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Short Note

(*S*)-(-)-Limonene Derivatives Containing (1H-1,2,3-Triazol-4-yl)methyl 4-Bromobenzoate

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Abstract: The synthesis of (S)-(-)-limonene derivatives containing (1H-1,2,3-triazol-4-yl)methyl 4-bromobenzoate were obtained by epoxidation, azidolysis and Huisgen's 1,3-dipolar cycloaddition. Two products were isolated and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, ESI-MS and optical rotation.

Keywords: Huisgen reaction; click chemistry; limonene

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1. Introduction

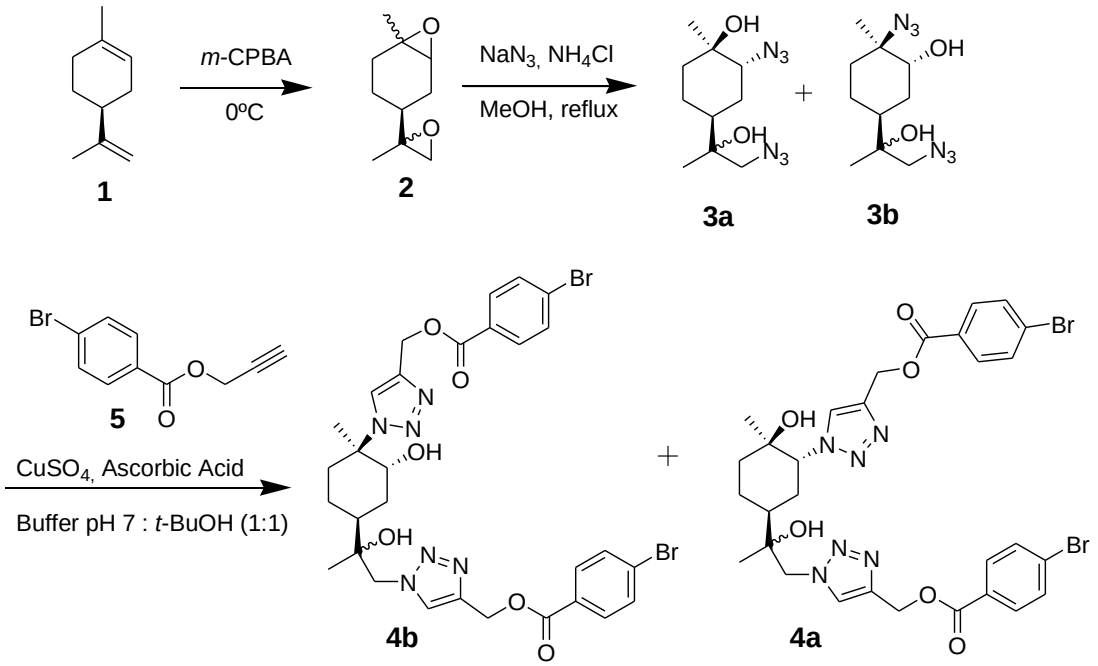
The use of natural products as starting material is a very attractive concept in order to use renewable, inexpensive and enantiomerically pure compounds. In this work, were synthesized two derivatives of (S)-(-)-limonene. These novel structures were created following the rules of click chemistry [1] and these reactions can be easily made over similar natural substrates.

2. Results and Discussions

Complete epoxidation of (S)-(-)-limonene was performed with *m*-chloroperbenzoic acid, followed by azidolysis of epoxides with sodium azide and ammonium chloride in refluxing methanol. In the azidolysis step, azide attacks the epoxide on the side chain of limonene at primary carbon and the epoxide of the ring by a trans-diaxial approach [2]. So this step yields a mixture of two azidoalcohols **3a** and **3b**. Then was performed the coupling of these azides and a terminal ethynyl block using Cu(I)-catalyzed click chemistry reaction. The Huisgen 1,3-dipolar cycloaddition using *in situ* reduced copper

(I) as catalyst, gives only 1,4-disubstituted 1,2,3-triazoles [3]. The products **4a** and **4b** were obtained by flash chromatography as epimeric mixtures.

Scheme 1. Synthesis of triazol containing products from (S)-(-)-limonene.



3. Experimental Section

(1-{2-[(1S,3R,4R)-3-(4-{[(4-bromophenyl)carbonyloxy]methyl}-1H-1,2,3-triazol-1-yl)-4-hydroxy-4-methylcyclohexyl]-2-hydroxypropyl}-1H-1,2,3-triazol-4-yl)methyl 4-bromobenzoate (**4a**) and *{1-[(1R,2R,4S)-4-[1-(4-{[(4-bromophenyl)carbonyloxy]methyl}-1H-1,2,3-triazol-1-yl)-2-hydroxypropan-2-yl]-2-hydroxy-1-methylcyclohexyl]-1H-1,2,3-triazol-4-yl}methyl 4-bromobenzoate* (**4b**)

A solution of *m*-chloroperbenzoic acid 70% w/w (930 mg, 3.76 mmol) in 8 mL of DCM was added dropwise (~ 30 min.) to solution of (S)-(-)-limonene (250 mg, 1.84 mmol) in 2 mL of DCM at 0 ℃. The reaction mixture was stirred for 3 h and then washed twice with saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM, dried over Na_2SO_4 and the solvent was removed at low pressure to obtain colorless oil. The crude epoxide obtained, was dissolved in 5 mL of MeOH, then NH_4Cl (393 mg, 7.34 mmol) and NaN_3 (477 mg, 7.34 mmol) were added to the stirred solution. The reaction mixture was refluxed for 6 h and then it was allowed to cool to room temperature. Water was added to the mixture and was extracted with Et_2O. The organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed at low pressure to obtain dark yellow oil. The crude reaction was dispersed with compound **5** (880 mg, 3.36 mmol) into a mixture of *t*-BuOH/Phosphate buffer pH 7 (1:1) (9 mL). A solution (0.87 mL) of $CuSO_4$ $5H_2O$ (43.5 mg, 0.17 mmol) was added. Ascorbic acid (165 mg, 0.96 mmol) was dissolved in 5 mL of water and neutralized with NaOH solution, and then this solution was added to the mixture. After TLC showed complete conversion, the mixture was diluted with water, and extracted with AcOEt. The organic layers were dried with Na_2SO_4, and the solvent was removed at low pressure. The crude reaction mixture was purified by flash silica gel column chromatography (AcOEt/*i*-PrOH 100:0.5) to afford **4a** (552mg, 0.72 mmol,

39.5% yield) and **4b** (272 mg, 0.37 mmol, 19.5% yield) as two white solids in a 59% yield for three steps.

Product **4a:** Ratio of epimers (57:43). m.p.: 79–80 ℃. $[\alpha]_D^{25}$= + 8.4 (c 1.02, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.90 (m, 8 H), 7.84 (s, 1 H), 7.82 (s, 1 H), 7.78 (s, 2 H), 7.58 (m, 8 H), 5.47 (m, 8 H), 4.79 (m, 2 H), 4.31 (m, 4 H), 2.38 (m, 2 H), 2.15 (m, 2 H), 1.98 (m, 2 H), 1.80 (m, 4 H), 1.52 (s, 3 H) , 1.51 (s, 3 H), 1.31 (m, 4 H), 0.95 (s, 3 H) , 0.92 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.82, 165.80, 165.78, 142.38, 142.28, 142.25, 131.79, 131.26, 128.56, 128.53, 128.49, 128.48, 126.18, 126.03, 122.16, 73.66, 73.52, 70.57, 70.53, 70.40, 64.15, 64.13, 58.29, 58.20, 58.17, 58.13, 57.63, 36.73, 36.47, 31.22, 31.06, 30.10, 28.70, 27.92, 22.56, 21.45, 21.32, 21.28, 21.11. IR (NaCl film, cm^{-1}): 2671, 1607, 1494, 1325, 1214, 1065, 988, 766, 747. HRMS (ESI): Found $[M+H]^+$ 731.0822. $C_{30}H_{33}Br_2N_6O_6$ requires 731.0823. $C_{30}H_{33}Br_2N_6O_6$ requires 731.0823. Anal. calc. for $C_{30}H_{33}Br_2N_6O_6$. $3H_2O$:C, 45.82, H, 4.87, N, 10.69. Found: C, 45.87, H, 4.72, N, 9.95.

Product **4b:** Ratio of epimers (55:45). m.p.: 111–112 ℃. $[\alpha]_D^{25}$= + 27.2 (c 1.08, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.89 (m, 8 H), 7.81 (s, 1 H), 7.76 (s, 1 H), 7.69 (s, 1 H), 7.68 (s, 1 H), 7.56 (m, 8 H), 5.45 (m, 8 H), 4.54 (m, 1 H), 4.50 (m, 1 H), 4.39 (m, 4 H), 2.36 (m, 2 H), 2.23 (m, 2 H), 2.03 (m, 2 H), 1.85 (m, 4 H), 1.73 (m, 4 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.81, 165.75, 142.42, 141.51, 131.81, 131.79, 131.76, 131.30, 128.60, 128.56, 128.49, 128.45, 128.42, 128.41, 126.03, 126.02, 125.94, 125.89, 73.88, 73.82, 70.37, 65.28, 65.23, 58.27, 58.24, 58.17, 58.13, 57.63, 39.17, 39.14, 34.31, 34.28, 28.26, 27.55, 27.25, 27.19, 22.14, 21.68, 21.35, 20.92. IR (NaCl film, cm^{-1}): 2967, 1719, 1589, 1398, 1271, 1101, 1013, 758, 737. HRMS (ESI): Found $[M+H]^+$ 731.0820. Anal. calc. for $C_{30}H_{33}Br_2N_6O_6$. $2H_2O$:C, 46.89, H, 4.72, N, 10.94. Found: C, 47.47, H, 4.84, N, 10.85.

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