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# Total Synthesis of (+)-*trans*-195A

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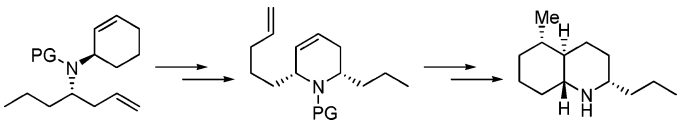
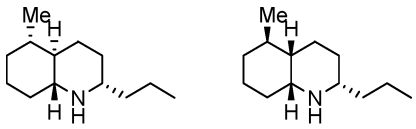
## ABSTRACT




**The first enantioselective synthesis of (+)-*trans*-195A is described. The structure has been constructed by ring-rearrangement metathesis (RRM) and zirconium-mediated Negishi-coupling, used for the first time to prepare 6,6-membered heterocycles, as key steps. By comparison of the synthesized material with the isolated natural product, the absolute configuration of natural *trans*-195A was determined to be (2*R*,4*aS*,5*R*,8*aS*)-(−).**

A remarkably diverse array of biologically active compounds occurs in amphibian skin.[1] One of the major classes of these alkaloids is the relatively untoxic decahydroquinolines, which have proven to be noncompetitive blockers of nicotinic receptor channels.[2] In addition, an inhibitory effect against sodium and potassium transport has been observed.[3] Decahydroquinolines occur mainly in skin extracts of neotropical frogs but were also isolated from bufanoid toads, marine flatworms, and myrmicine ants.[1] Since the discovery of the



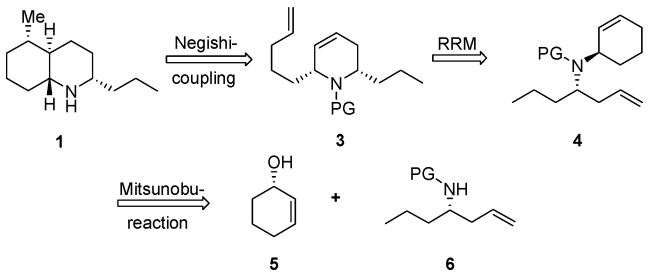

1 2

**Figure 1.** Structures of (+)-*trans*-**195A 1** and pumiliotoxine C (*cis*-**195A**) **2**.

first representative, pumiliotoxine C **2** (Figure 1),[4] both cis- and trans-fused decahydroquinolines have been found. *trans*-**195A** was first isolated as a trace compound from dendrobatid frogs of the species *Epipedobates bassleri* and later also from *Dendrobates imitator* and *Dendrobates variabilis*.[5] Due to the limited amounts available from natural sources, many structures are still tentative or incompletely defined. Further research and synthesis is required to confirm the configuration of the natural products by comparison with the synthesized material. In the case of **1**, whose structure and relative configuration could be solved,[6] the absolute configuration still remained tentative.

The aim of this work was to construct the decahydroquinoline structure of **1** by two metal-catalyzed, stereoselective steps, starting from easy accessible material (Scheme 1). First, the zirconium-mediated Negishi-coupling[7] of dienes

**Scheme 1.** Retrosynthetic Analysis for the Synthesis of **1**




was employed, leading stereoselectively to cis-1,2-disubstituted cyclohexanes.[7a] Successfully introduced into natural product synthesis by Mori et al.[8] to construct 5,6-membered

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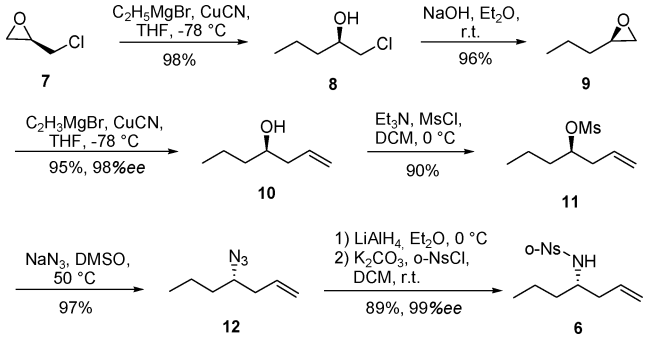
rings, this coupling has not been used to synthesize 6,6-annulated piperidines until now.

As a second key step, the concept of ring-rearrangement metathesis (RRM),[9] already established in natural product synthesis,[10] was used to construct the 2,6-disubstituted tetrahydropyridine derivative **3**. In recent work, we reported the enantioselective synthesis of α,α′-disubstituted piperidines via RRM of easily available carbocyclic secondary amines.[11] Since complete transfer of chirality was observed in this step, the enantiopure secondary amine **4** was chosen as a precursor for the planned RRM process. **4** was synthesized by Mitsunobu reaction[12] of the easily accessible compounds **5** and **6**. In conclusion, the desired decahydroquinoline **1** was constructed in only a few steps through our proposed strategy.

For synthesis of *ent*-**6**, we chose commercially available (*R*)-epichlorohydrin (**7**) as a starting material. Double copper-catalyzed epoxide ring-opening with Grignard reagents should lead to the corresponding enantiopure alcohol **10**.[13] The first ring-opening was carried out with ethylmagnesium bromide to afford **8** in quantitative yield (Scheme 2). Following transformation to epoxide **9** and second ring-opening with vinylmagnesium bromide gave (*R*)-hept-1-en-4-ol (**10**) in 91% overall yield. Comparison of its optical rotation with published data[14] corresponded to an enantiomeric excess of 98%.

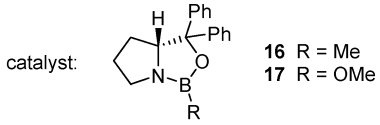
**Scheme 2.** Synthetic Route to **6**

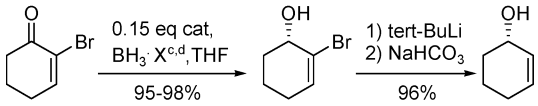



After formation of the corresponding mesylate **11**, substitution with sodium azide was carried out to yield **12**. Following reduction with $LiAlH_4$ and in situ protection of the corresponding amine intermediate with *ortho*-nitrobenzenesulfonyl chloride (*o*-NsCl) gave **6** in 89% yield. The *o*-Ns-group was chosen due to its electron-withdrawing effect, advantageous for subsequent Mitsunobu reaction[15] and for the planned RRM process. Subjection of **6** to chiral HPLC corresponded to an enantiomeric excess of 99%, which confirms complete inversion of the configuration in the transformation of **11** to **12**.

For synthesis of (*S*)-cyclohex-2-enol (**5**), the asymmetric CBS reduction of ketones, published first by Corey et al.,[16] was employed. As a prochiral ketone, we chose 2-bromocyclohex-2-en-1-one (**13**),[17] which was already successfully applied to synthesize *ent*-**5**.[18] Following the literature procedure, (*R*)-Me-CBS **16** was initially used as a chiral catalyst for the asymmetric reduction to yield **5** with only 70% ee. Reduction of the reaction temperature to −20 °C improved the enantiomeric excess to 83%. Lower temperatures, however, led to a decreased conversion, and the published 96% ee could not be reproduced (Table 1).[17] Due to these insufficient results, we tested (*R*)-MeO-CBS **17** as an oxazaborolidine system next, already used several times for

**Table 1.** Application of CBS Reduction for the Synthesis of **5**




| entry | catalyst | temp (°C)[a] | conversion (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 | **16**[c] | −10 | 100 | 70 |
| 2 | **16**[c] | −20 | 100 | 83 |
| 3 | **16**[c] | −30 | 40[e] | nd |
| 4 | **17**[d] | rt | 100 | 90 |
| 5 | **17**[d] | 0 | 100 | 99 |

[a] Temperature during addition of the ketone solution. [b] Detected by HPLC, Chiracel OJ column, flow rate 1.0 mL/min, temp 20 °C, eluent hexane/propan-2-ol (9/1), retention times (*R*)-**15** 5.73 min, (*S*)-**15** 6.58 min. [c] X = $SMe_2$. [d] X = diethylaniline. [e] Detected by $^1H$ NMR spectroscopy of the crude product.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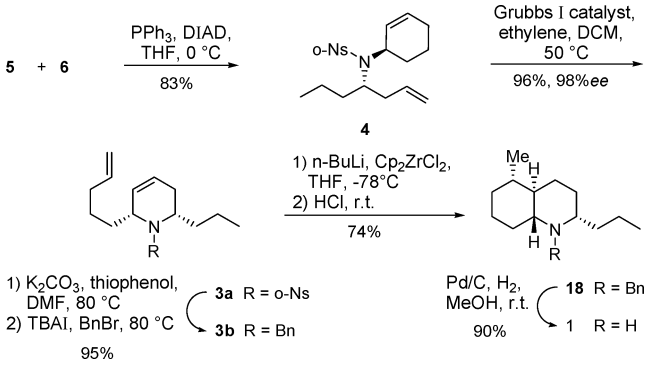
enantioselective reductions[19] but, to the best of our knowledge, never to synthesize *ent*-**5**.

Catalyst **17** was synthesized through in situ reaction of (*R*)-α,α-diphenylprolinol with $B(OMe)_3$ at room temperature. Addition of $BH_3$·diethylaniline followed by dropwise addition of a solution of **13** in THF afforded **15** with remarkably better enantiomeric excess. Carrying out the reaction at room temperature gave **15** with 90% ee. Temperature reduction to 0 °C, during addition of the ketone solution, finally yielded **15** with 99% ee. Subsequent dehalogenation was achieved by halogen-metal exchange with tert-BuLi and subsequent hydrolysis to give **5** in 96% yield.

Synthesis of **4** was achieved by Mitsunobu reaction[12] of **5** and **6** (Scheme 3). Employment of 1.3 equiv each of $PPh_3$,

**Scheme 3.** Synthesis of **1**




diisopropylazo dicarboxylate (DIAD), and **5** afforded **4** in 42% yield after 72 h. After testing different solvents, we finally succeeded in optimizing the reaction by use of THF and addition of an excess (2 equiv) of $PPh_3$, DIAD, and **5** to yield **4** in 83%. RRM of the obtained secondary amide **4** was undertaken with 5 mol % benzylidene-bis-(tricyclohexylphosphine)-dichloro ruthenium (Grubbs I catalyst)[20] under an ethylene atmosphere. The transformation resulted in complete conversion of the starting material and afforded stereoselectively the cis-2,6-disubstituted tetrahydropyridine derivative **3a** in 96% yield. The enantiomeric excess of **3a** was determined to be 98% by means of chiral HPLC analysis with comparison to the racemic material.

Unfortunately, subsequent Negishi-coupling[7] of **3a** did not lead to the desired cyclization product but resulted in dimerization of the aromatic nitro group. However, changing the protecting group to the corresponding *N*-benzyl derivative **3b**, we succeeded in constructing the required decahydroquinoline structure **18**. The cyclization reaction was carried out with *n*-BuLi and $Cp_2ZrCl_2$ under an argon atmosphere to afford **18** in 74% yield. Utilization of a nitrogen atmosphere proved to be unsuccessful, presumably due to the formation of an unreactive zirconium-nitrogen complex.[21] Final deprotection of **18** by hydrogenation with Pd/C afforded **1** as a colorless solid in 90% yield with an optical rotation of +27.4 (*c* 0.56, MeOH). Unfortunately, stereochemical determination of the product from Negishi cyclization was unsuccessful through NMR. Therefore, transformation of *rac*-**1** to the corresponding *N*-*p*-nitro-benzoate was carried out to form a crystallizable derivative. Subsequent analysis by X-ray crystallography,[22] coupled with the knowledge of the absolute configuration of the chiral precursor, indicates the absolute stereochemistry of the decahydroquinoline *ent*-**1** to be 2*S*,4*aR*,5*S*,8*aR*.

In cooperation with J. W. Daly et al. (Institutes of Health, Maryland), our synthetic (+)-enantiomer was compared with the isolated natural product by means of chiral GC. Both derivatives showed different retention times, indicating that natural *trans*-**195A** occurs as the (−)-enantiomer, whose absolute configuration is 2*R*,4*aS*,5*R*,8*aS*.

In conclusion, we successfully applied the concept of a stereoselective RRM and a diastereoselective Negishi coupling of dienes to the first enantioselective synthesis of (+)-*trans*-**195A**. Starting from (*R*)-epichlorohydrin **7** we synthesized **1** in 11 steps and in 35% overall yield. Subjection of **1** to chiral GC followed by comparison with the isolated natural product led to the determination of the absolute configuration of natural *trans*-**195A**.

**Acknowledgment.** We would like to thank the work group of J. W. Daly (Institutes of Health, Maryland), especially Thomas F. Spande for the chiral GC measurements of the synthesized material and for the provided chromatograms.

**Supporting Information Available:** Experimental procedures and full characterization for compounds **1**, **3**−**6**, **8**−**12**, **15**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Crystallographic data have been deposited with the Cambridge Crystallographic Data Center under desposition no. CCDC-239791.