Stereoselective synthesis of the C(1)—C(9) synthon of constanolactones by biomimetic cyclization of homoallylic epoxide

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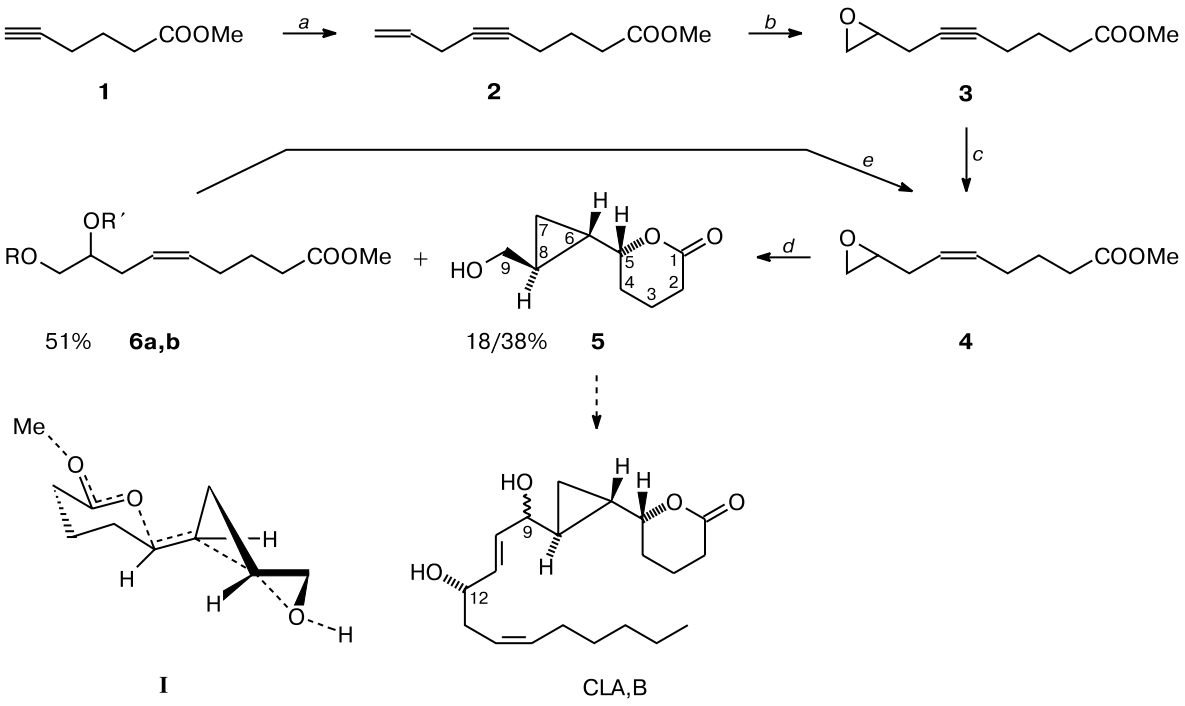
Constanolactones (CL), typically represented by CLA,B (Scheme 1) isolated from the sea algae *Constantinea simplex*, belong to the family of cyclopropane eicosanoids (CPE) (see review[1]). The pathway postulated for the biosynthesis of these eicosanoids includes lipoxygenase hydroperoxidation of arachidonic (or more polyunsaturated) acid followed by the homoallyl-cyclopropylcarbinyl (HA-CPC) rearrangement of the carbocation generated from the hydroperoxide. The expected biological activity of the "marine" CPE and the possibility of CPE biosynthesis upon the lipoxygenase metabolism of arachidonic acid in mammal organisms have stimulated considerable activity of synthetic chemists along this line.[2,3]

The total synthesis of CPE and other natural cyclopropane metabolites can be based on biomimetic cyclization of allylic carbocations (see review[4]). This strategy was successfully implemented for the synthesis of CLA,B back in 1995.[5] We attempted a different strategy using, together with the CA-CPC rearrangement, the intramolecular trapping of the cyclopropylmethyl carbocation by the methoxycarbonyl group.

Three standard steps starting from methyl hex-5-ynoate[6] (**1**) *via* the enyne **2** and homopropargyl epoxide **3**

Scheme 1



6: R = H, R′ = Ms (**a**), R = Ms, R′ = H (**b**)

Reagents and conditions: *a*. $H_2C{=}CHCH_2I$, CuI, K_2CO_3, NaI, MeCN, 20 °C, 15 min, 60%; *b*. MCPBA, $KHCO_3$, CH_2Cl_2, 20 °C, 5 h, 50%; *c*. H_2, Pd-Pb/$CaCO_3$, quinoline, benzene—hexane (1 : 1), 1 atm, 20 °C, 6 h, 38%; *d*. MsOH, H_2O-satur. CH_2Cl_2, 20 °C, 1 h; *e*. K_2CO_3, MeOH, 20 °C, 1.5 h, ~100%.

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(the yields were lowered by the volatility of the compounds) gave racemic homoallylic epoxide **4**, which was subjected to double cyclization on treatment with MsOH in CH_2Cl_2 in the presence of traces of water (CA-CPC rearrangement + lactonization) to afford cyclopropane hydroxylactone **5** (the atom numbering scheme is the same as in constanolactones). According to the ^{1}H NMR spectra, this cyclization was completely stereoselective, in particular, lactone **5** was a pure (5*R**,6*S**,8*S**)-stereoisomer. The *trans*-configuration of substituents in the cyclopropane can be deduced from the characteristic spin-spin coupling constant $^3J_{H(6),H(8)}$ = 4.3 Hz (obtained using computer simulation of the spectrum). The (5*R**,6*S**) relative configuration of the chiral centers was assigned on the basis of the established empirical dependence of the H(5) chemical shifts (for **5**, δ 3.80) on the relative configuration at the C(5) and C(6) atoms in closely related compounds (δ 3.85—3.90 and 4.06—4.21 for the *R*,*S*- and *R*,*R*-diastereomers, respectively).[5]

Together with lactone **5** (yield 18%), the reaction affords a mixture of isomeric mesylates **6a,b** (yield 51%), from which the starting epoxide **4** can be recovered in a nearly quantitative yield. This increases the yield of lactone **5** to 38% based on the unrecovered starting compound **4**. The cyclization of epoxide **4** to lactone **5** can be performed only in a narrow range of conditions. A similar cyclization also proceeds in the presence of CSA and in $CHCl_3$; the use of other acids (TsOH, H_2SO_4, HBF_4, $HClO_4$) or solvents (benzene, CCl_4) give, at the best, traces of lactone **5**, possibly due to the known instability of compounds with such structures.[5,7] Strangely enough, under conditions of cyclization of methyl ester **4**, the corresponding acid does not yield lactone **5**.

A similar cyclization of 9-hydroxymethyl homolog of epoxide **4** (free acid) induced by $SnCl_4$ has been reported.[5] In this publication, unlike our study, the cyclopropane lactone homologous to lactone **5** was prepared as a mixture (1 : 1.5) of 5-epimeric lactones, which indicates the intermediate generation of the 5-carbocation. The formation of lactone **5** as a single isomer in our case can be interpreted as being due to synchronous participation of the protonated epoxide and methoxycarbonyl groups in the cyclization step, as shown in model **I** of the transition state. In this model, two attacks of the double bond occur from the opposite sides of this bond, which is energetically more favorable and gives rise to this particular configuration of lactone **5**.

Hydroxylactone **5** (in the homochiral form) and the aldehydolactone prepared from it have already been used as key intermediates (synthons) in the total syntheses of CLA,B;[5,7] therefore, the short-step synthesis of **5** described here can be regarded as a formal synthesis of constanolactones A, B.

(1′*R,2′*R**,6*S**)-6-[(2′-(Hydroxymethyl)cyclopropyl)]tetrahydropyran-2(2*H*)-one (5).** 15 μL of MsOH (22.2 mg, 0.23 mmol) was added to a solution of epoxide **4** (20 mg, 0.11 mmol) in 9.4 mL of water-saturated CH_2Cl_2, and the resulting emulsion (pH 3) was vigorously stirred for 1 h at 20 °C. According to TLC, the starting compound was absent and the chromatogram showed spots for three more polar substances. The reaction mixture was diluted with 0.1 mL of a saturated aqueous solution of $NaHCO_3$, the mixture was stirred (pH 7), and the organic layer was separated and concentrated *in vacuo* to dryness. The oily residue (36.6 mg) was dissolved in benzene and chromatographed on a column (2 g of silica gel, Merck, 70—230 mesh), using the hexane—EtOAc (9 : 1 → 6 : 4) solvent system to give 3.4 mg (18%) of lactone **5**, R_f 0.18, 15.6 mg (51%) of a mixture of mesylates **6a,b** (2 : 1, according to NMR), R_f 0.57, and 2.6 mg of an unidentified product, R_f 0.25 (TLC was carried out on Silufol plates with silica gel, hexane—EtOAc, 3 : 7, two developments, for **4**, R_f 0.88). Characteristic signals in the ^{1}H NMR spectrum of lactone **5** (300.13 MHz, $CDCl_3$), δ*: 0.60 (dt, 1 H, H(7a)); 0.75 (dt, 1 H, H(7b)); 1.00 (tt, 1 H, H(6)); 1.11 (m, H(8)); 3.45 and 3.57 (both dd, each 1 H, C(9)H_2); 3.80 (dd, 1 H, H(5), J = 7.7 Hz, J = 10.1 Hz); spin-spin coupling constants/Hz (determined from iterative simulation of the H(5)—H(9) region of the spectrum using the NUTS-4.35 program): $^3J_{5,6}$ = 8.6 Hz, $^3J_{cis\text{-}6,7a}$ = 8.8 Hz, $^3J_{trans\text{-}6,7b}$ = 5.4 Hz, $^3J_{trans\text{-}6,8}$ = 4.3 Hz, $^2J_{7a,7b}$ = 5.1 Hz, $^3J_{trans\text{-}7a,8}$ = 5.4 Hz, $^3J_{cis\text{-}7b,8}$ = 8.2 Hz, $^3J_{8,9a}$ = 6.5 Hz, $^3J_{8,9b}$ = 7.2 Hz, $^2J_{9a,9b}$ = 10.1 Hz.

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* The signal multiplicities are presented as observed in the spectrum.