

### NOE STUDIES OF N-PROPIONYL DERIVATIVE OF CHIRAL AUXILIARY CHIRACAMPHOX SPIRO-OXAZOLIDIN-2-ONE

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تحضير المشتق N-بروبيونيل والمستبدل في وصلة كيرالية من نظام حلقة سبيرو-أوكسازوليدين-2-ون تم إنجازه بواسطة استعمال العديد من الكواشف والقواعد. من أجل زيادة محصلة الناتج المشتق N-بروبيونيل هناك طريقة جديدة استخدمت بواسطة كاشف الزنك الأكثر شيوعاً والمتاح تجارياً. وهو داي إيثايل زنك الذي يعطي ناتجاً قدره 100% من المركب المراد تحضيره.

المحاولات للتمييز بين بروتونا البروكيرال ميثيلين  $H_M$  و  $H_N$  وكل البروتونات الدياستيريوميرية الأخرى في مشتق N-بروبيونيل للكيرال المساعد Chiracamphox قد تم أداؤها باستخدام أطيف nOe المطروحة لرنين البروتون النووي المغناطيسي.

The synthesis of N-substituted propionyl-substituted chiral moiety based on the spiro-oxazolidin-2-one ring system has been achieved via the use of a variety of different reagents and bases. In order to increase the yield of the N-propionyl derivative, a new method was employed using the most commonly used and commercially available zinc reagent, diethyl zinc which gave a 100% yield of the desired product. Attempts to distinguish between the prochiral methylene protons  $H_M$  and  $H_N$  and all other diastereotopic protons in the N-propionyl derivative of the chiral auxiliary chiracamphox were carried out by using <sup>1</sup>H NMR nOe difference spectra.

#### INTRODUCTION

The camphene-derived reagent 1, termed chiracamphox, was synthesized by Banks *et al* [1,2] and turn out to be the most versatile of auxiliaries for use in organic synthesis. *Endo*-camphenol 2 (prepared from (-)-camphene 3 by hydroboration followed by treatment with KOH/H<sub>2</sub>O<sub>2</sub>) [3] was chosen by Banks *et al* [1,2] as the starting material and by nitrene-insertion methodology [4] yielded the spiro-oxazolidin-2-one 1 in good yield (70%) (Scheme 1).

Highly crystalline derivatives were synthesized from chiracamphox 1 and afforded excellent levels of diastereoselectivity in both lithium enolate mediated alkylation and acylation reactions, boron enolate aldol reactions and in 1,4-conjugate additions [5]. These versatile chemical manipulations were amply demonstrated in the synthesis of the tri-substituted  $\gamma$ -lactone referred to as (-)-dihydroprotolichesterinic acid 4 [6] containing three contiguous chiral centers in 5 steps and 57% overall yield. The successful

strategy is a considerable improvement on the previous synthesis of 4 by Mulzer *et al* [7] which involved 14 steps and led to 4 in only 0.4% overall yield.

#### EXPERIMENTAL

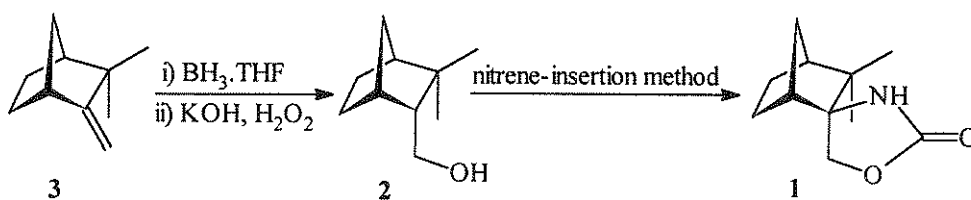
##### Preparation of (5S)-N-propionyl-4-aza-2-oxa-6,6-dimethyl-7,10-methylene-5-spiro[4.5]decan-3-one 5.

Diethylzinc (11.5ml of a 1.0M solution in hexane, 11.5mmol, 1.1eq) was added to a solution of the chiral auxiliary 1 (1.96g, 10.05mmol) in dry diethyl ether (40ml) under argon, and the mixture stirred at room temperature for 1 hour. The reaction mixture was then cooled to -78°C and after 10 minutes, a solution of freshly distilled propionyl chloride (3.10g, 33.5mmol, 3eq) in dry ether (10ml) was added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature and stirred under argon for 24 hours. TLC showed that the reaction was complete. The reaction was quenched by addition of a saturated

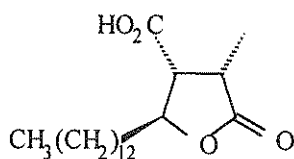
$H_N$  in this case. Irradiation of  $H_P$  gave a 18% enhancement of signal for  $H_Q$  and 3% enhancement of signal for  $H_K$ , that proves  $H_P$  in close position to  $H_K$ . Although, Irradiation of  $H_Q$  gave a 22% enhancement of signal for  $H_P$ , but did not affect on  $H_K$ . Irradiation of the bridgehead proton  $H_K$  gave a 3% enhancement of signal for  $H_D$ , and 2% for  $H_P$ . This result proves that discrimination between the diastereotopic methylene protons  $H_P$  and  $H_Q$  was achieved by irradiation of  $H_K$ . Irradiation of  $H_D$  gave a 14% enhancement of signal for  $H_L$ , 1.5% for  $H_J$  and 3% for  $H_K$ , confirming that  $H_K$  in close position to  $H_D$ .

Irradiation of the other bridgehead proton  $H_J$  gave 1.5% enhancement of signal for  $H_E$ , 1% for  $H_L$  and 1.5% for  $H_D$ , so is not possible to distinguish between  $H_D$  and  $H_L$  protons by irradiation of  $H_J$  because it affects both of them equally. Irradiation of  $H_N$  gave 10% enhancement for  $H_M$ , and irradiation of  $H_M$  gave a 1% enhancement for  $H_D$ .

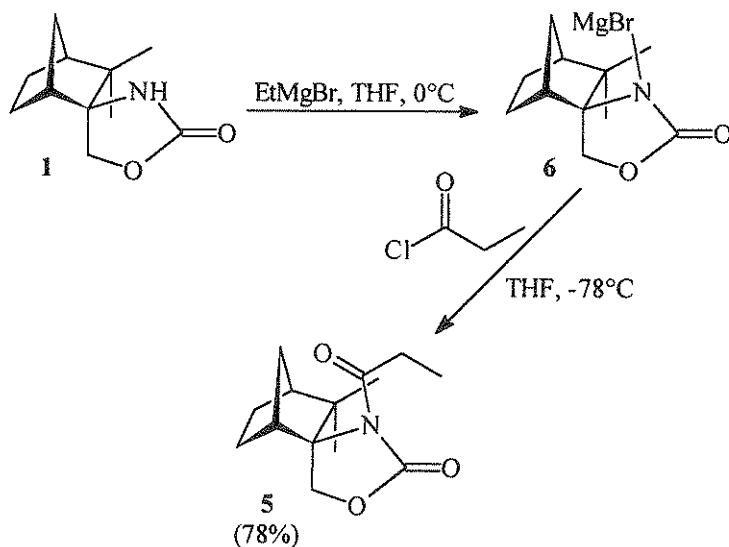
Unfortunately, coincidental irradiation of two methyl protons  $H_B$  and  $H_C$  affected both  $H_M$  and  $H_N$  equally, in other words, there is no differential enhancements of the prochiral protons  $H_M$  and  $H_N$ , *i.e.* the protons are not distinguishable.



Scheme 1



4



Scheme 2

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