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[A003]

ENANTIOSPECIFIC PREPARATION OF 10-(PIPERIDIN-1-YL)CAMPHOR: A MODEL PROCEDURE FOR 10-AMINOCAMPHORS.

Antonio Garc&#65533;a Mart&#65533;nez,[a] Enrique Teso Vilar,[b] Amelia Garc&#65533;a Fraile,[b] Cristina Diaz Morillo[b] and Santiago de la Moya Cerero[a]*

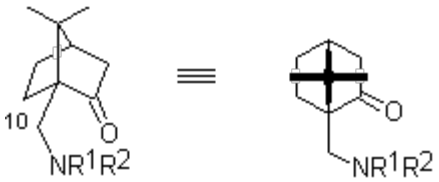
a) Universidad Complutense de Madrid, Departamento de Qu&#65533;mica Org&#65533;nica I, Ciudad Universitaria s/n, 28040-Madrid, Spain.

b) Universidad Nacional de Educaci&#65533;n a Distancia, Senda del Rey 9, 28040-Madrid, Spain.

Abstract. *&#65533; Enantiopure (1R)-10-(piperidin-1-yl)camphor has been straightforwardly obtained from natural camphor in five individual steps and with a high overall yield. The process involves a stereocontrolled double-Wagner-Meerwein-rearrangement strategy to generate 10-(triflyloxy)camphor as the key intermediate. This peculiarly-stable neopentylic-like triflate is able to react with piperidine easily and without producing Grob-like fragmentation of the* b*-(triflyloxy)ketone-based norbornane system. The described procedure constitutes a model procedure for the sterecontrolled preparation of interesting 10-aminocamphors*.

INTRODUCTION

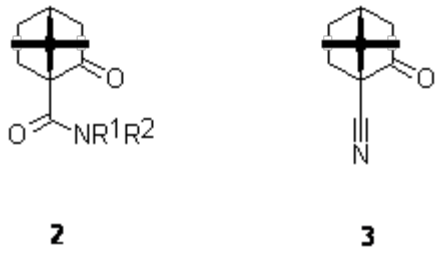
10-Aminocamphors [**1(NR^{1}R^2)** in Figure 1] and related derivatives (amido ketones, amino alcohols, etc.) constitute an interesting family of camphor derivatives, whose members can act as valuable chiral auxiliaries and catalysts in asymmetric synthesis,[1] or exhibit interesting biological activities.[2]



1(NR^{1}R^2)

Figure 1

Unfortunately, and differently to other 10-heteroatom-susbtituted-camphors,[3] the synthetic access to 10-aminocamphors is not easy. In fact, the only readily accessible 10-*N*-substituted camphors are amides derived from commercially available ketopinic acid (see amides **2** in Figure 2),[4] as well as ketopinic nitrile (**3** in Figure 2).[5] This fact has made such ketopinic-acid derivatives to be the only disposable synthetic intermediates for the preparation of other 10-*N*-substituted-camphor derivatives.[1,2,4,5]



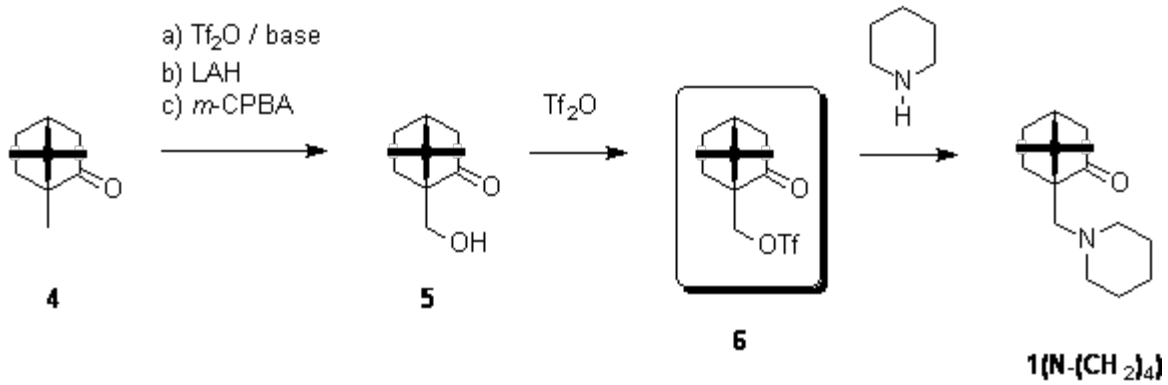
2 **3**

Figure 2

Additionally, the only previously described access to 10-aminocamphors **1(NR^{1}R^2)** based on ketopinic acid and developed by Schenone et al. in 1975,[2] is not general presenting a problematic oxidation step of an amino alcohol intermediate.
Therefore, the establishment of general and straightforward synthetic procedures to enantiopure 10-aminocamphors is of a great interest, due the high value (synthetic and pharmacological) of such camphor derivatives.

RESULTS AND DISCUSSION

In relation with this interest, we have developed a general synthetic procedure for enantiopure 10-aminocamphors, which is exemplified by the preparation of (1*R*)-10-(pyperindin-1-yl)camphor (Scheme 1).



Scheme 1

The synthetic route uses commercial camphor **4** as the enantiopure starting material, involving an initial stereocontrolled transformation of such chiral-pool material into 10-hydroxycamphor **5** (78% yield), according to a three-step double-Wagner-Meerwein-rearrangement-based methodology described previously by us.[3a] Initial intermediate **5** was then converted into key-intermediate 10-(triflyloxy)camphor **6**, by a straightforward treatment with triflic anhydride (Tf_2O) under mild reaction conditions (Scheme 1).

Neopentylic-like triflate **6** resulted to be peculiarly stable. Thus, it does not undergo any possible Wagner-Meerwein rearrangement of its framework (C6 or C7 alkyl migrations),[6] probably due to a destabilizing effect caused by the a-carbonyl group on the emergent bridgehead carbocation intermediate.
Finally, **6** was reacted with piperidine to give the corresponding *N*-alkylated amine **1(N-(CH$_2$)$_4$-)** with good yields. This neopentylic-like nucleophilic substitution takes place under mild reaction conditions and without producing Grob-like fragmentation of the b-(triflyloxy)ketone-based norbornane framework, due the high nucleofugacity of the triflyloxyl group.[7]

SUMMARY

For the first time, a straightforward and general synthetic method for the enantiospecific preparation of enantiopure 10-aminocamphors has been established. As validation of such methodology, (1*R*)-10-(piperidin-1-yl)camphor has been obtained from natural (1*R*)-camphor in 70% overall yield.

EXPERIMENTAL

(1*R*)-10-(Triflyloxy)camphor 6.

Over a cold (0 °C) solution of primary alcohol **5**[3a,8] in dry CH_2Cl_2 was added triflic anhydride (1.2 mol equiv.). The reaction mixture was stirred for 10 min and hydrolyzed with saturated sodium hydrocarbonate solution. After standard work up and purification by elution chromatography (silica gel, hexane/CH_2Cl_2 40:60) **6** was obtained as a colorless liquid (*ca.* quantitative). $[a]_D^{20}$ +30.8 (1.27 CH_2Cl_2). IR, ^1H and ^{13}C NMR, and MS agree with the structure.

(1*R*)-10-(piperidin-1-yl)camphor 1(N-$(CH_2)_5$-).

A solution of **6** and the piperidine (2.0 mol equiv) in dry acetonitrile was refluxed for 6 h. After standard hydrolysis (sat. sodium hydrocarbonate solution), work up and purification by elution chromatography (neutral alumina, ether/methanol 95:5), pure 10-(piperidin-1-yl)camphor **1(N-$(CH_2)_5$-)** (90% yield) was obtained as a colorless liquid. $[a]_D^{20}$ +40.1 (1.23, CH_2Cl_2). IR, ^1H and ^{13}C NMR, and MS agree with the structure.

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7.□□□□□□□□□ Highly-reactive triflyloxyl group makes its nucleophilic substitution to be the main process, avoiding a possible competitive (undesired) Grob-like fragmentation (on this synthetic problem, see reference 3b and other references cited therein).