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Synthesis of limonene β-amino alcohol from (*R*)-(+)-α-methylbenzylamine and (+)-limonene 1,2-epoxide

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ABSTRACT

Two new compounds of β-amino alcohol are obtained using (*R*) - (+) - α-methylbenzylamine as starting material which is converted into two amines. Each of these compounds reacted in excess with a 1: 1 mixture of *cis* and *trans*-limonene oxide in the presence of water as a catalyst. The products obtained show that β-amino alcohol derived from trans-limonene oxide is obtained and unreacted *cis*-limonene oxide from the reaction mixture as well as the amine is attained. Whereas the addition of the synthesized carbamate of the same primary amine over the 1: 1 mixture of *cis* and *trans* -limonene oxide in the presence of water results in the hydrolysis product and the recovery of unreacted *trans*-limonene oxide.

1. Introduction

Since leishmaniasis, which is considered by who as one of the six major neglected Tropical diseases, has brought about a considerable increase in the mortality rate in developing countries, and is reckoned as responsible for more than 20 million deaths per year [1,2], multiple research, in this sense [3,6], has been carried out on β-amino alcohols which have been considered as one of the major effective therapeutic ways in treating leishmaniasis as well as other diseases.

A study [7] has found 2 compounds. 1-methyl-2- (N-propylamino) –4-isopropenyl-cyclohexanol and 1-methyl-2- (N-phenylamino) –4-isopropenyl-cyclohexanol which exhibit activity 100 times more potent than the standard drug, pentamidine (antiparasitic drug from the trypanicide family). This study presents the first report of anti-leishmanial activity by limonene β-amino alcohol derivatives.

In addition, β-amino alcohols contain very interesting pharmaceutical and biological properties such as propanolol, a widely consumed drug which is a β-blocking agent in which the (*S*) enantiomer - propranolol is antihypertensive and anti-arrhythmic. It is used in the treatment of coronary heart disease while the (*R*) -enantiomer - propranolol is used as a contraceptive. β-amino alcohols are also found in the structure of serine protease inhibitors [8–11].

Many synthetic methods exist for the preparation of these compounds [12–14]. Racemic epoxides, which are readily available, can be easily transformed by reactions with various nucleophiles into 1, 2-substituted derivatives, especially 1,2-amino-alcohol [15–16].

β-amino alcohols are used as intermediates in the synthesis of a wide range of natural and synthetic biologically active products [17–19] as well as in unnatural amino acids. [20,21]. β-amino alcohols also play an important role as chiral ligands, most generally derived from natural sources. Chiral 1, 2-amino alcohols are common structural units found in a wide variety of natural and biologically active molecules. Amino alcohols are generally derived to be used in asymmetric synthesis. [22–25].

In the present work, we have synthesized and characterized, for the first time β-amino alcohols to be used in the field of biology. A synthesis of two secondary amine and carbamate was also carried out from the same primary amine which is (*R*)-(+)-α-Methylbenzylamine.

2. Experimental methods

In order to carry out an asymmetric synthesis of β-amino alcohols, as a first step, the secondary amines 2a and 3a were obtained as starting products as indicated in Fig. 1.

(*R*) -α-methylbenzylamine 1 was added to benzaldehyde and EtOH. Then, they were heated for 6 h under magnetic stirring at 110 °C. The imine 2 was obtained, and was subjected to a reduc-

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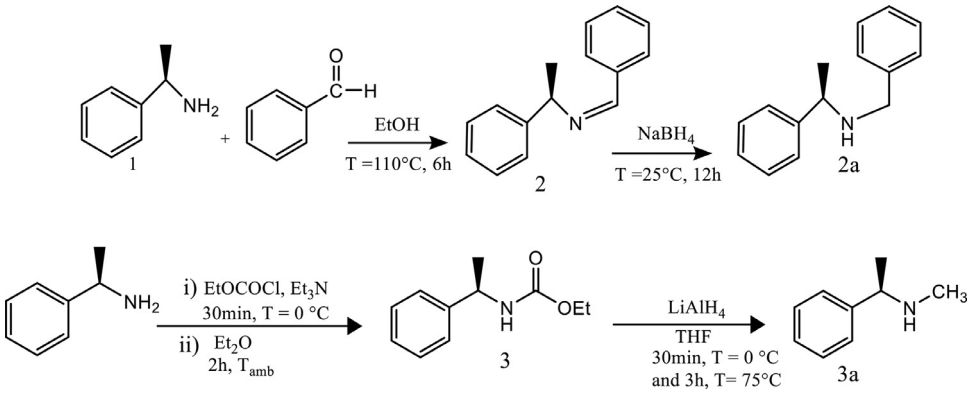

Fig. 1. Secondary amines 2a and 3a as starting products.

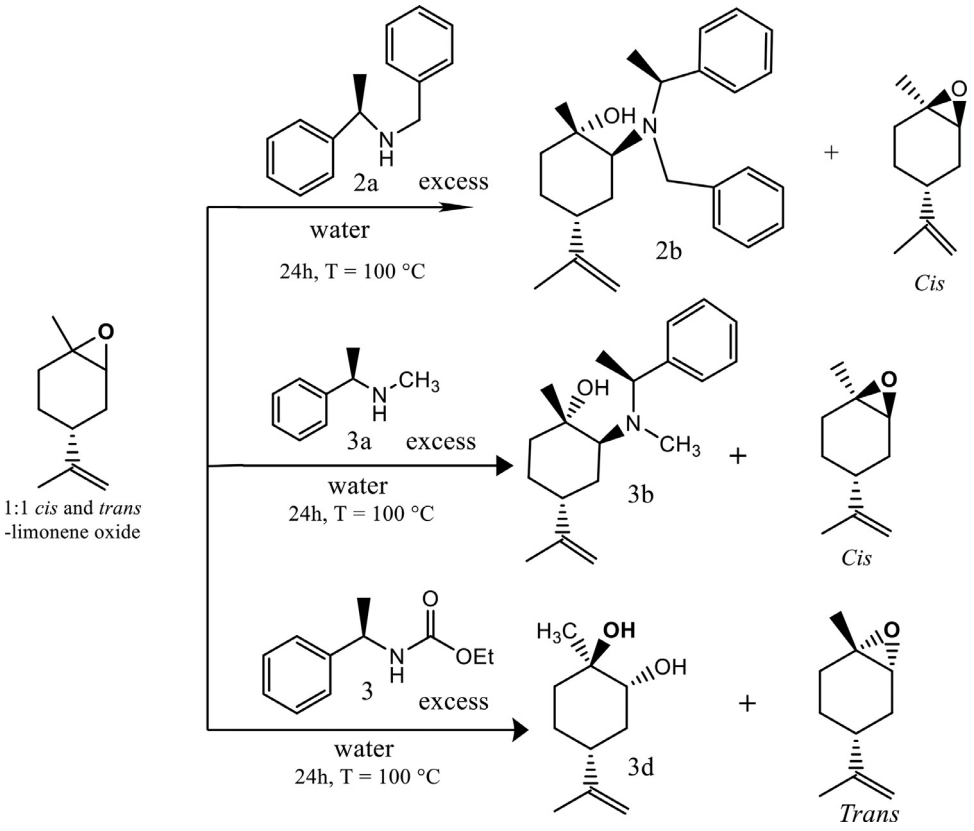

Fig. 2. Obtaining of beta -amino 2b, 3b and hydrolysis product 3d.

tion using $NaBH_4$ to produce amine 2a. The result obtained (amine 2a) was a pale yellow and oily liquid.

(*R*) -α-methylbenzylamine 1 was added to ethyl chloroformate. Carbamate 3 was obtained then reduced using lithium aluminum hydride to produce amine 3a. The result obtained (amine 3a) was a pale yellow, oily liquid.

The two amines 2a and 3a were purified by the crystallization of its hydrochloride obtained by treatment using 2 M HCl.

In a second step and as shown in Fig. 2, the amines 2a and 3a obtained were reacted in excess with a 1: 1 mixture of *cis* and *trans* limonene oxide in the presence of water as catalyst. The products obtained showed the obtaining β-amino alcohol 2b and 3b derived from *trans*-limonene oxide and recovery of unreacted limonene *cis* oxide, as well as excess amines from the reaction mixture. 2b and 3b were light brown and oily liquids.

When the carbamate 3 was reacted in excess with a 1: 1 mixture of *cis* and *trans* limonene oxide in the presence of water as a catalyst, we observed an unexpected result. The reaction involving carbamate catalyzed the selective hydrolysis of *cis*-limonene oxide, leaving *trans*- limonene oxide unreacted, the 3d hydrolysis products (a light brown oil) was derived from *cis*-limonene oxide were obtained and recovery of trans-limonene oxide as well as the unreacted carbamate. This result coincided with the work of [26] which showed that the addition of a secondary amine on a 1: 1 *cis* and *trans* limonene oxide mixture gave the β -amino alcohol and *cis* limonene as a result .On the other hand, the *trans* limonene and the hydrolysis product was obtained thanks to the addition of pyrazole, in our case the carbamate was used.

3. Conclusion

In summary, β-amino alcohols were synthesized because they are considered as a prominent effective therapeutic way in treat-

ing different diseases. They contain natural, pharmaceutical and biological properties [1–11].

The aim of this work is to show a simple way to the synthesis of pure β-amino alcohols and *trans*-limonene-1, 2-diol. We started by a synthesis of two secondary amine and carbamate. This was also carried out from the same primary amine which is (*R*)-(+)-α-Methylbenzylamine. We have also isolated both the *cis* and *trans* diastereomers of (*R*)-(+)-limonene oxide.

The results of this work is initial. Yet, they provide a starting point to design other modifications from the limonene oxide architecture in order to guide further structure activity relationship studies.

4. Results and discussion

*4.1. Synthesis of (*R*) -N-benzyl- (α-methyl-benzyl) amine, 2a*

The reaction was carried out by dissolving 5 g (45 mmol) of (*R*) -α-methylbenzylamine in 75 mL of ethanol, and adding 5 mL (19 mmol) of benzaldehyde (recently distilled) to it. The solution heated up to boiling (a bath temperature: 110 °C). After 6 h, the reaction mixture was cooled with an ice bath and 0.92 g (22.5 mmol) of NaBH4 was added. It allowed itself to react for 12 h. The ethanol evaporated and 25 ml of H_2O, solid KOH until pH> 10, and solid NaCl were added. The reaction mixture is extracted with ether, and the ethereal phase is washed with dissolution of saturated NaCl and H_2O. It was allowed to dry over anhydrous Na_2SO_4, the ether was filtered and evaporated, obtaining 8.71 g (99.5%) of 2a.

60 mL of hot 2 M HCl was added to 8.71 g of 2a. The crystalline hydrochloride was infiltrated and washed with H2O. 7.76 g (76%) of 2a hydrochloride was obtained.

To generate 2a as free amine, 7 g (28 mmol) hydrochloride of 2a was added to 80 mL of KOH (2 M) slowly, and it was carried out while stirring for 3 h. Then solid NaCl was added and extracted with ether. The organic phase was allowed to dry over anhydrous Na_2SO_4, which was infiltrated and the ether was evaporated, obtaining 5.20 g (89%) of 2a.

*4.2. Synthesis of (*R*) -N- (α-methyl-benzyl) ethyl carbamate, 3*

The reaction was carried out first by dissolving 5 g (45 mmol) of *R* -α-methylbenzylamine in 6.3 mL of triethylamine and 37.6 ml of diethyleter. After that, 4.8 mL of ethyl chloroformate is added dropwise at 0 °C for 30 min. Next, the reaction was stirred at a temperature room for 2 h. Then, 200 ml of ether was added. It was washed with HCl (2 M) and with dissolution of saturated $NaHCO_3$ and NaCl. Finally, it was dried over anhydrous Na_2SO_4, which was infiltrated and the ether was evaporated, obtaining 7.45 g of (95%) of 3.

*4.3. Synthesis of (*R*) -N-methyl- (α-methyl-benzyl) amine, 3a*

The reaction was carried out by dissolving 5.45 g (27.9 mmol) of 3 in 4 mL of THF and was added dropwise at 0 °C to a suspension of $LiAlH_4$ 3.15 g (82.3 mmol) in 40 mL of THF .It was stirred for 30 min. After that, the dissolution heated up to boiling at a bath temperature of 75 °C. After 3 h, the reaction mixture cooled down to 0 °C, and 10 ml of THF was added with 1 ml of H_2O little by little until the color changed from gray to white. It was filtered through silica and left to dry over anhydrous Na_2SO_4. The solvent was evaporated off. Finally, 2.37 g (17.6 mmol; 63%) of 3a was obtained.

*4.4. Synthesis of (1*R*, 2*R*, 4*S*) −1-methyl-2- (*R*) -N-benzyl (α-methyl-benzyl) amino −4-isopropenyl-cyclohexanol 2b and (1*R*, 2*R*, 4*S*) −1-methyl −2- (*R*) -N-methy (α-methyl-benzyl) amino −4-isopropenyl-cyclohexanol 3b*

The 1: 1 *cis* and *trans* limonene oxide (2.4 mmol), water (0.55 ml) and secondary amine 2a or 3a (5 mmol) were placed in a flask under magnetic stirring at 100 °C. After 24 h, the product reaction was obtained by column chromatography using as eluent hexane / ether 8: 2 β-aminoalcohol 2b was obtained in a yield of 50%, and β-aminoalcohol 3b with a yield of 60%.

*4.5. Synthesis of (1*R*, 2*R*, 4*R*) -Limonene-1, 2-diol*

The 1: 1 *cis* and *trans* limonene oxide (2.4 mmol), water (0.55 ml) and the carbamate 3 (5 mmol) were placed in a flask under magnetic stirring at 100 °C. After 24 h, the reaction product has been obtained by column chromatography, using hexane / ether 7: 3 as eluent. (1*R*, 2*R*, 4*R*) -Limonene-1, 2-diol was obtained with a yield of 80%.

Declaration of Competing Interest

No.

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(*R*)-N-benzyl-(α-methyl-benzyl) amine, 2a

IR (ν_{max}, cm^{-1}): 3400, 3200, 3050, 1600,710, ^1H NMR δ (ppm) (300 MHz, $CDCl_3$): 1.52 (3H, d, CH_3), 3.75 (1H, q, CH), 3.95 (2H, q, CH_2), 7.3–7.5 (10H, m, ArH), ^{13}C NMR δ (ppm) (50 MHz, $CDCl_3$): 24.5 (CH_3), 51.7 (CH_2), 57.8 (CH), 126.9–128.9 (10xCH, Ar), 141 (C, C_{ipso}), 145.9(C, C_{ipso}).

(*R*) -N-(α-methyl-benzyl) carbamate de ethyle, 3

IR (ν_{max}, cm^{-1}): 3324, 2980, 1699, 1537, 1248, 762, 700, ^1H NMR δ (ppm) (300 MHz, $CDCl_3$): 1.23 (3H, t, J = 6.8 Hz, OCH_2CH_3), 1.49 (3H, d, J = 6.4 Hz, CH_3), 4.11(1H, q, J = 6.4 Hz, CH), 4.10 (2H, q, J = 6.8 Hz, OCH_2CH_3), 7.28 (4H, m, Ar-H), ^{13}C δ(ppm) NMR (50 MHz, $CDCl_3$): 14.6 (CH_3, OCH_2CH_3), 22.5 (CH_3, C-2′), 50.6 (CH, C-1), 60.7(CH_2, OCH_2CH_3), 125.9 (2C, Ar-C_{orto}), 127.0 (C, Ar-C_{para}), 128.0 (2C, Ar-C_{meta}), 144.6 (C_{ipso}),156.8 (C, $NHCO_2CH_2CH_3$).

(*R*)-N-methyl-(α-methyl-benzyl) amine, 3a

IR (ν_{max}, cm^{-1}): 3320, 2980, 1671, 1439, 1451, 760, 700, NMR^1H δ (ppm) (300 MHz, $CDCl_3$): 1.37 (3H, d, J = 6.45 Hz, CH_3), 2.31(3H, s, CH_3), 3.57(1H, q, J = 6.4 Hz, CH),7.31 (m, Ar-H), ^{13}C NMR δ(ppm) (50 MHz, $CDCl_3$): 23.8(CH_3), 34.5(CH_3, CH_3), 60.2(CH), 126.5 (2C, Ar-C_{orto}), 126.8 (2C, Ar-C_{para}), 128.3 (2C, Ar-C_{meta}), 145.4(C_{ipso}).

(1*R*,2*R*,4*S*)−1-methyl-2-(*R*)-N-benzyl(α-methyl-benzyl) amino −4-isopropenyl-cyclohexanol 2b

HPLC-MS: 362.14786**,** IR (ν_{max}, cm^{-1}): 3500, 3200, 3050, 1600,710**,** ^1H δ (ppm) NMR (300 MHz, $CDCl_3$): 1.38 (3H, d, CH_3), 1.54 (2H, m, CH_2), 1.70 (3H, s, CH_3), 1.72 (3H, s, CH_3), 2.11 (3H, m, CH et CH_2), 2.27 (2H, m, CH_2), 3.65 (1H, q, CH), 3.89 (2H, c,CH_2), 4.68 (2H, s, CH_2), 4.71 (1H, s, CH), 7.25–7.36 (10H, m,ArH)**,** ^{13}C NMR δ (ppm) (50 MHz, $CDCl_3$): 21.20 (CH_3), 24.14 (CH_3), 26.27 (CH_2), 33.74 (CH_2), 34.57 (CH_2), 37.54 (CH), 51.39 (CH_2), 57.46 (CH), 71.33(C), 74 (CH), 109.10 (CH_2) 126.43–128.66 (10xCH, Ar), 140.90 (C, C_{ipso}), 150(C, C_q).

(1*R*,2*R*,4*S*)−1-methyl-2-(*R*)-N-methy(α-methyl-benzyl) amino −4-isopropenyl-cyclohexanol 3b

HPLC-MS:288.23239, IR (ν_{max}, cm^{-1}): 3500, 3200, 3050, 1600,710, ^{1}HNMR δ (ppm) (300 MHz, $CDCl_3$): 1.28 (3H, d, CH_3), 1.54 (2H, m, CH_2), 1.70 (3H, s, CH_3), 1.72 (3H, s, CH_3), 2.11 (3H, m, CH et CH_2), 2.27 (2H, m, CH_2), 4.05 (1H, q,CH), 4.62 (2H, s, CH_2), 4.69 (1H, s, CH), 7.20–7.28 (5H,m,ArH)**,** ^{13}C δ (ppm) NMR (50 MHz,

$CDCl_3$): 21.20 (CH_3), 23.43 (CH_3), 26.27 (CH_2), 31.50 (CH_2), 33.57 (CH_2), 37.54 (CH), 48.85 (CH), 57.16 (CH_3), 71.54(C_q), 73.96 (CH), 109.10 (CH_2) 126.43–129.66 (5xCH, Ar), 140.90 (C, C_{ipso}), 150(C, C_q).

(1*R*,2*R*,4*R*)-Limonene-1,2-diol 3d

HPLC-MS:170.80917, IR (ν_{max}, cm^{-1}): 3500, 2900, 1100,700, ^1H NMR δ (ppm) (300 MHz, $CDCl_3$): 1.25 (3H, s, CH_3), 1.53–1.59 (4H, m, 2xCH_2), 1.73 (3H, s, CH_3), 1.93 (2H, m, CH_2), 2.27 (1H, m, CH), 3.63 (1H, d, CH), 4.73 (1H, s, CH_2), ^{13}C NMR δ (ppm) (50 MHz, $CDCl_3$): 21.13 (CH_3), 26.12 (CH_2), 26.32 (CH_3), 33.66 (CH_2), 37.49 (CH), 71.54 (C), 73.71(CH), 109.09 (CH_2),149.28 (C).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130691.

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