ORGANIC LETTERS

2006
Vol. 8, No. 18
4051−4054

Synthetic Studies on Quinine: Quinuclidine Construction via a Ketone Enolate Regio- and Diastereoselective Pd-Mediated Allylic Alkylation

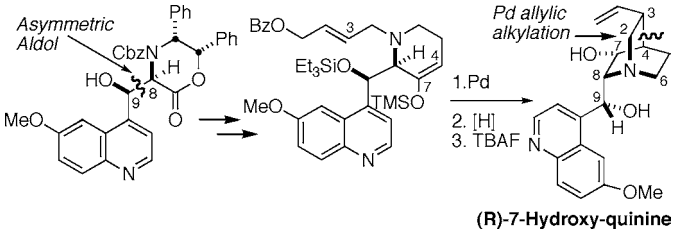
Deidre M. Johns, Makoto Mori, and Robert M. Williams*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523-1872

rmw@lamar.colostate.edu

Received June 21, 2006

ABSTRACT



7-Hydroxy-quinine was synthesized by an asymmetric aldol reaction that establishes the C8 and C9 stereochemistry, followed by construction of the 3-vinyl-quinuclidine azabicyclo[2.2.2]octane by C3–C4 ring closure using an intramolecular palladium-mediated allylic alkylation with excellent regio- and diastereoselectivity. This is the first report of a ketone-enolate-stereocontrolled allylic alkylation mediated by palladium. The title compound and a dehydro-quinine analogue were evaluated for antimalarial activity.

The *Cinchona* alkaloid, quinine (**1**),[1] was the first known effective treatment for malaria and has attracted considerable attention from synthetic chemists since its formula was determined by Strecker in 1854.[2] Initially, interest in quinine was driven by the need for a domestically produced malaria remedy and more recently because of its challenging architecture and utility as a catalyst or ligand for asymmetric synthesis.[3] Malaria kills over 1 million people every year, and this is projected to increase as a result of the ineffectivity of available treatments against widespread drug-resistant strains of the parasite. The first stereocontrolled synthesis of quinine was elegantly accomplished by Stork and co-workers in 2001 deploying a novel N1−C6 disconnection strategy.[4] Jacobsen[5] and Kobayashi[6] in 2004 completed the stereocontrolled synthesis of quinine via the historic Rabe N1−C8 disconnection strategy. In this communication, we report the first synthetic approach to quinine via a stereocontrolled C3−C4 ring-closure reaction to construct the quinuclidine azabicyclo[2.2.2]octane ring system (Scheme 1). This was accomplished using a modified Pd-mediated allylic alkylation to enable a TMS-enol ether (preformed ketone enolate equivalent) to participate as the nucleophile in an intramolecular cyclization. The observed diastereoselectivity at C3 suggests the reaction proceeds by a mechanism in which the C7-oxygen influences the forming vinyl

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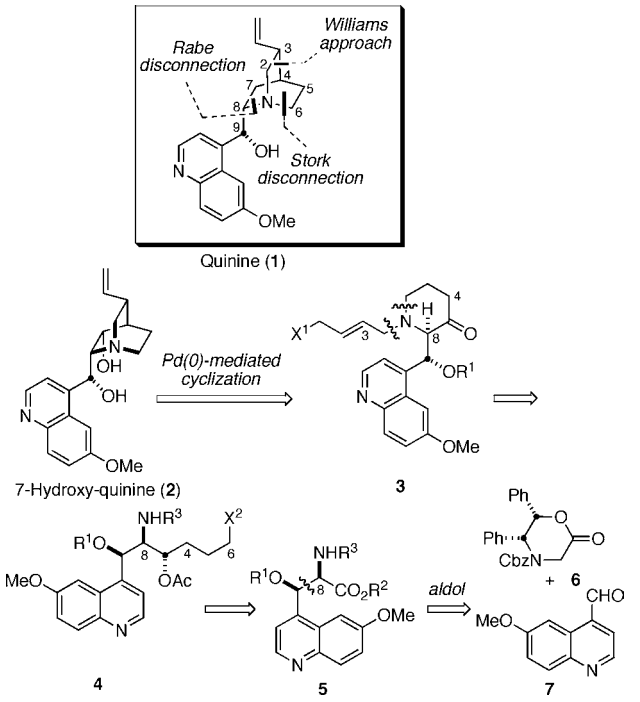
10.1021/ol061524s CCC: $33.50
Published on Web 08/04/2006

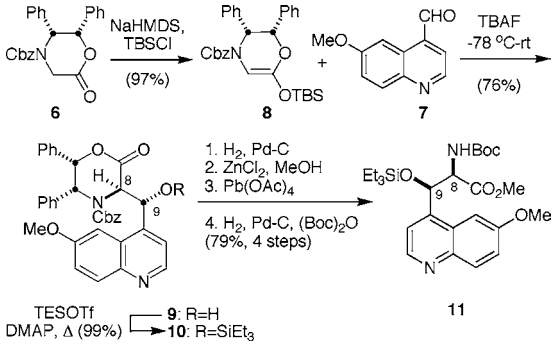
Scheme 1. Retrosynthetic Analysis



substituent. Preformation of the silyl enol ether facilitates regiocontrol; alkylation at elevated temperature occurs exclusively at the site of kinetic enolization. Another novel aspect of our approach is the establishment of the C8 and C9 stereogenic centers early in the synthesis through the use of an asymmetric aldol reaction.

The piperidinone **3** can be further disconnected to an α-amino-*β*-hydroxy ester (**5**), for which our laboratory has developed methods to prepare using the commercially available chiral, nonracemic 5,6-diphenylmorpholine-2-one templates (Williams lactones).[7] Lactone template (**6**) is known to participate in boron-mediated aldol reactions and provide *anti*-aldol products, which are well suited for preparing the historically challenging C8 and C9 stereogenic centers of quinine as illustrated in Scheme 2.[8] The boron-mediated aldol reaction of **6** with quinolinecarboxaldehyde **7**[9] resulted in an unsatisfactory yield (42% yield). However, the TBAF-promoted reaction of **7** with silyl enol ether **8** provided a significantly improved yield and excellent diastereoselectivity (>30:1 dr) of **9**, the relative configuration of which was secured by X-ray crystallography.[10] The desired *anti*-aldol product (**9**) is thermodynamically favored over the

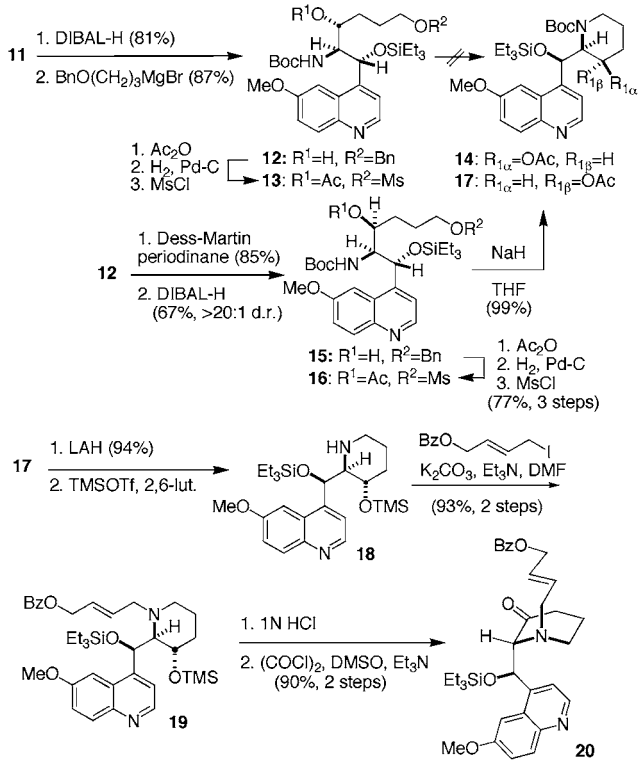
Scheme 2. Asymmetric Aldol Reaction



syn-isomer as illustrated by the decreased *syn*/*anti* selectivity for **9** when the reaction is maintained at −78 °C (1:1 to 2:1 dr). Optimal yields are obtained when the reaction is quenched at low temperature to minimize retro-aldol product formation. Protection of the C9-hydroxyl as a triethylsilyl ether (TES) (the largest silyl ether that it was found possible to install) provided compound **10**. Standard conditions for reductive cleavage of the chiral template (H_2, Pd−C) were sluggish as a result of the presence of the quinoline moiety and merely cleaved the N-Cbz group. The resulting free amine intermediate was converted in three steps to the desired α-amino-*β*-silyloxy-ester **11** in excellent yield.

With **11** in hand, the next task was to form the piperidine ring system (Scheme 3). Ester **11** was directly reduced to the corresponding aldehyde, and treatment with 3-(benzyl-

Scheme 3. Preparation of Piperidine Derivative **20**



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oxypropyl)magnesium bromide[11] resulted in the (*R*)-alcohol (**12**) selectively. This was converted to mesylate **13**, which resisted cyclization to piperidine **14**. We reasoned that gauche interactions preclude this substance from adopting the conformation required for cyclization as depicted in Figure 1. Fortunately, the epimeric C7-acetate (**16**) could be

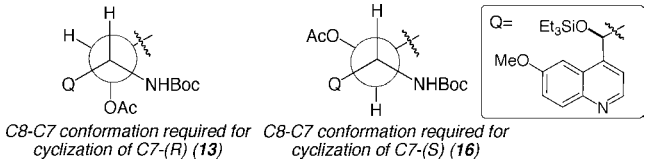


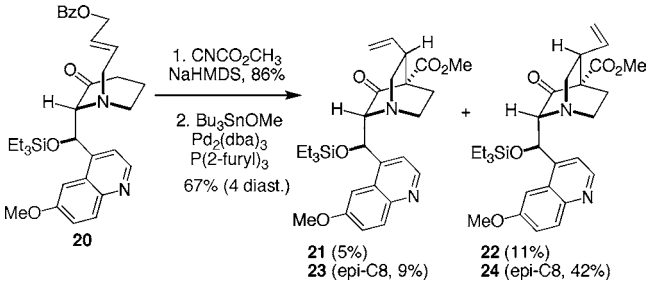
Figure 1. Conformations of **13** and **16**.

prepared from alcohol **12** via an oxidation−reduction sequence affording **15** (>20:1 dr). Indeed, the epimeric mesylate **16** cyclized to **17** when treated with NaH. Since removal of the C7-acetate required $LiAlH_4$, it was replaced with an *O*-TMS ether prior to N-alkylation. A five-step sequence involving first reductive cleavage of the acetate, followed by silylation of the C7-hydroxyl with simultaneous N-Boc deprotection,[12] N-alkylation, acid hydrolysis of the C7-OTMS, and finally Swern oxidation yielded piperidinone **20**.

Our laboratory has previously demonstrated the powerful directing ability of sodium enolates in stereoselective S_N2' cyclizations for the synthesis of complex prenylated indole alkaloid natural products such as the brevianamides and paraherquamides.[13] We envisioned a similar tight contact ion-pair, closed transition state between the enolate and forming vinyl group to control the C3-vinyl stereochemistry. The stereochemistry at C4 would be concomitantly established by facial control derived from the stereogenic center at C8.

After initial efforts to induce enolate species derived from ketones related to **20** (allylic halide substrates as opposed to the allylic benzoate were evaluated) to cyclize using various S_N2' conditions failed, we turned to palladium-mediated cyclizations. Piperidinone **20** was converted to the corresponding β-keto ester and subjected to Tsuji−Trost conditions (Scheme 4). Encouragingly, this provided quinuclidine products **21**−**24** after optimization. Attempts to decarboxylate, reduce, and deprotect all resulted in decomposition. This and the lack of stereoselectivity at C3 prompted us to investigate alternative substrates. Shortly after our initial studies, Trost reported a similar transformation in which a quinuclidine heterocycle lacking the problematic quinine C8

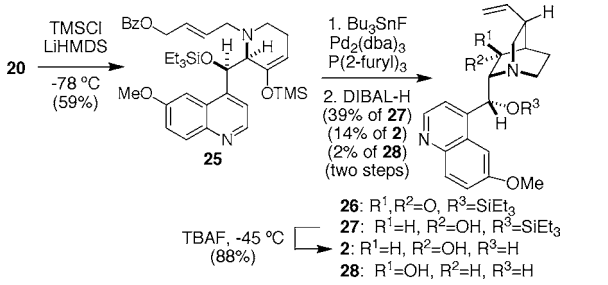
Scheme 4. Allylic Alkylation of Malonic Ester Derivative



functionality was prepared in 8:1 dr using chiral, nonracemic catalysts.[14]

The regio- and diastereselective allylic alkylation of ketone enolates is a versatile yet challenging synthetic transformation. Limited examples using ketone enolates have been reported.[15] The carbon nucleophiles used are predominantly stabilized carbanions, such as malonates, or enolate equivalents formed by the decarboxylation of allyl-β-keto carboxylates.[16] Ketone enolates as nucleophiles in this reaction offer several synthetic advantages as illustrated by our system (Scheme 5). The product C8-hydrogen is less prone to

Scheme 5. Regio- and Diastereoselective Allylic Alkylation of Ketone-Derived TMS Enol Ether



equilibration, and the need for subsequent decarboxylation is eliminated. Preformation of a silylenol ether enables alkylation exclusively at C4. After significant optimization, it was found that treatment of silylenol ether **25** with $Pd_2(dba)_3$, P(2-furyl)$_3$, and Bu_3SnF in toluene at 85 °C provides the desired quinuclidine ketone **26** having two additional

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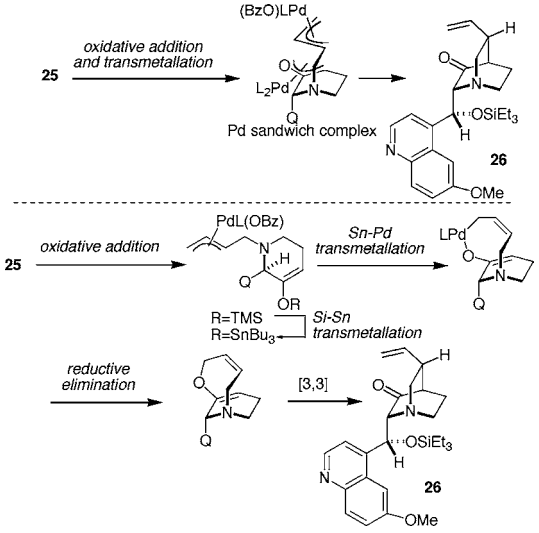
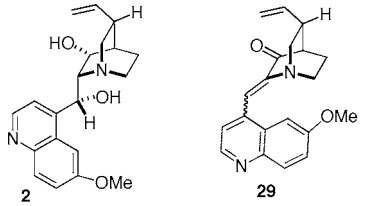
stereogenic centers established between C3−C4. Tributyltin fluoride is required to facilitate transmetalation of the silyl enol ether. Ketone **26** was immediately reduced to avoid equilibration at C8 and β-elimination. This provided the desired quinuclidine **27** and the diols **2** and **28**. Surprisingly, none of the undesired C3-vinyl stereoisomer was observed. Product **27** exists predominantly as two rotamers about C9 as determined by ROESY NMR and confirmed by variable temperature NMR ($\Delta G^\circ = 1.8$ kcal/mol). Removal of the silyl ether from **27** provided (*R*)-7-hydroxy-quinine **2**.

The mechanism of the net S_N2'-type cyclization reaction, particularly with respect to the diastereoselectivity observed, is interesting and deserves comment. The standard π-allyl Pd-based allylic alkylation mechanism fails to explain the observed stereoselectivity.[16] Two mechanisms can be envisioned (Scheme 6): (1) formation of a Pd-sandwich complex[17] involving an η^3 Pd-enolate and a π-allyl Pd species undergoing allylic alkylation, which could favor the desired C3 isomer; and (2) Pd-mediated etherification,[18] followed by a Claisen rearrangement.[19] The latter mechanism can only result in a single observed and desired stereoisomer (Scheme 5). Furthermore, the ethereal intermediate is reminiscent of the [5.3.1] AB ring system of taxane, which was conversely prepared from bicyclo[2.2.2]octanes by sigmatropic rearrangements.[20]

Scheme 6. (1) Pd-Sandwich Complex. (2) Pd-Mediated Etherification Followed by Claisen Rearrangement Mechanism



We were also interested to see if 7-oxygenated derivatives of quinine are effective against malaria parasites, as analogues of quinine of this type have not been reported. Diol **2** and dehydro-keto-quinine **29** (isolated as a cyclization byproduct during optimization studies; Figure 2) were evaluated against two strains of *Plasmodium falciparum*; surprisingly, both analogues were found to be inactive.



Inactive up to 5 μM, 60h against *Plasmodium* falciparum HB3, Dd2

Figure 2. Structures of 7-oxy-quinine analogues **2** and **29** evaluated for antimalarial activity.

In conclusion, the asymmetric synthesis of 7-hydroxy-quinine (**2**) has been accomplished via a novel quinuclidine-forming construction involving a C3−C4 Pd-mediated S_N2'-type cyclization reaction. Two 7-oxy analogues of quinine were evaluated and found to be inactive against malaria parasites. The application of this new conceptual approach to the total synthesis of the *Cinchona* alkaloids is currently under study in these laboratories.

Acknowledgment. We thank the National Institutes of Health (GM068011) for financial support. We are very grateful to Prof. Daniel Goldberg for evaluating the biological activity of analogues **2** and **29**, to Prof. L. S. Hegedus (Colorado State University) for helpful discussions, and to Dr. Chris Rithner for help with NMR spectroscopy. D.M.J. thanks the American Cancer Society, New England Division Broadway on Beachside for a postdoctoral fellowship, and M.M. thanks Sankyo Co., Ltd. for financial support.

Supporting Information Available: Experimental procedures and characterization of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061524S

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