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Asymmetric Synthesis of (+)-Mequitazine from Quinine

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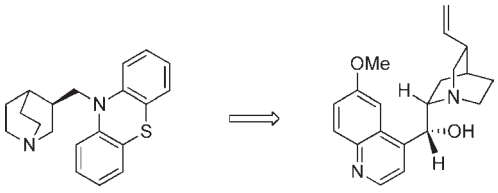
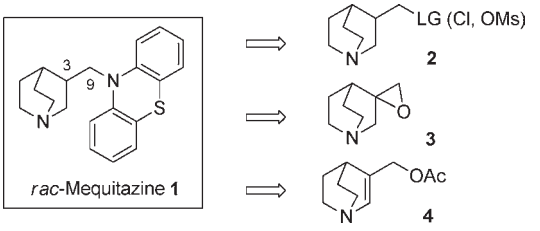
ABSTRACT



The first asymmetric synthesis of the antihistaminic drug mequitazine is reported. Our approach started from quinine, a *Cinchona* alkaloid, whose chiral information was exploited for setting up the stereogenic center of (+)-mequitazine.

Mequitazine **1** is a potent antihistaminic drug currently in use for the treatment of allergic conditions such as itching, rhinitis, urticaria, hay fever, and Quincke's edema.[1] Mequitazine is an H-receptor antagonist which competes with histamine on effector cells.[2] It belongs to the second generation of antihistaminic drugs and is currently marketed, as racemate, under various brand names such as Primalan. Several approaches have been reported in the literature for the synthesis of mequitazine, most of which have been patented. Strategies that have been devised so far relied on the coupling of a quinuclidine derivative with phenothiazine (Scheme 1). For example, alkylation of phenothiazine with 3-substituted quinuclidine electrophiles **2** permitted the efficient formation of the key C9−N bond.[3] Also, nucleophilic attack of a phenothiazine anion on epoxide **3**, followed by elimination of the resulting tertiary alcohol and double bond hydrogenation, allowed the multistep synthesis of mequitazine.[4] The most recent synthetic route reported to date for the synthesis of mequitazine is from the group of Baati who described the palladium catalyzed alkylation of phenothiazine by allylic acetate **4**.[5] The latter was prepared starting either from epoxide **3** by β-elimination or by using the Shapiro reaction. This approach permitted the elegant and straightforward construction of mequitazine's skeleton.

Scheme 1. Known Synthetic Approaches to *rac*-Mequitazine



However, the above strategies only provide access to *rac*-mequitazine and no enantioselective synthesis has yet been reported. Optically active mequitazine has nevertheless been obtained by kinetic resolution of a racemic synthetic intermediate, but this approach inexorably leads to 50% loss of

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(3) (a) Gueremy, C.; Labey, R.; Wirth, D.; Auclair, M. US Patent 3987042, 1976. (b) Guminski, Y.; Imbert, T.; Lesimple, P. WO Patent 9929692, 1999.

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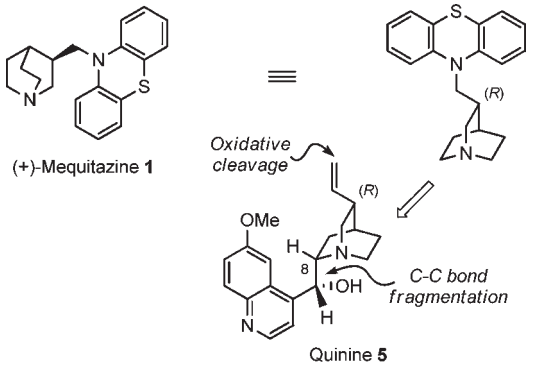
material.[6] In the present paper we would like to disclose the first asymmetric synthesis of (+)-mequitazine.

Stereochemistry of the C3 position is usually difficult to control because of the high symmetry of the quinuclidine core. This prompted us to investigate a novel synthetic route starting from widely available *Cinchona* alkaloids (Scheme 2).[7] Our choice was governed by the fact that these alkaloids (e.g., quinine **5**) already incorporate a C3-stereogenic center of the same absolute (*R*) configuration as that of (+)-mequitazine. The C3-borne vinyl group of the *Cinchona* alkaloid could afterward be transformed by oxidative cleavage and reduction for subsequent coupling with phenothiazine. Albeit, this pathway calls for the removal of the "superfluous" quinoline side chain linked to C8 in order to provide the required quinoline-free quinuclidine.

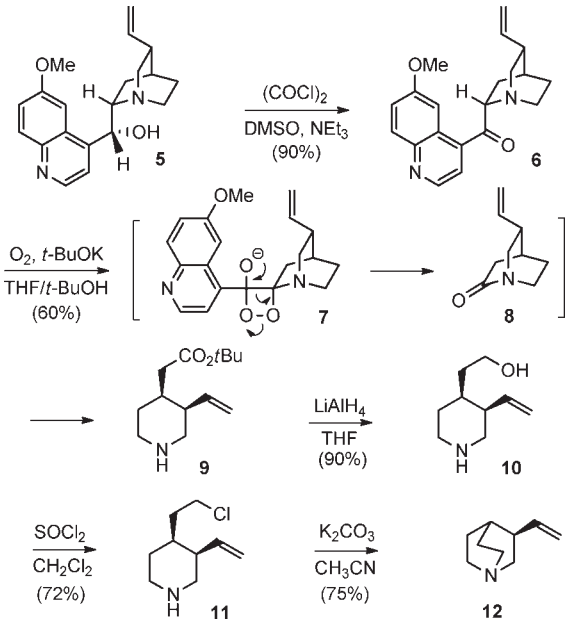
Scheme 2. Strategy for the Synthesis of (+)-Mequitazine Starting from Quinine



To remove the pendant side chain, we conceived that the carbon−carbon bond connecting the quinuclidine to the quinoline part could be cleaved by an autoxidation process, as originally demonstrated by Doering in 1946 for quininone.[8] The synthetic plan was thus divided into two stages: (i) isolation of the quinuclidine core from the *Cinchona* alkaloid and (ii) interconversion of the vinyl group for ultimate coupling with phenothiazine.

We chose quinine **5** as the starting alkaloid. Our synthesis thus commenced from **5** which was cleanly transformed to quininone **6** by Swern oxidation (Scheme 3). The resulting ketone was then reacted with potassium *tert*-butanolate in the presence of oxygen to induce autoxidation of the enolate. Fragmentation of the transient cycloadduct **7** however failed to give quinuclidinone **8** but rather provided meroquinene *tert*-butyl ester **9**.[9] The latter resulted from the *in situ* ring-opening of **8** by *tert*-butyl alcohol. The peculiar reactivity of the quinuclidinone intermediate **8** toward nucleophilic ring-opening can be rationalized by the intrinsic ring strain of the twisted amide that prevents classical stabilization by π-electron delocalization.[10] Meroquinene **9**, whose stereocenters were unaffected by the autoxidation step, was nevertheless exploited for the continuation of our synthesis of (+)-mequitazine.

Scheme 3. Stage 1: Isolation of the Quinuclidine Core from Quinine



Lithium aluminum hydride reduction of the *tert*-butyl ester of **9** gave the corresponding alcohol **10** which was treated with thionyl chloride to produce chlorinated quinuclidine precursor **11**. Intramolecular cyclization of **11** in refluxing acetonitrile finally afforded optically active vinyl quinuclidine **12**.

At this stage, we formally isolated the vinyl quinuclidine part from the quinoline part of quinine, while keeping intact the C3 stereogenic center. With vinyl quinuclidine **12** in hand, we next had to convert the olefinic side chain into an activated leaving group for the final coupling with phenothiazine. This transformation involved the ozone-mediated oxidative cleavage of the double bond (Scheme 4). The strongly basic nitrogen atom of **12** was first protected as the corresponding trifuoroacetate salt to prevent *N*-oxide formation and further side reactions. The protonated vinyl quinuclidine was then reacted with ozone at −78 °C in methanol, and to minimize potential risks of epimerization, the transient ozonide was directly reduced *in situ* at low temperature with sodium borohydride. Quinuclidine methyl alcohol **13** was recovered in 63% yield but of unknown optical purity as enantiomeric excess

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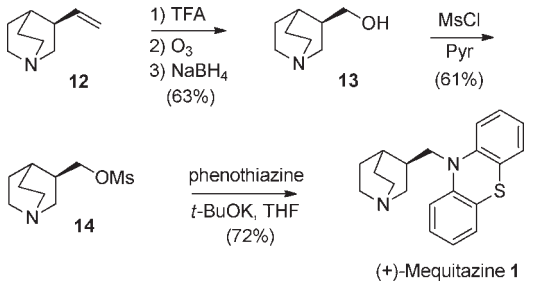
Scheme 4. Stage 2: Completion of the Synthesis of (+)-Mequitazine by Coupling with Phenothiazine



measurements by chiral HPLC were not feasible due to the lack of UV absorption of the substrate. The synthesis was nevertheless continued by activation of the alcohol as the corresponding mesylate **14** before phenothiazine was added. The coupling reaction proceeded in the presence of potassium *tert*-butanolate in refluxing THF to give (+)-mequitazine **1** in 72% yield.

Spectral data (^{1}H and ^{13}C NMR) of (+)-**1** are consistent with those of authentic mequitazine, and optical rotation measurement gave an α_D value of +43.4 (*c* 0.098, EtOH, 20 °C) to be compared to −40.5 (*c* 0.93, EtOH, 24 °C) for (−)-mequitazine (obtained by chiral resolution).[11] The enantiomeric excess of (+)-**1** was ultimately measured by chiral HPLC which indicated an ee value greater than 99%. These results unambiguously indicate that the C3 stereocenter of the starting *Cinchona* alkaloid was fully preserved throughout our synthesis of (+)-mequitazine which was achieved in eight linear steps.

The strategy we have developed to meet the synthetic challenge of the first asymmetric synthesis of mequitazine may be viewed as a general route for the preparation of optically active substituted quinuclidines from *Cinchona* alkaloids. The devised synthetic scheme permitted the straightforward access to (+)-mequitazine **1** of C3(*R*) absolute configuration.

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Supporting Information Available. Experimental procedures and copies of ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Guminski, Y.; Fabre, V.; Lesimple, P.; Imbert, T. *Org. Prep. Proc. Int.* **1999**, *31*, 319.