Communications to the Editor

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A FIRST AND STEREOSELECTIVE SYNTHESIS OF (±)-RADDEANAMINE

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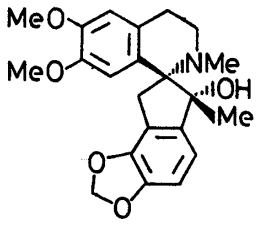
Raddeanamine (1), a unique spirobenzylisoquinoline alkaloid, was stereoselectively synthesized from the corresponding protoberberine (9) *via* 8-methyl-8,14-cycloberbine (12) through regioselective C_8-N bond cleavage and stereoselective hydroxylation at C_8.

KEYWORDS—— raddeanamine; ochotensimine; spirobenzylisoquinoline; protoberberine; 8,14-cycloberbine; stereoselective synthesis; photoisomerization

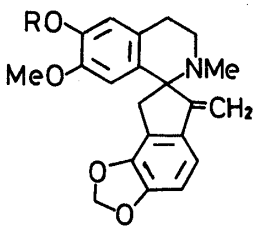
Raddeanamine (1),[1] isolated from *Corydalis ochotensis* var. *raddeana*, has been shown to be an unusual spirobenzylisoquinoline alkaloid possessing a tertiary hydroxy group *cis* to the nitrogen and a methyl group in the five-membered ring. Most of the spirobenzylisoquinoline alkaloids have no extra carbon on their five-membered ring.[2] Synthesis of the related alkaloids ochotensimine (2) and ochotensine (3), having one extra carbon, has been accomplished through the Wittig reaction of the corresponding ketone (4).[3,4]

A synthesis of raddeanamine (1) seems to be easily achieved by methylation of the ketone (4). From analogy with hydride reduction of such ketones,[5] however, a methylation reagent is presumed to approach the carbonyl group of 4 from the side of the nitrogen resulting in a *trans* alcohol instead of 1. In fact, on treatment with methyllithium, the ketone (5)[6] afforded the *trans* alcohol (6) [93%; δ 1.53 (3H, s, C-Me)] as a sole product.[7]

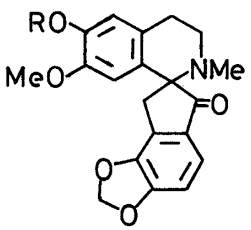
Therefore, another method should be developed for a stereoselective synthesis of a spirobenzylisoquinoline having a *cis* tertiary alcohol. This communication describes a first and stereoselective synthesis of raddeanamine (1) from the corresponding protoberberine (9) *via* the 8-methyl-8,14-cycloberbine (12) by regioselective C_8-N bond cleavage and stereoselective hydroxylation at C_8.



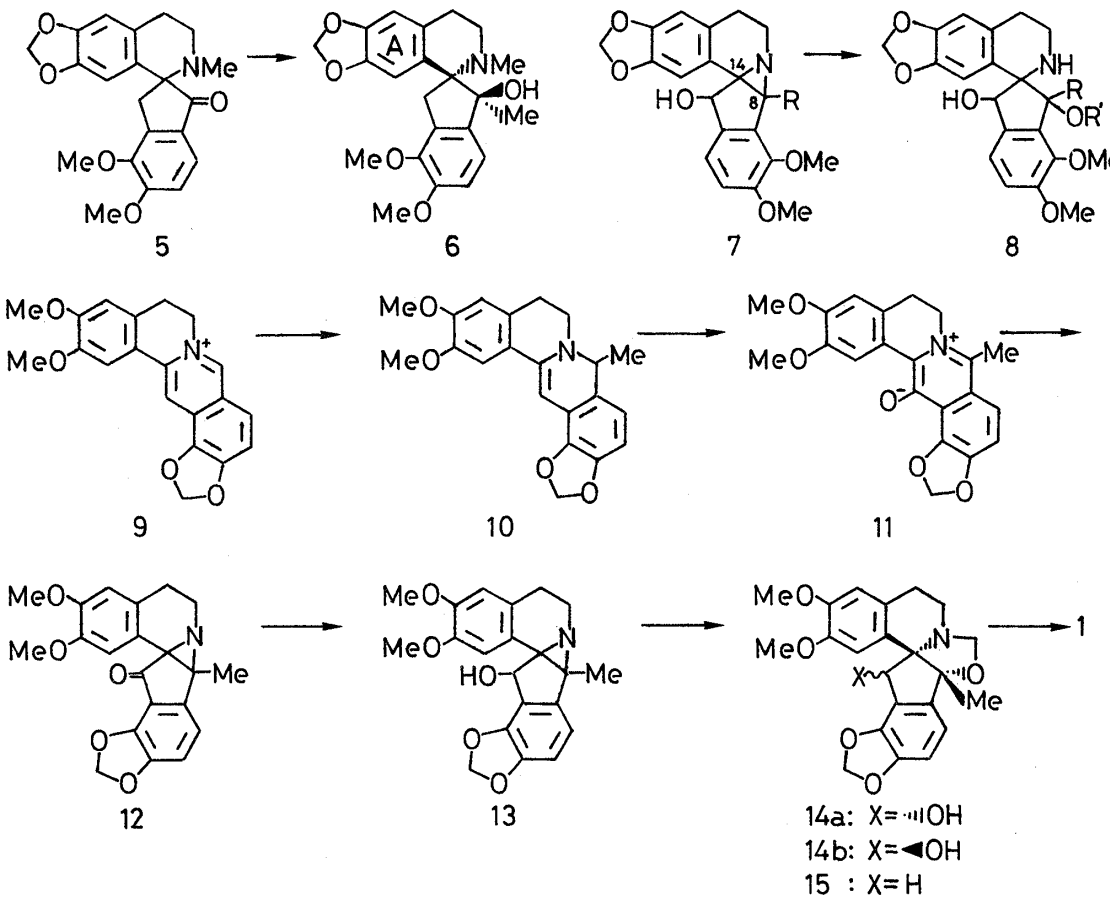
1
raddeanamine



2: R=Me
3: R=H



4



Treatment of the protoberberine (9)[8] with methylmagnesium iodide in ether afforded the 8-methyldihydroprotoberberine (10) (91%), which was oxidized with *m*-chloroperbenzoic acid in methylene chloride to furnish the phenolbetaine (11) [81%; *m/z* 365 (M^+); δ 9.24 (1H, s, C_1-H), 2.76 (3H, s, C-Me)]. This phenolbetaine was irradiated[9] in methanol with a high-pressure mercury lamp through a Pyrex filter to afford the 8-methyl-8,14-cycloberbine (12) [57%; mp 183-185°C; *m/z* 365 (M^+); ν 1715; δ 1.55 (3H, s, C-Me)]. Reduction of the cycloberbine (12) with sodium borohydride in methanol (method A) or lithium tri-*tert*-butoxyaluminum hydride in benzene-tetrahydrofuran (THF) (10:1) (method B) gave the alcohol (13) as a mixture of two diastereoisomers, which were difficult to separate.[10]

Previously we found that nucleophilic substitution of 8-alkyl-8,14-cycloberbines (7) effected regioselective C_8-N bond cleavage to give exclusively spirobenzylisoquinolines (8),[11] while the reaction of 8-unsubstituted cycloberbines led to benzindenoazepines through C_{14}-N bond cleavage.[12] Thus, an intramolecular nucleophilic opening of the aziridine ring in the 8-methylcycloberbine (13) is expected to afford a spirobenzylisoquinoline possessing a *cis* alcohol by a regio- and stereo-selective control.

Treatment of the alcohol (13) with 37% aq. formaldehyde solution[13] in methanol afforded the oxazolidine (14a and 14b) in 79% (from 12 *via* metjod A: 14a:14b=7.8:1) or 61% overall yield (from 12 *via* method B: 14a:14b=1:7.8) [14a: mp 191.5-192.5°C; *m/z* 397 (M^+); ν 3250; δ 6.28 (1H, s, C_1-H), 5.07 (1H, s, C_8-H), 4.49, 4.13 (2H, AB-q, *J*=7, NCH_2O); 14b: mp 196.5-197°C; *m/z* 397 (M^+); ν 3550; δ 6.28 (1H, s C_1-H),

5.42 (1H, s, C_8-H), 4.62, 4.56 (2H, AB-q, J=7, NCH_2O)]. Chlorination of the alcohol (14a or 14b) with thionyl chloride in methylene chloride followed by reduction with tri-*n*-butyltin hydride in THF in the presence of azobisisobutyronitrile yielded the deoxygenated product (15) [mp 138-139°C; *m/z* 381 (M^+); δ 4.55, 4.49 (2H, AB-q, J= 7.5, NCH_2O), 3.42, 3.31 (2H, AB-q, J=18.5, C_8-H)] in 52 or 46% yield, respectively.

Finally, the oxazolidine (15) was treated with sodium cyanoborohydride in methanol in the presence of hydrochloric acid[14] to provide (±)-raddeanamine (1) [94%; mp 144.5-146°C; *m/z* 383 (M^+); ν 3250; δ 6.88, 6.73 (2H, AB-q, J=8, C_{11}- and C_{12}-H), 6.56 (1H, s, C_4-H), 6.19 (1H, s, C_1-H), 5.96 (2H, s, OCH_2O), 3.83, 3.43 (each 3H, s, OMe x 2), 3.46, 3.15 (2H, AB-q, J=16, C_8-H), 2.58 (3H, s, NMe), 1.24 (3H, s, C-Me)]. The synthetic product was proved by spectral comparisons to be identical with natural raddeanamine.

Thus, we have accomplished a first and stereoselective synthesis of (±)-raddeanamine and the present conversion of the oxazolidine (15) to 1 confirmed unambiguously the *cis* relationship between the hydroxy group and the *N*-methyl group in raddeanamine. The present synthesis of 1 also amounts to a formal synthesis of ochotensimine (2), since 1 has been transformed to 2 by dehydration.[1]

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