New approach for the synthesis of pinane-derived bis-phosphines

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Abstract: The new approach to the synthesis of rigid bicyclic chiral bisphosphines derived from α-pinene is described. Thus, α-pinene is transformed into isopinocamphone or verbanone and these ketones are converted to spiro-epoxides. Controlled reduction of epoxides with borane gives allylic alcohols, which are transformed into bisphosphines by previously developed methods

Keywords: bis-phosphines; spiro-epoxides; pinane, monoterpenes

1. Introduction

A very important part of organic synthesis is the enantioselective synthesis. Many research programs are carried out to develop new chiral reagents, ligands and catalysts. Currently, catalytic reactions have become one of the most important areas of organic chemistry, therefore the search for new chiral catalysts is now widely explored and developed [1]. One of the directions of research is the use of chiral natural compounds as substrates because they are readily available, cheap, and in many cases enantiomerically pure compounds.

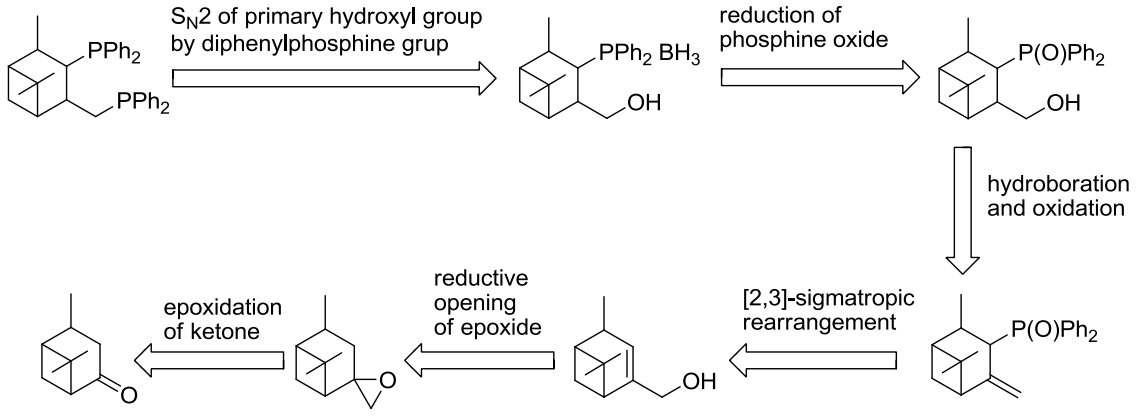
In our studies, we chose monoterpenes as a cheap source of chirality for the synthesis of chiral ligands. Monoterpenes are natural compounds present in optically active form. They are not expensive and the presence of several stereogenic centers in the molecule gives a lot of synthetic possibilities for transformations into the corresponding derivatives [2].

In this paper, we want to present our research devoted to the synthesis of bis-phosphines attached to the rigid bicyclic pinane ring system utilizing spiro-epoxides as a key intermediates. In our previous studies, we synthesized bis-phosphine derivatives of pinane, but we encountered many problems with the nucleophilic substitution of the secondary hydroxyl groups with diphenylphosphine [3]. This led us to conclusion that diphenylphosphine group should be introduced by the nucleophilic substitution of mesylate on the primary hydroxyl group. (Scheme 1)

2. Results and Discussion

We selected verbenone and isopinocamphone as substrates for the synthesis of bisphosphine derivatives. Verbenone is a commercially available compound, but the reagent of higher optical purity can be obtained by the oxidation of α-pinene with lead(IV) acetate. The resulting acetate derivatives after hydrolysis and oxidation lead to verbenone [4]. Hydrogenation of the conjugated double bond, in the presence of platinum oxide as catalyst, led to verbanone (*cis*-pinan-4-on) [5]. In turn,

isopinocamphone was obtained in a two step reaction. In the first step, α-pinene reacted with borane-dimethylsulfide adduct ($BH_3{\cdot}SMe_2$, BMS) giving crystalline diisopinocampheylborane (Ipc_2BH, in this step, optical purity of the hydroborated α-pinene is upgraded), followed by oxidation of dialkylborane to isopinocampheol by dihydrogen peroxide. Next, the hydroxyl group was converted to carbonyl group by oxidation with potassium dichromate (VI). Reaction was carried out applying Brown-Garg methodology and isopinocamphone was obtained in high yield [6].

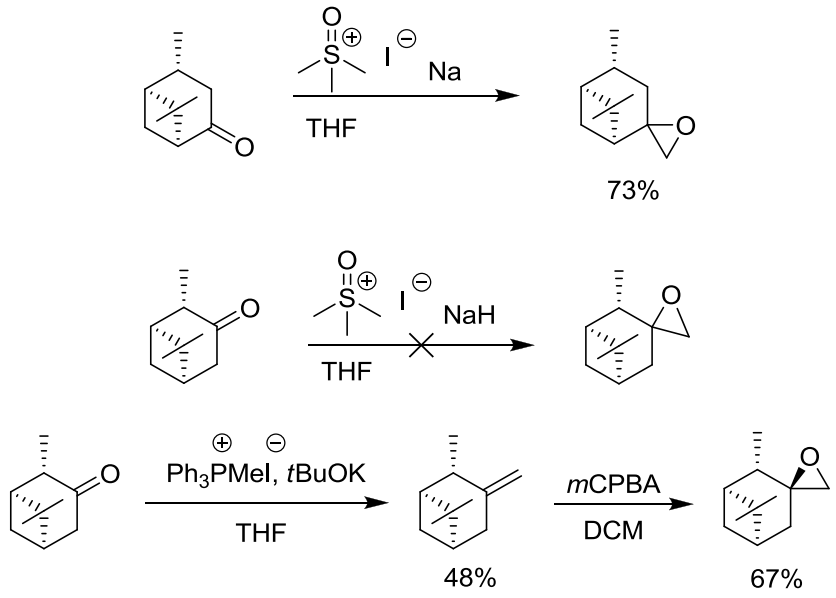


Scheme 1. Retrosynthethic analysis of bisphosphine derivatives of pinane system

The direct method of converting a ketone into an epoxide is the Corey-Chaykovsky reaction (CCR), which was discovered in 1961 by A. William Johnson and developed significantly by E. J. Corey and Michael Chaykovsky [7]. The mechanism for the Corey-Chaykovsky epoxidation consists of nucleophilic addition of the ylide to the carbonyl group. A negative charge is transferred to the oxide atom and because the sulfonium cation is a good leaving group it gets removed forming the ring [8]. In the related Wittig reaction, the formation of the much stronger phosphorus-oxygen double bond disturbs oxirane formation and olefination takes place through a 4-membered cyclic intermediate [9].

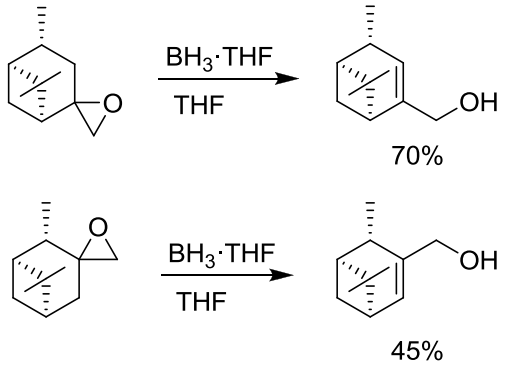
The Corey-Chaykovsky epoxidation reaction was carried out both for verbanone and isopinocamphone. Dimethyloxosulfonium methylide (known as the Corey-Chaykovsky reagent), which was generated from trimethylsulfoxonium iodide, was used as sulfonium ylide. The epoxidation reaction of verbanone furnished spiro-epoxide in good yield (73%). In the same reaction, isopinocamphone did not give the epoxidation product. We suspect that this was due to the steric hindrance of the carbonyl group, which results from the proximity of the methyl group in the pinane bridged bicyclic ring system. (Scheme2)

In the case of isopinocamphone, we applied a two steps procedure converting ketone to epoxide. In the first step, ketone was converted to methylene group by the Wittig reaction. 3-Methylene-*cis*-pinane was isolated in 48% yield. The double bond was then oxidized to the epoxide with *meta*-chloroperoxybenzoic acid (*m*CPBA) in 67% yield. (Scheme 2)



Scheme 2. Epoxidation reactions

In the following step, epoxides were reductively opened with the formation of double bonds. We applied methodology described by Yvonne Bessierre-Chretien and borane-tetrahydrofuran complex was used to obtain appropriate allylic alcohols [10]. 4-(Hydroxymethyl)-*cis*-3-pinene was isolated in 70% yield and 3-(hydroxymethyl)-*cis*-3-pinene in 45% yield. (Scheme 3)

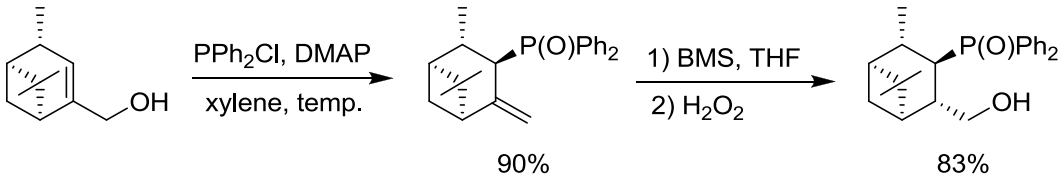


Scheme 3 Reductive opening of epoxides

Allylic alcohols were used as substrates in the second part of bis-phosphines synthesis, which is the same for both derivatives.

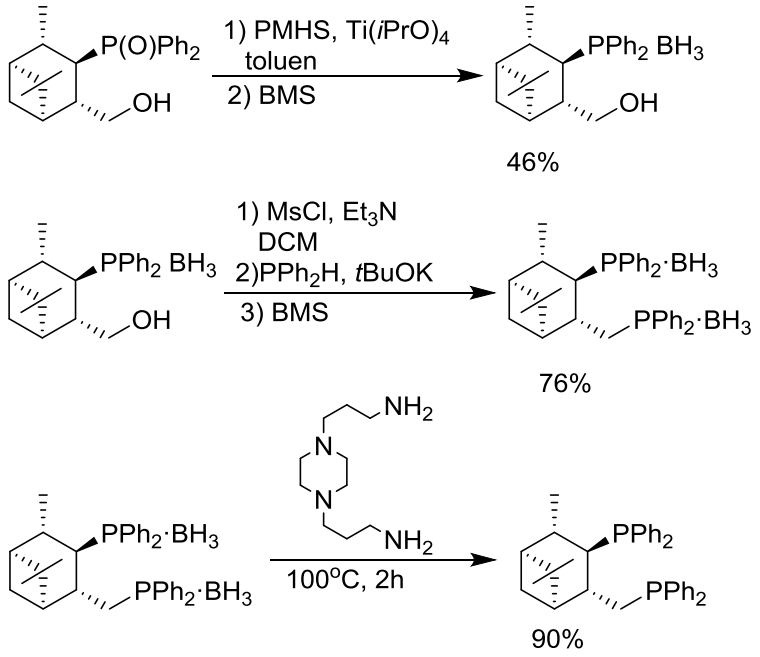
The key transformation to the further course of the synthetic pathway was the reaction of the thermal [2,3]-sigmatropic rearrangement of the allylic diphenylphosphinite to diphenylphosphine oxide [11] It was carried out in xylene as a solvent, which allowed to keep the temperature of the reaction mixture at around 130°C to finish rearangement in very good yield (90%). The obtained products, 3-(4-methylenepinanyl)-diphenylphosphinoxide and 4-(3-methylenepinanyl)-diphenyl-phosphinoxide, were fully characterized using spectroscopic methods. Then, the

hydroboration/oxidation reaction was carried out providing a derivative with a primary hydroxyl group with 83% yield. (Scheme 4)



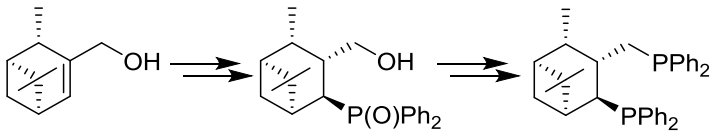
Scheme 4

Finally, in the last three steps of the synthesis diphenylphosphine oxide was reduced with polimethylhydrosiloxane (PMHS) in the presence of $Ti(O^iPr)_4$ and protected as a borane complex. Next, the primary hydroxyl group, after conversion to mesylate, was substituted with diphenylphosphine, which was protected as borane adduct. In the last step, deprotection of the diphenylphosphine groups was achieved using 1,4-bis(3-aminopropyl)piperazine and the bis-diphenylphosphine derived from verbenone was obtained. (Scheme 5)



Scheme 5

Analogous transformations to those shown in Schemes 4 and 5 were carried out starting with 3-(hydroxymethyl)-*cis*-3-pinene, which was obtained from isopinocamphone. (Scheme 6)



Scheme 6

3. Summary

We have shown the new approach to the synthesis of regio-isomeric bis-phosphines built on the pinane ring system. The key transformation was the conversion of ketones into spiro-epoxides followed by the reductive opening of epoxides to allylic alcohols. We are going to employ the obtained bis-phosphines as chiral ligands with rhodium and iridium complexes for the asymmetric hydrogenation reactions.

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