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Synthesis of optically active macroheterocycles containing of hydrazide (1*R*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid fragment from Δ^3-carene, (+)-α-pinene and *l*-menthol

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Abstract

It is known that (1*R*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid has been widely used in the synthesis of cardiac drugs, prostaglandin analogues, etc. We previously used this acid dihydrazide in its [1+1]-condensation with α,ω-diketodiester, available from tetrahydropyran, in the synthesis of a potentially useful 31-member macrocycle with a yield of 64%. In this paper we propose to use dihydrazide (1*R*,2*S*,3*R*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2,3-dicarboxylic acid for the synthesis of optically active macrocycles. For this purpose, from of natural monoterpenoids by the decyclization in several stages (for l-menthol) or in one stage (for Δ^3-Karen and (+)-α-pinene), the corresponding hydroxylamines ((6*R*)-8-hydroxy-2,6-dimethyloctan-3-on,1-[(1*S*,3*R*)-3-(2-hydroxyethyl)-2,2-dimethylcyclopropyl]acetone and 1-[(1*S*,3*S*)-)-3-(2-hydroxyethyl)-2,2-dimethylcyclobutyl]ethanol), were synthesized. These hydroxyketone were involved in the reaction of [2+1]-condensation with adipic acid chloranhydride as a result, α,ω-diketones with two ester functions were obtained. [1+1]-Condensation of the intermediate α,ω-diketodiesters with hydrazide (1*R*,4*S*)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid were obtained three optically active macroheterocycles, containing two ester groups and two hydrazide fragment. In [1+1]-condensation at room temperature under conditions of high dilution in dioxane α,ω-diketodiester, available from Δ^3-carene, with bicyclic dihydrazide, the formation of a macrocycle after 48 h was observed only in trace amounts. For α,ω-diketodiesters available from l-menthol and (+)-α-pinene, respectively, macrocyclization did not occur under similar conditions. The addition of water to increase the solubility of the initial crystalline hydrazide during the macrocyclization reaction allowed the synthesis of macrolides with yields of 37, 25 and 16%, respectively. The structures of the obtained macrocycles were determined by IR, NMR ^{1}H and ^{13}C spectroscopy and chromatomass spectrometry, and the purity was controlled by HPLC.

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