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Heck Arylation of Endocyclic Enecarbamates with Diazonium Salts. Improvements and a Concise Enantioselective Synthesis of (–)-Codonopsinine

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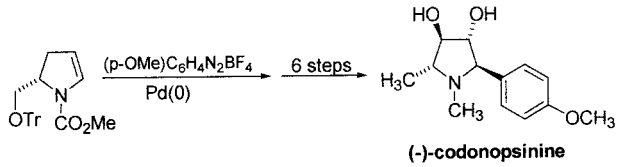
ABSTRACT



Total enantioselective synthesis of the natural (–)-codonopsinine was accomplished in seven steps with an overall yield of ~16% starting from the five-membered endocyclic enecarbamate 4. The total synthesis features a highly efficient and stereoselective Heck arylation of endocyclic enecarbamate 4 with *p*-methoxybenzenediazonium tetrafluoroborate and a stereoselective epoxidation/epoxide opening sequence as key steps.

(−)-Codonopsinine **1** and (−)-codonopsine **2** are rather complex pyrrolidine alkaloids isolated from *Codonopsis clematidea* that display antibiotic activity and hypotensive activity without affecting the central nervous system in animal tests.[1] Interest in the synthesis of codonopsine and codonopsinine stems mainly from their pharmacological activity associated with the synthetic challenge they constitutes in view of their 1,2,3,4,5-pentasubstituted molecular structures bearing four contiguous stereogenic centers (2*R*,3*R*,4*R*,5*R*) around a pyrrolidine ring in an all trans arrangement.[2]

We envisioned the synthesis of these alkaloids starting from an enantiomerically pure five-membered endocyclic enecarbamate by means of a stereoselective Heck arylation as the key transformation. The Heck arylation would introduce the required phenyl ring adjacent to the pyrrolidine nitrogen with the concomitant placement of a strategic double bond, which would later provide access to the required trans-diol functionality (Figure 1).[3]

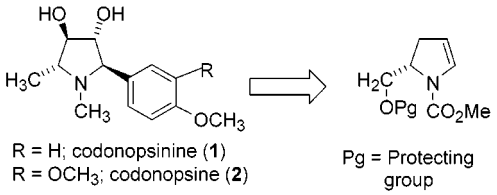


Figure 1. Retrosynthetic analysis for the synthesis of (−)-codonopsinine and (−)-codonopsine.

Recently, we reported a formal total synthesis of (−)-codonopsine and (−)-codonopsinine employing a Heck

(1) Codonopsinine and codonopsine were isolated by Russian researchers in 1969, who later on made incorrect stereostructural assignments based on ^{1}H NMR coupling constants. The correct stereochemistry of codonopsinine was established by C. Kibayashi in 1986. For details, see: Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5393.

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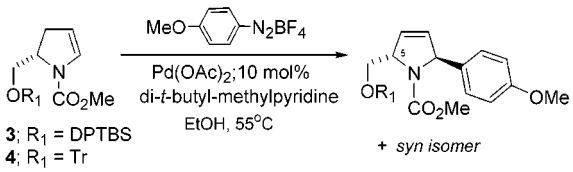
reaction of endocyclic enecarbamates with diazonium salts as effective arylating agents.[4] Herein we report a concise total synthesis of the natural product (−)-codonopsinine, as well as significant improvements on the key Heck arylation of five-membered endocyclic enecarbamates with diazonium salts which clearly demonstrates the generality and synthetic potential of this arylation reaction.

Enantiomerically pure endocyclic enecarbamates **3** and **4** were obtained from L-pyroglutamic acid with overall yields of 52−70% following procedures developed in our laboratory.[5] As previously reported by us, Heck arylation of enecarbamates using "traditional" conditions (aryl triflates and/or aryl iodides in the presence of phosphine ligands) provided the desired aryl-3-pyrrolines in very low yields (10−20%).[4] We were thus pleased to find out that benzenediazonium tetrafluoroborates could act as suitable arylating agents for endocyclic enecarbamates, when the reaction was carried out in methanol using 2,6-di-*tert*-butyl-4-methylpyridine or 2,6-di-*tert*-butyl-pyridine (2 equiv) as base. Heck arylation of enecarbamates **3** and **4** were then performed as indicated in Scheme 1 to afford a diastereomeric mixture of

Scheme 1. Heck Arylation of Endocyclic Enecarbamate **3** and **4** with *p*-Methoxybenzenediazonium Tetrafluoroborate



Product	R_1	Yield(%)	ds*
5a,b	Tr	79	88:12
6a,b	DPTBS	96	82:18

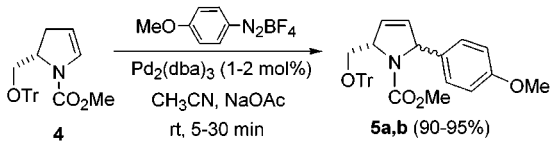
*determined by capillary GC.

aryl-3-pyrroline **5a**,**b** and **6a**,**b** in good to high yields (79−96%). Arylation proceeded rapidly (within 10−15 min) with moderate stereoselectivity without detection of regioisomeric products resulting from isomerization of the primary 2-pyrroline adduct.[6] In our initial studies of the Heck arylation, we kept the amount of the starting enecarbamate to a maximum of 1.5−2 equiv with good results (Scheme 1). Normally, excess enecarbamate could be recovered (60−80% recovery) after column chromatography and recycled into the synthetic scheme. By comparison, literature procedures using aryl triflates usually require large excesses of the olefin or enecarbamate undergoing Heck reaction (4−5 equiv).[7]

The Heck 3-pyrroline adducts **5a**,**b** and **6a**,**b** were consistently obtained as an unseparable mixture of diastereomers.[8] Stereoselectivity of the Heck arylation was moderate (4.5:1 for the *tert*-butyldiphenylsilyl ether protecting group and 7.3:1 for the triphenylmethyl ether protecting group) as determined by capillary gas chromatography of the corresponding free alcohols (see discussion ahead).

During attempts to further improve yields with the tritylated enecarbamate **4**, we found out that the Heck arylation can be performed in high yields and with good stereoselectivity using only 1% of $Pd_2(dba)_3$[9] in acetonitrile at room temperature, in the presence of sodium acetate as base as described in Scheme 2. Using this protocol the aryl-

Scheme 2. Improved Heck Arylation of Endocyclic Enecarbamate **4** with *p*-Methoxybenzenediazonium Tetrafluoroborate



3-pyrrolines **5a**,**b** were obtained in yields ranging from 90 to 95%, with a diastereomeric ratio of 90:10 favoring the anti aryl-3-pyrroline **5a**. This procedure is simpler, milder, and more economic than the one depicted in Scheme 1. It also seems to be a general arylation procedure for moderate electron rich olefins.[10]

Noteworthy in this reaction is that no excess of the endocyclic enecarbamate or diazonium salts was required to attain high yields of the Heck adduct. Arylations in acetonitrile were exothermic and usually very fast (from less than 5 min with 1 mol % of the palladium catalyst, to up to 30 min with 0.5 mol %).[11] Reaction rates also seem to be dependent on the solubility of NaOAc, so diluted reactions

(2) For previous syntheses of codonopsinine and codonopsine, see: (a) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531. (b) Wang, C. L. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341. (c) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 1956. (d) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255. This last reference actually marks the first total synthesis of the unnatural (+)-codonopsinine. However, the stereochemical representation for (+)-codonopsinine made in this work was latter revised; see ref 1.

(3) Reviews on the Heck reaction: (a) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (c) Shibasaki, M.; Boden, D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (d) Negishi, E.; Coperet, C.; Ma, S; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl*. **1994**, *36*, 2379. (f) Cabri, W.; Candiani, E. *Acc. Chem. Res.* **1995**, *28*, 8.

(4) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083.

(5) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646. In more recent experiments, the endocyclic enecarbamate **4** was obtained after three steps in 85% overall yield from the commercially available (S)-(+)-5-(trityloxymethyl)-2-pyrrolidinone using the protocol described therein.

(6) Recently, Tietze and Ferraccioli reported on a Heck reaction of a five-membered endocyclic enecarbamate under Jeffrey conditions that afforded a 1.2:1 ratio of regioisomeric Heck products in 63% yield. See: Tietze, L. F.; Ferraccioli, R. *Synlett* **1998**, 145.

(7) (a) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267. (b) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464. (c) Loiseleur, O.; Meier, P.; Pfaltz, A. Angew. *Chem., Int. Ed. Engl*. **1996**, 35, 200.

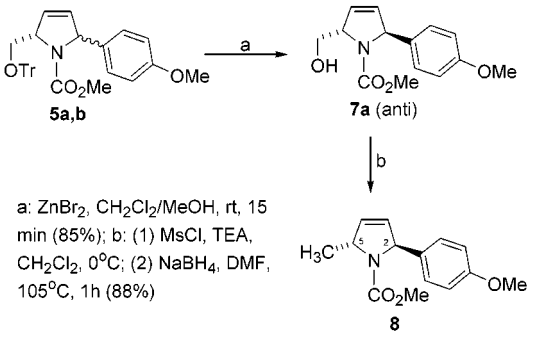
(8) The Heck products are obtained as homogeneous material by TLC. Capillary gas chromatography and HPLC were ineffective to resolve the two diastereomers. Capillary GC led to significant decomposition, and HPLC (hexanes/EtOAc) provided only partial resolution of the two diastereomers.

(9) $Pd_2(dba)_3$·dba was obtained according to the procedure described in Takahashi, Y.; Ito, Ts.; Ishii, Y. *J. Chem. Soc. Chem. Commun.* **1970**, 1065.

(0.16 M) were faster than concentrated ones (0.30 M) in which NaOAc is not entirely soluble.

Separation of the two diastereomers was easily accomplished after removal of the trityl (HCO_2H, EtOAc, rt, 1 h, or $ZnBr_2$, CH_2Cl_2/MeOH) or silyl (HF·pyr, THF, rt, 72 h, ~85%) protecting groups (Scheme 3). Removal of the

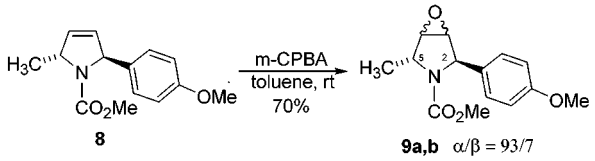
Scheme 3. Conversion of Heck Product **5** into Pyrroline **8**



protecting groups gave two isomeric hydroxymethyl pyrrolines whose TLC retention factors were quite distinct: ~0.30 for the anti stereoisomer **7a** and ~0.60 for the syn stereoisomer **7b**.[12] The anti 3-arylpyrroline **7a** was obtained in 70% yield when employing zinc bromide for removal of the trityl protecting group (the same yield was obtained when using formic acid). Compound **7a** was then submitted to deoxygenation, which was best carried out by mesylation of the primary alcohol, followed by reduction with $NaBH_4$ at 90° C to yield the desired 5-methyl-3-pyrroline **8** in 88% yield for the two steps (Scheme 3). The stereocontrolled synthesis of the trans-pyrroline **8** provided an outstanding opportunity for the total synthesis of (−)-codonopsinine.[13]

Introduction of the required trans diol functionality was carried out by the intermediacy of an epoxide. Olefin **8** reacted slowly with 3-chloroperoxybenzoic acid (*m*-CPBA); however, use of 5 equiv (toluene, rt, 24 h) afforded the α -and *β*-epoxides **9a**/**9b** in 70% yield in a diastereomeric ratio of 93/07 as observed by capillary GC (Scheme 4).[14]

Scheme 4. Conversion of Pyrroline **8** into Epoxide **9**



Epoxidation occurred mainly from the least congested face of the double bond and provided the α-oriented epoxide **9a** as the major product. The stereochemistry for the major product was assigned as due to the larger coupling constant between H4 and H5 ($^3J_{4,5} \cong 1.5$ Hz), when compared to that found in the *β*-epoxide **9b** ($^3J_{4,5} \cong 0$). These coupling constants are in agreement with those reported in the literature for similar systems.[15] Epoxide stereochemistry played a decisive role for the total synthesis of (−)-codonopsinine as concluded from the reactivity of the isolated stereoisomers. Acidic hydrolysis of the major α-epoxide **9a** afforded the desired (2*R*,3*R*,4*R*,5*R*)-diol as the major product, whereas exposure of the minor *β*-epoxides **9b** to the same conditions afforded none of the expected trans-diol (analysis by TLC and capillary GC).

Although we did not perform any mechanistic studies, it is conceivable that the *β*-epoxide **9b**, which is more sterically congested, undergoes epoxide ring opening, generating a carbocation that disproportionates to other products. On the other hand, α-epoxide **9a**, being more stable, undergoes attack by the incoming nucleophile at C4, minimizing steric repulsion with the C2 aryl group and the C5 methyl group.

Acidic hydrolysis was performed on epoxides **9a** to provide the expected trans-diol **10** in 55% yield (Scheme 5).[16] To conclude the total synthesis, the last step was a straightforward reduction of the carbamate moiety with lithium aluminum hydride that provided the natural product

(10) After much experimentation, these were conditions we have found optimum for the Heck arylation of endocyclic enecarbamates with diazonium salts. These were conditions almost identical to those previously reported by Matsuda to perform Heck arylation of cyclic olefins with diazonium salts (see: Kikukawa, K.; Nagira, K.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31). However, they reported that these conditions gave poor results when applied to enamines and to some other cyclic olefins. Preliminary results from our laboratory indicate that these conditions could be applied to six- and seven-membered ring enecarbamates with good yields. Moreover, the nature of the functional group at C5 of the five-membered enecarbamates plays a critical role in the diastereoselectivity of the Heck arylation. These results should be reported in due course.

(11) **Typical experimental procedure:** To a solution of 627 mg of enecarbamate **4** (1.57 mmol) in 10 mL of anhydrous acetonitrile was added, at once, a mixture of 340 mg of *p*-methoxybenzenediazonium tetrafluoroborate (1.57 mmol), 380 mg of sodium acetate (4.50 mmol), and 20 mg of $Pd_2(dba)_3$·dba (0.017 mmol). Upon addition, strong evolution of nitrogen ensued with a noticeable warning of the reaction mixture. Evolution of gas ceased after ~5 min with a concomitant darkening of the reaction medium. At this stage TLC indicated complete consumption of the starting enecarbamate. Then, ~10 mL of saturated $NaHCO_3$ was added to the reaction, followed by addition of 30 mL of EtOAc. The organic layer was separated, washed with saturated $NaHCO_3$, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue obtained was flash chromatographed on silica gel (hexane:EtOAc; 2:1) to afford 734 mg (93% yield) of a diastereomeric mixture of Heck adduct **5a**,**b** (90:10 dr by capillary GC of the free alcohols) as a single spot on TLC ($R_f = 0.22$; hexane:EtOAc; 3:1).

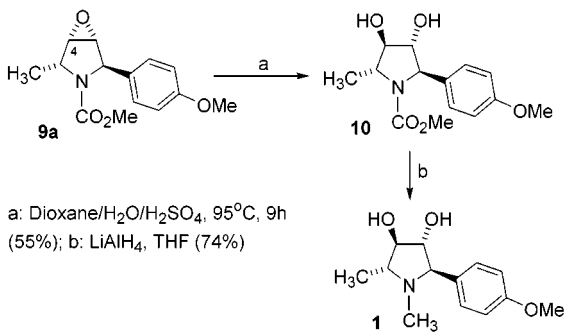
(12) This large difference in retention factors led us to a previous incorrect conclusion about the diastereoselectivity of the Heck arylation (see ref 4). The Heck arylation, although stereoselective (90:10), gives a mixture of two diastereomers. After deprotection, chromatography on silica gel furnishes the trans aryl-3-pyrroline **7a** as a pure compound as analyzed by capillary GC and HPLC.

(13) The synthesis of codonopsine **2** by Wang and Calabrese relied on a diastereomeric mixture (1.3:1 ratio) of 3-pyrrolines very similar to ours. See: Wang, C. L. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341.

(14) Three epoxidizing agents were tested: *m*-CPBA, dimethyldioxirane (DMD), and magnesium monperoxyphthalate (MMPP). A period of 24 h was necessary for the epoxidation of **8** with 5 equiv of *m*-CPBA (90% conversion). DMD epoxidation was much faster (10 equiv of DMD, acetone, 0 °C, 3.5 h or at room temperature for 2.5 h), resulting in the same diastereomeric mixture (~90:10), but in somewhat lower yields (55−61%). MMPP provided results very similar to those obtained with *m*-CPBA.

(15) The presence of conformational isomers makes ^{1}H NMR spectra complex. Nevertheless, we have noticed in several instances a good correlation between the vicinal coupling involving H4 and H5 and the stereochemistry of substituted pyrrolidines and proline systems. Large coupling constants are associated with cis H4−H5, whereas smaller coupling constants (between 0 and 4 Hertz) are associated with trans H4−H5. For a full analysis of related systems (3,4-epoxyprolines), see: Robinson, J. K.; Lee, V.; Claridge, T. D. W.; Baldwin, J. E.; Schofield, C. J. *Tetrahedron* **1998**, *54*, 981.

Scheme 5. Conversion of Epoxide **9a** into (−)-Codonopsinine **1**



(−)-codonopsinine **1** in 74% yield. Spectroscopic data obtained for our synthetic (−)-codonopsinine **1** were in excellent agreement with data reported in the literature.[2c]

In summary, the Heck arylation of endocyclic enecarbamates was greatly improved by the use of 1% $Pd_2(dba)_3$·dba in acetonitrile and sodium acetate as base without the need of an excess of the valuable enecarbamate. This process proved to be very practical, economic, and stereoselective. The characteristics of this novel protocol for the Heck arylation of enecarbamates permitted a rather concise and enantioselective total synthesis of (−)-codonopsinine **1** in seven steps from enecarbamate **4** with good overall yield (∼16%). Additionally, the synthetic strategy features a stereoselective epoxidation/epoxide opening sequence that was also key to the present synthesis and that should prove valuable to other targets. A similar strategy can be also applied to the total synthesis of (−)-codonopsine, although we have not carried that through.

Further studies applying this methodology to the synthesis of other nitrogen-containing heterocycles are in progress and should be reported in due course.

Acknowledgment. We thank FAPESP (Research Supporting Foundation of the State of São Paulo) for financial support and CNPq (Brazilian National Research Council) for fellowships.

Supporting Information Available: Spectroscopic data for compounds **3**, **4**, **5a**,**b**, **7a**, **7b**, **8**, **9a** **10**, and **1** and ^{1}H NMR and IR spectra of compounds **7a**, **7b**, **8**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The amount of sulfuric acid employed for hydrolysis seems to be critical. Best results were obtained with dioxane/H_2O/H_2SO_4 concentrated in a ratio of 3/2/0.2 mL. Higher concentrations of the acid (3/2/0.5 mL) led to a diastereomeric diol whose structure was not determined yet. Basic hydrolysis of epoxide **9a** (DMSO/KOH 10% solution, 90−100 °C, 15 h) provided trans diol **10** in ∼ 40% yield.