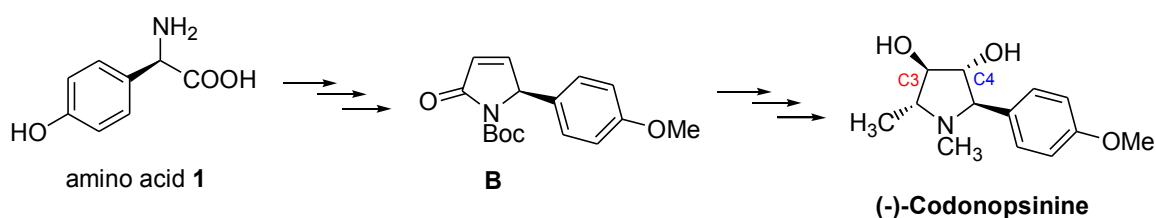


STUDIES TOWARDS THE TOTAL SYNTHESIS OF (-)- CODONOPSININE, AN ANTI-HYPERTENSIVE COMPOUND FROM *Codonopsis clematidae*

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ABSTRACT

In this study (-)-codonopsinine was chosen as our synthetic target molecule due to its unique *trans* pentasubstituted pyrrolidine structure as well as remarkable antibiotic and hypotensive activity. Our synthetic approach towards total synthesis of codonopsinine requires an appropriate diketo pyrrolidinone ring template, formed by Dieckmann cyclization of an intermediate diester which provided the β,β -diketo pyrrolidinone. Performing series of successive functional group modification on the ring template, which include demethoxycarbonylation, keto reduction, *O*-protection and β -elimination, successfully furnished us an important intermediate of unsaturated lactam **B** in 9 steps towards total synthesis of (-)-codonopsinine with an overall yield of 18%.

KEYWORDS: Alkaloids, anti-hypotensive, pyrrolidine, Dieckmann cyclization

INTRODUCTION

Azasugars, or polyhydroxylated alkaloids are low molecular-weight compounds isolated from plants or microorganisms and considered to have high potential therapeutic values due to their glucosidase inhibition properties. Polyhydroxylated alkaloid structures containing at least two hydroxyl groups and one heterocyclic nitrogen atom may be mono or bicyclic and represented by rings consisting of four (azetidene), five (pyrrolidine), six (piperidine) atoms, or fused ring systems (pyrrolizidine, indolizidine) built up from the above monocycles. Among the naturally occurring polyhydroxylated alkaloids, hydroxy-pyrrolidine in particular has been one of the subjects of extensive research for decades. Besides having outstanding medicinal properties, hydroxy-pyrrolidine has important

structural motifs in many naturally occurring biologically active include (-)-codonopsinine.

(-)-Codonopsinine is a complex hydroxy pyrrolidine alkaloid, isolated by a Russian group from a plant *Codonopsis clematidae* in 1969. This compound exhibits antibiotic and hypotensive activities without affecting the central nervous system observed in animal testing. After structural characterization, codonopsinine was revealed as a new class of pyrrolidine alkaloid possessing 1,2,3,4,5-*penta*substituted structure and carrying an aromatic substituent on the ring. Such alkaloid is very rare in nature.

The total synthesis of codonopsinine has always been the interests of many synthetic chemists not only because of its significant biological activities, but also because of its synthetic challenges since all its 1,2,3,4,5-*penta*substituted pyrrolidine nuclei are *trans* relative to each other. For the reasons described above, (-)-codonopsinine was chosen as our synthetic target molecule. Thus, the objectives of this study are given as follows:

- (1) To develop simple, flexible and stereocontrolled synthesis of (-)-codonopsinine and its derivatives.
- (2) To explore some chemical transformations of the synthesized intermediates.

RESULTS AND DISCUSSION

Our initial synthetic methodology towards the total synthesis of codonopsinine began with the esterification of amino acid **1** using thionyl chloride in methanol. This esterification reaction proceeded by the conversion of the acid functionality **1** to an acyl chloride which then reacted with methanol *in situ* to give the hydroxy phenyl glycine methyl ester as the product at a nearly quantitative yield. Subsequent amino group protection of the resulted methyl ester product using Boc anhydride, Et₃N in THF gave the required *N*-Boc product in high yield.

With the *N*-Boc protected compound in hand, our next chemical transformation was the etherification of the hydroxy phenol functionality. This reaction was carried out by employing K₂CO₃, MeI and DMF as the solvent at room temperature for 8 hours. Following purification gave the methyl ether compound in an excellent yield. Related transformation proceeded through the formation of the corresponding alkoxide anion of the phenol which then attacked the electrophilic MeI to give the ether product. With all the initial conversion reactions completed, we proceeded to the next step of condensation reaction. This attempt toward installation of the β,β-diketo ester functionality to the *N*-amide site was prove to be very troublesome. Nevertheless, by refluxing the *N*-amide compound with methyl malonyl chloride in anhydrous benzene finally furnished us the condensation product of the *N*-Boc carbamate compound in quantitative yield before proceeding to the Dieckmann cyclization.

Dieckmann cyclization is an intramolecular Claisen reaction which commonly carried out under thermodynamic conditions, although kinetic control can also be used to form stable five- or six-membered cyclic enone. These ring sizes are preferred over strained three- or four-membered ring. Initially, we proceeded the Dieckmann cyclization of the *N*-Boc carbamate compound using sodium methoxide as the base, *in situ* generated from sodium metal and anhydrous methanol, in refluxing toluene. This gave us the deprotected β,β -diketoester pyrrolidinone ring template, but in a very poor yield of 1.5%. Interestingly, changing the base to non-nucleophilic of NaH also led to similar poor results. However, by performing the cyclization using *t*BuOK as the base and anhydrous toluene as the solvent at room temperature finally gave us the β,β -diketoester pyrrolidinone ring template in moderate yield of 61%.

Having prepared the β,β -diketoester ring template, we then attempted to remove the methyl ester group or decarboxylation reaction at the *C*-3 position before proceeding with the reduction of carbonyl at the *C*-4 position. Decarboxylation, which involves 1,3-elimination reaction, is an ester-functionality removal reaction commonly employed onto cyclic and acyclic β -keto acids, β -carboxyl esters and 1,3 diacids. This will lead to the corresponding products of ketone which is commonly done by thermal decarboxylation in acidic or basic condition. Another interesting decarboxylation method was also reported by Heinicke which involved refluxing the substrate in acetonitrile.

Following Heinicke's protocol we managed to perform the decarboxylation of our β,β -diketoester pyrrolidinone by refluxing the compound in acetonitrile for 6 hours to yield the decarboxylated product of diketo pyrrolidinone in quantitative yield. An attempt to optimize the decarboxylation reaction by refluxing the β,β -diketoester pyrrolidinone under acidic acetonitrile managed to reduce the amount of solvent used and reaction time needed to complete the chemical conversion. Following the decarboxylation, the diketo compound was then subjected to carbonyl reduction at the *C*-4 position using NaBH₄ in methanol at 0°C. This gave us the unexpected stereoselective reduced product of hydroxyl pyrrolidone in moderate yield of 80%. The reduced compound allegedly to be *cis*-enantiomer as shown by the single X-ray crystallography result.

With the reduced compound available in good yield, the next step in our synthesis involved successive *OH*-protection-elimination reaction strategy towards the targeted unsaturated lactam. This strategy was successfully demonstrated by Schmidt *et al.* during the synthesis of *syn*-Statin. Employing excess of Boc and DMAP to the hydroxyl pyrrolidone protection successfully furnished us the *di*-protected of *O*-Boc/*N*-Boc compound in 80% yield. With such compound in hand we then proceeded to the subsequent elimination reaction.

Finally, by treating the *di*-protected compound with cesium carbonate (Cs₂CO₃) as a base furnished us the unsaturated lactam **B** at a reasonable yield of 45%. The proposed mechanism involved the *O*-Boc functionality as a labile nucleofuge during the elimination reaction upon abstraction of the acidic *C*-3 proton. At this stage we had in hand the most advanced intermediate of unsaturated lactam **B** in nine steps with an overall yield of 18% on a gram scale towards total synthesis of (-)-codonopsinine.

Three key chemical transformations are yet to be explored which include epoxidation of the unsaturated lactam **B**, Grignard reaction for installing the methyl at the C-2 position, followed by *N*-Boc reduction to obtain the *N*-Me functionality. All these transformations are well established and were reported by Celebrese, Yoda and Correia accordingly.

CONCLUSION

In summary, an essential intermediate of unsaturated lactam **B** towards the total synthesis of (-)-codonopsinine was synthesized in the best pathway of nine steps with an overall yield of 18% on a gram scale

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REFERENCES

1. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. (2001). *Phytochemistry*, **56**, 265-295.
2. Matkhalikova, S. F.; Malikov, V. M.; Yunosov, S. Y.(1969). *Khim. Prir. Soedin*, **5**, 30-32.
3. Heinicke, G. W.; Morella, A. M.; Orban, J.; Prager, R. H; Ward, A.D.(1985). *Aust. J. Chem.*, **38**(12), 1847-1856.
4. Mohammat, M. F.; Shaameri, Z.; Hamzah, A. S.; Kamarulzaman, N.; Fun, H. K.; Chantrapromma, S.(2008). *Acta. Cryst. E.*, **E64**, o578-o579.
5. Mohammat, M. F.; Shaameri, Z.; Hamzah, A. S.; Fun, H. K.; Chantrapromma, S. (2008). *Acta. Cryst. E.*, **E64**, o661-o662.
6. Mohammat, M. F.; Shaameri, Z.; Hamzah, A. S.; Kamarulzaman, N.; Fun, H. K.; Chantrapromma, S.(2008). *Acta. Cryst. E.*, **E64**, o663-o664
7. Mohammat, M. F.; Shaameri, Z.; Hamzah, A.S.(2009). *Molecules*, **14**, 250-256.
8. Schmidt, U.; Riedl, B.; Haas, G.; Griesser, H.; Vetter, A.; Weinbrenner, S.(1992). *Synthesis*, 216-220.
9. Yoda, H.; Nakajima, T.; Takabe, K.(1996). *Tetrahedron Lett.*, **37**, 5531-5534
10. Wang, C.-L. J.; Calabrese, J.C.(1991). *J.Org.Chem.*, **56**, 4341-4343.
11. Oliveira, D. F.; Severino, E. A.; Correia, C. R. D.(1999). *Tetrahedron Lett.*, **40**, 2083-2086