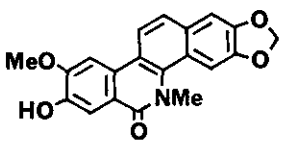
A NEW TOTAL SYNTHESIS OF OXYTERIHANINE

Miyoji Hanaoka,* Nobuyuki Kobayashi, and Chisato Mukai
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

Abstract——Oxyterihanine (1), a phenolic benzo[*c*]phenanthridine alkaloid, was efficiently synthesized from the corresponding protoberberine (4) through C_6-N bond cleavage and subsequent cyclization *via* the acetal (12).

Oxyterihanine (1), a phenolic benzo[*c*]phenanthridine alkaloid, was isolated from *Xanthoxylum nitidum* (Roxb.) D.C. (*Fagara nitida* Roxb.) in 1984[1] and its structure was established by the synthesis.[2] The oxygenation pattern in ring A and D of 1 is the same as that of fagaronine (2) and nitidine (3), both of which possess strong antileukemic activities.[3]



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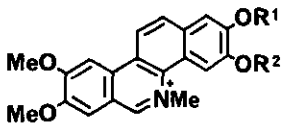
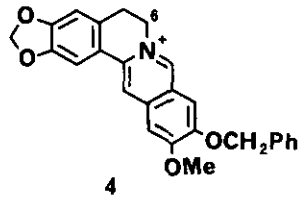


2 : R^1 = H, R^2 = Me
3 : R^1 + R^2 = CH_2



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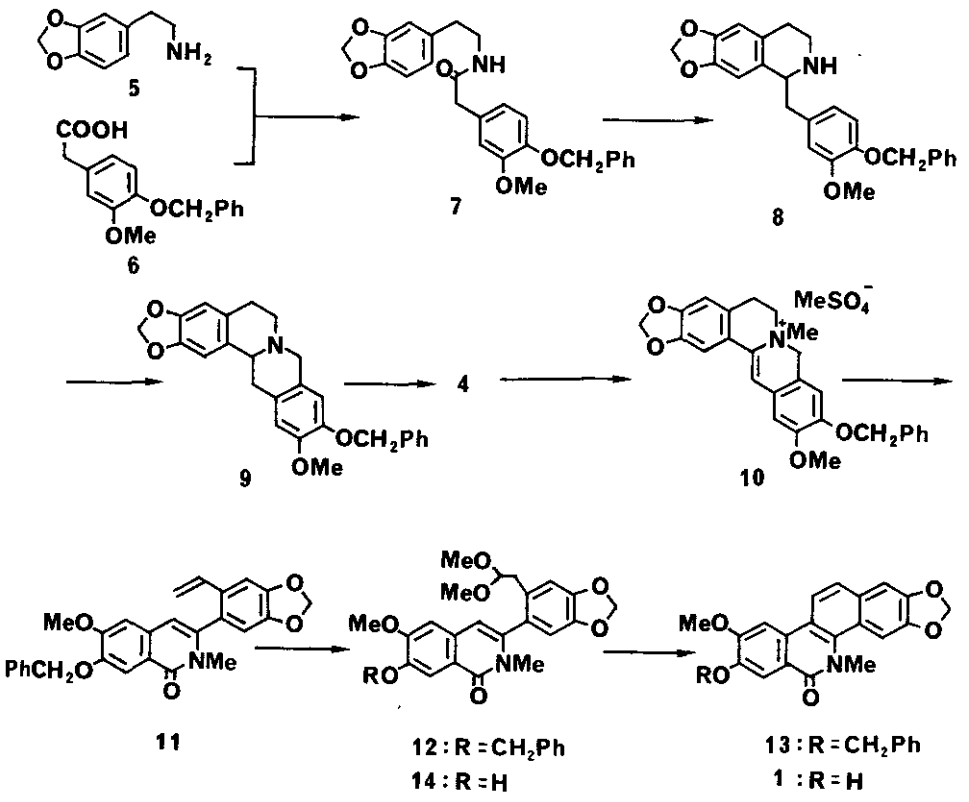
Recently we have developed[4] a biomimetic and efficient transformation of protoberberine alkaloids to benzo[*c*]phenanthridine alkaloids and this transformation was successfully applied to a convenient synthesis of the alkaloids (2 and 3).[5] This communication deals with a new synthesis of oxyterihanine (1) from the corresponding protoberberine (4) with protection of the phenolic hydroxyl group as a common benzyl ether.

The starting protoberberine (4) was synthesized by a conventional method. Condensation of the phenethylamine (5) with the phenylacetic acid (6)[6] at 190-200°C afforded the amide (7) in 88% yield. The Bischler-Napieralski reaction of 7

using phosphorus oxychloride in benzene followed by reduction with sodium borohydride yielded the benzylisoquinoline (8) in 72% yield. On treatment with 37% aqueous formaldehyde solution, 8 was converted to the protoberberine (9, 93%), which was dehydrogenated with iodine in ethanol in the presence of potassium acetate to give the desired protoberberine (4) in 93% yield.

Reduction of 4 with lithium aluminum hydride followed by quaternization with dimethyl sulfate afforded the methosulfate (10, 76%). Sequential treatment of 10 with potassium hydroxide, DDQ, and potassium ferricyanide effected C_6-N bond cleavage, dehydrogenation, and oxidation to lead to the enamide [11: *m/z* 441 (M^+), ν 1640] in 32% yield.

On exposure to thallium trinitrate[7] in methanol the enamide (11) was quantitatively transformed to the acetal (12), treatment of which with 10% hydrochloric acid underwent hydrolysis, cyclization, and dehydration to produce directly *O*-benzyl-oxyterihanine [13: mp 236-238°C; *m/z* 439 (M^+); ν 1635; δ 7.99 (1H, s), 7.96 (1H, d, *J*=8.5)] in 88% yield. Hydrogenolysis of 13 over 10% Pd-C in acetic acid



provided oxyterihanine [1: mp >300°C (lit.[1] mp >300°C); *m/z* 349 (M^+); ν 3100, 1630; δ 8.31, 7.68 (2H, AB-q, *J*=8.5), 7.84, 7.78, 7.68, 7.41 (each 1H, s), 6.18 (2H, s), 4.03, 3.85 (each 3H, s)[8]] in 20% yield. The synthetic oxyterihanine was identical with authentic sample by Ir spectral comparison and thin-layer chromatographic behavior.

Because of an unsatisfied yield in the last step, we tried another route to oxyterihanine. The acetal (12) was first hydrogenolyzed over 10% Pd-C in methanol to afford the phenolic acetal [14: mp 170-173°C; *m/z* 413 (M^+)] in quantitative yield. Heating of 14 in 10% hydrochloric acid provided oxyterihanine (1) in 63% yield. Thus, we have completed a new synthesis of oxyterihanine (1) from the corresponding protoberberine (4) by application of our biomimetic transformation.

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8. In $(CD_3)_2SO$.

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