420; δ 9.89 (1H, s), 8.76, 8.15 (2H, AB-q, *J*=9), 8.28, 8.13, 7.86, 7.57 (each 1H, each s), 4.98, 4.21, 4.09, 4.03 (each 3H, each s)] was obtained in 97% yield as yellow needles by debenzylation of 1b with 6N hydrochloric acid in refluxing ethanol. The spectral data of the synthetic fagaronine was in good agreement with those of natural fagaronine.[1a]

In a similar manner, nitidine (1c) was also efficiently synthesized from the corresponding protoberberine, tetrahydropseudoberberine (2c). Dehydrogenation of 2c with iodine gave pseudoberberine (3c)[11] (81%), reduction of which with $LiAlH_4$ followed by methylation with dimethyl sulfate afforded the methosulfate (4c) [83%; mp 274-274.5°]. Hofmann elimination of 4c followed by oxidation furnished the styrene derivative (5c) [41%; mp 196-197°; *m/z* 365 (M^+); ν 1645; δ 6.41 (1H, dd, *J*=17.5 and 11), 6.34 (1H, s), 5.59 (1H, d, *J*= 17.5), 5.11 (1H, d, *J*=11)]. Treatment of 5c with TTN and ring closure of the resulting acetal (6c) [*m/z* 427 (M^+); ν 1640; δ 4.38 (1H, dd, *J*=6 and 5), 3.23, 3.17 (each 3H, each s), 2.81 (1H, dd, *J*=14.5 and 6), 2.61 (1H, dd, *J*=14.5 and



5)] produced oxynitidine (7c)[quant.; mp 284-285°(lit.[5b] 284-285°); *m/z* 363 (M^+); ν 1640; δ 7.95, 7.53 (2H, AB-q, *J*=9), 7.91 (1H, s)]. Since oxynitidine (7c) has already been converted into nitidine (1c),[5d] the present synthesis amounts to a formal synthesis of 1c. In addition, we have accomplished an alternative conversion of 7c into 1c. Reduction of 7c with $LiAlH_4$ in dry THF at room temperature yielded dihydronitidine (8c)[79%; mp 215-216°(lit.[5a] 217-218°); *m/z* 349 (M^+); δ 7.69, 7.50 (2H, AB-q, *J*=8.5), 4.14 (2H, s)], which was oxidized with DDQ to furnish nitidine (1c)[88%; mp 272-275°(lit.[5e] 274-278°); *m/z* 333 (base peak); δ 9.88 (1H, s), 8.90, 8.28(2H, AB-q, *J*=8.5), 8.31 (2H, s), 7.90, 7.77 (each 1H, each s), 6.35 (2H, s), 4.90, 4.24, 4.05 (each 3H, each s)] as yellow needles. The synthetic nitidine, dihydronitidine, and oxynitidine were identical with natural ones by mixed melting point, spectral comparison, and thin-layer chromatographic behavior.

Thus, we have completed a novel and efficient synthesis of fagaronine (1a) and nitidine (1c), antileukemic benzo[*c*]phenanthridine alkaloids, starting from the corresponding protoberberines, *O*-benzyldiscretine (2b) and tetrahydropseudoberberine (2c), respectively. These protoberberines having oxygenated substituents at 2,3,10, and 11 positions can easily be prepared in the usual manner. Therefore, the present synthetic method of fagaronine and nitidine provides a general method for the preparation of benzo[*c*]-phenanthridine alkaloids possessing oxygenated substituents at 2,3,8, and 9 positions.

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