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Enantioselective Total Synthesis of the Natural γ-Tocopherol Metabolite (*S*)-γ-CEHC [(*S*)-LLU-α]

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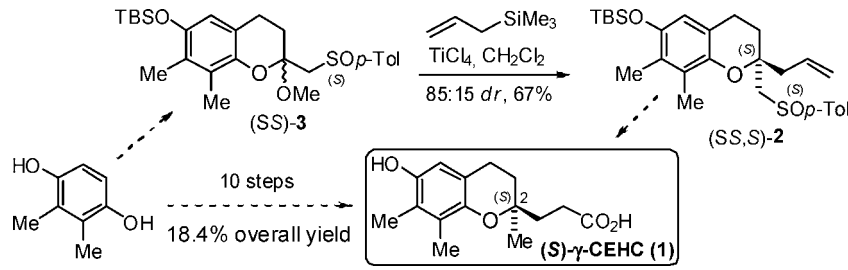
ABSTRACT



The asymmetric synthesis of the natural γ-tocopherol metabolite (*S*)-γ-CEHC (1) is described in 10 steps and 18.4% overall yield starting from 2,3-dimethylhydroquinone. The key step is a stereoselective $TiCl_4$-mediated homochiral sulfoxide-directed allylation of ketal (S*S*)-3 to efficiently generate the challenging C-2 stereogenic carbon of chroman (S*S*,*S*)-2 with the correct absolute configuration.

(2*S*)-2,7,8-Trimethyl-2-(2′-carboxyethyl)-6-hydroxychroman, (*S*)-γ-CEHC (**1**), was originally discovered as an endogenous natriuretic factor in patients suffering from uremia and named (*S*)-LLU-α by Wechter et al. in 1995.[1] The structure of this compound was determined by spectroscopic analysis[2] and proven by a racemic synthesis from 2,3-dimethylhydroquinone.[2,3] The absolute stereochemistry at C-2 was secured by X-ray analysis of an enantiopure amide and the resolution of the enantiomers was accomplished by chiral HPLC.[3] (*S*)-γ-CEHC was later found to be a major metabolite of (2*R*)-γ-tocopherol,[4] a component of the vitamin E family, and recent studies showed that (2*R*)-γ-tocotrienol is also metabolized to **1** in rats[5] and humans.[6]

The study of racemic γ-CEHC (**1**) in vitro in various model oxidative reactions has shown that, by its high antioxidant properties, it is comparable with α-tocopherol, ascorbic acid, and Trolox, a cardioprotective short-chain tocopherol analogue.[7] On the other hand, short-chain hydrophilic analogues of tocopherols, such as **1**, are water-soluble metabolites of Vitamin E possessing unique properties distinguishing them from the

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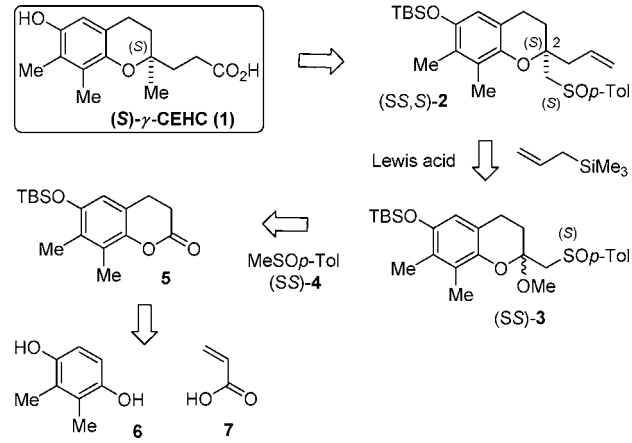
initial liposoluble tocopherols.[8] They exhibit antiinflammatory and natriuretic action, being endogenous ligands.[9] Unlike other diuretics, γ-CEHC selectively promotes the excretion of sodium ions without affecting the potassium ions.[1,4,10] Furthermore, **1** has been shown to inhibit the generation of prostaglandin E_2, an important mediator synthesized during inflammation via the cyclooxygenase-2-catalyzed oxidation of arachidonic acid.[11] Thus, (*S*)-γ-CEHC is expected to be a useful therapeutic agent.

These multiple biological activities make (*S*)-γ-CEHC (**1**) an attractive target for total synthesis. To achieve this goal, the main challenge and non-well-resolved task is the efficient generation of the C-2 stereogenic center at the chroman unit.[12] Besides several racemic approaches,[2,3,13] the only total synthesis of the natural (*S*)-enantiomer of γ-CEHC (**1**), reported in 1999 by Jung et al., was accomplished in 13 steps and 18% overall yield, starting from geraniol.[14] The key steps were a Sharpless asymmetric epoxidation of geraniol to generate the required stereogenic center, a Gassman−Sato process to join the alkyl chain to the phenolic moiety, and the cyclization of a triol with acid to give the corresponding chroman with retention of configuration at the tertiary alcohol center.

We have recently developed an enantioselective access to C-2-substituted chromans using the cyclization/nucleophilic substitution of several 2-(*p*-tolylsulfinylmethyl)-2-chromanols.[15] Herein, we describe a new and shorter enantioselective total synthesis of (*S*)-γ-CEHC (**1**) using, as the key step, a diastereoselective homochiral sulfoxide-directed[16] allylation to efficiently generate the challenging (*S*) stereogenic center at C-2 of the chroman moiety present in the final target.

The retrosynthetic analysis of (*S*)-γ-CEHC (**1**) is depicted in Scheme 1. As can be seen, (*S*)-**1** could be obtained from an advanced intermediate such as (*SS*,*S*)-**2**, after desulfinylation, double bond transformation, and OTBS deprotection. Compound **2**, showing the correct absolute configuration at the C-2 stereogenic center, would be formed after a Lewis acid-promoted diastereoselective (*S*)-sulfoxide-directed allylation of ketal intermediate (*SS*)-**3**, which could be obtained from 3,4-dihydrocoumarin **5** and (*SS*)-methyl *p*-tolyl sulfoxide (**4**).

Scheme 1. Retrosynthesis Toward (*S*)-γ-CEHC (**1**)



Finally, lactone **5** could be easily accessible from commercially available starting materials such as 2,3-dimethylhydroquinone (**6**) and acrylic acid (**7**).

One of the methods used to synthesize 3,4-dihydrocoumarins is the Friedel−Crafts alkylation of phenols with an excess of acrylic acid in the presence of the ion-exchange resin Amberlyst 15 as acid catalyst.[17] Thus, the hitherto unknown dihydrocoumarin derivative **9** could be synthesized from commercially available reagents 2,3-dimethyl-1,4-hydroquinone (**6**) and acrylic acid (**7**) under these conditions (Scheme 2). Nevertheless, in our hands, the formation of **9** was always accompanied with variable amounts of dicoumarin **8**, which could not be avoided. After several trials, we found the best conditions to minimize the undesired presence of **8**, by carrying out the reaction between **6** (1 equiv) and **7** (1.05 equiv) and an excess of Amberlyst in refluxing toluene for 2 days. From the crude reaction mixture formed under these conditions, the dicoumarin **8** was precipitated with EtOAc (10% yield). The mother liquors were later concentrated and purified by flash column chromatography to obtain a 65% yield of 3,4-dihydrocoumarin **9**.

Then, the phenolic OH group of **9** was protected as its silyl ether (TBSOTf, 2,6-lutidine, CH_2Cl_2, 12 h, 100%) and the resulting OTBS-protected lactone **5** was submitted to reaction with the Li anion of (*SS*)-methyl *p*-tolyl sulfoxide (**4**)[18] (LDA, THF, −78 °C, 1 h) furnishing sulfinyl lactol (*SS*)-**10**, in 75% yield. After methylation of lactol (*SS*)-**10** [TMSOTf, $MgSO_4$, CH_2Cl_2, MeOH, 0 °C to rt, 3 h, 85%),[19] the resulting 2-methoxy-3,4-dihydrobenzopyran (*SS*)-**3**, obtained as a mixture of stereoisomers at C-2, was submitted to the key-step formation of the C-2 stereogenic center of the chroman unit through a sulfoxide-directed Lewis acid-promoted nucleophilic allylation reaction.[20] After trying different Lewis acids ($TiCl_4$, $ZrCl_4$) and experimental conditions, we found that the best results, in terms

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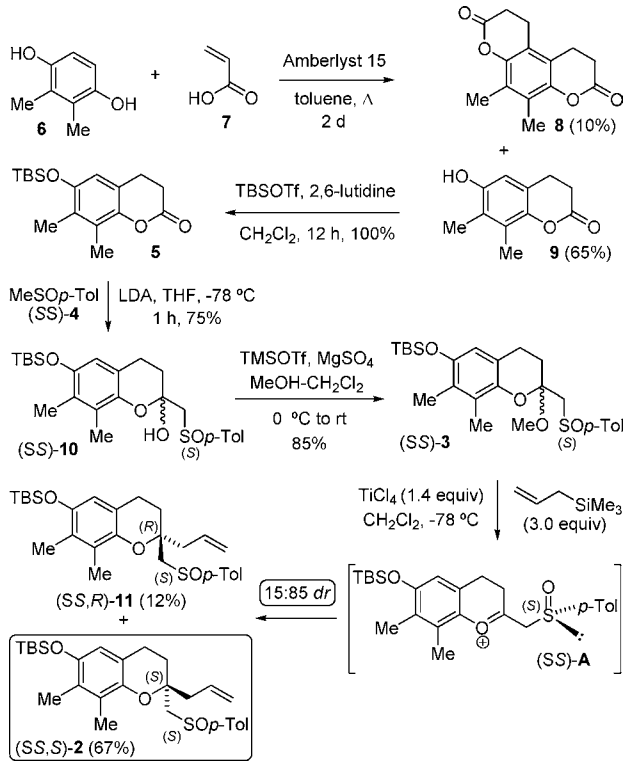
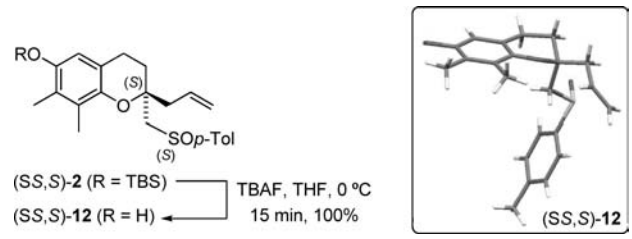
Scheme 2. Stereoselective Synthesis of Chroman (*SS*,*S*)-**2** En Route to (*S*)-γ-CEHC (**1**)



Scheme 3. Synthesis and X-ray ORTEP of Sulfinyl Chroman (*SS*,*S*)-**12**

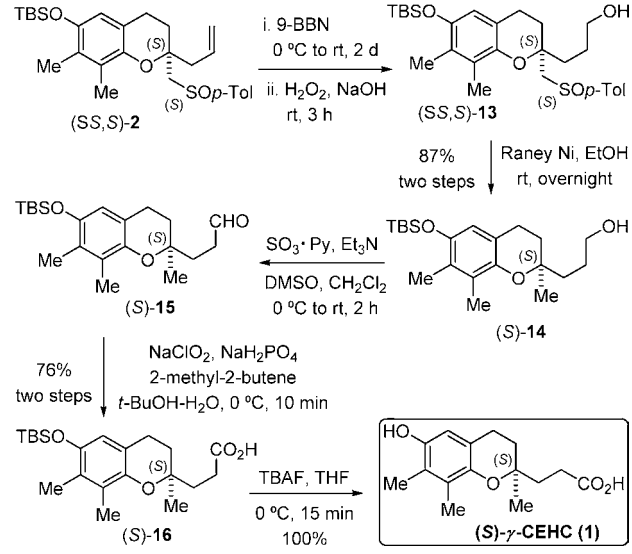


of diastereoselectivity and yield, were achieved from reaction of (*SS*)-**3** with allyl trimethyl silane (3 equiv) in the presence of $TiCl_4$ (1.4 equiv) at −78 °C in CH_2Cl_2. Under these conditions, a 15:85 mixture[21] of allyl sulfinyl chroman epimers at C-2, (*SS*,*R*)-**11** and (*SS*,*S*)-**2**, was obtained after stereoselective (*S*)-sulfoxide-directed addition of the allyl group of the reagent to the upper face of oxocarbenium intermediate (*SS*)-**A**, formed after the $TiCl_4$-promoted elimination of the methoxy group present in the starting material (*SS*)-**3**. Both diastereoisomers (*SS*,*R*)-**11** and (*SS*,*S*)-**2** could be separated after flash chromatography, being isolated in 12% and 67% yield, respectively (Scheme 2).

The (*S*) absolute configuration of the newly created stereogenic center at C-2 of chroman (*SS*,*S*)-**2** could not be determined at this stage but, after transformation into the corresponding free-OH derivative (*SS*,*S*)-**12** (TBAF, THF, 0 °C, 15 min, 100%), suitable crystals were collected for X-ray analysis[22] (Scheme 3).

With allyl sulfinyl chroman (*SS*,*S*)-**2** in hand, we undertook the final steps toward the total synthesis of (*S*)-γ-CEHC (**1**), as shown in Scheme 4. First, the reaction of the allyl moiety of **2** with 9-BBN (0 °C to rt, 2 d) followed by treatment with H_2O_2 and NaOH (rt, 3 h) gave rise to the corresponding sulfinyl alcohol (*SS*)-**13**, which, without further purification, was submitted to desulfinylation with Raney Ni (EtOH, rt, overnight) furnishing the 1-hydroxypropyl chroman (*S*)-**14** with 87% yield for the two last steps. Then, we tried to perform the direct oxidation of the primary OH of (*S*)-**14** into the corresponding carboxylic acid present in the final target. In our hands, this one-pot oxidation using different protocols[23] [(*t*-BuOOH, 5% mol CuCl, CH_3CN, rt),[23a] (0.03 equiv of $RuCl_3$, $NaIO_4$, H_2O/CH_3CN/CCl_4, rt),[23b] (TPAP, NMO, CH_3CN/H_2O, rt),[23c] (2.5% mol $NiCl_2$, NaOCl aq, CH_2Cl_2, rt),[23d] (CrO_3, H_5IO_6, CH_3CN/H_2O, rt)][23e] afforded complex reaction mixtures containing the desired carboxylic acid, the aldehyde intermediate, and/or degradation products. Thus, we decided to perform this oxida-

Scheme 4. Completion of the Synthesis of (*S*)-γ-CEHC (**1**)



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(21) When the reaction was carried out with the OAc-protected analogue of (*SS*)-**3**, we observed a 37:63 diastereoisomeric ratio, indicating a remarkable effect of the remote protecting group in the selectivity of the process.

(22) CCDC-742661 for (*SS*,*S*)-**12** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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tion process in two steps. First, the treatment of alcohol (*S*)-**14** with SO_3•Py in the presence of Et_3N (DMSO−CH_2Cl_2, 0 °C to rt, 2 h) gave rise to the aldehyde intermediate (*S*)-**15**, which, without further purification, was transformed into the corresponding carboxylic acid (*S*)-**16** after $NaClO_2$ oxidation (NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O, 0 °C, 10 min),[24] in 76% yield for the two last steps. Finally, desilylation of compound (*S*)-**16** with TBAF (THF, 0 °C, 15 min) took place in quantitative yield to afford (*S*)-γ-CEHC (**1**) {$[\alpha]^{20}_D$ +5.5 (*c* 1.43, MeOH); lit[3] $[\alpha]^{20}_D$ +5.1 (*c* 1.27, MeOH)}, showing >99% enantiomeric excess.[25] All physical and spectroscopic data of synthetic **1** were identical with those reported for the natural metabolite.[2,3]

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(25) The optical purity was determined by chiral HPLC (Daicel Chiralpack IA, 9.5% *i*-PrOH and 0.5% AcOH in hexane, 1 mL min^{-1}, 25 °C, 254 nm): $t_{R(2R)}$ = 23.5 min and $t_{R(2S)}$ = 28.8 min.

In conclusion, we have successfully achieved a new, short, and highly stereoselective total synthesis of the natural γ-tocopherol metabolite (*S*)-γ-CEHC [(*S*)-LLU-α], in 10 steps and 18.4% overall yield, using an enantiopure (*S*)-sulfoxide-directed nucleophilic allylation of a sulfinyl ketal intermediate as the key step to efficiently generate the challenging stereogenic center at C-2 of the chroman moiety.

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Supporting Information Available: Experimental procedures, characterization data, NMR spectra, and X-ray data (CIF) for (S*S*,*S*)-**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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