

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

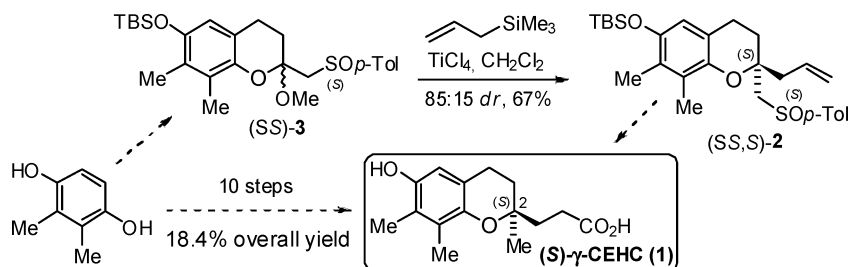
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ABSTRACT



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 (*SS*)-**3** to efficiently generate the challenging C-2 stereogenic carbon of chroman (*SS,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 analysis² 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 rats⁵ 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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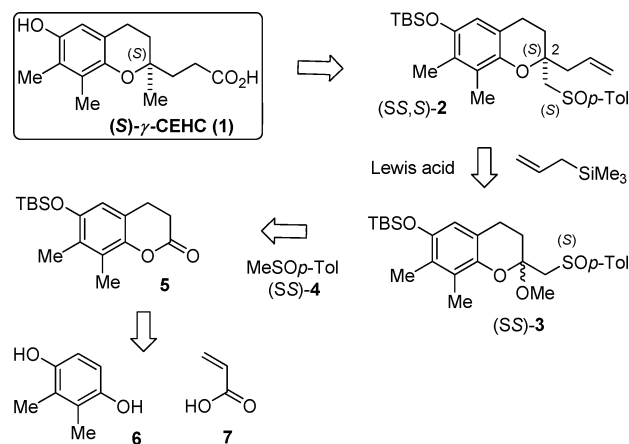
initial liposoluble tocopherols.⁸ They exhibit antiinflammatory and natriuretic action, being endogenous ligands.⁹ Unlike other diuretics, γ -CEHC selectively promotes the excretion of sodium ions without affecting the potassium ions.^{1,4,10} Furthermore, **1** has been shown to inhibit the generation of prostaglandin E₂, 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-directed¹⁶ 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, CH₂Cl₂, 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, MgSO₄, CH₂Cl₂, 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 (TiCl₄, ZrCl₄) and experimental conditions, we found that the best results, in terms

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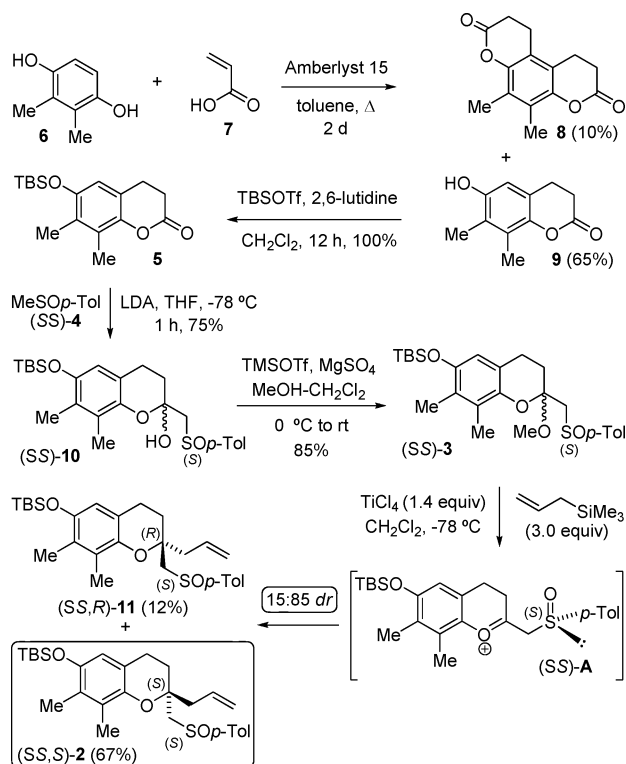
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Scheme 2. Stereoselective Synthesis of Chroman (SS,S)-2 En Route to (S)- γ -CEHC (1)

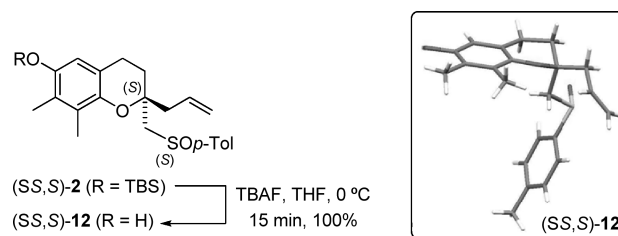


of diastereoselectivity and yield, were achieved from reaction of (SS)-3 with allyl trimethyl silane (3 equiv) in the presence of TiCl_4 (1.4 equiv) at -78°C in CH_2Cl_2 . Under these conditions, a 15:85 mixture²¹ of allyl sulfinyl chroman epimers at C-2, (SS,R)-11 and (SS,S)-2, was obtained after stereoselective (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 analysis²² (Scheme 3).

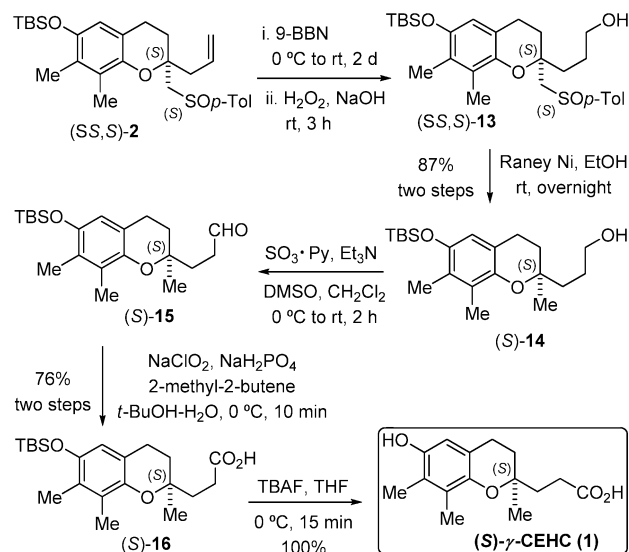
With allyl sulfinyl chroman (SS,S)-2 in hand, we undertook the final steps toward the total synthesis of (S)- γ -CEHC (1), as

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



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 protocols²³ [(*t*-BuOOH, 5% mol CuCl , CH_3CN , rt),^{23a} (0.03 equiv of RuCl_3 , NaIO_4 , $\text{H}_2\text{O}/\text{CH}_3\text{CN}/\text{CCl}_4$, rt),^{23b} (TPAP, NMO, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, rt),^{23c} (2.5% mol NiCl_2 , NaOCl aq, CH_2Cl_2 , rt),^{23d} (CrO_3 , H_5IO_6 , $\text{CH}_3\text{CN}/$

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



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-

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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 SO₃·Py in the presence of Et₃N (DMSO–CH₂Cl₂, 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 NaClO₂ oxidation (NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH–H₂O, 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**) {[α]_D²⁰ +5.5 (*c* 1.43, MeOH); lit³ [α]_D²⁰ +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 (SS,S)-**12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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