A TOTAL SYNTHESIS OF (±)-TACAMONINE (PSEUDOVINCAMONE I) THROUGH RADICAL CYCLIZATION#

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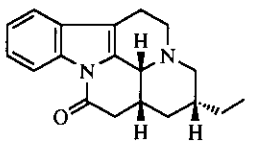
Abstract——The radical cyclization of the bromo ester (**11**), prepared from 2-hydroxymethylbutan-1-ol (**7**), giving the diastereoisomeric mixture of lactones (**12**) was examined under various conditions. Treatment of the bromo ester (**17**), derived from **7**, with tris(trimethylsilyl)silane in the presence of 2,2-azoisobutyronitrile provided the epimeric mixture of lactams (**18**), convertible to (±)-tacamonine (pseudovincamone I) (**1**) in three steps.

Tacamonine (**1**), isolated from *Tabernaemontana eglandulosa* in 1982,[1] is an indole alkaloid of *Iboga* type. Massiot and coworkers synthesized the racemate of **1** (pseudovincamonone I) prior to the isolation.[2] Although its synthesis would be important due to the structural similarity to a *Hunteria* alkaloid, eburnamonine (**2**) possessing a vasodilator activity, only few efforts have been devoted to the synthesis. We envisaged that the possible synthetic precursor (**3**) of tacamonine (**1**) could be produced by two different approaches (A and B) utilizing radical cyclization as the key step as shown in the Scheme 1. It was further considered that two radical synthons (**5**) and (**6**) could be derived from 2-hydroxymethylbutan-1-ol (**7**).



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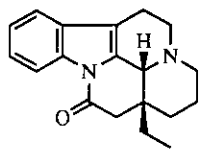
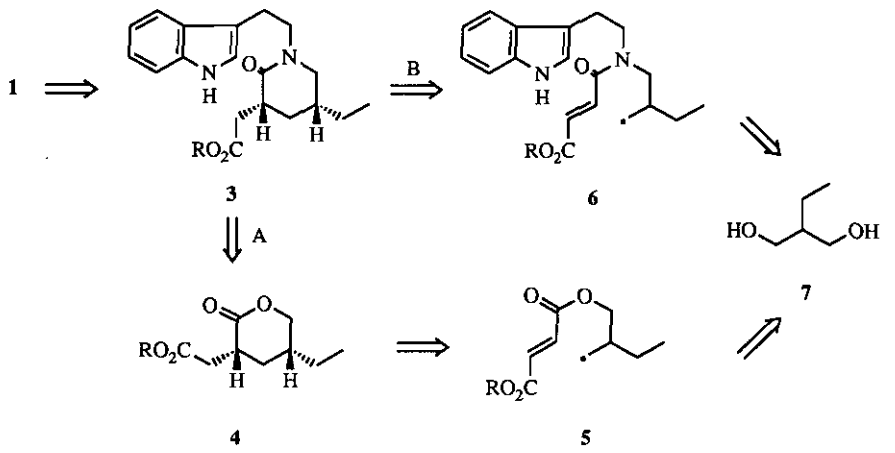


2

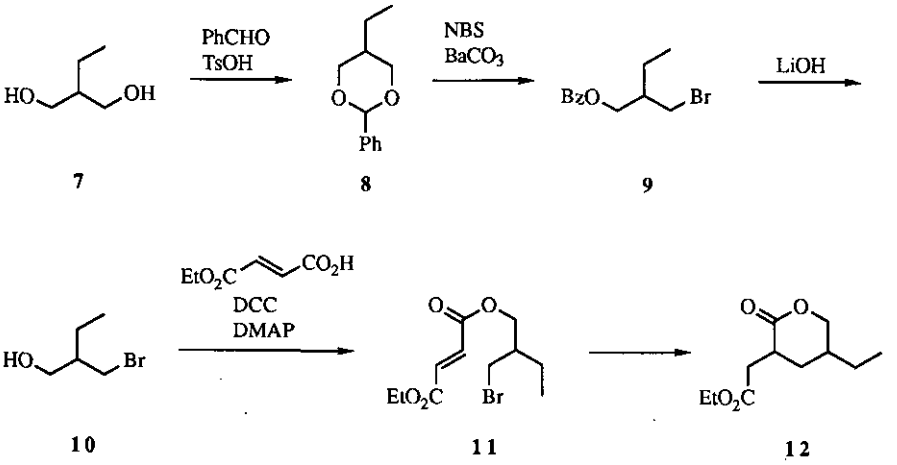
First, the radical cyclization of **5** according to the approach A was investigated (Scheme 2). The synthesis of a suitable substrate for this strategy began with the acetalization of the diol (**7**). Benzylidene (**8**), obtained in 94%

Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.



Scheme 1

yield, was readily converted to the benzoate (**9**) in 79% yield using the Hanessian ring opening.[3] After hydrolysis of **9** (95% yield), the resulting alcohol (**10**) was reacted with fumaric acid monoethyl ester in the presence of dicyclohexylcarbodiimide (DCC) and *N,N*-dimethylaminopyridine (DMAP) to give the substrate (**11**) in 97% yield. The cyclization was examined by using tributyltin hydride (Bu_3SnH) and tris(trimethylsilyl)-silane [$(TMS)_3SiH$][4] in the presence of 2,2-azoisobutyronitrile (AIBN). The desired lactone (**12**) was provided as a mixture of two diastereoisomers in a ratio of 1 : 1.2. As shown in the Table 1, the yield of **12** depended on the concentration when the reaction was carried out using Bu_3SnH. The replacement of the bromine atom of **11** with hydrogen atom mainly occurred under the concentrated conditions. On the other hand, the effect of the concentration to the yield of the cyclized product (**12**) was small for the radical cyclization using $(TMS)_3SiH$. However, the trial for the conversion of **12** to the lactam (**3**) resulted in a failure.



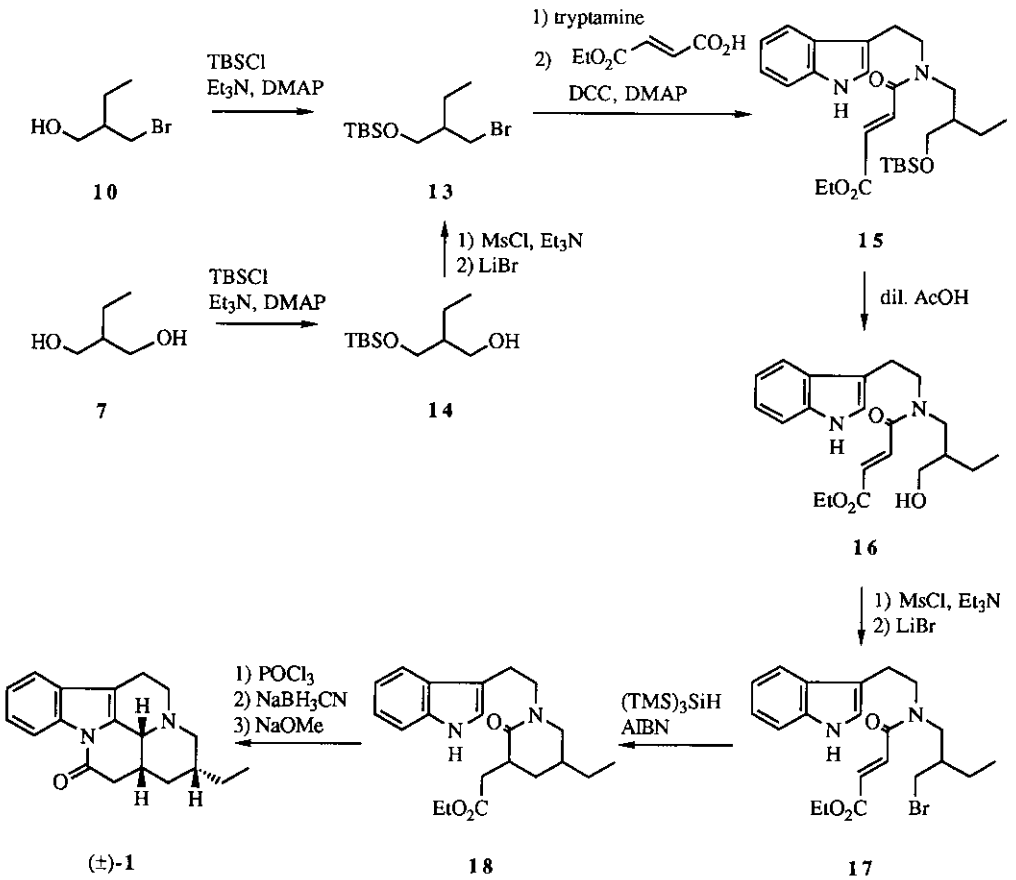
Scheme 2

Tabele 1 Radical cyclization of **11** carried out in the presence of AIBN in refluxing benzene for 5 h.

concentration[a]	Bu_3SnH	$(TMS)_3SiH$
× 100	0%	82%
× 1000	92%	90%

[a] The ratio of the volume (ml) of the solvent for the substrate (g).

Next, the approach B producing directly the desired lactam (**3**) was examined as depicted in the Scheme 3. Protection of the hydroxy group of the alcohol (**10**) with *tert.*-butyldimethylsilyl group afforded the ether (**13**) in 96% yield. The ether (**13**) was also prepared from **7** in three steps; monosilylation of **7** (62% yield), followed by



Scheme 3

the mesylation of the hydroxy group of the resulting **14**, and the subsequent bromination (95% overall yield for two steps). The reaction of the bromide (**13**) with two equivalent moles of tryptamine in dimethylformamide at 70 °C gave the corresponding secondary amine, which was then condensed with fumaric acid monoethyl ester to afford the amide (**15**) in 60% overall yield for two steps. Deprotection of the *tert.*-butyldimethylsilyl group of **15**, followed by mesylation of the resulting alcohol (**16**) and the substitution reaction, provided the bromo ester (**17**) in 88% overall yield for three steps. The radical cyclization of **17**, conducted with $(TMS)_3SiH$ in the presence of AIBN in hot benzene for 16 h, furnished the required lactam (**18**) in 62% yield. The ratio of the epimeric isomers of **18** could not be determined by the high resolution of ^1H nmr spectroscopy due to their rotational isomers. The lactam (**18**) was transformed, by the standard three step procedure, to the (±)-tacamonine (**1**) (pseudovincamone I), mp 146-147 °C (lit.,[2] mp 143 °C), together with diastereoisomers. The spectral and chromatographic properties of the synthetic product (**1**) were identical with those of the authentic sample.

Thus, a convenient synthesis of (±)-tacamonine (**1**) has been accomplished by way of the radical cyclization of the amide (**17**). A chiral synthesis of the alkaloid (**1**) utilizing the chiral 1,3-propanediol derivative[5] is in progress.

ACKNOWLEDGMENT

We thank Dr. G. Massiot of University of Reims for his generous gift of the authentic specimen.

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Received, 13rd October, 1993