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Tetrahedron Letters 45 (2004) 8685–8686
Tetrahedron Letters

The absolute stereochemistry of cascarillic acid

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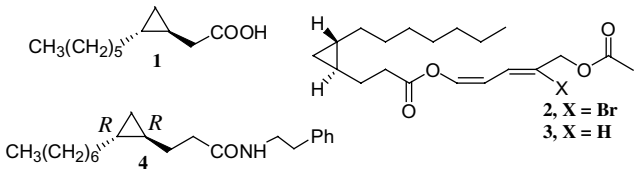
Received 13 August 2004; revised 13 September 2004; accepted 21 September 2004

Abstract—((1*S*,2*R*)-2-Hexylcycloprop-1-yl)acetic acid has been synthesised from *cis*-1,2-dihydroxymethylcyclopropane and shown to be identical to cascarillic acid obtained from cascarilla essential oil.

1. Introduction

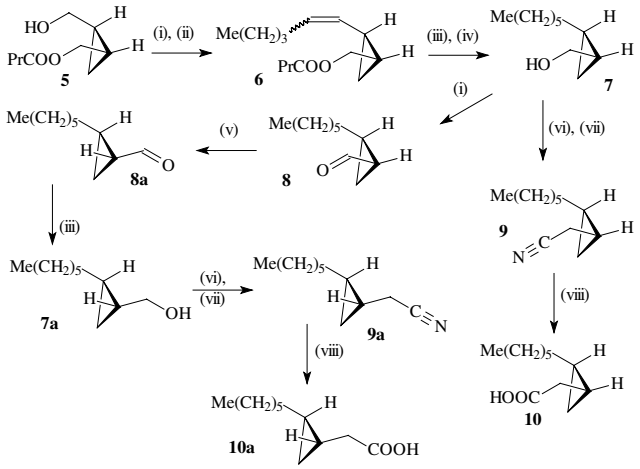
Cascarillic acid **1** is a cyclopropane containing fatty acid found in cascarilla essential oil, derived from the bark of the medicinal shrub *Croton eluteria* L. (Scheme 1). The oil has been used for many years to treat the symptoms of colds and influenza as well as respiratory ailments including bronchitis, via its use as an inhalant. It is unusual because the cyclopropane has been shown to have a *trans*-stereochemistry,[1] whereas more common cyclopropane fatty acids, such as lactobacillic acid,[2] and dihydrosterculic acid,[3] are of *cis*-stereochemistry. Compounds such as grenadadiene **2**, debromogrenada-diene **3** and grenadamide **4**,[4] are of *trans*-stereochemistry and indeed the latter has been determined to have an *R*,*R*-stereochemistry.[5] *trans*-Cyclopropanes are also reported in some more complex fatty acids such as mycolic acids, but in these cases there is a methyl-group on one of the adjacent carbons.[6] As part of a study to determine and compare the absolute stereochemistry of each of these cyclopropane fatty acids, we now report the synthesis of cascarillic acid as the single natural isomer.



Scheme 1.

2. Results and discussion

cis-1,2-Dihydroxymethylcyclopropane was converted into the monobutyrate ester **5**[7] by reaction with trifluoroethyl butyrate and lipase.[8] Oxidation to the aldehyde using PCC followed by a Wittig reaction led to the *E*/*Z*-alkenyl esters **6** (Scheme 2). Reduction to the alcohols, then di-imide reduction of the alkene led to the *cis*-cyclopropane **7**. To form the *trans*-cyclopropane, the alcohol **7** was oxidised to the aldehyde **8** and this was epimerised under basic conditions to **8a**. The ^{1}H NMR spectrum of the crude product showed two aldehyde protons and a *trans*/*cis* de of 87%; chromatography



Scheme 2. Reagents and conditions: (i) PCC, CH_2Cl_2; (ii) $Br^-P^+Ph_3(CH_2)_4Me$, BuLi, THF, −40 °C; (iii) $LiAlH_4$, THF; (iv) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH; (v) NaOMe, MeOH; (vi) 1,2-*bis*-diphenylphosphinoethane, Br_2, CH_2Cl_2; (vii) NaCN, DMSO; (viii) NaOH, H_2O, EtOH.

Keywords: Cascarillic acid; CPFA; Cyclopropane.
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doi:10.1016/j.tetlet.2004.09.141

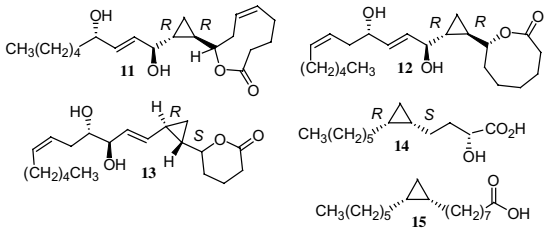
resulted in a 92% de. Chromatography after each following step improved the de further. Reduction of **8a** to the *trans*-alcohol **7a**, then bromination, formation of the nitrile **9a** and hydrolysis gave [(1*S*,2*R*)-2-hexylcycloprop-1-yl]-acetic acid (**10a**).

Cascarillic acid was obtained from cascarilla oil,[9] by base extraction followed by chromatography; the spectroscopic properties of the extracted material were in agreement with those already published.[1b] The ^{1}H NMR spectra reported and obtained in this work for natural cascarillic acid show the presence of a small amount of what appears to be a *cis*-disubstituted cyclopropane. The corresponding methyl ester showed one major peak on GCMS, together with a minor component (ca. 5%) at a slightly longer retention time showing an essentially identical MS to that of the major isomer. The spectroscopic properties of **10a** synthesised above (^{1}H, ^{13}C NMR, IR, MS) and the GCMS were identical to those of the naturally obtained material. Furthermore, the $[\alpha]_D^{20}$ values for the natural and synthetic samples were −8.9 and −10.9, respectively, while synthetic methyl cascarillate was found to have an $[\alpha]_D^{20}$ of −9.8, which compares favourably with the literature value of −10.5.[1] Taking into account the slightly lower purity of the natural sample of free acid than the synthetic sample, the above results represent proof that the two molecules are of identical stereochemistry.

cis-Cascarillic acid (**10**) was obtained in three steps from [(1*S*,2*R*)-2-hexylcyclopropyl]methanol **7**, bromination, formation of the nitrile and hydrolysis to the acid. Its ^{1}H NMR spectrum, GC retention time and MS were identical to those of the minor component in the natural sample.

The stereochemistry of natural cascarillic acid matches that of grenadamide (**4**) (though the Cahn–Prelog–Ingold descriptors are different). The absolute stereochemistries of the cyclopropane reported for the acid and alkyl derived side chains of halicholactones such as **11**,[11] and solande-lactones such as **12**,[12] are also the same.

Other natural derivatives such as costanolactone E (**13**) are reported to have the opposite absolute stereochemistries of the two chains.[10] The related *cis*-cyclopropane fatty acids, lactobacillic acid[2,13] and dihydrosterculic acid[3] are reported to be 11*R*,12*S*, and 9*S*,10*R*, respectively. Cepaciamide, a derivative of the acid **14**,[14] the corresponding hydroxy acid chain of plakoside A,[15] and a derivative of acid **15** from the slime mould *Pyhysarum polycephalum*,[16] all have an *S*,*R*-configuration of fatty acid and alkyl chains, respectively (Scheme 3). A number of other natural *cis*-cyclopropane fatty acids are of unknown absolute stereochemistry.[17]



Scheme 3.

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