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Asymmetric Synthesis

Gold-Catalyzed Asymmetric Allylic Substitution of Free Alcohols: An Enantioselective Approach to Chiral Chromans with Quaternary Stereocenters for the Synthesis of Vitamin E and Analogues

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Abstract: The enantioselective synthesis of α- and γ-tocopherol (the most biologically active members of vitamin E family) and analogues has been accomplished employing a new enantioselective gold catalyzed intramolecular allylic alkylation reaction followed by an olefin cross-metathesis as key steps. The methodology proved to be applicable to different olefins highlighting its potential for the synthesis of diverse libraries.

The chiral chroman core constitutes a privileged framework of numerous natural products and synthetic analogues that display significant biological properties. For example, vitamin E is a radical scavenger that exhibits potent antioxidant properties, and is considered an essential compound against lipid peroxidation.[1] Vitamin E is the generic descriptor for a family of eight fat-soluble compounds (tocopherols and/or tocotrienols **I** and **II**) that depending on the degree of methylation on the aromatic ring are specified as α-, β-, γ-, or δ-isoforms (Figure 1).[2] Moreover, all the isoforms possess a chroman core with a *R* stereogenic centre at C-2. Trolox (**III**) is a water-soluble analogue of α-tocopherol with potent antioxidant properties. It is commonly used as a standard or positive control in antioxidant assays (trolox equivalent antioxidant capacity).[3] (*S*)-LLU-α (**IV**) is a metabolite of γ-tocopherol and γ-tocotrienol and has been isolated as an endogenous natriuretic factor.[4] Several biological studies prove that it has diuretic activity and antioxidant properties comparable with α-tocopherol, trolox, and ascorbic acid[5] and that it inhibits the generation of prostaglandin E_2.[6] MDL-73404 (**V**) is an antioxidant, which inhibits lipid peroxidation, scavenges superoxides more effectively than α-tocopherol, and exhibits cardioprotective effects during myocardial infarction.[7] Clusifoliol (**VI**) is a natural product isolated from a *Peperomia* species and has been used in the treatment of cancer tumors.[8] Finally, daurichromenic acid (**VII**) has shown potent anti-HIV activity.[9] In consequence, there is great interest in developing new methodologies for the synthesis of chiral chromans,[10] specially for the chiral chroman nucleus of vitamin E (Figure 1).

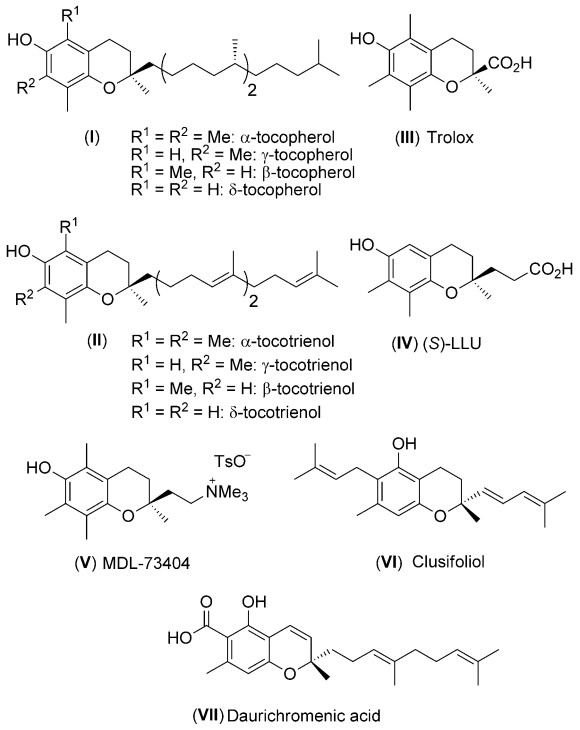
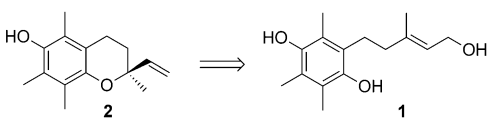


Figure 1. Representative chiral chromans and chromens.

However, while a variety of enantioselective approaches for the synthesis of the chiral chroman framework of α-tocopherol have been described (enzymatic methods,[11] Sharpless dihydroxylation,[12] palladium catalysis,[13] ruthenium catalysis,[14] organocatalysis,[15] or biomimetic cyclisation[16]), novel, easy, and efficient methods are still indispensable. In retrosynthetic analysis (Scheme 1), (*R*)-vinylchroman **2** might be formed by an intramolecular enantioselective allylic alkylation of allylic alcohol **1**.



Scheme 1. Retrosynthesis of the α-tocopherol precursor.

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Based on our experience in asymmetric ion pair and hydrogen-bond catalysis,[17] we decided to examine the enantioselective synthesis of the desired chiral chromans employing a chiral Brønsted acid as catalyst. However, in all the cases tested, the compounds were obtained with poor enantiomeric ratios. After these discouraging results, we attempted the chiral counterion strategy using chiral Au^{I}–phosphate complexes as reaction promoters,[18–20] but in these cases enantiomeric ratios remained low (up to 64.5:35.5). Finally, we decided to employ chiral gold–phosphine complexes in the intramolecular allylic alkylation reaction to generate the quaternary stereogenic center at C-2 of the chroman core in an asymmetric fashion. Indeed, gold catalysis has attracted widespread attention in organic synthesis over the past years, promoting a great number of enantioselective reactions.[21] Specifically, allylic alcohols have been employed as substrates for some enantioselective[22] or diastereoselective[23,24] alkylation reactions, but the formation of a quaternary carbon center through an allylic alkylation reaction still constitutes a major challenge.

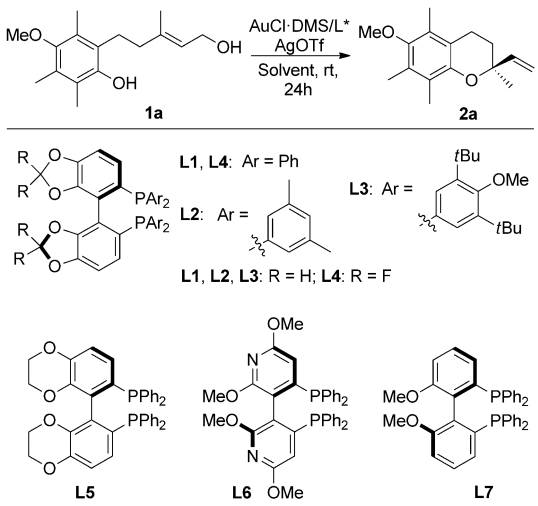
Herein, we describe an intramolecular enantioselective allylic alkylation reaction catalyzed by gold–phosphine complexes to synthesize chiral vinyl chromans as precursors for vitamin E and analogues.

With allylic alcohol (*E*)-**1a**[25,26] as a model substrate, we carried out a series of experiments to identify the best chiral phosphine ligand (Table 1).[27] For the first set of reactions, a mixture of toluene/CH_2Cl_2 (4:1) was used as solvent owing to the low solubility of (*E*)-**1a** in pure toluene. Several ligands with different electronic and steric properties were tested and generally better results were obtained with the SEGPHOS ligand family (**L1**–**L4**) (Table 1, entries 1–4), (*R*)-DM-SEGPHOS (**L2**) being the most promising one (Table 1, entry 2). Then, we focused on improving the enantioselectivity of the reaction by modifying the solvent. Surprisingly, even if the substrate was not initially fully dissolved, toluene gave better results (Table 1, entry 8) affording the desired compound with 95% yield and an e.r. of 92.5:7.5. Nevertheless, it should be pointed out that good enantioselectivity could also be obtained if different ether solvents were used (Table 1, entries 9–11). We also evaluated different temperatures (lower or higher), but only a drop in enantioselectivity was observed. The addition of different silver salts and additives did not improve the results. Finally, we found that the catalyst loading could be reduced to 2.5 mol% without observing any influence on the yield or enantiomeric ratio of chroman **2a** (Table 1, entry 12).

Having established an optimal protocol for the reaction,[28] the scope of the methodology with regard to the allylic alcohol was studied (Table 2). The reaction proceeded well with most of the alcohols, furnishing the corresponding vinyl chromans **2a**–**i** with excellent yields and good levels of enantioselectivity.

Thus, compatibility of the process with a wide range of substituted aromatic rings is given. As specified in Table 2, the use of substrates with different alkoxy groups (OMe, OEt, OBn) in the *para* position of the phenol ring gave good results (Table 2, entries 1–3). A bulkier compound led to the isolation of the desired adduct **2g** with similar results (Table 2, entry 7), as did less substituted compounds (Table 2, entries 6, 8–9). Excellent yields and slightly better levels of enantioselectivity were obtained when the methyl group present in the substrate was replaced with the longer ethyl group (Table 2, entries 4 and 5). Finally, we decided to investigate the influence of the configuration of the double bond of the substrate, and observed that the opposite enantiomer of the chiral chroman was formed with lower selectivity.

Table 1. Optimization of the reactions conditions for the enantioselective allylic alkylation of (*E*)-**1a**.[a]



Entry	Ligand	Solvent	Yield [%][b]	e.r.[c]
1	**L1** (5%)	toluene/CH_2Cl_2 (4:1)	90	70:30
2	**L2** (5%)	toluene/CH_2Cl_2 (4:1)	96	86:14
3	**L3** (5%)	toluene/CH_2Cl_2 (4:1)	94	85:15
4	**L4** (5%)	toluene/CH_2Cl_2 (4:1)	89	79:21
5	**L5** (5%)	toluene/CH_2Cl_2 (4:1)	93	57:43
6	**L6** (5%)	toluene/CH_2Cl_2 (4:1)	96	67.5:32.5
7	**L7** (5%)	toluene/CH_2Cl_2 (4:1)	91	67:33
8	**L2** (5%)	toluene	95	92.5:7.5
9	**L2** (5%)	Et_2O	92	91.5:8.5
10	**L2** (5%)	TBME	84	91.5:8.5
11	**L2** (5%)	CpME	94	92.5:7.5
12[d]	**L2** (2.5%)	toluene	96	93:7
13[e,f]	**L2** (1.25%)	toluene	98	92.5:7.5

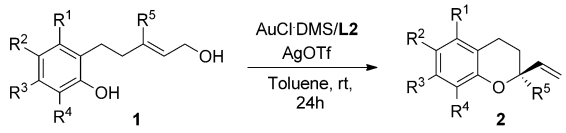
[a] Reaction conditions: (*E*)-**1a** (0.057 mmol), solvent (1 mL) at rt under Ar atmosphere. [b] Yield of isolated product after flash chromatography. [c] Determined by chiral supercritical fluid chromatography (SFC) by using a Chiralcel OD-H column. [d] 2.5 mol% of DMS·AuCl and AgOTf. [e] 1.25 mol% of DMS·AuCl and AgOTf. [f] (*E*)-**1a** (0.23 mmol), solvent (4 mL) under Ar atmosphere. DMS = dimethylsulfide, TBME = *tert*-butylmethylether, CPME = cyclopentylmethylether.

With all these results in hand, we decided to apply the methodology for the synthesis of biologically active and valuable compounds, including vitamin E. The absolute configuration of the chromans obtained by the newly developed asymmetric gold-catalyzed allylic alkylation is the appropriate one to synthesize the desired natural products.

Thus, we started to explore the preparation of α- and γ-tocopherol (**4** and **5**), the most active isoforms, by employing a cross-metathesis between vinyl chroman **2** and olefin **3**.

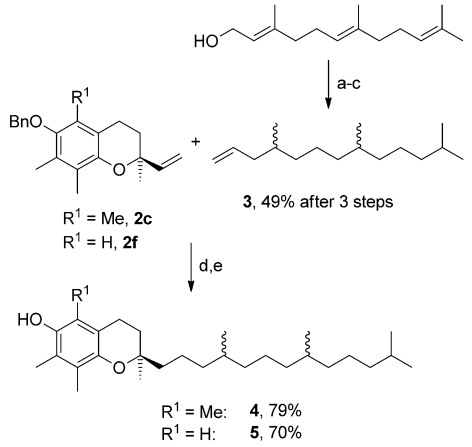
The lipophilic alkyl chain **3** was obtained in 49% overall yield following a three-step synthetic approach, as described

Table 2. Scope for the intramolecular enantioselective allylic alkylation catalyzed by gold (I).[a]



Entry	$R^1/R^2/R^3/R^4/R^5$	2	Yield [%][b]	e.r. (*R*/*S*)[c]
1	Me/MeO/Me/Me/Me	**2a**	98 (95)[d]	92.5:7.5 (22:78)[d]
2	Me/EtO/Me/Me/Me	**2b**	94	91:9
3	Me/BnO/Me/Me/Me	**2c**	99 (98)[d]	92:8 (15:85)[d]
4	Me/MeO/Me/Me/Et	**2d**	98 (94)[d]	93:7 (26:74)[d]
5	Me/BnO/Me/Me/Et	**2e**	99 (95)[d]	94:6 (23:77)[d]
6	H/BnO/Me/Me/Me	**2f**	98	93:7
7	Me/BnO/CH=CH-CH=CH[e]/Me	**2g**	62	90:10
8	Me/H/BnO/Me/Me	**2h**	97 (81)[d]	92:8 (16:84)[d]
9	H/H/H/EtO/Me	**2i**	91	91:9

[a] Reaction conditions: AuCl·DMS (2.5 mol%), **L2** (1.25 mol%), AgOTf (2.5 mol%), (*E*)-**1** (0.23 mmol), toluene (4 mL) at rt under Ar atmosphere. [b] Yield of isolated product after flash chromatography. [c] Determined by SFC on chiral support. [d] In parenthesis, results when (*Z*)-**1** was used. [e] R^3 and R^4 are represented together.



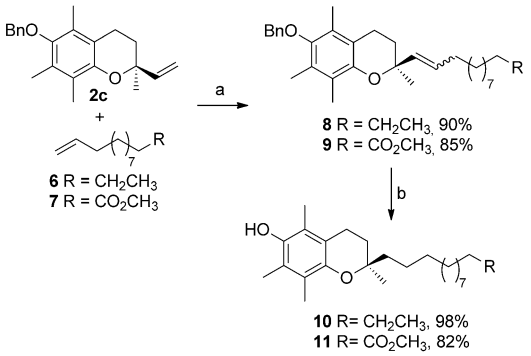
Scheme 2. Synthesis of the α-(2*R*,4′*RS*,8′*RS*)-tocopherol **4** and γ-(2*R*,4′*RS*,8′*RS*)-tocopherol **5**. Reagents and conditions: a) Pd/C (5%), H_2, EtOH, rt, 1 day, 92%; b) PCC, CH_2Cl_2, 2 h, 56%; c) Ph_3PCH_3Br, *t*BuOK, THF, 3 h, 95%; d) Second-generation Hoveyda–Grubbs ruthenium catalyst (HG-II, 20 mol%), 65 °C (MW), 10 h; e) Pd/C (5%), H_2, MeOH, rt, overnight. PCC = pyridinium chlorochromate.

in Scheme 2. It is noteworthy that racemic mixtures are usually prepared instead of enantiopure mixtures as recent studies have shown that the configuration of the stereogenic center of the isopropenoid chain does not have any influence on the antioxidant activity of the vitamin E.[29] Nevertheless, **3** could be prepared in enantiopure form by using the remarkable enantioselective hydrogenation reported by Pfaltz.[30]

With the substrates for the metathesis in hand we carried out an extensive study to find good conditions to introduce the lipophilic chain onto the chroman scaffold. Given that substrates with quaternary centers are slow to react in cross-metathesis reactions, several catalysts and diverse reaction conditions needed to be examined. The best results were achieved by employing 2.5 equivalents of olefin **3**, 20 mol% of second-generation Hoveyda–Grubbs ruthenium catalyst (HG-II) and a reaction temperature of 65 °C under microwave irradiation (Scheme 2).

The following reduction of the double bond with simultaneous deprotection of the benzyl ether led to the two vitamin E isoforms. Thus, α- and γ-(2*R*,4′*RS*,8′*RS*)-tocopherol (**4** and **5**) were obtained with good yields following olefin cross-metathesis and reduction/deprotection carried out as a one-pot procedure. Additionally, different analogues of α-tocopherol were synthesized to demonstrate the potential and utility of the present methodology.

The metathesis is compatible with different side chains and functional groups, including esters to afford desired compounds **10** and **11** with good to excellent yields (Scheme 3).

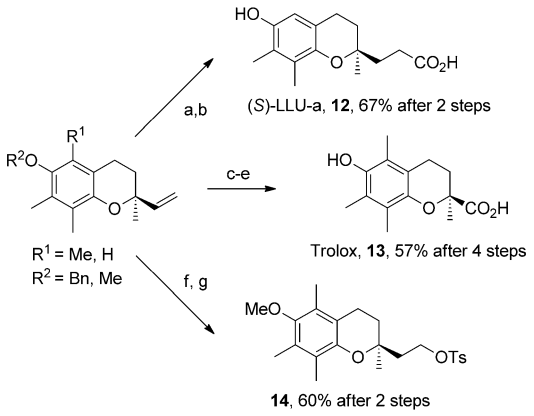


Scheme 3. Synthesis of the α-tocopherol analogues. Reagents and conditions: a) HG-II (10 mol%), 65 °C (MW), 2 h; b) Pd/C (5%), H_2, MeOH, rt, overnight.

Furthermore, it is also possible to perform the enantioselective allylic alkylation/metathesis operation in a one-pot procedure maintaining good yields for **8** and **9** (77 and 78% yield, respectively).

Given the value of the chroman core structure in important synthetic precursors, we decided to study further chemical modifications. In this respect, (*S*)-LLU-α, trolox, and tosylated chromanol, all compounds with biological activity, were prepared following literature procedures or optimized protocols thereof (Scheme 4).

In conclusion, we have developed a new synthesis of α- and γ-tocopherol as well as analogues employing a novel asymmetric gold-catalyzed intramolecular allylic alkylation reaction and an olefin cross-metathesis as key steps. The methodology presented herein proved to be compatible with different olefins, highlighting its potential for the synthesis of diverse libraries of valuable biologically active compounds. Furthermore, the new gold-catalyzed intramolecular asymmetric allylic alkylation provides various chromans with quaternary stereocenters with excellent yields and high levels of enantioselectivity.



Scheme 4. Synthesis of other vitamin E analogues. Reagents and conditions: a) HG-II (20 mol%), acrylic acid (3 equiv), CH_2Cl_2, 65 °C (MW), 5 h, 79%; b) Pd/C (5%), H_2, MeOH, rt, overnight, 85%; c) 1) OsO_4, NMO, CH_2Cl_2, H_2O, rt, 14 h, 2) $NaIO_4$, acetone, H_2O, rt, 25 min, 72% (two steps); d) $NaClO_2$, NaH_2PO_4, *t*BuOH, 2-methyl-2-butene, 0 °C, 2 h, 82%; e) Pd/C (5%), H_2, MeOH, rt, 8 h, 97%; f) BH_3·THF, THF, 0 °C to rt then NaOH, H_2O_2, 60 °C, 87%, 3:1 regioselectivity; g) TsCl, pyridine, 0 °C, 70%. NMO = *N*-methyl-morpholine-*N*-oxide.

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Keywords: allylic alkylation · chromans · gold catalysis · tocopherol · vitamin E

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