รายงานฉบับสมบูรณ์

โครงการ วิธีการใหม่ในการสังเคราะห์สารประกอบโปรโตเบอร์เบอรีน อัลคาลอยด์

โดย ดร. อณุชา น้ำสอาด

มิถุนายน 2549

สัญญาเลขที่ TRG4780013

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อณุชา น้ำสอาด

ห้องปฏิบัติการผลิตภัณฑ์ธรรมชาติ สถาบันวิจัยจุฬาภรณ์

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย
(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว. ไม่จำเป็นต้องเห็นด้วยเสมอไป)

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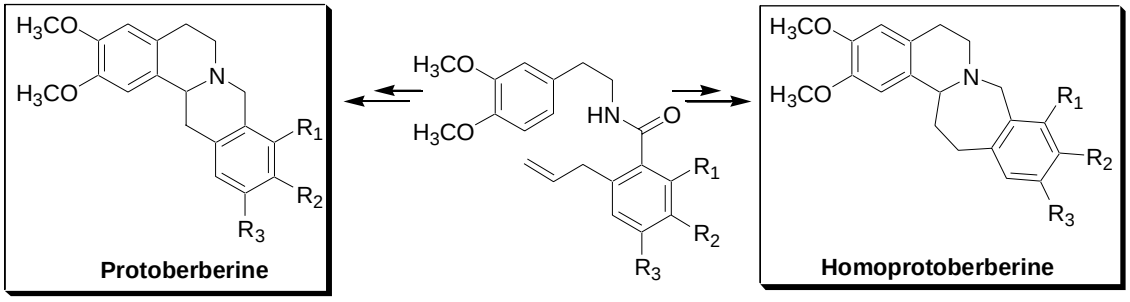
วิธีการใหม่ในการสังเคราะห์สารประกอบโปรโตเบอร์เบอรีน อัลคาลอยด์

หัวหน้าโครงการ : ดร. อณุชา น้ำสอาด (TRG4780013)

นักวิจัยพี่เลี้ยง : ศ. ดร.สมศักดิ์ รุจิรวัฒน์

บทคัดย่อ

เนื่องมาจากความสามารถในการแสดงฤทธิ์ชีวภาพที่หลากหลายของสารโปรโตเบอร์เบอรีนและโฮโมโปรโตเบอร์เบอรีนนั้น จึงได้มีการศึกษาและสังเคราะห์สารในกลุ่มนี้เป็นจำนวนมาก อย่างไรก็ตามในอดีตได้มีการศึกษาสารในกลุ่มนี้เป็นจำนวนมากแล้ว แต่มีวิธีการสังเคราะห์ที่หลายขั้นตอนและยังซับซ้อน รวมถึงปริมาณของผลิตภัณฑ์นั้นยังไม่ดีและเหมาะสมเท่าที่ควร



ดังนั้นเราจึงได้ศึกษาและสังเคราะห์สารโปรโตเบอร์เบอรีนและโฮโมโปรโตเบอร์เบอรีนโดยเน้นทางด้านการหาวิธีสังเคราะห์แบบใหม่ให้สั้น ง่าย และมีประสิทธิภาพสูงสุดเพื่อให้ได้ปริมาณผลิตภัณฑ์ที่ดีกว่าในอดีต โดยได้ทำการเสนอวิธีการสังเคราะห์สารมัธยันต์ที่สำคัญด้วยปฏิกิริยาสติลล์คลอสคัพพลิ่งระหว่างสารโบรโมเบนซามายด์และอัลลิลแสตนเนน ซึ่งผลิตภัณฑ์ที่ได้จากกระบวนการข้างต้นจะถูกเปลี่ยนไปเป็นโปรโตเบอร์เบอรีนและออกโซโปรโตเบอร์เบอรีนด้วยกระบวนการออกซิไดซ์และการปิดวงโดยใช้กรดเป็นตัวทำปฏิกิริยาตามลำดับ

นอกจากนี้สารมัธยันต์อัลลิลแสตนเนนที่สำคัญข้างต้นนี้จะถูกเปลี่ยนไปเป็นผลิตภัณฑ์โฮโมโปรโตเบอร์เบอรีนและออกโซโฮโมโปรโตเบอร์เบอรีนได้อีกด้วยโดยใช้กระบวนการออกซิไดซ์ที่แตกต่างจากการสังเคราะห์โปรโตเบอร์เบอรีนและสุดท้ายสารมัธยันต์ที่ได้จะนำมาทำปฏิกิริยาปิดวงโดยใช้กรดเป็นตัวทำปฏิกิริยาอีกครั้งหนึ่ง

คำหลัก : โปรโตเบอร์เบอรีน, โฮโมโปรโตเบอร์เบอรีน, ปฏิกิริยาสติลล์คลอสคัพพลิ่ง

Project Code : TRG4780013

Project Title : A New Method for the Synthesis of Protoberberine Alkaloids

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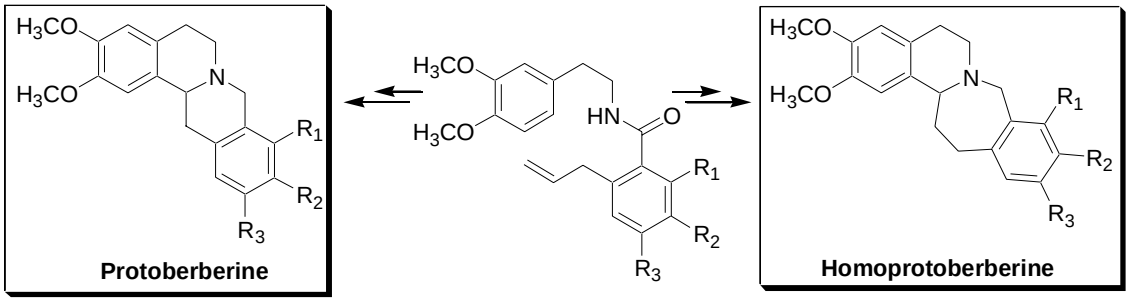
Project Period : 24 Months

ABSTRACT

Due to very diverse interesting biological activities exhibited by the protoberberine and homoprotoberberine alkaloids, various approaches for the syntheses of these unique alkaloids have been investigated. However, there are some drawbacks in these reported syntheses regarding the yields, number of steps and complexity in the operation as well as the ready availability of the starting materials.



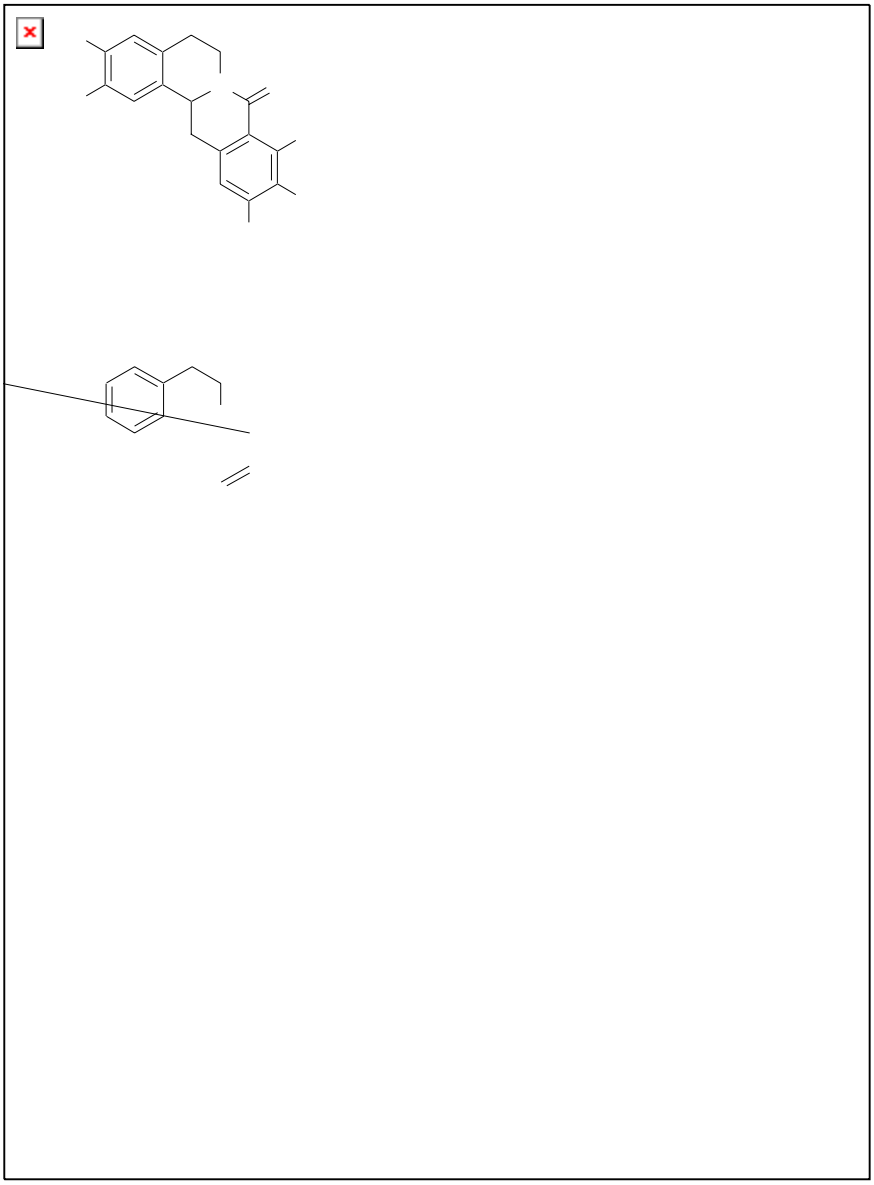
The synthesis of protobeberines and homoprotoberberines has been reported. Key allyl aryl amide intermediates prepared by the Stille cross coupling reaction of bromo benzamides to allyl stannanes were converted into protoberberines and oxoprotoberberine by oxidative cleavage and subsequent acid-induced cyclization.

Moreover, the allyl arylamides could be also transformed to homoprotoberberines and oxohomoprotoberberines by other different oxidations followed with the previous cyclization condition.

Key word: Protoberberine, Homprotoberberine, Stille cross coupling reaction

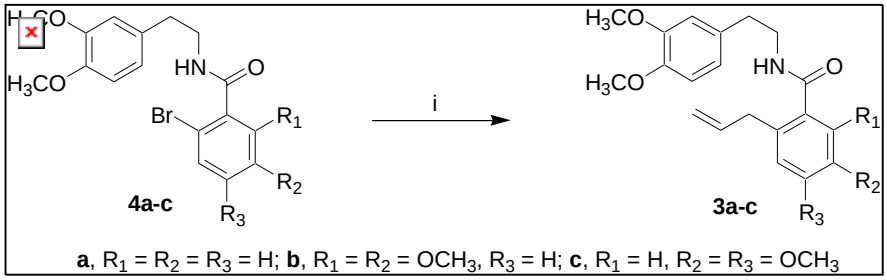
Exclusive Summary

We have designed the retrosynthesis for both protoberberine and homoprotoberberine in two different pathways, which derive from the key allyl arylamide intermediate **3**. For the synthetic pathway A (**Scheme 1**), it was planed that the aldehyde intermediate **2** could be simultaneously cyclized in the acidic condition to get the ring B and C of protoberberine **1**. The aldehyde intermediate **2** would be synthesized by a specific oxidation of allyl arylamide **3** which was cleaved one carbon of an olefinic moiety. The allyl arylamide **3** could conceivably be prepared by the reaction of a commercially available tributyl allylstannane with bromobenzamide which was synthesized from the condensation of commercially available homoveratrylamine with benzoylcholride derivative. For another synthesis, a pathway B could be exhibited the homoprotoberberine synthesis which would share the same intermediate **3** as pathway A to construct the alternative aldehyde compound **5** by the different oxidations. Cyclization of aldehyde **5** in acid condition could be gotten the oxohomoprotoberberine **6**.



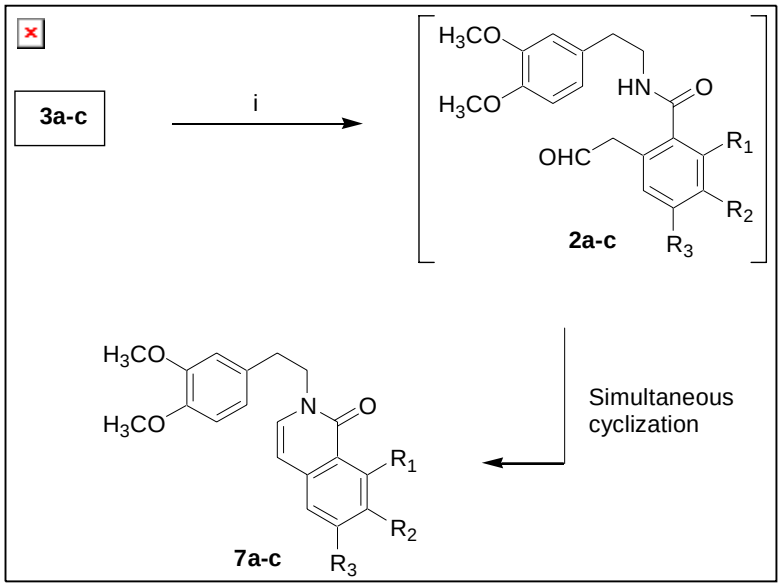
Scheme 1. Retrosynthetic analysis

In practice, the Stille cross coupling reaction between bromo amide **4a** and commercially available tributyl allylstannane gave an expected allyl arylamide derivative **3a** in high yield. Having successfully carried out the couple of three carbon unit, the Stille reaction was then extended to the other bromoamides **4b-c**. It was found that the **4b-c** were reacted, the allyl arylamide **3b-c** were smoothly obtained in good yield as well (**Scheme 2**).



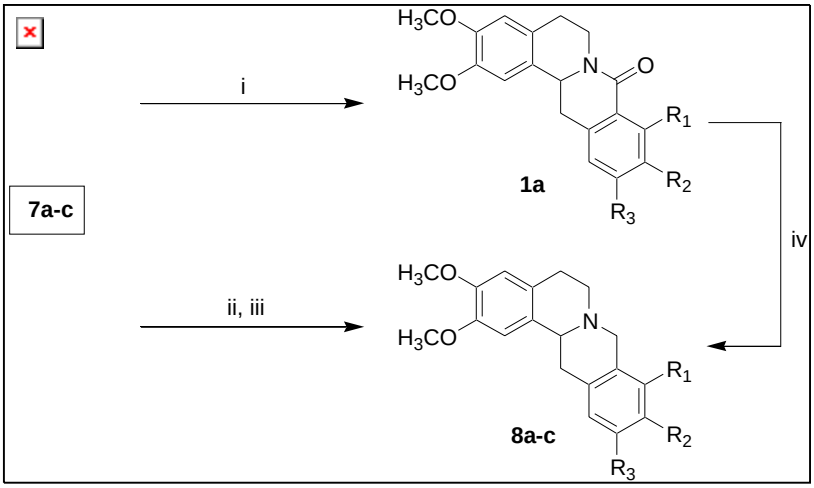
Scheme 2. Reagents and conditions: (i) 10mol % $Pd(Ph_3)_4$, tributyl allylstannane, toluene, refulx, 24h, 86% (**3a**), 85%, (**3b**), 85% (**3c**)

According to the retrosynthetic plan (**Scheme 1**), the oxidative cleavage reaction, ozonolysis, was performed by treatment of allyl compound **3b-c** with bubbly ozone containing a trace of iodine. Unfortunately, the ozonolysis afforded a complex mixture, which was possible for an over oxidative cleavage reaction, preferably breaking some parts of aromatic system.



Scheme 3 Reagents and conditions: (i) 4% in water OsO_4, $NaIO_4$, THF : H_2O (3:1), rt, 6h, 85% (**7a**), 83% (**7b**), 89% (**7c**)

The ozonolysis problem was solved with the OsO_4-$NaIO_4$-mediated oxidation in the presence of THF-H_2O mixture. In this experiment, the substrates **3a-c** were converted immediately to the isoquinoline derivatives **7a-c** which were derived from the cyclization of oxidative cleavage products, aldehydes **2a-c** (**Scheme 3**).

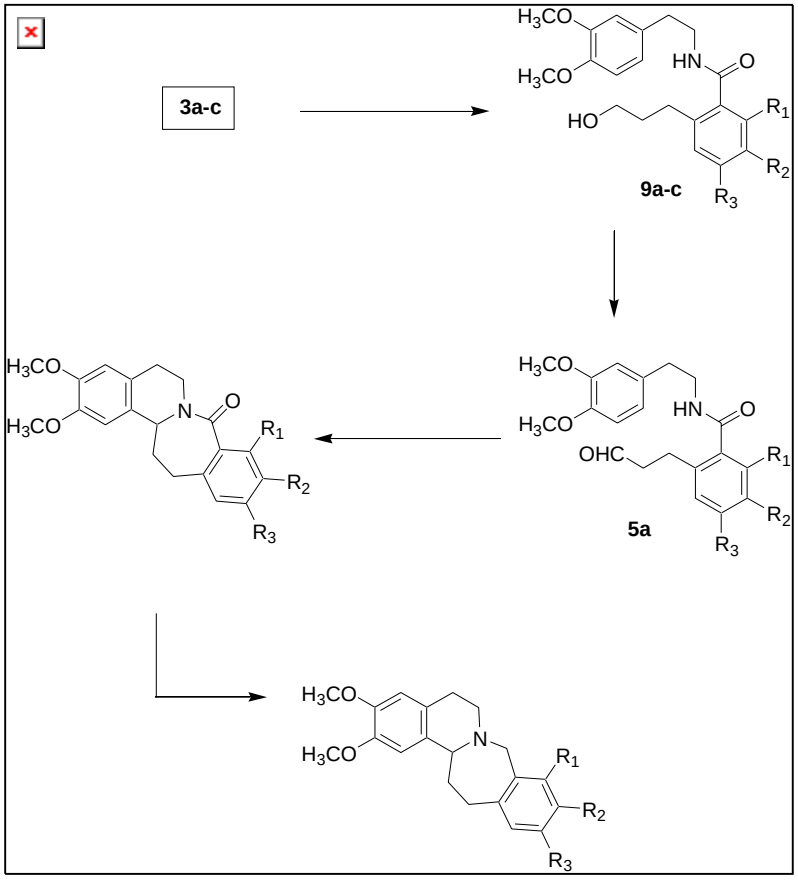


Scheme 4. Reagents and conditions: (i) TFA, reflux, 4h, 76% (**1a**); (ii) LAH, THF, relux, 6h; (iii) TFA, reflux, 4h, 80% (**8a**), 71% (**8b**), 83% (**8c**); (iv) LAH, THF, reflux, 6h, 89% (**8a**)

Further cyclization of isoquinolines **7a-c** was performed in acidic condition as well as TFA. The result afforded the only one oxoprotoberberine product **1a**, whereas the other products **1b-c** were disappeared because the donating effect of methoxy at R_2-position caused to the lack of immide formation of isoquinolone. Even through, the acid-induced cyclization to form the oxoprotoberberine was effective with non-para activation, the remained isoquinolune substrates **7b-c** including **7a** could be transformed to protoberberine **8a-c** by the reduction with lithium alluminium hydride in THF, then followed with TFA to completely close the ring B to the desired

protoberberine **8a-c** in high yield (**Scheme 4**). The reduction of oxoprotoberberine **1a** with LAH in THF was also yielded the protoberberine **8a** in 98%.

For the synthesis of the related protoberberines, homoprotoberberines, we attempted to synthesize the homoprotoberberines by oxidation at the olefinic position of the key allyl amide to generate a hydroxyl group at the end of double bond, so the hydroboration reaction was introduced in this case. Treatment of allyl amide **3a-c** with 9-BBN in THF at refluxing condition for 4h followed with H_2O_2 and NaOH to afford the desired hydroxyl compound **9a-c** in good yield (**Scheme 5**).



Scheme 5. Reagents and conditions: 9-BBN, THF, reflux, 4h; (ii) 35% H_2O_2, NaOH, rt, 1h, 88% (**9a**), 80% (**9b**), 83% (**9c**); (iii) PCC, CH_2Cl_2, rt, 8h, 71% (**5a**), 77% (**5b**), 75% (**5c**); (iv) TFA, reflux, 4h, 88% (**6a**), 94% (**6b**), 96% (**6c**); (v) LAH, THF, reflux, 6h, 82% (**10a)**, 90% (**10b**), 86% (**10c**)

The treatment of PCC with hydroxyl derivatives **9a-c** in the presence of dichloromethane at room temperature for 8h was exhibited the aldehyde compound **5a-c** as liquid in good yield as shown in scheme 5. Again with the acid-induced cyclization, the aldehyde derivatives **5a-c** were treated with TFA which simultaneously induced the ring closure of both B and C ring to give the oxohomoprptoberberines **6a-c**. Finally, the reduction of oxohomeprotoberberines **6a-c** performed with the same condition as oxoprotoberberine **1a** were obtained homoprotoberberines **10a-c**.

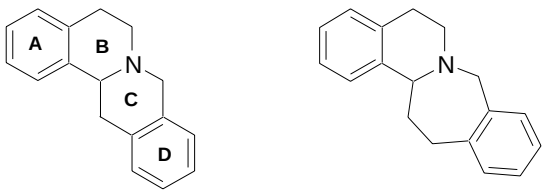
Completed Report (July 2004-June 2006)

TRG4780013

A New Method for the Synthesis of Protoberberine Alkaloids

Introduction

Natural protobebrberine alkaloids constitute a large group of metabolites which occur in the plants of families, *Papaveraceae*, *Berberidaceae*, *Ranunculaceae*, *Menisperaceae* and *Rutaceae*.[1]



Protoberberine **Homoprotoberberine**

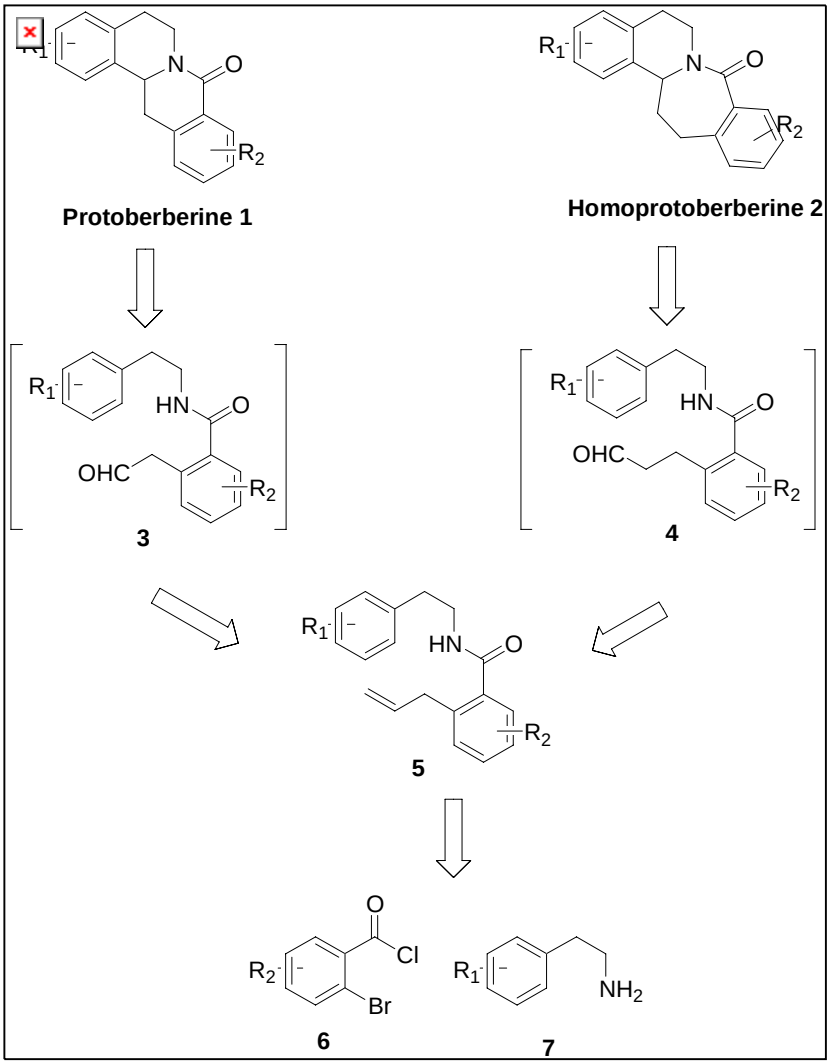
Figure 1. Skeleton of protoberberine and homoprotoberberine alkaloid

The main skeleton of protoberberine and homoprotoberberine is consisted of a tetracyclic ring contained an isoquinoline core (**Fig. 1**). Protoberberines have represented continuing challenge for organic synthesis[2] due to their widespread occurrence in nature and broad range of biological properties such as anticancer[3], antiameobic[4], antimicrobial[5] or antiplatelet aggregation[6] activity. Much interest has been focused on their effectiveness as antileukemic agents, and research in this area has revealed that the intercalation of coralyne and berberine with DNA may play a critical role in their antileukemic action.[7] Moreover, the dimeric protoberberines[8] are developed to be the DNA-binding agents

which have highly potential application for either elucidating the action mechanism of antitumor and antiviral drugs[9] or developing new chemotherapeutic agent.[10] In this paper, we planed to synthesize the protoberberines from effective key allyl arylamide derivatves as intermediates. Besides, the related protoberberines, homoprotoberberines, exhibited the antimalarial activity[11] can be also prepared from allyl arylamide intermediate.

Results and discussion

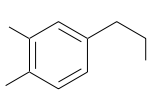
Retrosynthetic analysis

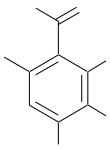


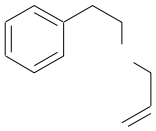
Scheme 1

It was planned to develop a new route for the synthesis of protoberberine **1** and homoprotoberberine **2** by using the same key intermediate **5**.

The target protoberberine **1** will be synthesized from allyl compound **5** *via* an aldehyde intermediate **3** which will be prepared by the specific oxidation reaction. Moreover, the homoprotoberberine target **2** will be also carried out from allyl compound **5** by oxidation which used the different oxidation reaction. For preparation of allyl compound **5**, the condensation of bromobenzoic acid derivative **6** and amine compound **7** will be afforded the bromoamide compound, and then the bromo group of bromoamide compound will be substituted to allyl group by insertion reaction. The adopted route was based on the retrosynthetic analysis shown in **scheme 1**.





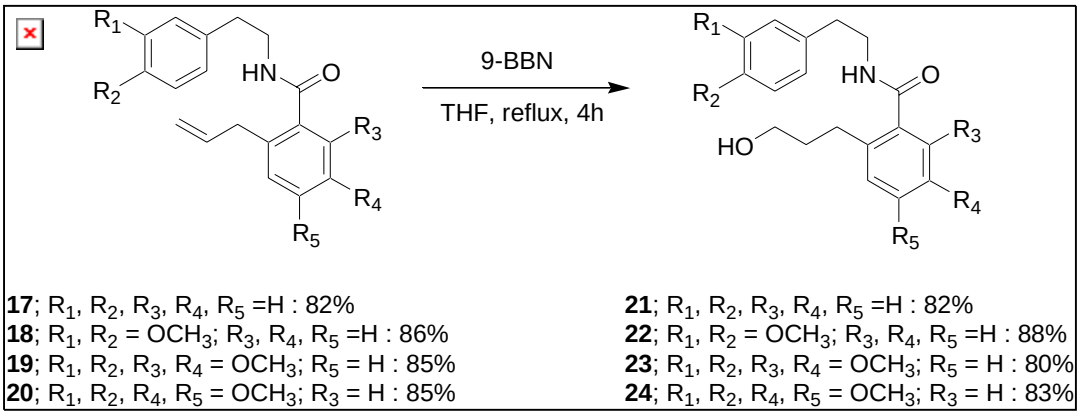


Scheme 2

In practice, we recently described the condensation of homoveratrylamines **8-9** and benzoyl chloride derivatives **10-12** in the presence of $NaHCO_3$ to give

bromobenzamide **13-16** in good yield. The synthesis of key allyl intermediateds was obtained by transformation of bromoamide **13-16** with tributyl(allyl)tin in the presence of $Pd(PPh_3)_4$ in toluene, Stille reaction[12], under refluxing condition provided the crucial intermediates **17-20** in high yield as depicted in **scheme 2**.

Now we have the key allyl amide intermediates in hand. For the first try, we attempted to synthesize the homoprotoberberines by oxidation at the olefinic position of allyl amide to generate a hydroxyl group at the end of double bond, so the hydroboration[13] reaction was introduced in this case. Treatment of allyl amide **17-20** with 9-BBN in the presence of THF at refluxing condition for 4h to afford the desired hydroxyl compound **21-24** in good yield **(Scheme 3).**

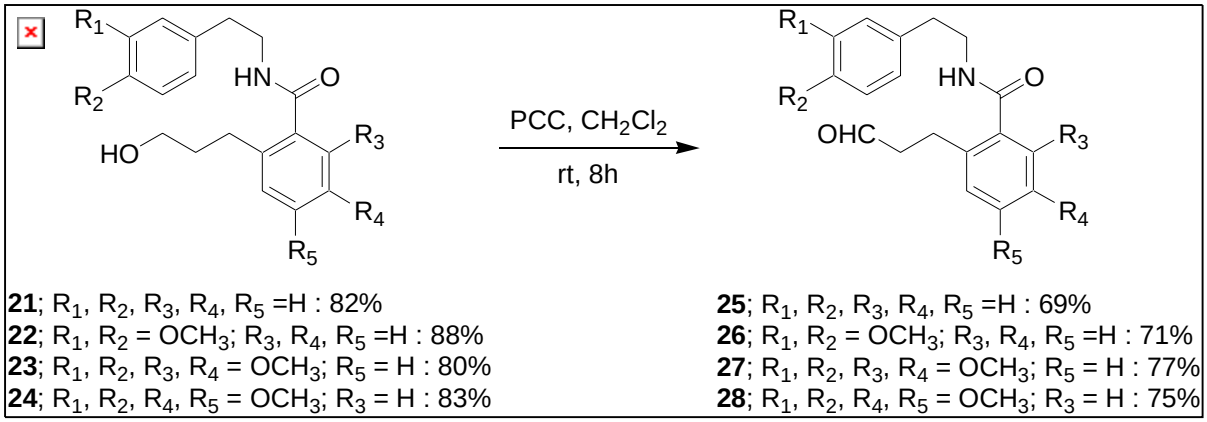


17; R_1, R_2, R_3, R_4, R_5 =H : 82%
18; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H : 86%
19; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 85%
20; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 85%

21; R_1, R_2, R_3, R_4, R_5 =H : 82%
22; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H : 88%
23; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 80%
24; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 83%

Scheme 3

From the successful preparation of hydroxyl compound **21-24**, we then further converted the hydroxyl function of compound **21-24** to the aldehyde function by oxidation with PCC[14] in the presence of dichloromethane at room temperature for 8h. After work up as unual, aldehyde compound **25-28** was obtained as liquid in good yield as shown in **scheme 4**.

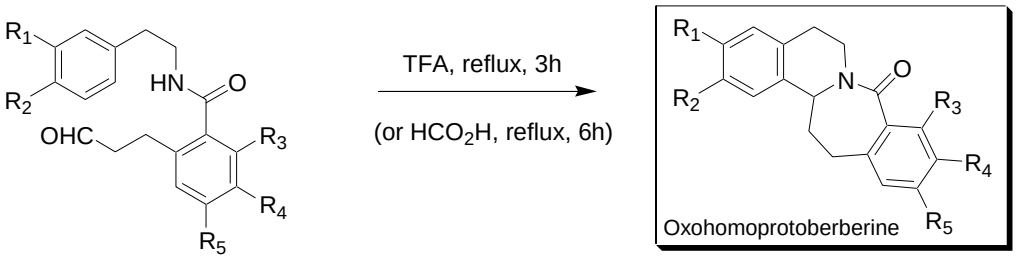


21; R_1, R_2, R_3, R_4, R_5 =H : 82%
22; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H : 88%
23; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 80%
24; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 83%

25; R_1, R_2, R_3, R_4, R_5 =H : 69%
26; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H : 71%
27; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 77%
28; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 75%

Scheme 4

In the final step, the aldehyde derivatives **25-28** were treated with TFA or formic acid, and then the formation of homoprotoberberine was obtained in a case of acid-induced cyclization to give the expected product **29-31** in high yield as obtained in **scheme 5**.



25; R_1, R_2, R_3, R_4, R_5 = H : 69%
26; R_1, R_2 = OCH_3; R_3, R_4, R_5 = H : 71%
27; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 77%
28; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 75%

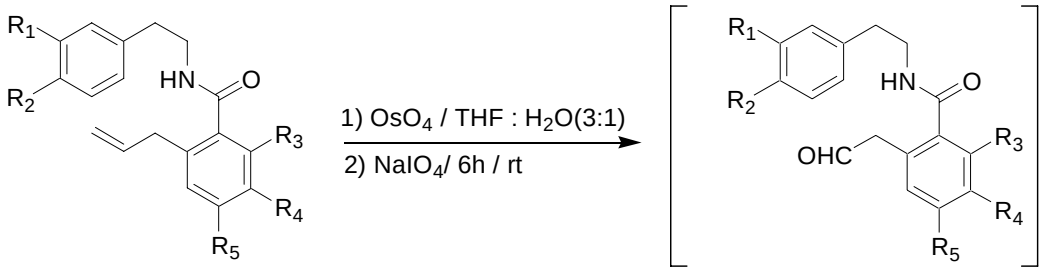
29; R_1, R_2 = OCH_3; R_3, R_4, R_5 = H : 94% (94%)
30; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 93% (90%)
31; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 94% (93%)

Scheme 5

In the case of aldehyde compound **25** was shown the failure of homoprotoberberine formation due to the activating group, para-methoxy R_1, didn't contain a molecule.

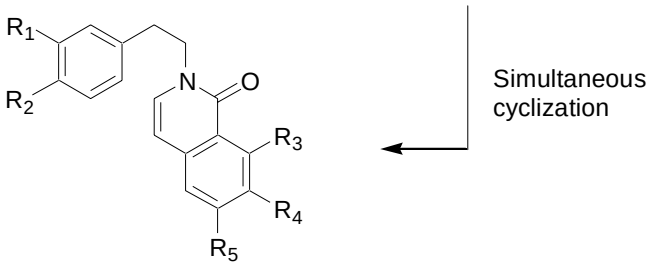
With the success of a synthesis of homoprotoberberine **29-31**, it prompted us to further investigate the method for the synthesis of protoberberine, starting with the key allyl amide **17-20** as proposed in **scheme 1**.

According to the retrosynthetic plan in **scheme 1**, the oxidative cleavage reaction, ozonolysis, was performed by treatment of allyl compound **17-20** with bubbly ozone containing a trace of iodine. Unfortunately, the ozonolysis afforded a complex mixture, which was possible for an over oxidative cleavage reaction, preferably breaking some parts of aromatic system[15].



17; R_1, R_2, R_3, R_4, R_5 =H
18; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H
19; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H
20; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H

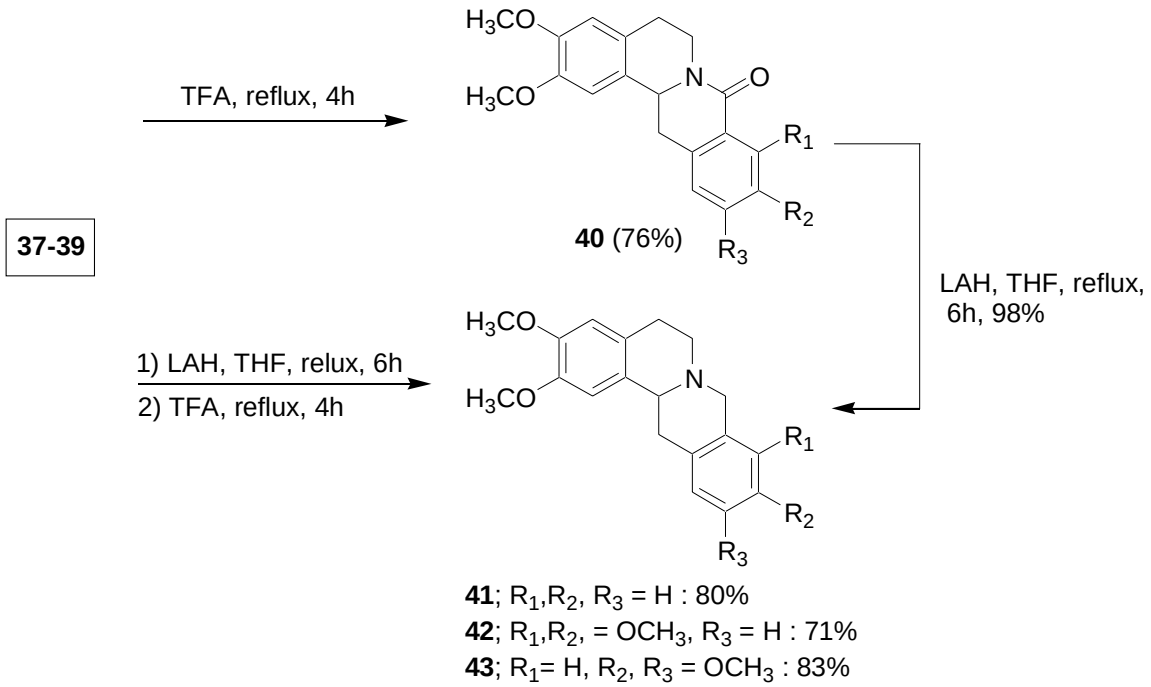
32; R_1, R_2, R_3, R_4, R_5 =H
33; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H
34; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H
35; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H



36; R_1, R_2, R_3, R_4, R_5 =H : 88%
37; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H : 85%
38; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H : 83%
39; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H : 89%

Scheme 6

The ozonolysis problem was solved with the OsO_4-$NaIO_4$-mediated oxidation[16] in the presence of THF-H_2O mixture. In this experiment, the substrates **17-20** were converted immediately to the isoquinolone derivatives **36-39** which were derived from the cyclization of oxidative cleavage products, aldehydes **32-35** (Scheme 6).



Scheme 7

Further cyclization of the isoquinolines **37-39** was performed in acidic condition as well as TFA. The result afforded the only one oxoprotoberberine product **40**, whereas the other products were disappeared because the donating effect of methoxy at R_2-position caused to the lack of immide formation of isoquinolone. Even through, the acid-induced cyclization to form the oxoprotoberberine was effective with non-para activation, the remained isoquinolune substrates **37-39** including **36** could be transformed to protoberberine by the reduction with lithium alluminium hydride in THF, and then

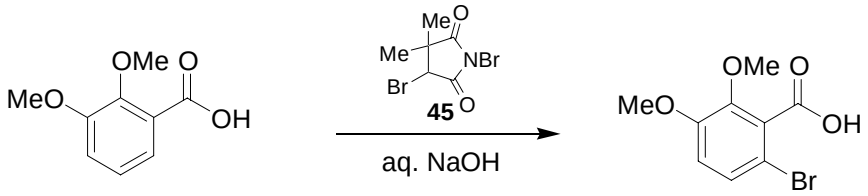
followed with TFA to completely close the ring B to the desired protoberberine **41-43** in high yield **(Scheme 7)**. The reduction of oxoprotoberberine **37** with LAH in THF was also yielded the protoberberine **40** in 98%.

Conclusion

In summary, we have shown that the allyl arylamides prepared from the stille coupling reaction are versatile intermediates for the synthesis either protoberberine or homoprotobebrberine alkaloids. The oxidative cleavage reaction with OsO_4-$NaIO_4$ is suitable performance to create the important aldehyde intermediates. Furthermore, the hydroboration and PCC-oxidation are obtained the different aldehydes without the cleavage of olefin. Conveniently, TFA treatment of both types of aldehyde intermediates affords the final protoberberine, protoberberine or homoprotoberberine in perfect yield.

Experimental

Synthesis of 2-bromo-5,6-dimethoxy benzoic acid (46)



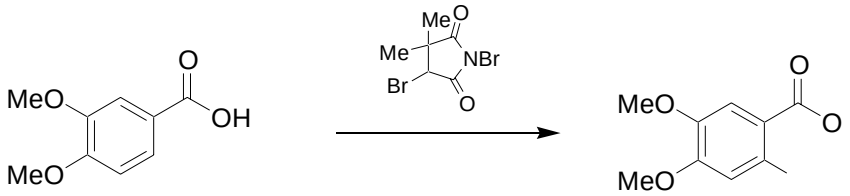
44 **46**

Scheme 8

1g (5.49 mmol) of 2,3-dimethoxy benzoic acid **44** was dissolved in a 0.6M NaOH solution at room temperature until complete dissolution. The solution was

cooled to 0^0 C and 800mg (2.8 mmol) of dibromodimethyl hydantoin **45** was added in portions over 5 min. The solution was allowed to warm to room temperature and stirred for 24h. The reaction was quenched by addition of sodium sulfite and filtered was added to tert- butyl methyl ether (TBME) and the two phase systems acidified to pH 2 (conc. HCl) with rapid stirring. The aqueous layer was extract with TBME and combined organic layer washed with water. Removal of the solvents provided crude 2-bromo-5, 6-dimethoxybenzoic acid **46** 1.40 g, 98% **(Scheme 8).**

Synthesis of 2-bromo-4,5-dimethoxy benzoic acid (48)

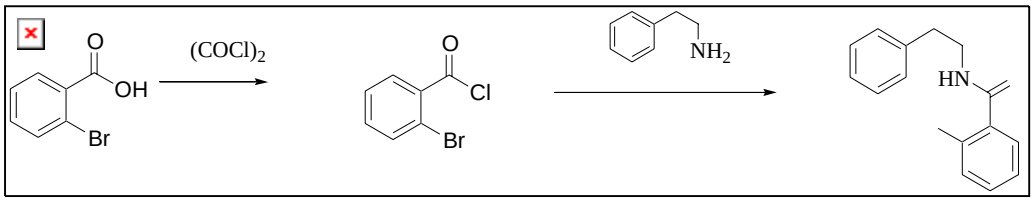


47 **48**

Scheme 9

To follow the previous bromination, (3g, 16.48 mmol) of 3,4-dimethoxybenzoic acid **47** was dissolved in a 0.6 M NaOH solution at room temperature until complete dissolution. Dibromodimethyl hydantoin **33** 2.37 g (8.30 mmol) was added then the reaction was followed the previous condition to give 2-bromo-4,5-dimethoxy benzoic acid **48** 4.0 g, 93% **(Scheme 9).**

The condensation of phenyl ethylamine (8) with 2-bromo benzoyl chloride(10)

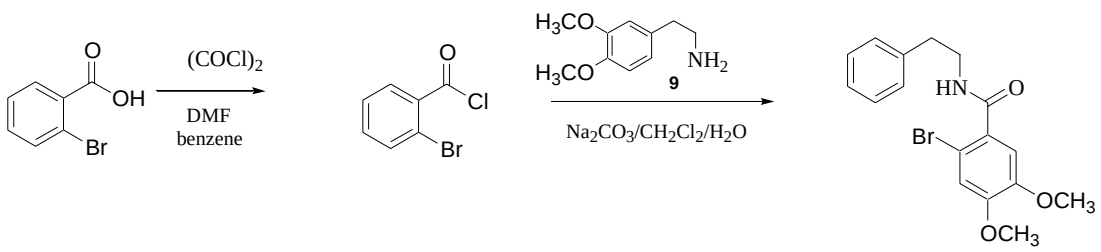


37 **10** **13**

Scheme 10

A solution of 2-bromo benzoic acid **37** (5.01 g, 24.87 mmol), oxalyl chloride (3.80 mL, 44.98 mmol) and dimethylformamide (3 drops) as catalyst in benzene (30 mL) was stirred at room temperature under argon atmosphere for 2 h, then solvent was removed under reduced pressure (aspirator and then *vacuo*) to give acid chloride **10**. The obtained acid chloride **10** in dichloromethane (7 mL) was added to a solution of homoveratrylamine **8** (3.91 g, 32.33 mmol) and sodium carbonate (6.0 g, 56.22 mmol) in dichloromethane : water (5 mL: 1 mL). The resulting solution was stirred at room temperature for 2 h. The crude was purified by column chromatography on silica gel to give bromoamide compound **13** (15.75 g, 87%) as a white solid **(Scheme 10).**

The condensation of phenyl ethylamine (9) with 2-bromo benzoyl chloride (10)

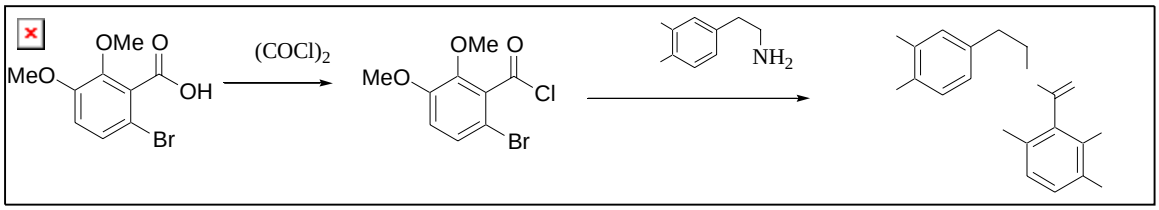


37 **10** **14**

Scheme 11

A solution of 2-bromo benzoic acid **37** (10.00 g, 49.75 mmol), oxalyl chloride (7.60 mL, 89.96 mmol) and dimethylformamide (3 drops) as catalyst in benzene (60 mL) was stirred at room temperature under argon atmosphere for 2 h, then solvent was removed under reduced pressure (aspirator and then *vacuo*) to give acid chloride **10**. The obtained acid chloride **10** in dichloromethane (15 mL) was added to a solution of homoveratrylamine **9** (9.05 g, 50.00 mmol) and sodium carbonate (12.0 g, 112.44 mmol) in dichloromethane : water (5 mL: 1 mL). The resulting solution was stirred at room temperature for 2 h. The crude was purified by column chromatography on silica gel to give bromoamide compound **14** (16.66 g, 92%) as a white solid **(Scheme 11).**

The condensation of homoveratrylamine (9) with 2-bromo-5,6-dimethoxy benzoic acid (11)



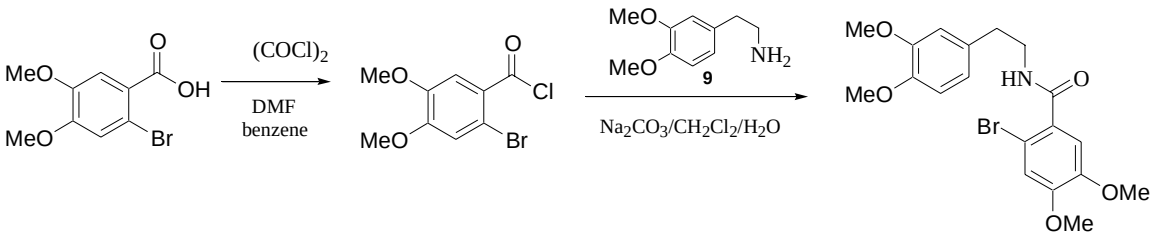
38 **11** **15**

Scheme 12

A solution of 2-bromo-5,6-dimethoxy benzoic acid **38** (4.98 g, 18.74 mmol), oxalyl chloride (1.90 mL, 22.49 mmol) and dimethylformamide (3 drops) as catalyst in benzene (30 mL) was stirred at room temperature under argon atmosphere for 2 h, then solvent was removed under reduced pressure (aspirator and then *vacuo*) to give acid chloride **11**. The obtained acid chloride **11** in dichloromethane (7 mL) was added

to a solution of homoveratrylamine **9** (3.40 g, 18.74 mmol) and sodium carbonate (6.0 g, 56.22 mmol) in dichloromethane : water (5 mL: 1 mL). The resulting solution was stirred at room temperature for 2 h. The crude was purified by column chromatography on silica gel to give bromoamide compound **15** (7.27 g, 81%) as a white solid **(Scheme 12)**.

The condensation of homoveratrylamine (9) with 2-bromo-3,4-dimethoxy benzoic acid (12)



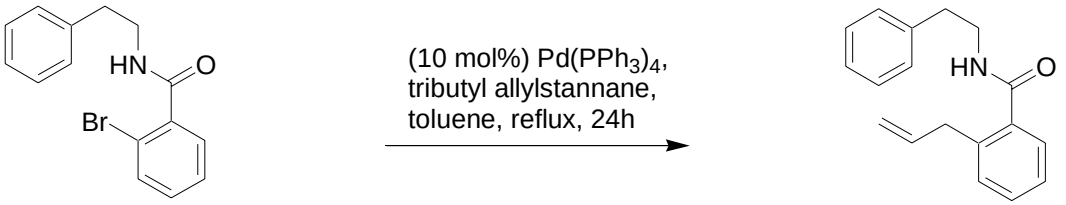
36 **12** **16**

Scheme 13

A solution of 2-bromo-3,4-dimethoxy benzoic acid **36** (2.02 g, 7.67 mmol), oxalyl chloride **12** (0.79 mL, 9.20 mmol) and dimethylformamide (3 drops) as catalyst in benzene (20 mL) was stirred at room temperature under argon atmosphere for 2 h, then solvent was removed under reduced pressure (aspirator and then *vacuo*) to give acid chloride **12**. The obtained acid chloride **12** in dichloromethane (20 mL) was added to a solution of homoveratrylamine **9** (1.67 g, 9.20 mmol) and sodium carbonate (2.4 g, 23.00 mmol) in dichloromethane : water (5 mL: 1 mL). The resulting solution was stirred at room temperature for 2 h. The crude was purified by

column chromatography on silica gel to give bromoamide compound **16** (2.82 g, 87%) as a white solid **(Scheme 13).**

Allyl amide (17)

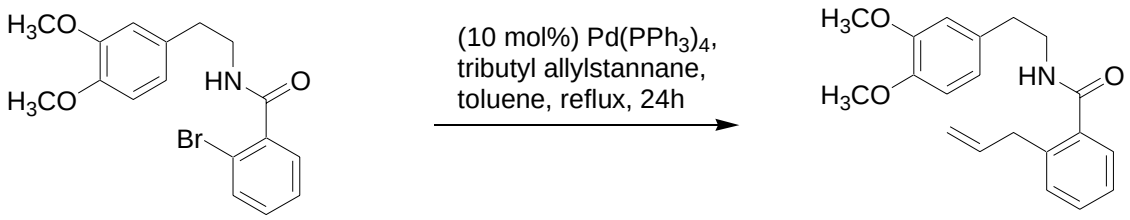


13 **17**

Scheme 14

Tetrakistriphenylphosphinepalladium 20 mg and tributyl allylstannane (2.54 mL, 8.28 mmol) were added to a stirred suspension of bromoamide **13** (2.01 g, 6.90 mmol) in dry toluene (15 mL) under argon atmosphere. The mixture was refluxed for 12 h. The solution was cooled to room temperature and saturated aqueous potassium fluoride (10 mL) was added and stirred for 15 min. The reaction mixture was filtered through celite. The filtrate was extracted with dichloromethane (3x20 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to dryness. The residue was purified by preparative thin layer chromatography on silica gel (40% ethyl acetate-hexane as a developing solvent) to give allyl amide **17** (1.46 g, 82%, **scheme 14**).

Allyl amide (18)

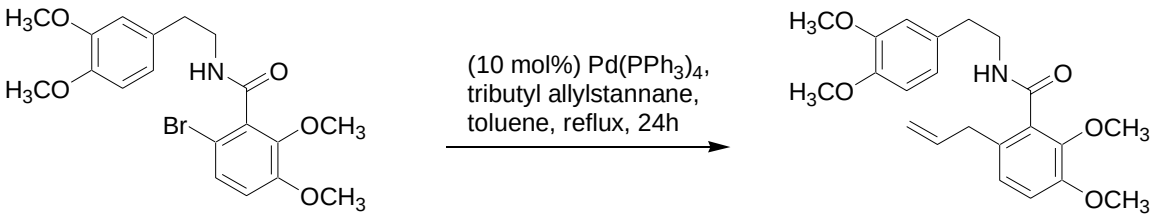


14 **18**

Scheme 15

Tetrakistriphenylphosphinepalladium 10 mg and tributyl allylstannane (0.92 mL, 3.01 mmol) were added to a stirred suspension of bromoamide **14** (1.0 g, 2.74 mmol) in dry toluene (10 mL) under argon atmosphere. The mixture was refluxed for 12 h. The solution was cooled to room temperature and saturated aqueous potassium fluoride (10 mL) was added and stirred for 15 min. The reaction mixture was filtered through celite. The filtrate was extracted with dichloromethane (3x10 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to dryness. The residue was purified by preparative thin layer chromatography on silica gel (50% ethyl acetate-hexane as a developing solvent) to give allyl amide **18** (765 mg, 86%, **scheme 15**).

Allyl amide (19)

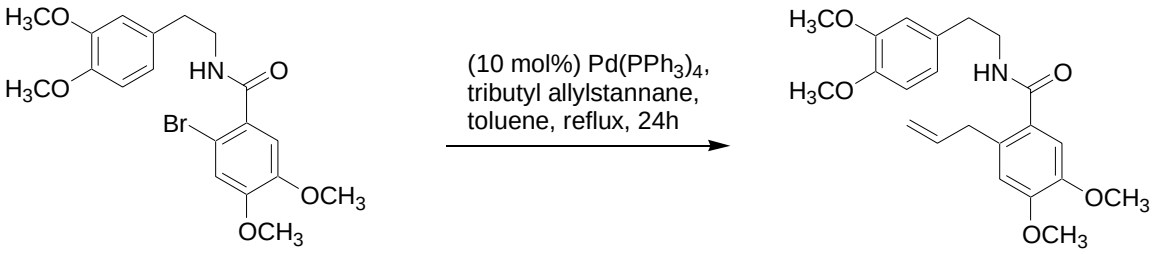


15 **19**

Scheme 16

Tetrakistriphenylphosphinepalladium 10 mg and tributyl allylstannane (0.10 mL, 0.31 mmol) were added to a stirred suspension of bromoamide **15** (100 mg, 0.24 mmol) in dry toluene (6 mL) under argon atmosphere. The mixture was refluxed for 12 h. The solution was cooled to room temperature and saturated aqueous potassium fluoride (10 mL) was added and stirred for 15 min. The reaction mixture was filtered through celite. The filtrate was extracted with dichloromethane (3x15 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to dryness. The residue was purified by preparative thin layer chromatography on silica gel (60% ethyl acetate-hexane as a developing solvent) to give allyl amide **19** (79 mg, 85%, **scheme 16**).

Allyl amide (20)

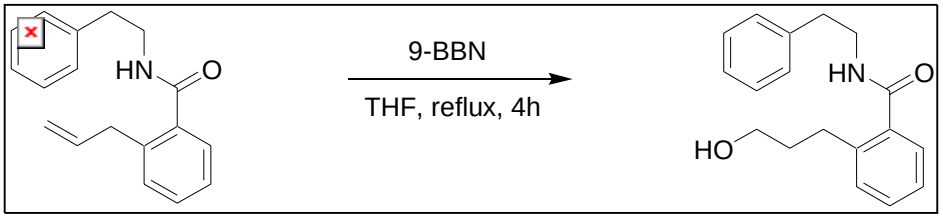


16 **20**

Scheme 17

Tetrakistriphenylphosphinepalladium 10 mg and tributyl allylstannane (0.10 mL, 0.31 mmol) were added to a stirred suspension of bromoamide **16** (100 mg, 0.24 mmol) in dry toluene (6 mL) under argon atmosphere. The mixture was refluxed for 12 h. The solution was cooled to room temperature and saturated aqueous potassium fluoride (10 mL) was added and stirred for 15 min. The reaction mixture was filtered through celite. The filtrate was extracted with dichloromethane (3x15 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to dryness. The residue was purified by preparative thin layer chromatography on silica gel (70% ethyl acetate-hexane as a developing solvent) to give allyl amide **20** (79 mg, 85%, **scheme 17**).

Hydroboration of allyl amide (17)

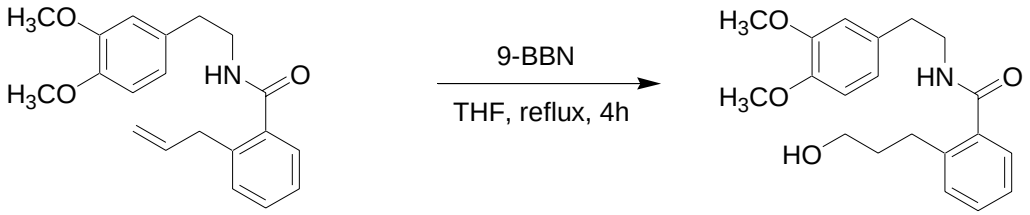


17 **21**

Scheme 18

To a solution of 9-BBN (439 mg, 3.60 mmol) in dry THF (10 mL) was added to a solution of allylamide **17** (500 mg, 1.89 mmol) in dry THF at room temperature under argon atmosphere. The reaction mixture was then refluxed for 12 h, quenched with NaOH (200 mg, 5.0 mmol), followed with addition of 37% H_2O_2 (2mL). The reaction mixture was stirred for 30 min at room temperature. The solution was further extracted with dichloromethane (3x25 mL), then washed with water (20 ml), dried over anhydrous sodium sulfate and evaporated to dryness in *vacuo*. The crude product was purified by PLC on silica gel using 60% ethyl acetate-hexane as developing solvent to give hydroxyl compound **21** (438 mg, 82%, **scheme 18**).

Hydroboration of allyl amide (18)

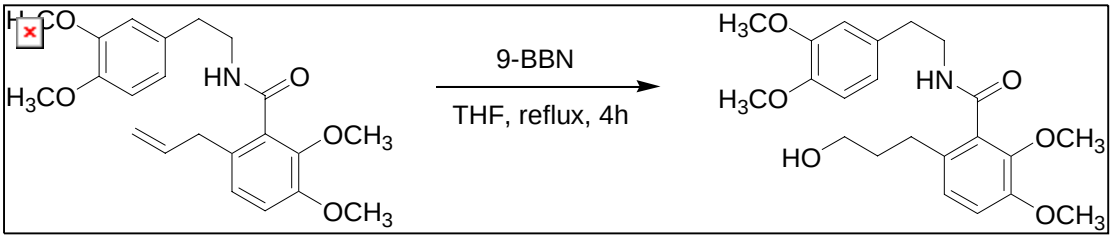


18 **22**

Scheme 19

To a solution of 9-BBN (525 mg, 4.30 mmol) in dry THF (10 mL) was added to a solution of allylamide **18** (700 mg, 2.15 mmol) in dry THF at room temperature under argon atmosphere. The reaction mixture was then refluxed for 12 h, quenched with NaOH (206 mg, 5.15 mmol), followed with addition of 37% H_2O_2 (2 mL). The reaction mixture was stirred for 30 min at room temperature. The solution was further extracted with dichloromethane (3x25 mL), then washed with water (20 ml), dried over anhydrous sodium sulfate and evaporated to dryness in *vacuo*. The crude product was purified by PLC on silica gel using 80% ethyl acetate-hexane as developing solvent to give hydroxyl compound **22** (649 mg, 88%, **scheme 19**).

Hydroboration of allyl amide (19)



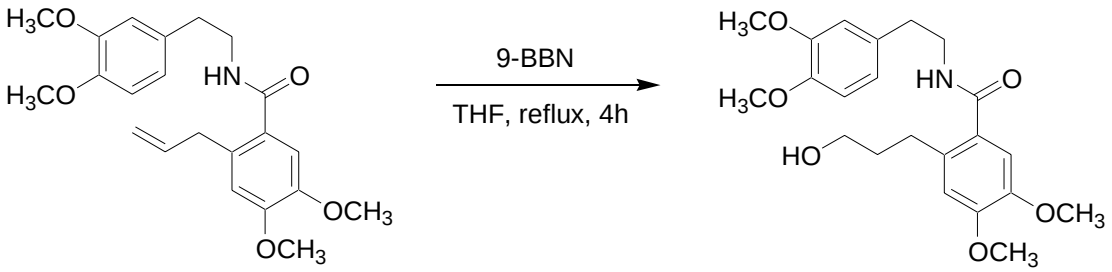
19 **23**

Scheme 20

To a solution of 9-BBN (381 mg, 3.12 mmol) in dry THF (10 mL) was added to a solution of allylamide **19** (600 mg, 1.56 mmol) in dry THF at room temperature under argon atmosphere. The reaction mixture was then refluxed for 12 h, quenched with NaOH (200 mg, 0.5 mmol), followed with addition of 37% H_2O_2 (2mL). The reaction mixture was stirred for 30 min at room temperature. The solution was further extracted with dichloromethane (3x25 mL), then washed with water (20 ml), dried over anhydrous sodium sulfate and evaporated to dryness in *vacuo*. The crude product

was purified by PLC on silica gel using 80% ethyl acetate-hexane as developing solvent to give hydroxyl compound **23** (503 mg, 80%, **scheme 20**).

Hydroboration of allyl amide (20)

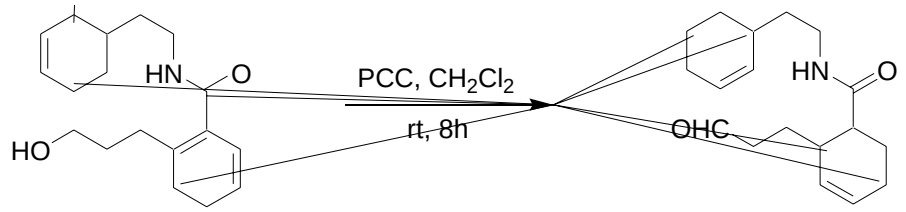


20 **24**

Scheme 21

To a solution of 9-BBN (349 mg, 2.86 mmol) in dry THF (10 mL) was added to a solution of allylamide **20** (550 mg, 1.43 mmol) in dry THF at room temperature under argon atmosphere. The reaction mixture was then refluxed for 12 h, quenched with NaOH (200 mg, 0.5 mmol), followed with addition of 37% H_2O_2 (2mL). The reaction mixture was stirred for 30 min at room temperature. The solution was further extracted with dichloromethane (3x25 mL), then washed with water (20 ml), dried over anhydrous sodium sulfate and evaporated to dryness in *vacuo*. The crude product was purified by PLC on silica gel using 80% ethyl acetate-hexane as developing solvent to give hydroxyl amide 24 (478 mg, 83%, **scheme 21**).

Preparation of aldehyde derivative (25)



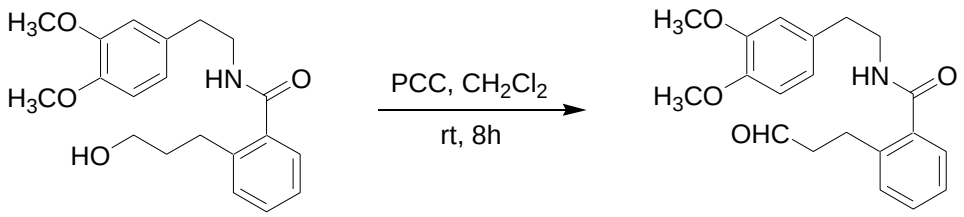
21 **25**

Scheme 22

A solution of hydroxyl amide **21** (250 mg, 0.88 mmol) in dry dichloromethane (20 ml) was added to a suspension of pyridinium chlorochromate, PCC, (247 mg, 1.14 mmol) and then stirred for 4h at room temperature. The mixture became homogeneous and the formed a smeary black precipitate.

The solution was decanted from the black residue and the flask was rinsed three times with ether. The combined organic phases were column filtered through coarse silica gel. The column is rinsed with 100 mL of ether. The ether solution was washed with 2M HCl (3 mL), saturated $NaHCO_3$ (10 mL) and NaCl (10 mL) solutions, dried over Na_2SO_4 and evaporated. The crude product was purified by PLC on silica gel using 30% ethyl acetate-hexane as developing solvent to give hydroxyl amide **25** (170 mg, 69%, **scheme 22**).

Preparation of aldehyde derivative (26)



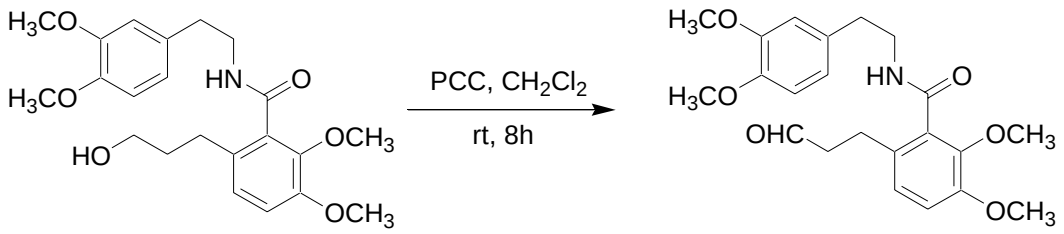
22 **26**

Scheme 23

A solution of hydroxyl amide **22** (100 mg, 0.29 mmol) in dry dichloromethane (10 ml) was added to a suspension of pyridinium chlorochromate, PCC, (76 mg, 0.35 mmol) and then stirred for 4h at room temperature. The mixture became homogeneous and the formed a smeary black precipitate.

The solution was decanted from the black residue and the flask was rinsed three times with ether. The combined organic phases were column filtered through coarse silica gel. The column is rinsed with 50 mL of ether. The ether solution was washed with 2M HCl (3 mL), saturated $NaHCO_3$ (10 mL) and NaCl (10 mL) solutions, dried over Na_2SO_4 and evaporated. The crude product was purified by PLC on silica gel using 30% ethyl acetate-hexane as developing solvent to give hydroxyl amide **26** (170 mg, 69%, **scheme 23**).

Preparation of aldehyde derivative (27)



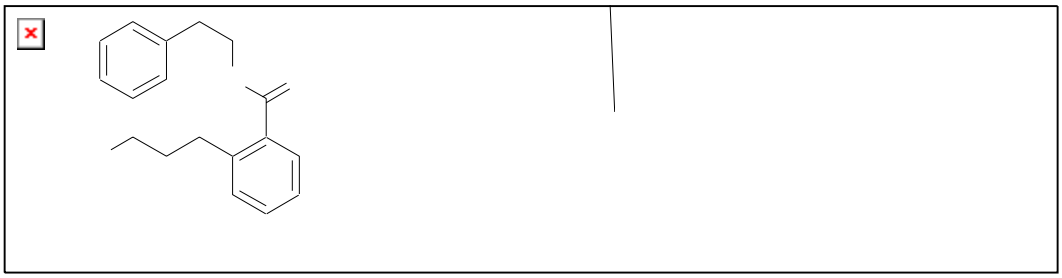
23 **27**

Scheme 24

A solution of hydroxyl amide **23** (100 mg, 0.25 mmol) in dry dichloromethane (10 ml) was added to a suspension of pyridinium chlorochromate, PCC, (81 mg, 0.38 mmol) and then stirred for 4h at room temperature. The mixture became homogeneous and the formed a smeary black precipitate.

The solution was decanted from the black residue and the flask was rinsed three times with ether. The combined organic phases were column filtered through coarse silica gel. The column is rinsed with 50 mL of ether. The ether solution was washed with 2M HCl (3 mL), saturated $NaHCO_3$ (10 mL) and NaCl (10 mL) solutions, dried over Na_2SO_4 and evaporated. The crude product was purified by PLC on silica gel using 80% ethyl acetate-hexane as developing solvent to give hydroxyl amide **27** (71 mg, 71%, **scheme 24**).

Preparation of aldehyde derivative (28)



24 **28**

Scheme 25

A solution of hydroxyl amide **24** (200 mg, 0.50 mmol) in dry dichloromethane (20 ml) was added to a suspension of pyridinium chlorochromate, PCC, (130 mg, 0.60 mmol) and then stirred for 4h at room temperature. The mixture became homogeneous and the formed a smeary black precipitate.

The solution was decanted from the black residue and the flask was rinsed three times with ether. The combined organic phases were column filtered through coarse silica gel. The column is rinsed with 100 mL of ether. The ether solution was washed with 2M HCl (5 mL), saturated $NaHCO_3$ (15 mL) and NaCl (15 mL) solutions, dried over Na_2SO_4 and evaporated. The crude product was purified by PLC on silica gel using 90% ethyl acetate-hexane as developing solvent to give hydroxyl amide **28** (150 mg, 75%, **scheme 25**).

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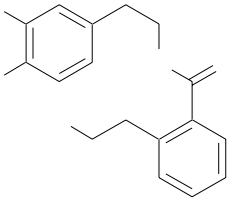
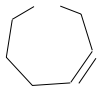
Preparation of oxohomoprotoberberine (29)



26

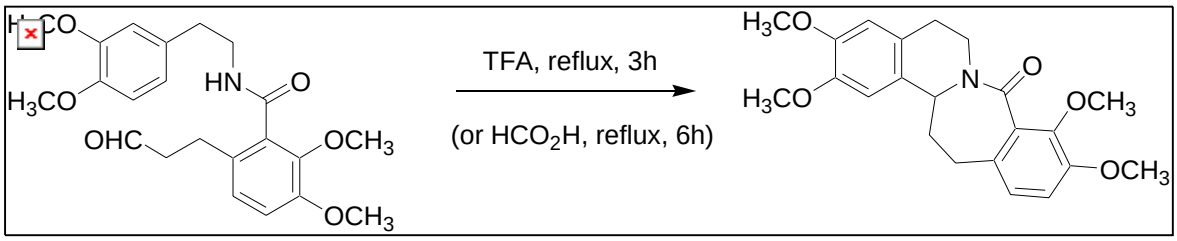


29

Scheme 26

A mixture of aldehyde derivative **26** (60 mg, 0.25 mmol) and trifluoroacetic acid (3 mL) or formic acid (3 mL) was refluxed for 12 h. After cooling the reaction mixture, water was added then extracted with dichloromethane (3x15 mL). The organic layer was dried over anhydrous sodium sulfate, and then removed off solvent *in vacuo* to give crude product. Purification by preparative thin layer chromatography (70% ethyl acetate-hexane as developing solvent) followed by recrystallization from ethyl acetate-hexane yielded pure oxohomoprotoberberine **29** (76 mg, 94% and 94% with formoc acid **scheme 26**).

Preparation of oxohomoprotoberberine (30)

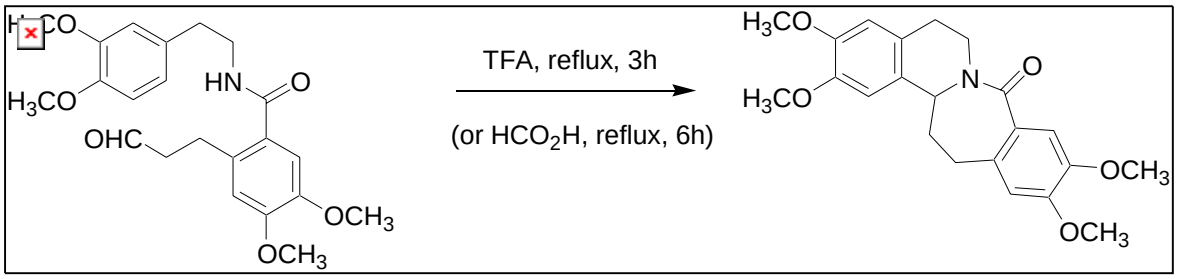


27 **30**

Scheme 27

A mixture of aldehyde derivative **27** (30 mg, 0.075 mmol) and trifluoroacetic acid (2 mL) or formic acid (2 mL) was refluxed for 12 h. After cooling the reaction mixture, water was added then extracted with dichloromethane (3x10 mL). The organic layer was dried over anhydrous sodium sulfate, and then removed off solvent *in vacuo* to give crude product. Purification by preparative thin layer chromatography (70% ethyl acetate-hexane as developing solvent) followed by recrystallization from ethyl acetate-hexane yielded pure oxohomoprotoberberine **30** (26 mg, 90% and 90% with formic acid **scheme 27**).

Preparation of oxohomoprotoberberine (31)

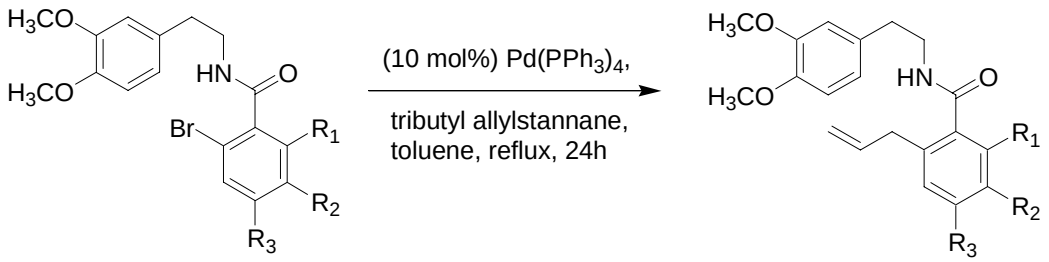


28 **31**

Scheme 28

A mixture of aldehyde derivative **28** (20 mg, 0.05 mmol) and trifluoroacetic acid (2 mL) or formic acid (2 mL) was refluxed for 12 h. After cooling the reaction mixture, water was added then extracted with dichloromethane (3x10 mL). The organic layer was dried over anhydrous sodium sulfate, then removed off solvent *in vacuo* to give crude product. Purification by preparative thin layer chromatography (60% ethyl acetate-hexane as developing solvent) followed by recrystallization from ethyl acetate-hexane yielded pure oxohomoprotoberberine **31** (20 mg, 94%, and 93% with formic acid **scheme 28**).

Preparation Of Allyl arylamide 17-20



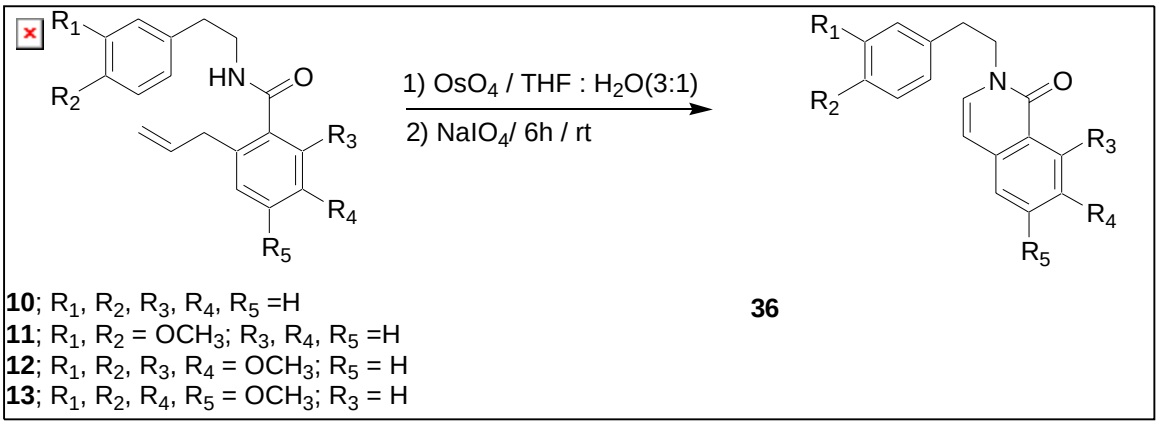
13; R_1, R_2, R_3, R_4, R_5 =H
14; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H
15; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H
16; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H

17; R_1, R_2, R_3, R_4, R_5 =H
18; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H
19; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H
20; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H

Scheme 29

General procedure for the preparation of **17-20**: Tetrakistriphenylphosphinepalladium (10 mol %) and tributyl allylstannane (0.31 mmol) were added to a stirred suspension of bromoamide **13-16** (0.24 mmol) in dry toluene (6 mL) under argon atmosphere. The mixture was refluxed for 24 h. The solution was cooled to room temperature and saturated aqueous potassium fluoride (10 mL) was added and stirred for 15 min. The reaction mixture was filtered through celite. The filtrate was extracted with dichloromethane (3x15 mL). The combined organic extracts were washed with water (20 mL) and saturated aqueous sodium chloride (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to dryness. The residue was purified by preparative thin layer chromatography on silica gel to give allyl arylamide **17-20(Scheme 29)**.

Oxidative cleavage of allyl arylamide 17-20



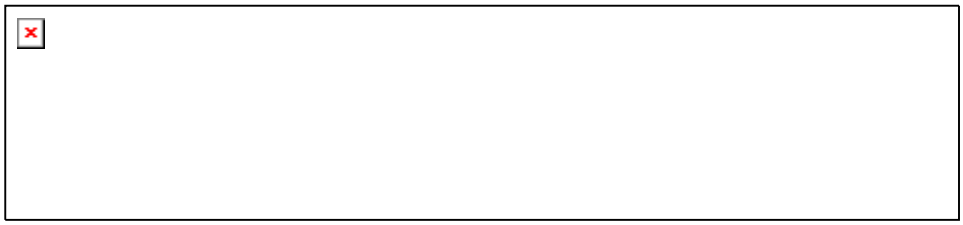
10; R_1, R_2, R_3, R_4, R_5 =H
11; R_1, R_2 = OCH_3; R_3, R_4, R_5 =H
12; R_1, R_2, R_3, R_4 = OCH_3; R_5 = H
13; R_1, R_2, R_4, R_5 = OCH_3; R_3 = H

36

Scheme 30

General procedure for the preparation of **36-39**: to a solution of allyl arylamide **10-13** (0.3 mmol) in a mixture of tetrahydrofuran and water (5 mL, 4:1) was added osmium tetraoxide (0.1 mL, 4% in water), and the resulting mixture turned from light tan to black within 10 min. At this point, $NaIO_4$ (1.2 mmol) was added, and the resulting solution was then stirred for 6h at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to give desired products, isoquinolone derivatives **36-39 (Scheme 30)**.

Acid-induced cyclization to 8-oxoprotoberberine (40)

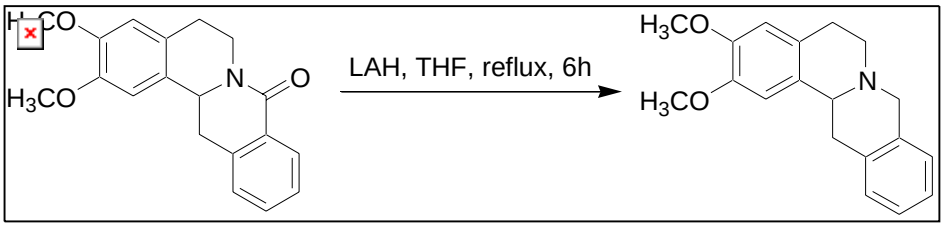


37 **40**

Scheme 31

To a solution of isoquinolone derivative **37** (18 mg, 0.058 mmol) in trifluoroacetic acid (2 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL). The combined organic extracts were washed with distilled water (2x10 mL), saturated aqueous sodium carbonate (10 mL), and saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to dryness to give crude product. Recrystallization from ethyl acetate-hexane afforded 8-oxoprotoberberine **40** in 14 mg (76%) **(Scheme 31)**.

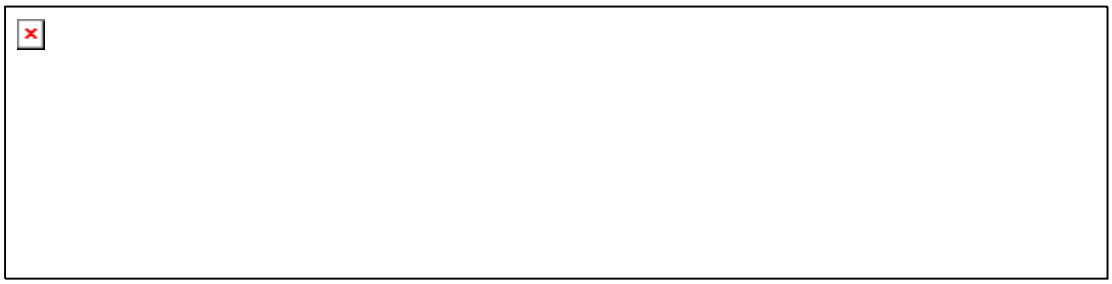
Reduction of 8-oxoprotoberberine (40) to protoberberine (41)



Scheme 32

To a solution of 8-oxoprotoberberine **40** (22 mg, 0.017 mmol) in dry tetrahydrofuran (3 mL) was slowly added to a stirred suspension of lithium aluminium hydride (11 mg, 0.28 mmol) in dry tetrahydrofuran (5 mL) cooled in an ice bath under argon atmosphere. The reaction mixture was kept in the ice bath during the addition and left stirring at room temperature for about 6 h. Water was slowly added dropwise to the ice cold mixture to destroy an excess lithium aluminium hydride. The precipitate was filtered and washed with dichloromethane. The combined filtrate was washed with water, saturated sodium chloride, dried over anhydrous sodium sulfate. Removal of solvent *in vacuo* gave crude protobebrberine. Recrystallization from ethyl acetate-hexane afforded protoberberine **41** in 19 mg (89%) **(Scheme 32).**

Synthesis of protoberberine (40)



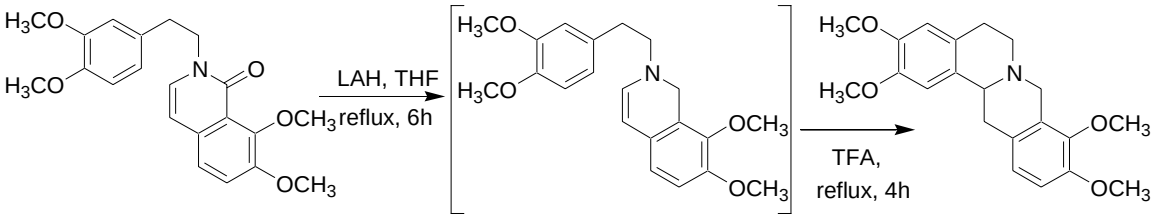
37 **37a** **40**

Scheme 33

To a solution of 8-oxoprotoberberine **37** (80 mg, 0.26 mmol) in dry tetrahydrofuran (3 mL) was slowly added to a stirred suspension of lithium aluminium hydride (39 mg, 1.04) in dry tetrahydrofuran (10 mL) cooled in an ice bath under argon atmosphere. The reaction mixture was kept in the ice bath during the addition

and left stirring at room temperature for about 6 h. Water was slowly added dropwise to the ice cold mixture to destroy an excess lithium aluminium hydride. The precipitate was filtered and washed with dichloromethane. The combined filtrate was washed with water, saturated sodium chloride, dried over anhydrous sodium sulfate. Removal of solvent *in vacuo* gave crude **37a**. Then, the crude product **37a** was treated with trifluoroacetic acid (2 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL). The combined organic extracts were washed with distilled water (10 mL), saturated aqueous sodium carbonate (10 mL), and saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to dryness to give crude product. Recrystallization from ethyl acetate-hexane afforded the prtoberberine **40** (61 mg, 80%) **(Scheme 33).**

Synthesis of protoberberine (41)



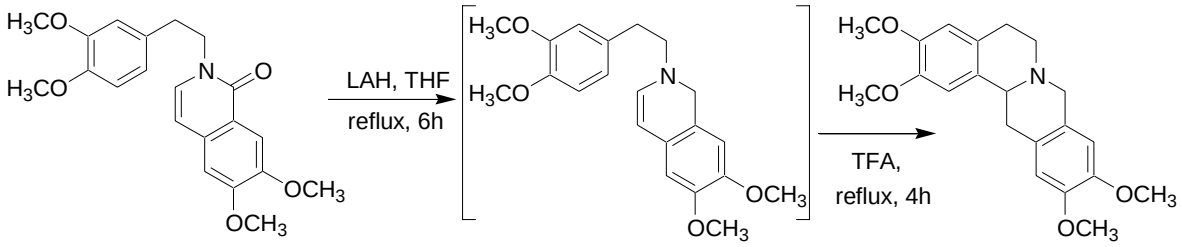
38 **38a** **41**

Scheme 34

To a solution of 8-oxoprotoberberine **38** (74 mg, 0.20 mmol) in dry tetrahydrofuran (3 mL) was slowly added to a stirred suspension of lithium aluminium hydride (31 mg, 0.80 mmol) in dry tetrahydrofuran (10 mL) cooled in an ice bath

under argon atmosphere. The reaction mixture was kept in the ice bath during the addition and left stirring at room temperature for about 6 h. Water was slowly added dropwise to the ice cold mixture to destroy an excess lithium aluminium hydride. The precipitate was filtered and washed with dichloromethane. The combined filtrate was washed with water, saturated sodium chloride, dried over anhydrous sodium sulfate. Removal of solvent *in vacuo* gave crude **38a**. Then, the crude product **38a** was treated with trifluoroacetic acid (2 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL). The combined organic extracts were washed with distilled water (10 mL), saturated aqueous sodium carbonate (10 mL), and saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to dryness to give crude product. Recrystallization from ethyl acetate-hexane afforded the prtoberberine **41** (50 mg, 71%) **(Scheme 34).**

Synthesis of protoberberine (42)



98 **39a** **42**

Scheme 35

To a solution of 8-oxoprotoberberine **39** (97 mg, 0.26 mmol) in dry tetrahydrofuran (3 mL) was slowly added to a stirred suspension of lithium aluminium hydride (40 mg, 1.05 mmol) in dry tetrahydrofuran (10 mL) cooled in an ice bath

under argon atmosphere. The reaction mixture was kept in the ice bath during the addition and left stirring at room temperature for about 6 h. Water was slowly added dropwise to the ice cold mixture to destroy an excess lithium aluminium hydride. The precipitate was filtered and washed with dichloromethane. The combined filtrate was washed with water, saturated sodium chloride, dried over anhydrous sodium sulfate. Removal of solvent *in vacuo* gave crude **39a**. Then, the crude product **39a** was treated with trifluoroacetic acid (2 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (10 mL). The combined organic extracts were washed with distilled water (10 mL), saturated aqueous sodium carbonate (10 mL), and saturated aqueous sodium chloride. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to dryness to give crude product. Recrystallization from ethyl acetate-hexane afforded the prtoberberine **42** (82 mg, 89%) **(Scheme 35).**

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Out put จากโครงการที่ได้รับทุนจาก สกว.

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ

อยู่ในระหว่างขั้นตอนการจัดทำ

2. การนำผลงานวิจัยไปใช้ประโยชน์

- เชิงสาธารณะ ได้มีเครือข่ายความร่วมมือในการทำงานวิจัยกับ Nagoya University, Japan

3. การเสนอผลงานในที่ประชุมวิชาการ

3.1 การประชุมนักวิจัยรุ่นใหม่พบเมธีวิจัยอาวุโส สกว. วันที่ 13-15 ตุลาคม 2548 ณ โรงแรมรีเจนท์ ชะอำ จ.เพชรบุรี ในหัวข้อ “Effienct Synthesis of Protoberberines and Homoprotoberberines”

3.2 การประชุมวิชาการครั้งที่ 5 สถาบันวิจัยและพัฒนาวิทยาศาสตร์และเทคโนโลยี ม. มหิดล วันที่ 30 พ.ย. -1 ธ.ค. 2548 ณ หอประชุมณัฐ ภมรประวัติ อาคารสถาบันพัฒนาการสาธารณสุขอาเซียน ม.มหิดล ศาลายา ในหัวข้อ “Effienct Synthesis of Protoberberines and Homoprotoberberines”

3.3 IUPAC International conference on biodiversity and natural products: Chemistry and Medical Applications (ICOB-4 & ISCNP – 24) January 26-31, 2004, New Delhi (India) ในหัวข้อ “Synthesis of Protoberberine Alkaloids via Latheral Lithiation and Heck Reaction”

3.4 Chemistry Biology Interface: Synergistic New Frontiers (CBISNF 2004), November 21-26, 2004, New Delhi (India) ในหัวข้อ “Synthesis of Indolonaphthyridine and Indolopyridonaphthyridine Alkaloids via Latheral Lithiation”