HETEROCYCLES, Vol. 106, No. 5, 2023, pp. 858 - 867. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 28th February, 2023, Accepted, 27th March, 2023, Published online, 4th April, 2023
DOI: 10.3987/COM-23-14837

ASYMMETRIC SYNTHESIS OF THE UNNATURAL ENANTIOMER OF CODONOPSININE AND A STEREOISOMER VIA ALKOXYALLENES

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Abstract – The unnatural enantiomer of the alkaloid codonopsinine was prepared employing a suitably substituted alkoxyallene equipped with a D-fructose-derived auxiliary. The crucial lithiated 1-alkoxy-3-arylallene was generated *in situ* from easily available 1,2:4,5-di-*O*-isopropylidene-3-*O*-[3-(4-methoxyphenyl)-1,2-dien-1-yl]-*β*-D-fructopyranose and treated with an *N*-tosyl imine to afford a diastereomeric mixture of the corresponding allenyl adducts. Their cyclization with silver nitrate in acetonitrile in the presence of potassium carbonate furnished highly substituted 2,5-dihydropyrrole derivatives. After separation, straightforward synthetic operations, with highly diastereoselective hydroborations as key step, provided (+)-codonopsinine (≥95% ee) and one of its stereoisomers.

INTRODUCTION

Hydroxylated pyrrolidine derivatives such as (–)-codonopsine and its close relatives (–)-codonopsinine, (+)-radicamine A and (+)-radicamine B (Figure 1) display interesting biological activities.[1] The pentasubstituted alkaloid (–)-codonopsinine features four contiguous stereogenic centers bearing all substituents in *trans* arrangement. It was first isolated from *Codonopsis clematidea* by Russian scientists who subsequently elucidated the structure.[2] The absolute configuration of natural codonopsinine was determined by synthesis to be (2*R*,3*R*,4*R*,5*R*)[3] which was later confirmed by an X-ray crystallographic analysis.[4] Due to the moderate complexity of its structure, (–)-codonopsinine frequently served as target for the examination of new synthetic methods.[5] Although the biological activity of the unnatural enantiomer (+)-codonopsinine should also be of interest – e.g. as glycosidase inhibitor – this compound has been prepared only occasionally.[3c,6]

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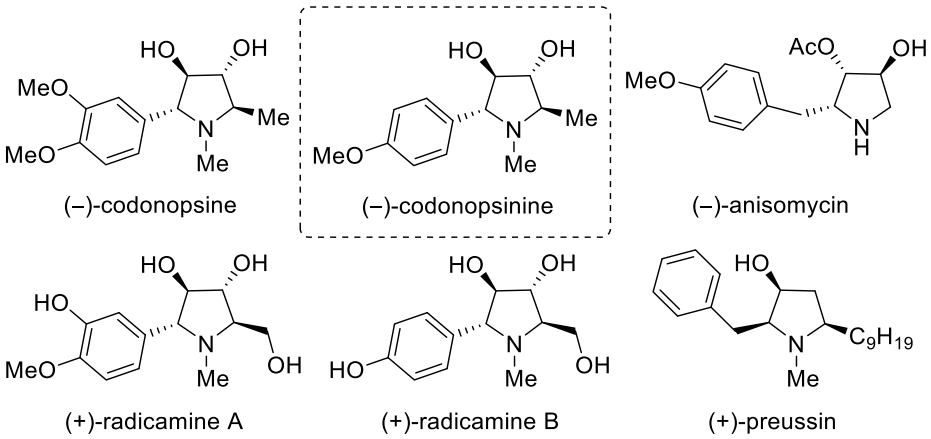
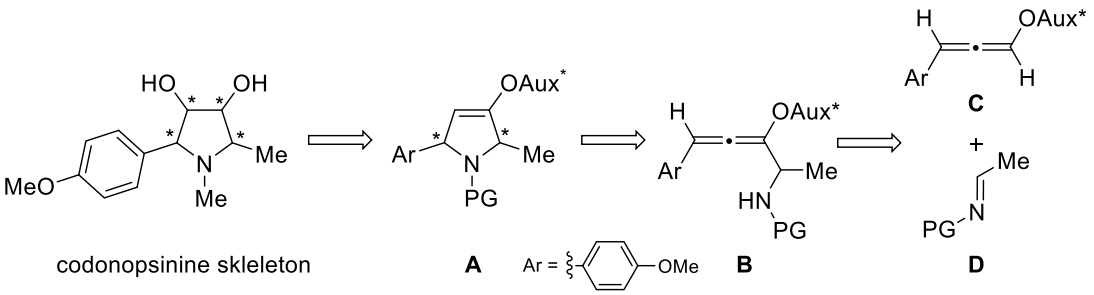


Figure 1

Employing alkoxyallenes as crucial C3 building blocks,[7] our group developed efficient and flexible routes to related hydroxylated pyrrolidine natural products such as detoxinine,[8] anisomycin[9] and preussin[10] (Figure 1); appropriate imines delivered the required CN moiety of the target structures. Base-promoted or Lewis-acid-catalyzed cyclizations of the intermediate allenyl imines under differing conditions provided the pyrrolidine core of the natural products. Earlier we reported the preparation of racemic codonopsinine by our established protocol via an aryl-substituted methoxyallene as precursor.[6a] Based on these results and the previously studied routes to anisomycin and preussin, we now report the asymmetric synthesis of (+)-codonopsinine and a stereoisomer as shown in the retrosynthetic analysis (Scheme 1). It was planned to generate the codonopsinine skeleton by stereoselective hydroboration of 2,5-dihydropyrrole derivative **A** which should be obtained by cyclization of a suitably substituted allenyl amine **B**. This crucial intermediate can be disconnected into alkoxyallene derivative **C** and imine **D**. The absolute configuration of the compounds should be steered by an appropriate chiral auxiliary Aux* at the allene oxygen.



Scheme 1

Crucial questions are connected with the approach designed in Scheme 1:

a) Which auxiliaries steer the addition of the lithiated alkoxyallene to the imine and which absolute

configuration is induced?

b) How does the axial chirality of the allene moiety influence the diastereoselectivity of the addition step?

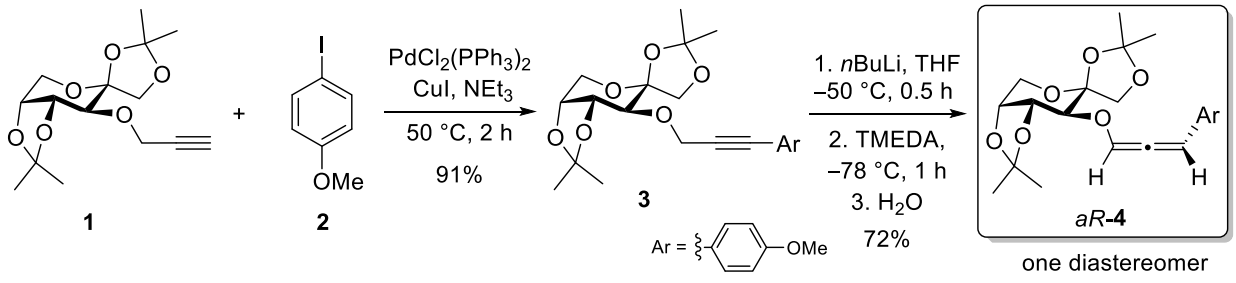
c) Is the achieved stereoselectivity of the addition cleanly transferred to the cyclization products?

d) Is the hydroboration sufficiently stereoselective?

In previous studies we employed carbohydrate-derived auxiliaries at the alkoxallenes and investigated their hetero Diels-Alder reactions.[11] Alternatively, these alkoxyallenes were lithiated and the resulting strong nucleophiles were added to electrophiles such as carbonyl compounds[12] or imines,[9,13] resulting in moderate to very good asymmetric inductions triggered by the auxiliaries. For the reactions with imines, the diacetone-fructose derived auxiliary gave good inductions with diastereoselectivities of up to 90:10,[13] but a considerable dependence on the structure of the imine employed was observed. By use of a 3-nonyl-substituted 1-alkoxyallene with the diacetone-fructose auxiliary we could prepare cytotoxic (–)-preussin.[10] For the current study, we decided to examine a similar 1-alkoxyallene, now bearing a *p*-methoxyphenyl group at C-3 of the allene moiety.

RESULTS AND DISCUSSION

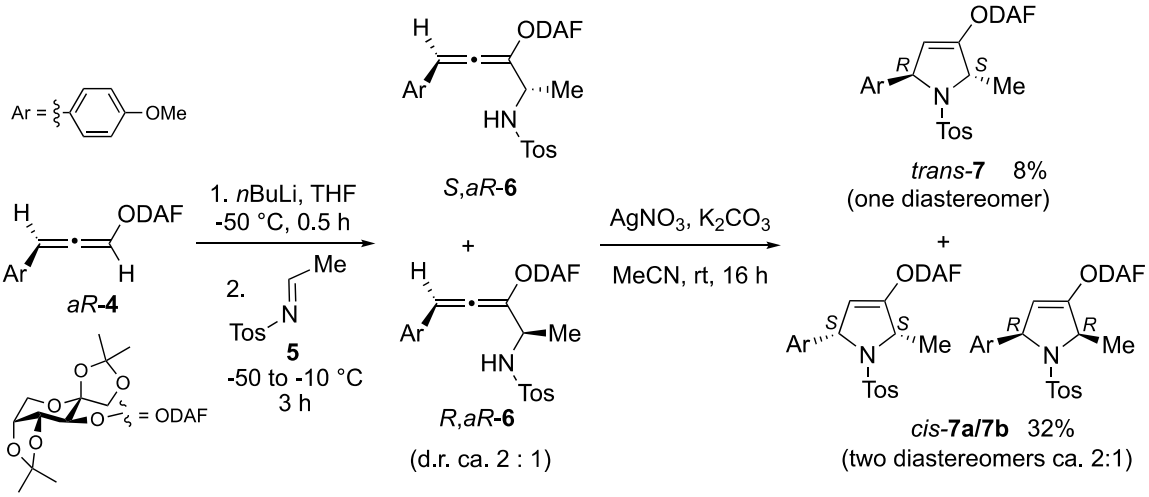
Starting from cheap and readily available 1,2:4,5-di-*O*-isopropylidene-D-fructose and propargyl bromide, a Williamson ether synthesis furnished compound **1** in good yield (Scheme 2).[14,15] A subsequent Sonogashira reaction[16] of **1** with *p*-iodoanisole (**2**) under standard conditions very efficiently provided the disubstituted alkyne **3** on a multigram scale, which served as precursor of the required alkoxyallene. Alkyne **3** was isomerized to the required axially chiral alkoxyallene **4** by treatment with *n*-butyllithium at –50 °C, followed by addition of TMEDA at –78 °C and finally protonation of the intermediate lithiated species with water (Scheme 2). The method has earlier been developed for the isomerization of *alkyl*-substituted alkynes, which afforded the diastereomeric alkoxyallenes in an *aR*/*aS* ratio of 75:25.[17] This protocol perfectly worked for the conversion of **3** into *aryl*-substituted allene *aR*-**4** which was isolated after column chromatography as single diastereomer in 72% yield; the compound is only moderately stable and has to be stored at –25 °C. Although *aR*-**4** is a solid we could not obtain suitable crystals to unambiguously determine its configuration by an X-ray analysis.



Scheme 2

However, its conversion into (+)-codonopsinine (see below) allowed the assignment of the chiral axis to be *aR* as depicted in Scheme 2.[18] We cannot rigorously exclude that small amounts of the *aS*-**4**-diastereomer are also formed and removed during the chromatographic purification. Nevertheless, the alkyne-to-allene isomerization process seems to proceed with higher selectivity when the alkyne bears an aryl group instead of an alkyl substituent.

With reasonably quantities of the diastereomerically pure aryl-substituted allene *aR*-**4** in hand, its addition to the respective *N*-tosyl-substituted imine was attempted. This type of electrophiles turned out to be particularly reactive and complete consumptions of lithiated alkoxyallenes in short reaction times were generally observed.[19] By treatment with *n*-butyllithium at –50 °C compound a*R*-**4** was lithiated at C-1 and *N*-ethylidene-4-methylbenzenesulfonamide (**5**)[20] was subsequently added at –78 °C (Scheme 3). After warm-up to –50 °C and aqueous work-up the expected allenyl amines **6** were isolated, which were provisionally purified by quick flash chromatography on silica gel to obtain a mixture of diastereomers *S,aR*-**6** and *R,aR*-**6** (ca. 60%, d.r. ca. 2:1). The moderate diastereoselectivity in this step was disappointing and is probably due to the small size of the alkyl group at the imine carbon. Alternative auxiliaries in order to optimize this step were not examined. Due to the low stability of adducts **6** no efforts were made for their thorough purification or separation. Instead, they were immediately used for the next cyclization reaction (see below). The shown configurations of *S,aR*-**6** and *R,aR*-**6** are based on our experience with alkyl-substituted alkoxyallenes revealing that the intermediate lithiated allenes are configurationally stable under the applied reaction conditions[13] and supported by the subsequent reactions providing the final products (+)-codonopsinine and 5-*epi*-codonospsinine.

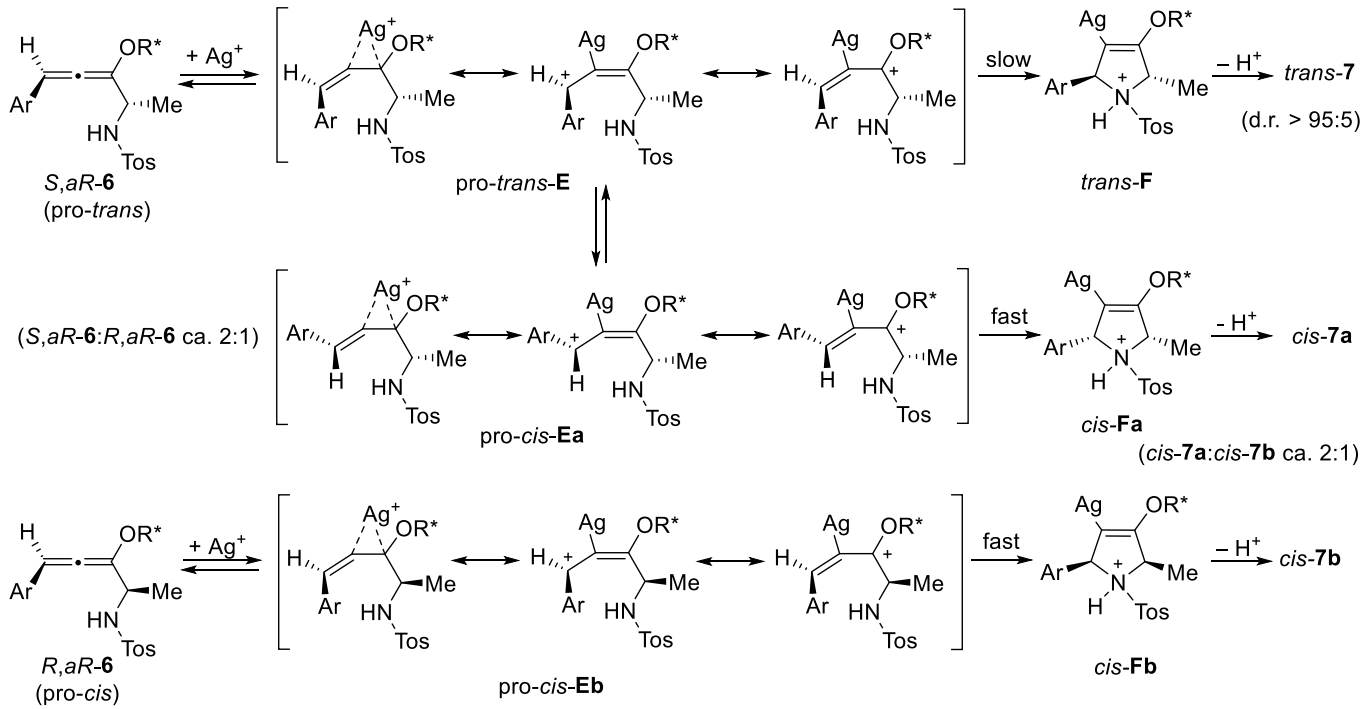


Scheme 3

Cyclization of semi-purified **6** with silver nitrate in acetonitrile in the presence of potassium carbonate[21] furnished 2,5-dihydropyrrole derivatives **7**. Purification by column chromatography on silica gel gave a

mixture of diastereomers (*cis*:*trans* ca. 4:1) which were separated by HPLC (hexanes/EtOAc, 7:3) to furnish as minor isomer the desired *trans*-**7** (8% overall yield) as colorless solid and as major component *cis*-**7** (32%) as a yellowish foam. NMR analysis showed that *trans*-**7** was isolated as single (enantiopure) compound with 2*S*,5*R* configuration as depicted in Scheme 3. On the other hand, the major product consisted of the two diastereomers *cis*-**7a** and *cis*-**7b** (ratio ca. 2:1), which differ in the absolute configurations of the stereogenic centers of the 2,5-dihydropyrrole part (2*S*,5*S* versus 2*R*,5*R*).

In Scheme 4 we try to rationalize the puzzling observation that two diastereomers at the allene stage (compounds **6**) provide three diastereomers at the 2,5-dihydropyrrole stage (compounds **7**). It is assumed that the allene/2,5-dihydropyrrole isomerization starts with a complexation of the soft Lewis acidic silver ion at the electron-rich central allene carbon giving the resulting intermediate **E** which can be described as π-complex and/or as allyl cation.[19] This activation allows the nucleophilic nitrogen to attack the terminal allene carbon to give the cyclized intermediate **F** which after protonation delivers the products **7**. Diastereomer *S*,*aR*-**6** (pro-*trans*) first provides the complex pro-*trans*-**E** which apparently cyclizes with relatively slow rate. The lifetime of pro-*trans*-**E** allows a rotation within the allyl cation moiety and partial conversion into the diastereomeric pro-*cis*-**Ea**. The cyclizations of pro-*trans*-**E** and pro-*cis*-**Ea** hence afford a mixture of products *trans*-**7** and *cis*-**7a**. The homogeneous configuration of the allene axis is therefore lost during this isomerization process.

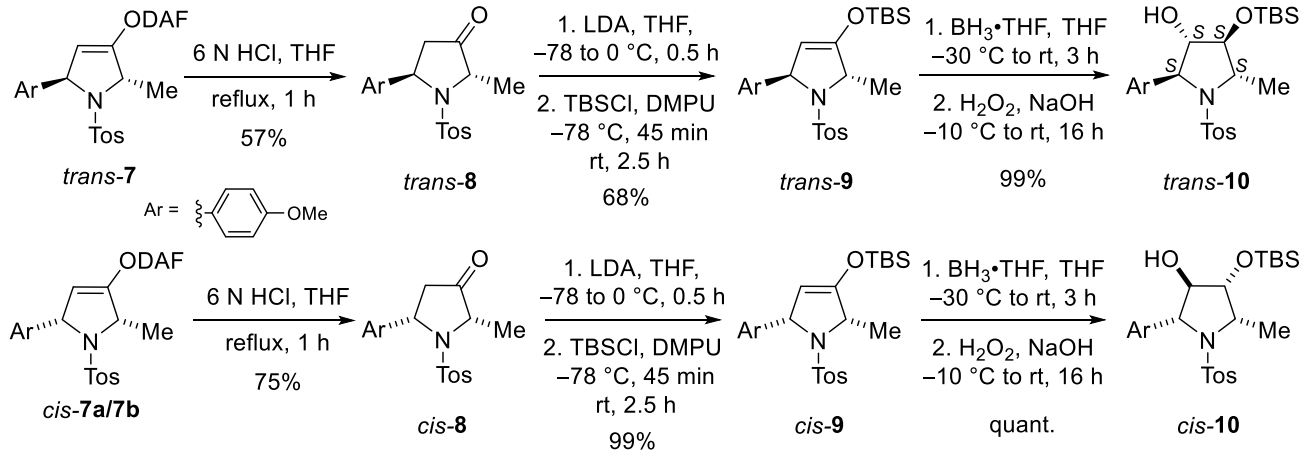


Scheme 4

The *R*,*aR*-**6** (pro-*cis*) gives pro-*cis*-**Eb** which undergoes faster cyclization to *cis*-**Fb** and hence affords *cis*-**7b**. Overall, compound *trans*-**7** was diastereomerically pure whereas a 2:1 mixture of diastereomers of *cis*-**7a** and *cis*-**7b** was isolated. We propose that major isomer *cis*-**7a** is 2*S*,5*S* configured and minor isomer *cis*-**7b** has 2*R*,5*R* configuration. The observation that pro-*cis* allene diastereomers undergo faster cyclizations than their pro-*trans* isomers is in agreement with the already reported results in the racemic series[6a] and with 3-alkyl-substituted allenyl amines.[10,13] The origin of the faster rate is not known, however, we assume that steric effects make the cyclization to the *cis*-compounds more favorable.[22]

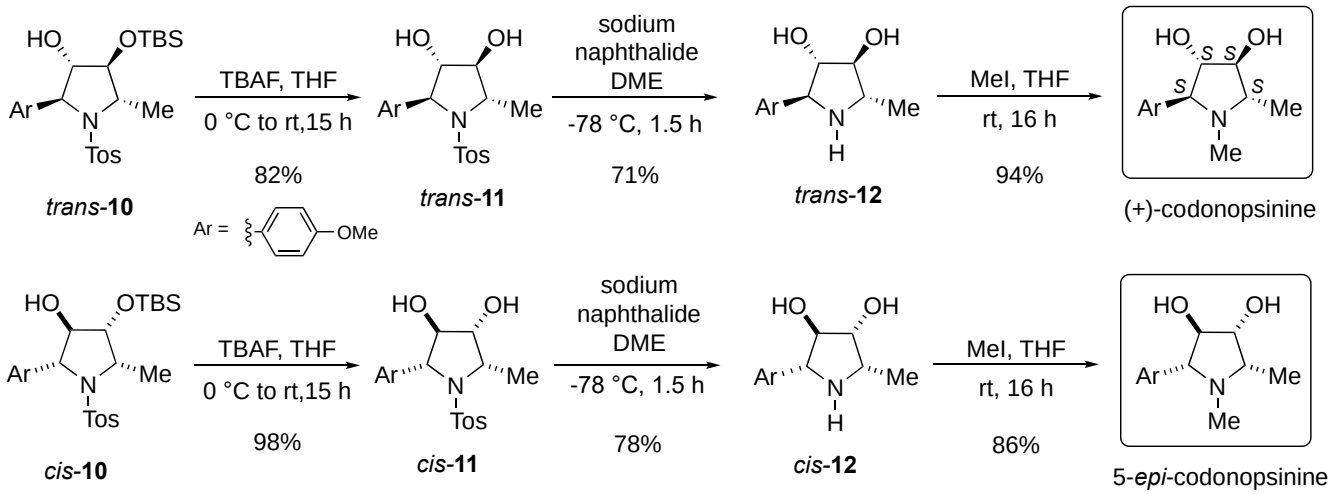
For the planned synthesis of codonopsinine we require *trans*-**7**. Unfortunately, the route to this compound is not very efficient, due to the isomerization process depicted in Scheme 4, but the obtained amount of material was sufficient to continue and to confirm the proposed configurational assignments. For completeness we also performed the identical chemical transformation with the diastereomeric mixture of *cis*-**7a**/**7b** to achieve the synthesis of 5-*epi*-codonopsinine.

To avoid harsh reaction conditions at later stages, the carbohydrate auxiliary has to be replaced by an apt silyl group. For this purpose, the alkyl enol ether moiety of compounds **7** was cleaved and subsequently silyl enol ethers were prepared from the intermediate ketones (Scheme 5).[23] Treatment of *trans*-**7** and of *cis*-**7a**/**7b** with 6 N aqueous hydrochloric acid furnished the corresponding pyrrolidin-4-ones *trans*-**8** and *cis*-**8**, respectively, in moderate to good yields. The high enantiopurity of *trans*-**8** was confirmed at this stage by employing NMR analysis with a chiral shift reagent. A $CDCl_3$ solution of *trans*-**8** and praeseodymium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate provided a ^{1}H-NMR spectrum without splitting of signals, whereas a control experiment with racemic *trans*-**8**[6a] showed clear splitting of most signals. An enantiomeric excess of ≥95% was deduced from these measurements. Subsequently, compounds *trans*-**8** and *cis*-**8** were transferred into the silyl enol ethers *trans*-**9** and *cis*-**9** under standard conditions employing LDA and *tert*-butyldimethylsilyl chloride in the presence of DMPU (*N*,*N*´-dimethylpropyleneurea). The crucial hydroboration with borane-THF complex, followed by oxidative work-up, furnished pentasubstituted pyrrolidine derivatives *trans*-**10** and *cis*-**10**, respectively, in excellent yields. Whereas the high selectivity in favor of the depicted structure can be expected for the *cis* series we were pleased to observe that the transformation of *trans*-**9** into *trans*-**10** also occurred with the required selectivity. Apparently, the fairly bulky 4-methoxyaryl group at C-5 of *trans*-**9** steers the borane reagent to attack the opposite face of the molecule.



Scheme 5

Two standard deprotection steps involving desilylation with TBAF (tetra-*n*-butylammonium fluoride) in tetrahydrofuran and detosylation with sodium naphthalide in DME (dimethoxyethane)[24] afforded the *N*-unsubstituted compounds *trans*-**11** and *cis*-**11** in good overall yields (Scheme 6). Finally, *N*-methylation was smoothly achieved by stirring these intermediates with methyl iodide at room temperature to obtain (+)-codonopsinine and the 5-*epi*-codonopsinine.



Scheme 6

The obtained sample of (+)-codonopsinine should have high enantiopurity due to the diastereomeric homogenity of *trans*-**7** and the enantiomeric excess determined at the stage of *trans*-**8** (see above). The optical rotation $[\alpha]_D$ of +5.5 (in methanol) of our sample deviates considerably from the reported value of +12.5 (in methanol),[3c] however, it should be noted that the optical rotations reported for the enantiomeric (–)-codonopsinine scatter very strongly, reaching from –7.2 to –20.0 (all in methanol),[5] showing that this value is no suitable criteria to determine the enantiopurity of this compound. Along our route from *trans*-**8**

to (+)-codonopsinine no configurational changes are possible (without epimerization) and hence we assume that the high enantiomeric excess of *trans*-**8** has been transferred to the final product.

The spectroscopic data of 5-*epi*-codonopsinine are in reasonable agreement with those reported in the literature,[3c,1g] but the compound cannot be enantiomerically pure since a 2:1 mixture of diastereomers *cis*-**7a**/**7b** was used as precursor. Its enantiomeric excess should therefore be ca. 30% and we assume that the 2*S*,3*R*,4*R*,5*R* enantiomer is in moderate excess. This assumption is based on the sign of the optical rotation which was –6.6 (in methanol) which has to be compared with a literature value of –5.0 (in dichloromethane) was reported for this enantiomer in the literature.[1g]

CONCLUSION

We demonstrate that enantiomerically highly enriched allene **4** allows the preparation of (+)-codonopsinine. Although its addition to imine **5** occurs with reasonable diastereoselectivity a considerable amount of the correctly configured intermediate *S*-*aR*-**6** is lost during the subsequent cyclization step to *trans*-**7** due to an isomerization of the allene moiety. The subsequent steps proceed highly selective and with good yield. Our approach again demonstrates the potential of alkoxyallene-based chemistry to prepare natural products with pyrrolidine skeleton.

EXPERIMENTAL

General Information, all experimental procedures and analytical data with assignments of spectroscopic data can be found in the Supporting Information.

ACKNOWLEDGEMENT

Generous support of this work by the Deutsche Forschungsgemeinschaft and by the Alexander von Humboldt Foundation (fellowship for MAC) is gratefully acknowledged.

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22. After completion of this study we found that gold-catalyzed cyclizations of allenyl imines occur much faster (see for instance ref. 19b). Under these improved conditions the cyclization of *R*,*aR*-**6** to the desired *trans*-**7** may be more efficient.
23. Since all compounds in the *cis* series of Schemes 5 and 6 are scalemic (mixture of enantiomers different from 1:1) we indicate the relative configurations by use of bold and hashed bonds only, whereas in the *trans* series the absolute configuration of the compounds is expressed by wedged bonds and wedged hashed bonds.
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