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A concise and efficient synthesis of tetrahydroquinoline alkaloids using the phase transfer mediated Wittig olefination reaction

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ABSTRACT

The present study describes the total synthesis of 1,2,3,4-tetrahydroquinoline alkaloids (±)-galipinine, (±)-cuspareine, (±)-galipeine and (±)-angustureine, in three steps and high yields (78%, 76%, 74%, and 66%, respectively) from common aldehyde and the ylide respectives. The key step of this approach is based on an unusual Wittig reaction by using the phase transfer medium (aq. $NaOH/CH_2Cl_2$ 1:1 or *t*-BuOK/*t*-BuOH/CH_2Cl_2 1:1), affording olefinic intermediates in high yields.

Tetrahydroquinoline alkaloids

1,2,3,4-Tetrahydroquinoline (THQ) alkaloids are important pharmacological structures that are currently among the most popular targets for the development of new synthetic methodologies.[1] Among the natural alkaloids containing the 1,2,3,4- tetrahydroquinoline nucleus, angustureine and its congeners – galipinine, cuspareine, and galipeine – stand out (Fig. 1).

These alkaloids were isolated from the stem bark of *Galipea officinalis* Hancock, a South American shrub known as angostura and characterized for the first time by Jacquemond-Collet et al.[2] and Rakotoson et al.[3] Extracts of the stem bark of this shrub have been used in Venezuelan folk medicine to treat various diseases, including dyspepsia, dysentery, and diarrhea, and symptoms such as fever.[4] Additional biological assessments of alkaloids also revealed a prominent *in vitro* antimalarial activity (IC_{50} 0.09–38 μg mL^{-1}) against chloroquine-resistant (CQR) strains.[5]

In this context, these compounds have emerged as reference standards for the application of new methodologies to prepare tetrahydroquinoline-type structures. In the literature, there are more than 24 publications to date concerning the synthesis of these tetrahydroquinolinic alkaloids,[6] in addition to a recent review covering this subject.[1]

A Wittig reaction

The Wittig reaction is one of the most versatile synthetic methods for the preparation of olefins from carbonyl compounds. This reaction classically requires the use of hydrides or organometallic bases, anhydrous aprotic organic solvents, and an inert atmosphere.

However, in recent years, the use of water instead of the use of organic solvents, whether totally or partially, in various organic reactions, especially in the Wittig reaction, have become increasingly popular. These studies have contributed to the development of new environmentally benign chemical methodologies. Some representative examples on this topic can be seen in the works of Wu, J. & Yue, C.; and Bergdahl et al.; among others.[7]

Inserted in a research program for the synthesis of natural products with remarkable biological activities, which allows for advances in the bioprospecting of new drugs, mainly against neglected tropical diseases (leishmaniasis, Chagas disease, and schistosomiasis), the present study seeks to describe a new approach to the racemic synthesis of 2-alkyl-substituted tetrahydroquinolinic alkaloids: galipinine, cuspareine, galipeine, and angustureine. The preparation of these compounds was facilitated by the use of a phase transfer medium in the Wittig reaction, applied as a new protocol, to prepare the olefin intermediates for the synthesis of these alkaloids. Our main interest focused on a

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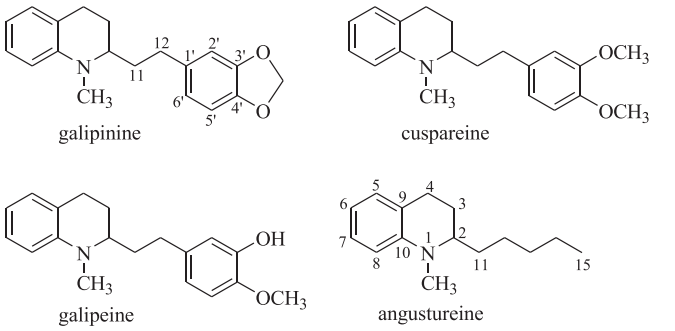


Fig. 1. Structures of THQ alkaloids galipinine, cuspareine, galipeine, and angustureine.

simple, direct, and environmentally friendly approach that would allow for the synthesis of these alkaloids.

From our point of view, the key reaction in alkaloid synthesis, according to the retrosynthetic analysis shown in Scheme 1, is the Wittig olefination between quinaldehyde **7** and phosphorus ylides (phosphoranes) **11**, **17**, **25**, and **30** (prepared *in situ* from the respective phosphonium salts by treatment with a base). Quinaldehyde **7** can be readily obtained from the commercially available quinaldine acid (**5**). The Wittig salts **10**, **16**, **24**, and **29**, which are phosphorane precursors, can be prepared from the piperonyl alcohol (**8**), 3,4-dimethoxybenzyl alcohol (**14**), 3-benzyloxy-4-methoxy)benzyl alcohol (**22**), and bromobutane (**28**), respectively.

Synthesis of quinaldehyde 7 and the benzyl alcohol 22

Our synthesis started with the preparation of aldehyde **7** and (3-benzyloxy-4-methoxy)benzyl alcohol (**22**). The sequence of esterification followed by reduction with DIBAL at −78 °C from the quinaldine acid (**5**), led to aldehyde **7** in 83% yield (2 steps) (Scheme 2). Benzyl alcohol **22** was obtained in a two-step one-pot synthesis from isovanillic acid (**20**). The protection of phenolic hydroxyl and simultaneous esterification of **20**, was done by treatment with benzyl bromide and K_2CO_3 in DMF. Reduction of the ester function with DIBAL at **21**, with no purification, afforded alcohol **22** in 98% yield (2 steps).

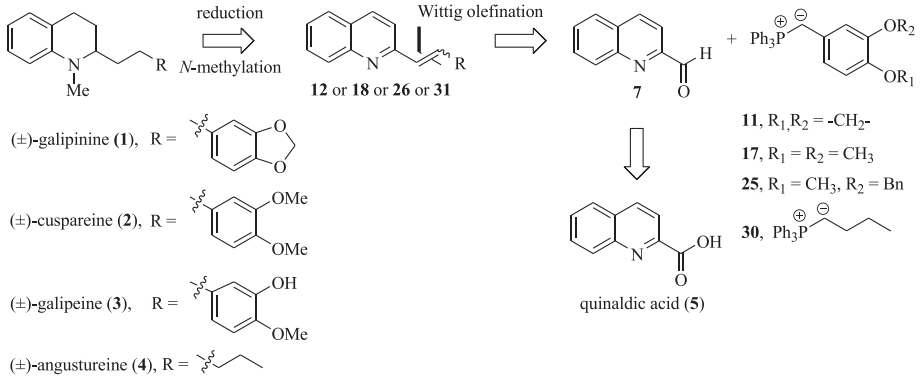
Synthesis of Wittig's salts 10, 16, 24, and 29

Treatment with PBr_3 in CH_2Cl_2 of benzyl alcohols **8**, **14**, and **22**, produced bromides **9**, **15**, and **23**, respectively (Scheme 3). These bromides, which are very unstable when exposed to chromatographic column purification, were treated with Ph_3P immediately after their preparation, producing Wittig's salts **10** and **16** in 83% yield (2 steps) after recrystallization with ethanol, and Wittig's salt **24** in 89% yield (2 steps) after purification by column chromatography. However, Wittig's salt **29** was prepared directly from bromobutane (**28**) by treatment with Ph_3P, affording salt **29** in 85% yield after purification by column chromatography.

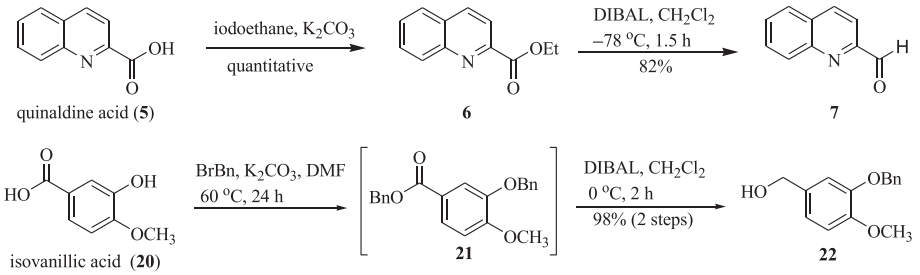
Synthesis of THQ alkaloids galipinine, cuspareine, galipeine, and angustureine

With the quinoline aldehyde (**7**) and the respective phosphonium salts **10**, **16**, **24**, and **29**, we attempted to carry out the Wittig olefination reaction between these substrates. It was believed that it would be a simple task; however, exhaustive attempts, employing conventional methods (PhLi/Et_2O,[8] *n*-BuLi/hexanes,[9] NaHMDS/THF,[10] *t*-BuOK/THF,[11] *t*-BuOK/toluene,[12] etc) led to fruitless results (yields of less than 5% and obtaining unwanted products).

In light of these results, we rationalized that the problem could be a consequence of the low solubility of the phosphonium salts in the organic solvents used to conduct this study. Hence, another Wittig olefination attempt between **7** and **10**, employing NaHMDS



Scheme 1. Retrosynthetic analysis of the THQ alkaloids (±)-galipinine, (±)-cuspareine, (±)-galipeine and (±)-angustureine.



Scheme 2. Preparation of aldehyde **7** and benzyl alcohol **22**.