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Confirmation of the absolute configuration of (−)-aurantioclavine

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Dedicated to Professor Harry H. Wasserman on behalf of his 90th birthday

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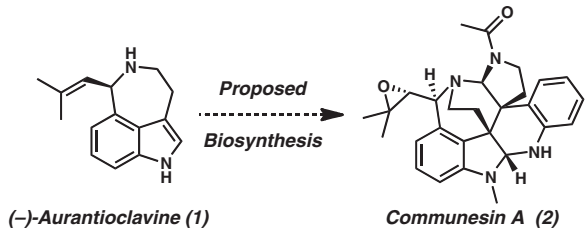
ABSTRACT

We confirm our previous assignment of the absolute configuration of (−)-aurantioclavine as 7*R* by crystallographically characterizing an advanced 3-bromoindole intermediate reported in our previous synthesis. This analysis also provides additional support for our model of enantioinduction in the palladium(II)-catalyzed oxidative kinetic resolution of secondary alcohols.

As part of a research program in oxidative catalysis, we have developed a palladium(II)-catalyzed oxidative kinetic resolution (OKR) of secondary alcohols.[1] To demonstrate the utility of this methodology, we have carried out several natural product syntheses that rely on OKR to induce asymmetry.[2] Specifically, we completed the first enantioselective synthesis of (−)-aurantioclavine (**1**), which allowed the assignment of the absolute configuration of the natural product as 7*R* (Scheme 1).[2c] Aurantioclavine was a focal point of our interest in the calycanthaceous alkaloids (e.g., communesin A (**2**))[3] and allowed us to demonstrate the utility of the enantioenriched secondary alcohols produced from our OKR reaction as precursors to enantioenriched amines. However, a recent personal communication from Professor Jia called into question our stereochemical assignment.[4] This coupled with our recent experience with an attempted S_N2 reaction that proceeded with retention of configuration[5] prompted us to reinvestigate our assignment.

Our synthesis of the ergot natural product (−)-aurantioclavine (**1**) employed an OKR of racemic diol **3**, which produced enantioenriched diol (−)-**3** and ketone **4** (Scheme 2). Incorporation of the required nitrogen atom was achieved by treating diol (−)-**3** with hydrazoic acid under low temperature Mitsunobu conditions to give the displacement product, azide **5**, which was expected to be of inverted configuration. A sequence of azide reduction, nosyl protection, and bromination provided bromoindole **7**. Elaboration of the indole 3-position and dehydration provided alcohol **9** underwent smooth cyclization to form indoleazepine **10**.[6] Deprotection



Scheme 1. Alkaloid natural products of interest.

of bis-sulfonamide **10** afforded (−)-aurantioclavine, which matched the optical rotation of the natural material in both sign and magnitude.[7]

It should be noted that the assignment of the absolute configuration of diol (−)-**3** in our previous paper was based entirely on the extrapolation of our model for enantioinduction in the OKR reaction and our extensive experience with such secondary benzylic alcohol substrates.[8] No definitive proof of the absolute configuration of diol (−)-**3** was obtained at that time. While this was a reasonable course of action given the complete agreement between the experimental data from other substrates of known absolute configuration and our model, we chose to reexamine the route.

In scrutinizing our synthesis, we judged that the two most probable, albeit unlikely, opportunities for an unanticipated stereochemical outcome were the OKR and Mitsunobu steps (Scheme 3). In one scenario (path A), alcohol **3** might act as an anomalous substrate, such that under the OKR conditions the (*S*)-enantiomer is oxidized more rapidly. Alternatively, we considered the possibility that during the Mitsunobu reaction the pendant

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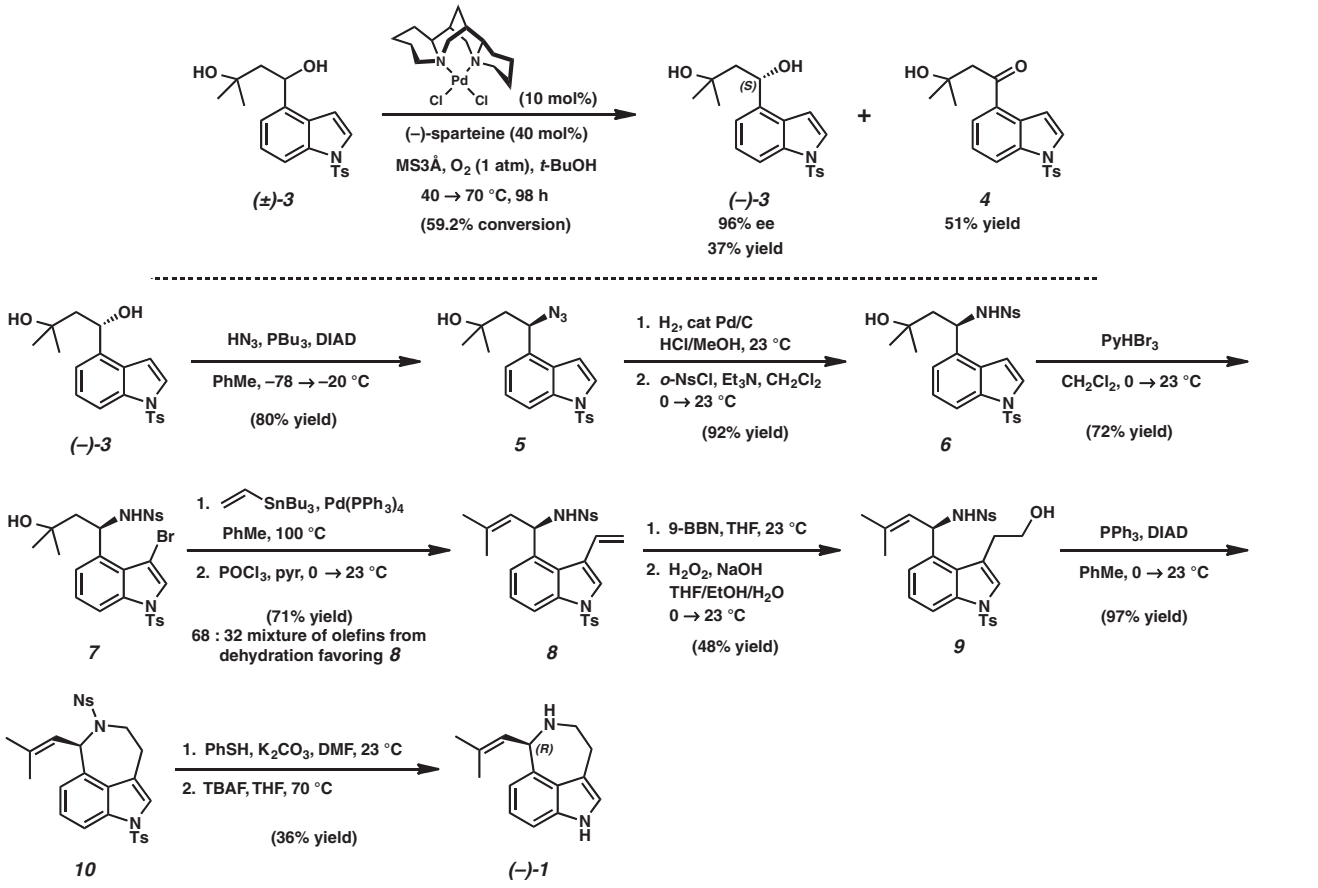
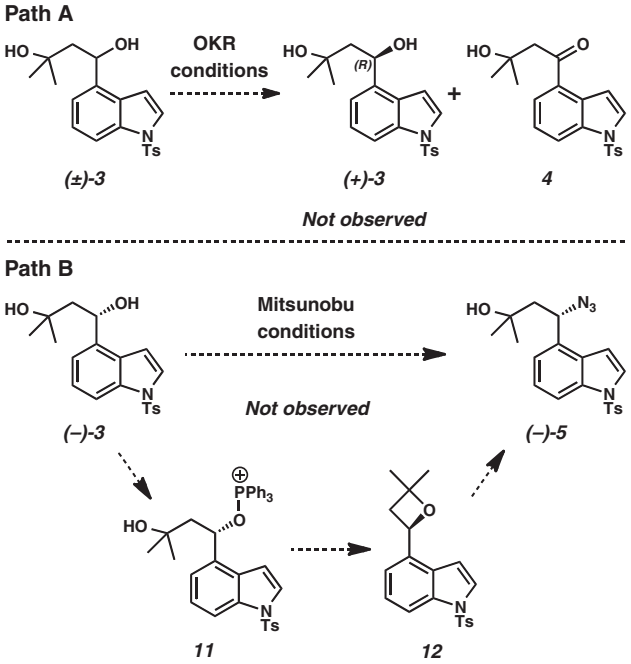


Scheme 2. Synthesis of (−)-aurantioclavine.



Scheme 3. Potential pathways for unanticipated stereochemical outcomes in the functionalization of diol **3**.

tertiary alcohol could displace an activated intermediate to form oxetane **12**, which could be opened by the azide nucleophile and give the product with an overall retention of configuration (path

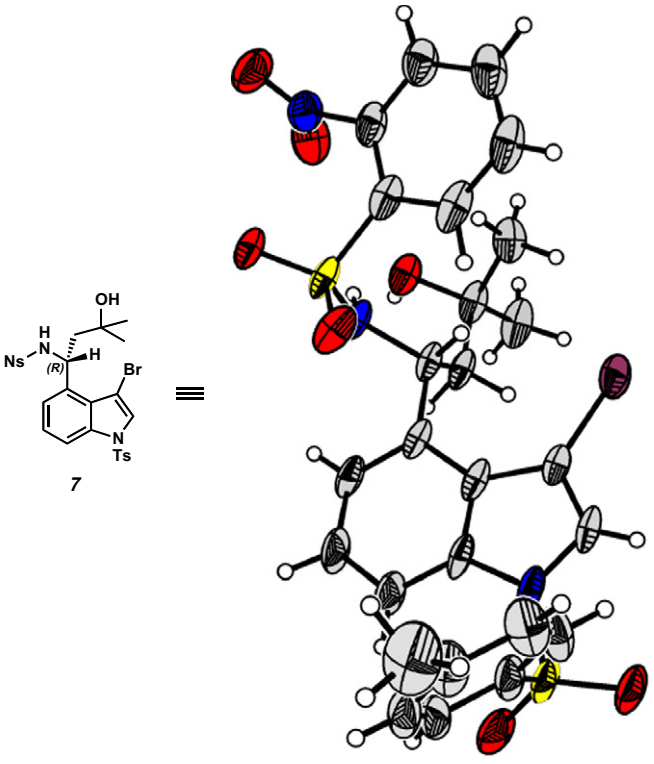


Figure 1. ORTEP representation of compound **7**.

B).[5,9] While it seemed possible, a priori, that later steps in the synthesis might erode the enantiomeric excess of advanced intermediates, no step subsequent to the azide displacement appeared capable of completely inverting the stereocenter.

In order to address these possibilities, we initiated efforts to obtain definitive evidence regarding the absolute configuration generated by our synthesis. Fortunately, intermediate bromide **7** proved to be crystalline and provided crystals of sufficient quality for single crystal X-ray diffraction studies. Calculation of the Flack parameter[10] clearly indicated that the absolute stereochemistry of the C(7) stereocenter is *R* (Fig. 1).

This structural data reaffirms our assertion that the natural product (−)-aurantioclavine (**1**) is of the (7*R*)-configuration and provides further support for our model of asymmetric induction in the OKR reaction.

Acknowledgments

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Supplementary data

Crystallographic data for compound **7** can be obtained from this journal or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK by quoting the deposition number (772069). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.074.

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