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INVERSION OF A HYDROXYL GROUP BY THE NEIGHBORING-GROUP PARTICIPATION OF A URETHANE —A GENERAL AND STEREOSELECTIVE SYNTHESIS OF (±)-RADDEANONE, (±)-YENHUSOMIDINE, AND RELATED SPIROBENZYLISOQUINOLINE ALKALOIDS

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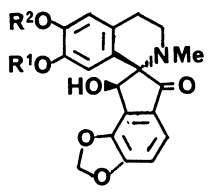
(±)-Raddeanone (**1**) was stereoselectively synthesized from the corresponding protoberberine (**5**) via the ketal (**17**) in four steps. Inversion of a hydroxyl group in the ketal (**17**) was realized by the neighboring-group participation of a urethane to afford the diastereoisomeric ketal (**22**), which was easily converted to (±)-yenhusomidine (**3**). These alkaloids (**1** and **3**) were converted to (±)-raddeanine (**18**), (±)-raddeanidine (**20**), and (±)-yenhusomine (**25**).

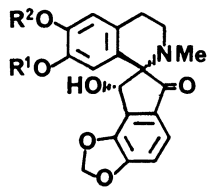
KEYWORDS —spirobenzylisoquinoline alkaloid; protoberberine; raddeanone; yenhusomidine; raddeanine; raddeanidine; yenhusomine; neighboring-group participation; urethane

Various types of spirobenzylisoquinoline alkaloids have been isolated from Fumariaceae[1-3] and a number of synthesis methods for these alkaloids have also been developed.[1] The most challenging target for a synthesis is alkaloids having a carbonyl and a hydroxyl group on a five-membered ring such as raddeanone (**1**), sibiricine (**2**), yenhusomidine (**3**), and corydaine (**4**), because of their stereochemistry, functionalities, and possibility for deriving other types of alkaloids. Although several syntheses of these alkaloids have been achieved,[4-7] no report has been published so far on a stereoselective synthesis of both diastereoisomeric alkaloids (**1** and **3**) and (**2** and **4**) from common synthetic intermediates.

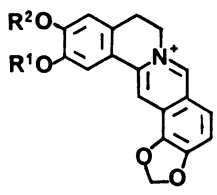
In a previous paper,[7] we reported a simple and stereoselective synthesis of (±)-sibiricine (**2**), an alkaloid having a trans-alcohol, from the corresponding protoberberine (**6**) in four steps. However, this method cannot be used to synthesize alkaloids having a cis-alcohol. If we could develop an easy way to invert the hydroxyl group, it would enhance the versatility of the above method. We describe here a new inversion procedure effected by the neighboring-group partici-



1: $R^1=R^2=Me$
2: $R^1+R^2=CH_2$



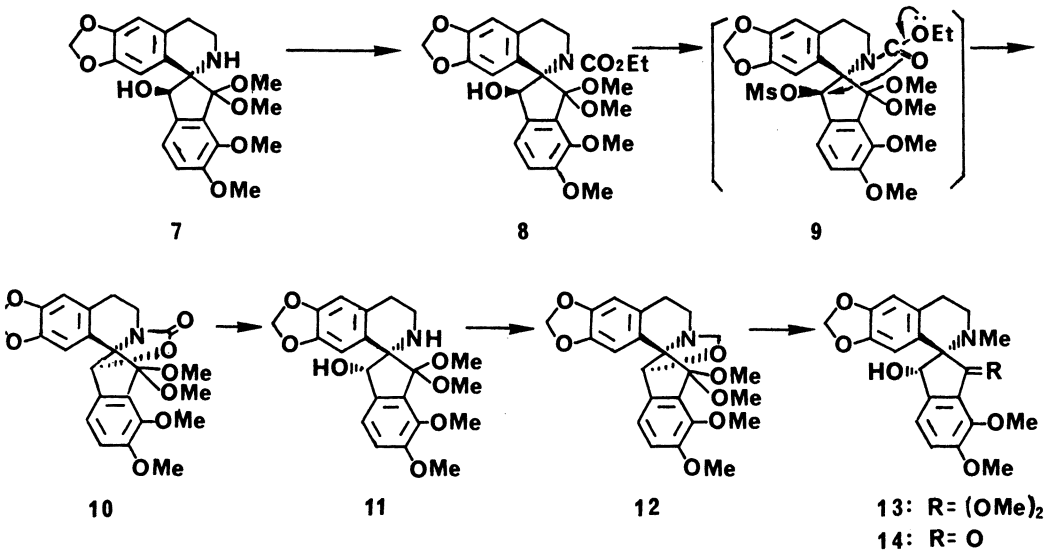
3: $R^1=R^2=Me$
4: $R^1+R^2=CH_2$



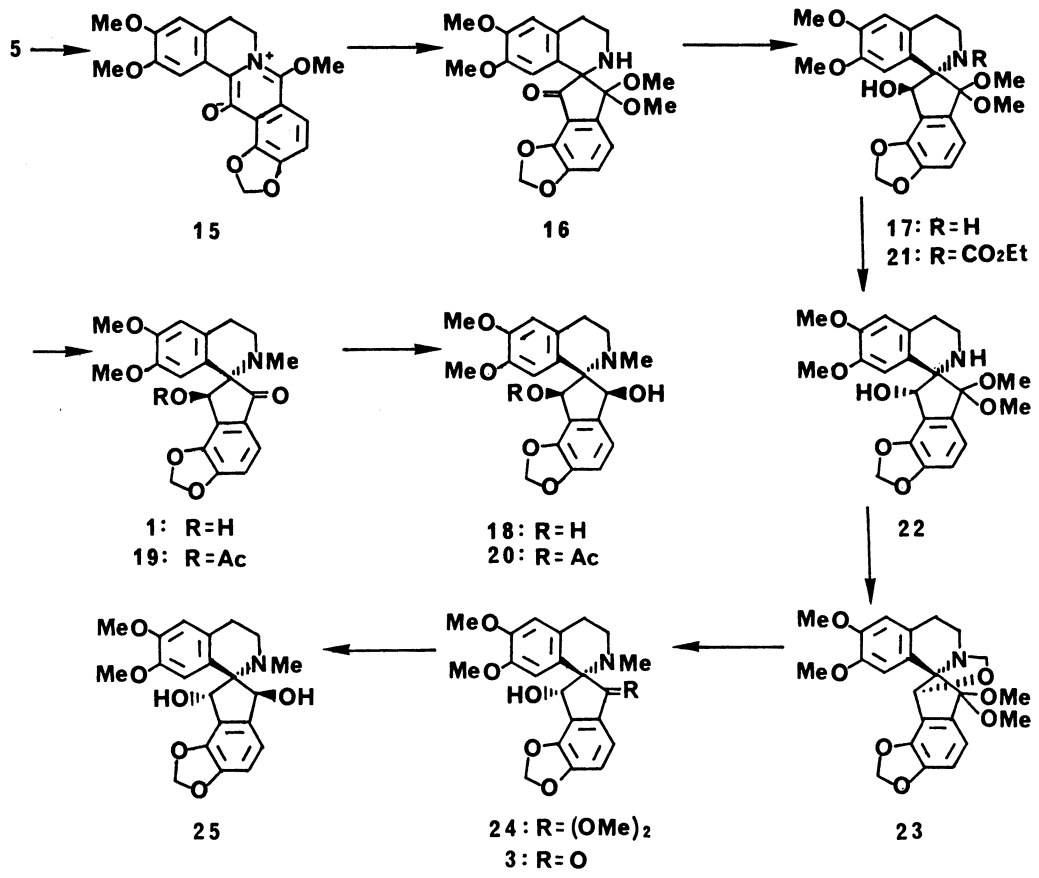
5: $R^1=R^2=Me$
6: $R^1+R^2=CH_2$

pation of a urethane and its application to a stereoselective synthesis of both diastereoisomeric alkaloids, (±)-raddeanone (**1**) and (±)-yenhusomidine (**3**) from the protoberberine (**4**) via a common intermediate.

After several unsuccessful experiments including the Mitsunobu reaction[8] and isomerization through retro-aldol followed by aldol recyclization,[4,5] we proceeded to develop a new inversion procedure using the spirobenzylisoquinoline (**7**)[9] readily available from berberine. Treatment of the urethane (**8**),[9] derived from **7**, with methanesulfonyl chloride in tetrahydrofuran in the presence of triethylamine at 0°C afforded the oxazolidinone (**10**) [95%; mp 206-207.5°C; m/z 441 (M^+); ν 1740; δ 5.23 (1H, s, H-13)]. The formation of **10** was rationalized in terms of the intermediacy of the methanesulfonate (**9**), the methanesulfonyloxy group of which was replaced by the ethoxycarbonyl group from the backside.[10] Hydrolysis of **10** with potassium hydroxide furnished the cis-hydroxy-ketal (**11**) [97%; mp 156-158°C; m/z 400(M^+-15); ν 3350; δ 4.71 (1H, d, J=0.5, H-13)], a diastereoisomer of **7**. The stereochemistry of **11** was verified by the appearance in the ^{1}H-NMR spectra of H-13 at a higher chemical shift[3,7] in comparison with that of **7** (δ 4.89).[9] Thus, the trans-alcohol (**7**) was smoothly converted to the cis-alcohol (**11**) employing the neighboring-group participation of a urethane.



The cis-alcohol (**11**) was heated with 37% formaldehyde[5] in methanol under reflux to give the oxazolidine (**12**) [98%; mp 146-148°C; m/z 427 (M^+); δ 5.02, 4.64 (2H, AB-q, J=5.5, -OCH_2N-), 4.97 (1H, s, H-13)], reduction of which with sodium cyanoborohydride in methanol[5] in the presence of hydrochloric acid followed by acidic treatment of the resulting ketal (**13**) furnished the desired yenhusomidine analog (**14**) [86% from **12**; m/z 383 (M^+); ν 3400, 1710; δ 4.93 (1H, d, J=0.5, H-13)]. Next, a synthesis of raddeanone (**1**) and its related alkaloids was undertaken according to our previous method.[7] Photooxygenation[9] of **5** by irradiation with a halogen lamp in methanol containing sodium methoxide and rose bengal in a stream of oxygen at 0°C and subsequent irradiation[9] of the resulting phenolbetaine (**15**) with a mercury lamp through a Pyrex filter in methanol at 0°C afforded the spiro-ketal (**16**) [42% form **5**; mp 181-183°C; m/z 413 (M^+), ν 1720]. This was reduced with sodium



borohydride in methanol-dichloromethane (3:1) to give stereoselectively the trans-alcohol (**17**) [99%; mp 165-166°C; δ 5.12 (1H, s, H-8)]. On treatment with formaldehyde-formic acid, **17** afforded (±)-raddeanone (**1**) [91%; mp 177-179°C (lit.[4] mp 181-182°C); m/z 383 (M^+)].[11] Reduction of **1** with sodium borohydride furnished stereoselectively (±)-raddeanine (**18**) [90%; mp 201-202°C (lit.[12] mp 218-220°C); m/z 385 (M^+)]. Acetylation of **1** with acetic anhydride in pyridine gave the acetate (**19**) [94%; m/z 425 (M^+); ν 1740, 1720]. This was reduced with sodium borohydride to produce (±)-raddeanidine (**20**)[93%; mp 169-171°C; m/z 427 (M^+)].[4] The synthetic (±)-raddeanone and (±)-raddeanine were identical in their ^{1}H-NMR spectra with the corresponding authentic samples.

The inversion procedure described above was now applied to the trans-alcohol (**17**). Treatment of **17** with ethyl chloroformate in benzene in the presence of triethylamine under reflux afforded the urethane (**21**) [83%; mp 172-172.5°C; m/z 457 (M^+-30); ν 3450, 1670; δ 5.12 (1H, s, H-8)]. Sequential treatment of **21** with methanesulfonyl chloride, potassium hydroxide, and 37% formaldehyde in methanol gave the oxazolidine (**23**) [41% from **21**; mp 183-184°C; m/z 412 (M^+); δ 5.14 (1H, s, H-8), 5.00, 4.71 (2H, AB-q, J=5.5)] via the cis-alcohol (**22**) [δ 4.82 (1H, s, H-8)]. The oxazolidine (**23**) was reduced with sodium cyanoborohydride in methanol in the presence of hydrochloric acid to furnish the N-methyl ketal (**24**) [98%; m/z 429 (M^+)], which was hydrolyzed with hydrochloric acid to produce (±)-yenhusomidine (**3**)

[90%; mp 228-229°C (lit.[4] 239-240°C), m/z 383 (M^+)].[11] Synthetic (±)-yenhusomidine was identical with the authentic sample. As **3** has already been converted to (±)-yenhusomine (**25**),[4] the present synthesis amounts to a formal synthesis of **25**.

Thus, we developed a new inversion of a hydroxyl group by the neighboring-group participation of a urethane, and a stereoselective synthesis of raddeanone (**1**) and yenhusomidine (**3**) from the corresponding protoberberine (**5**) via a common intermediate (**17**). The present synthesis provides a general and stereoselective method for synthesizing any type of spirobenzylisoquinoline alkaloids possessing two oxygen functional groups on a five-membered ring.

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(±)-raddeanone (**1**): ν 3550, 1710; δ 7.53 (1H, d, J=8), 7.03 (1H, d-d, J=8; 0.5), 6.66 (1H, s), 6.23, 6.19 (2H, AB-q, J=1), 6.02 (1H, s), 5.59 (1H, br-d, J=7.5), 3.84, 3.51 (each 3H, s), 2.41 (3H, s).
(±)-raddeanine (**18**): ν 3550; δ 6.93 (1H, d-d, J=8; 1), 6.85 (1H, d, J=8), 6.69 (1H, s), 6.17 (1H, s), 6.03, 6.00 (2H, AB-q, J=1), 5.48 (1H, br-d, J=7.5), 5.27 (1H, br-d, J=6.5), 3.84, 3.42 (each 3H, s), 2.65 (3H, s).
(±)-raddeanidine (**20**): ν 3350, 1740; δ 6.90 (1H, d-d, J=8; 1), 6.84 (1H, d, J=8), 6.72 (1H, s), 6.62 (1H, s), 6.22 (1H, s), 5.98 (2H, s), 5.22 (1H, s), 3.85, 3.44 (each 3H, s), 2.53 (3H, s), 1.95 (3H, s).
(±)-yenhusomidine (**3**): ν 3250, 1705; δ 7.49 (1H, d, J=8), 7.01 (1H, d-d, J=8; 0.5), 6.60 (1H, s), 6.24, 6.21 (2H, AB-q, J=1), 6.08 (1H, s), 5.10 (1H, s), 3.86, 3.64 (each 3H, s), 2.27 (3H, s).
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