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Heck Reaction of Endocyclic Enecarbamates with Diazonium Salts. Formal Enantioselective Syntheses of Alkaloids (-)-Codonopsine and (-)-Codonopsinine, and the Synthesis of a New C-Aryl Azasugar.

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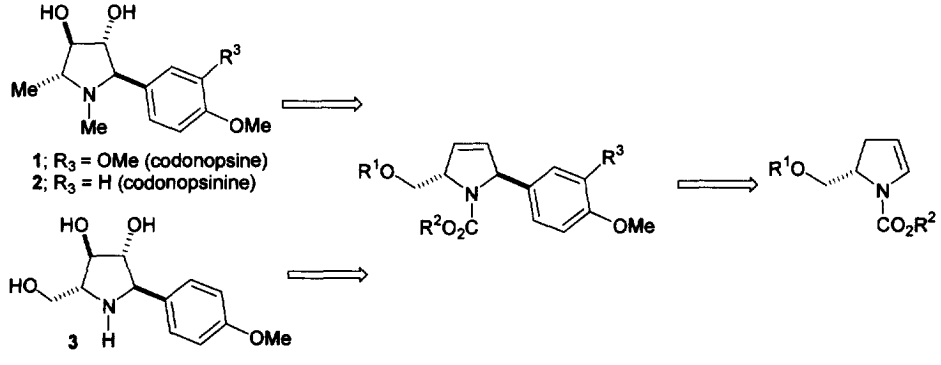
Abstracts: Formal total syntheses of the pyrrolidine alkaloids (-)-codonopsine and (-)-codonopsinine, as well as the synthesis of a new C-aryl azasugar were accomplished from a common 5-membered, enantiomerically pure endocyclic enecarbamate. The key step in those syntheses relies on a novel and practical version of the Heck reaction involving endocyclic enecarbamates and diazonium salts.

Keywords: Heck reactions; alkaloids; enecarbamates; pyrrolidines

The Heck reaction constitutes a powerful methodology in organic synthesis for the controlled construction of C-C bonds. Its most frequent variation, the Heck arylation, has found widespread use in synthesis, relying mostly on aryl iodides and triflates as arylating agent of the olefin acceptor [1].

The outstanding potential of Heck arylation process combined with the versatility of endocyclic enecarbamates [2] was envisioned as a key synthetic element in planning the syntheses of α-*N*-arylated alkaloids, as well as C-arylated azasugars. As initial targets, we focused our attention on the synthesis of pyrrolidine alkaloids codonopsine **1** and codonopsinine **2**, and on C-aryl azasugar **3**, all coming from a five-membered endocyclic enecarbamate readily prepared from L-proline or (S)-pyroglutamic acid (Scheme 1) [3]. Codonopsine and codonopsinine were isolated from *Codonopsis clematidea* and have shown hypotensive activity without any effect on the central nervous system on animal studies [4].



Scheme 1. Synthesis Plan to Compounds **1**, **2** and **3** Based on a Stereoselective Heck Arylation.

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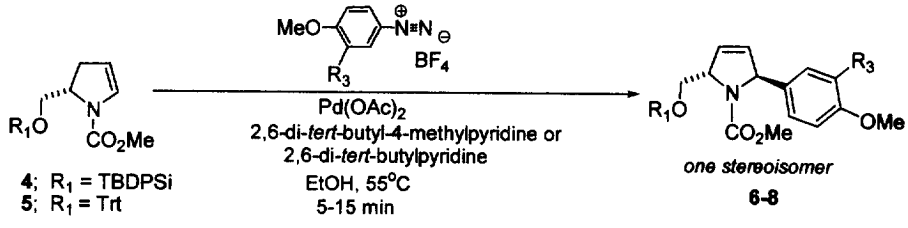
We commenced our synthetic route by applying standard Heck arylating conditions on enantiomerically pure endocyclic enecarbamates (EPEE) **4** and **5** [3]. However, most of the standard protocols tested failed to provide the desired Heck product, or afforded it in low yields (10-20%). Model studies with simpler enecarbamates and non-substituted aromatic compounds also led to low yields of the desired Heck product. In view of these results, we were attracted to Kikukawa-Sengupta's protocol employing diazonium salts as the aryl partner in Heck reactions [5]. The reactions involving diazonium salts are usually milder and faster than the traditional Heck protocols employing aryl triflates and iodides. Although electron rich and electron poor olefins have already been used in Heck reactions with diazonium salts, to the best of our knowledge, enecarbamates or enamides have never been tested before under these conditions [6]. Initial attempts using Sengupta's conditions led only to decomposition products. However, most gratifyingly when the reaction was carried out in presence of 2,6-di-*t*-butylpyridine or 2,6-di-*t*-butyl-4-methylpyridine as base the desired Heck product was obtained in reasonable yields in a highly regio- and stereoselective manner (Scheme 2). After some experimentation, we found out that using 1.5 to twofold excess of the EPEE improved yields to the 68-85% range, with partial recovering of starting EPEE[1]. Use of EtOH as solvent and the presence of a base proved crucial for the success of the Heck reaction. With MeOH as solvent (no base added) we observed methanolysis of enecarbamate **4** to yield the corresponding C-2 methoxy pyrrolidine (~36% yield). So far only 2,6-lutidine and KOAc were tested as alternative bases. However, both proved ineffective to promote coupling and only starting material was recovered.



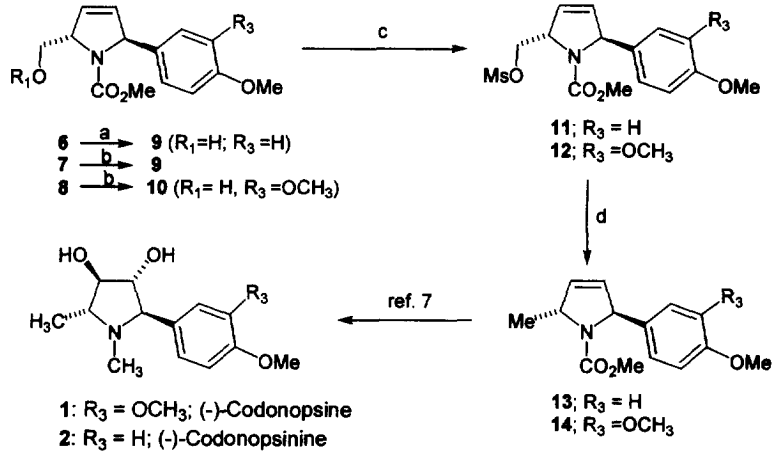
cmpd	equiv. 4 or 5	R^1	R^3	Yield (%)[a]
6	1.0	TBDPSi	H	55
7	1.0	Trt	H	45
8	1.0	Trt	OCH_3	36
7	1.5	Trt	H	68
8	1.5	Trt	OCH_3	68
7	2.0	Trt	H	79
8	2.0	Trt	OCH_3	85

a: Yields based on the diazonium salts employed.

Scheme 2: Heck Reaction of Endocyclic Enecarbamates with Diazonium Salts

[1] This reaction is still under investigation in our laboratory, nevertheless a typical procedure is as follows: To a solution of enecarbamate **5** (100mg, 0.25mmol), 2,6-di-*tert*-butyl-4-methylpyridine (205 mg; 1mmol) in 1 mL of EtOH under argon atmosphere (may not be necessary) was added $Pd(OAc)_2$ (5.6 mg; 10 mol %) and 3,4-$(OMe)_2$-$C_6H_3N_2BF_4$ (32 mg; 0.13mmol). The reaction mixture (dark brown) was immersed in an oil bath at ~55°C when it started bubbling intensely. After 10 min, bubbling ceased and the reaction was dark red. After cooling, water was added (5 mL) and the mixture extracted with EtOAc (3x5mL). The combined organic phase was dried with anhydrous Na_2SO_4, concentrated *in vacuo* and the residue chromatographed on SiO_2 (EtOAc/hexane; 1:4 to 1:1) to provide 58 mg of 3,4-dihydropyrrole **8** (85% yield) as a viscous oil and 43 mg of the starting enecarbamate **5**.

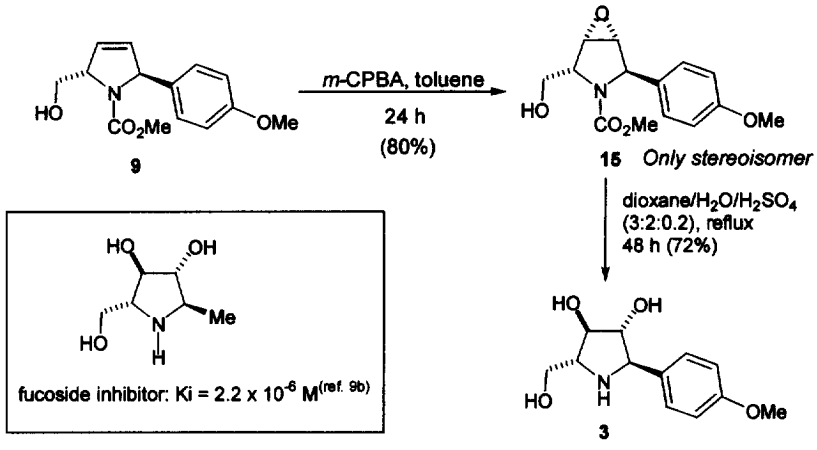
With the critical step resolved we moved forward to convert the Heck arylated products into the monocyclic alkaloids. With the aim of intercepting known advanced intermediates, deoxygenation of position C-6 was undertaken. Thus, the TBDPS group of **6** was removed with HF/pyr to afford hydroxy pyrrolidine **9** (74% yield), while the trityl group of **7** and **8** were removed with formic acid in ethyl acetate to give the hydroxyl pyrrolidines **9** and **10** in 70% and 78% yield respectively (Scheme 3). The hydroxymethyl pyrrolidine **10** was next converted into mesyl pyrrolidine **12** as an appropriate substrate for deoxygenation, and immediately reduced with sodium borohydride to provide the desired C-5 methyl pyrroline **14** in 68% overall yield. Spectroscopic characterization of **14** revealed it identical to a known intermediate previously prepared by Wang and Calabrese [7] thus completing our formal total synthesis of (-)-codonopsine. The same sequence of events were applied to deprotected Heck product **9** thus affording the monomethoxylated intermediate **13** that, in principle, can be converted to (-)-codonopsinine by the same sequence applied by Wang and Calabrese [7].



Reagents and Conditions: a) HF-pyr, THF, rt, 72 h (74%); b) HCO_2H. EtOAc (70% for **9** and 78% for **10**); c) MsCl, Et_3N, CH_2Cl_2, 0°C to rt, 30 min; d) $NaBH_4$, DMF, 105°-110°C, 1 h (yields for steps c and d combined: 72% for **13** and 68% for **14**)

Scheme 3: Conversion of Heck products to Codonopsine and Codonopsinine.

Although the above approach to codonopsine and codonopsinine did not require a stereocontrolled epoxidation, a substrate-directed epoxidation [8] was attempted in order to provide some insights on the directing capability of the primary hydroxyl group at C-6 of the pyrrolidine ring, which could be explored synthetically concerning other targets. Thus, epoxidation of **9** was carried out employing m-CPBA and to our satisfaction, only one stereoisomeric epoxide was observed (Scheme 4). Stereochemical assignments using ^{1}H-NMR, ^{13}C-NMR and NOEdif confirmed the stereoisomeric epoxide as the α-epoxide **15** depicted in Scheme 4 demonstrating the anticipated directing power of the C-6 hydroxyl group. Aiming at the synthesis of an azasugar epoxide **15** underwent an acidic hydrolysis to cleanly provide polyhydroxylated pyrrolidine **3**. This new polyhydroxylated azasugar is an aryl analogue of a potent α-fucoside and α-mannoside inhibitor [9].



Scheme 4: Synthesis of a C-aryl azasugar from Heck adduct **9**.

The results shown above clearly demonstrate the utility of the enantiomerically pure endocyclic enecarbamates as starting material in organic synthesis which coupled to this novel combination of Heck reaction partners employing diazonium salts opened up new routes to the preparation of important compounds of pharmacological importance. The generality of this new Heck process is under investigation in our laboratories, as well as its application to other target alkaloids.

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References and Notes

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