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Graphical Abstract

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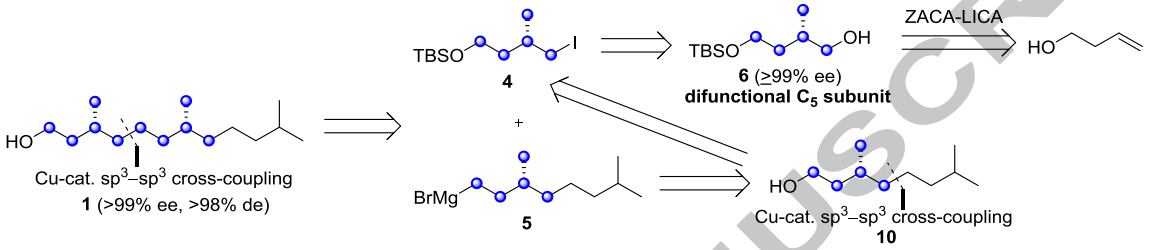

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A novel highly enantio- and diastereoselective synthesis of vitamin E side-chain

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ABSTRACT

A novel highly enantioselective (>99% ee) and diastereoselective (>98% de) method for the synthesis of chiral C_{15} vitamin E side-chain **1** was developed. ZACA–lipase-catalyzed acetylation protocol to provide a key *α,ω*-dioxyfunctional C_5 synthon **6** (≥99% ee), and two subsequent Cu-catalyzed alkyl–alkyl cross-coupling reactions of enantiomerically pure C_5 iodide **4** were employed as key steps. ^{1}H NMR analysis of MαNP ester was found to be a convenient method for measuring the enantiomeric purity of the C_{15} vitamin E side-chain **1**.

Saturated isoprenoids represent a large and diverse class of naturally occurring organic compounds including vitamins,[1] pheromones,[2] antioxidants,[3] marine natural products,[4] and archaebacterial lipids.[5] The saturated isoprenoids play widely varying roles in the physiological processes in living organisms such as archaea, bacteria, and human. Archaea are distinct from bacteria and eukaryotes. One characteristic feature of archaea is the chemical structure of its core membrane lipids consisting of saturated isoprenoid chains connected to glycerol through ether linkages.[6]

(3*R*,7*R*)-3,7,11-Trimethyldodecanol **1** is a very important saturated isoprenoid derivative, which can be used as a versatile intermediate for the syntheses of vitamin E,[7] vitamin K_1,[8] and

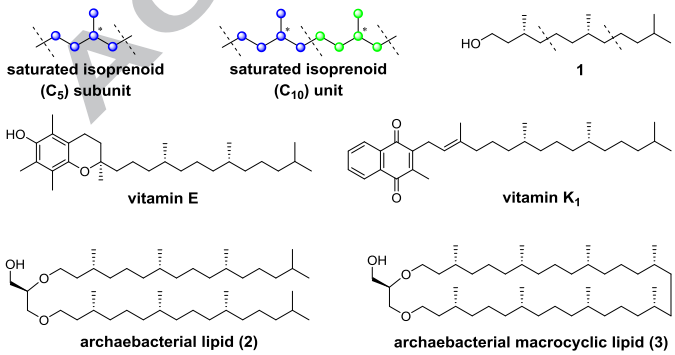

Figure 1. Some natural products containing chiral saturated isoprenoid units.

related antioxidants.[9] It has also been identified as a precursor of many isoprenoid compounds in plants,[10] geological sediments,[11] and archaebacterial lipids in archea.[12] Thus, numerous synthetic strategies have been developed for the synthesis of such important building block. Current synthetic approaches include chiral auxiliary-based methods,[13] chiral pool synthesis,[14] and enzymatic protocols.[15] However, these methods have several disadvantages including long and multi-step processes, the use of stoichiometric quantities of chiral reagents, and low stereoselectivity. At present, only a very few transition metal-catalyzed methods are known, of which catalytic asymmetric hydrogenation by Noyori[16] and Pfaltz[17] are noteworthy. We also developed a concise and efficient synthesis of **1** via **Z**r-catalyzed **a**symmetric **c**arboalumination of **a**lkenes (ZACA).[18] However, all these methods lack high (≥98%) stereoselectivity leading to diastereomeric mixtures which are very difficult to purify.

We recently developed highly enantioselective (≥99% ee) and catalytic routes to a wide range of 1-alkanols including those of isotopic cryptochirality via ZACA–Cu- or Pd-catalyzed cross-coupling.[19-21] The development of these methods relied on the following four critical findings: (i) ZACA–*in situ* iodinolysis of allyl alcohol to produce either (*S*)- or (*R*)-$ICH_2CH(R)CH_2OH$ in 80–90% ee,[19] (ii) ZACA–*in situ* oxidation of TBS-protected ω-alkene-1-ols to afford both (*R*)- and (*S*)-α,ω-dioxyfunctional intermediates in 80–86% ee,[20,21] (iii) enantiomeric purification by **li**pase-**c**atalyzed **a**cetylation (LICA) of the above functionally rich intermediates to the ≥99% ee level through exploitation of their high selectivity factors (*E*),[22] and (iv) essentially perfect (>99%) stereochemical fidelity with retention observed widely in the subsequent Cu- or Pd-catalyzed cross-coupling reactions.[18e,23] Herein we report a highly reliable and predictable method for the

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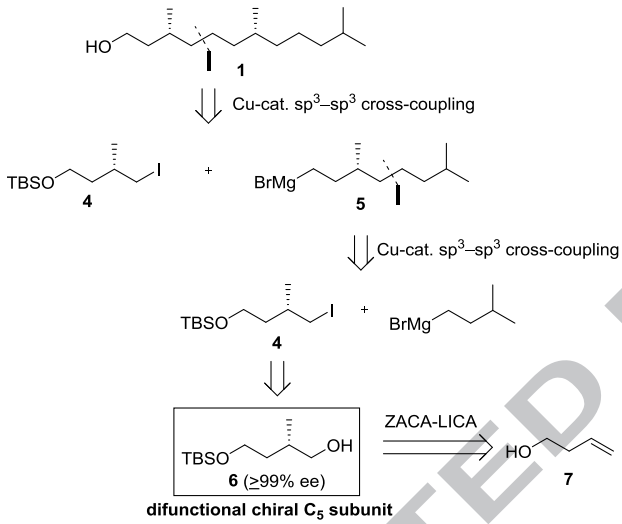
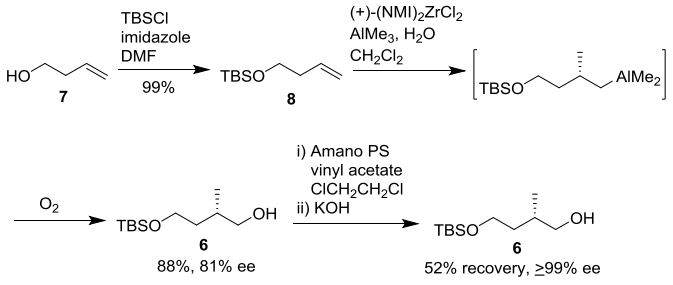
preparation of both enantiomerically and diastereomerically pure C_{15} vitamin E side-chain **1** using our ZACA–Cu-catalyzed cross-coupling strategy.

A retrosynthetic scheme for preparation of the C_{15} vitamin E side-chain **1** is shown in Scheme 1. It was planned to couple C_5 iodide **4** and C_{10} Grignard reagent **5** through Cu-catalyzed alkyl–alkyl cross-coupling reaction.[23] Segment **5** should be readily prepared by another Cu-catalyzed alkyl–alkyl cross-coupling reaction of isopentylmagnesium bromide with iodide **4**, which, in turn, should be derived from the key *α,ω*-dioxyfunctional chiral C_5 subunit **6**. We envisioned that a highly enantioselective synthesis of chiral C_5 synthon **6** could be achieved via our ZACA–LICA protocol. If the key C_5 subunit **6** could be obtained in high enantiomeric purity (≥99% ee), the subsequent Cu-catalyzed cross-coupling reactions would proceed with essentially full (>99%) retention of all carbon skeletal features of key C_5 synthon **6** to provide **1** with excellent enantiomeric and diastereomeric purity (ee > 99%, de > 98%).



Scheme 1. Retrosynthetic analysis of C_{15} vitamin E side-chain **1**.

The *α,ω*-dioxyfunctional C_5 synthon **6** (≥99% ee) was prepared as shown in Scheme 2. 3-Buten-1-ol **7** was protected with TBSCl and was subjected to ZACA reaction. A solution of 1 mol% of (+)-bis(neomenthylindenyl)zirconium dichloride [(+)-$(NMI)_2ZrCl_2$][24] in CH_2Cl_2 was treated with trimethylaluminum (2 equiv) and H_2O (1 equiv), then TBS-protected 3-buten-1-ol **8** was added to the above solution for asymmetric methylalumination. After the completion of methylalumination, the initial alkylalane intermediate was oxidized *in-situ* with O_2 to provide **6** in 88% yield and 81% ee.



Scheme 2. The synthesis of key *α,ω*-dioxyfunctional C_5 synthon **6** (≥99% ee).

Enantiomeric purification of *α,ω*-dioxyfunctional intermediate **6** obtained by the ZACA reaction was carried out by lipase-catalyzed acetylation. Thus, crude intermediate **6** (81% ee) was readily purified to the level of ≥99% ee in 52% recovery yield by Amano lipase PS-catalyzed acetylation with vinyl acetate in 1,2-dichloroethane. The high enantiomeric purity of **6** was evidenced by Mosher ester analysis[25] as shown in Figure 2. Two diastereomeric Mosher esters of β-chiral alcohol **6** showed the expected chemical shift differences. The absence of peaks at 4.23 ppm of MTPA ester **9** derived from alcohol **6** and (*R*)-MTPA-Cl indicated the high enantiomeric purity of alcohol **6** (Figure 2).

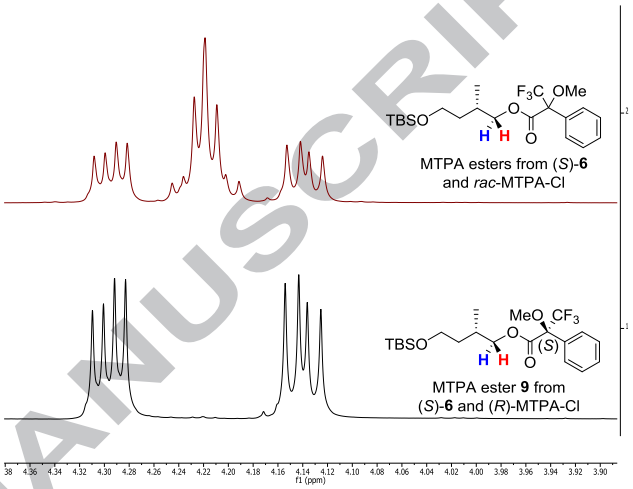
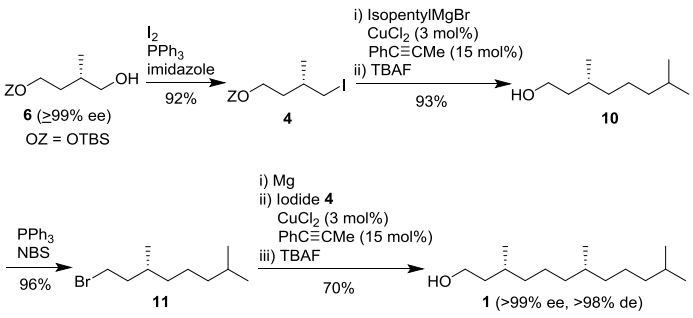


Figure 2. ^{1}H NMR spectra of two diastereomeric MTPA esters of β-chiral alcohol **6** ($CDCl_3$, 600MHz).

With the enantiomerically pure C_5 intermediate **6** in hand, we proceeded to investigate the synthesis of C_{15} vitamin E side-chain **1** by using **6** as the key building block. Thus, the chiral C_5 alcohol **6** was readily converted to iodide **4** with triphenylphosphine, imidazole and iodine in CH_2Cl_2. Next, $CuCl_2$-catalyzed alkyl–alkyl cross-coupling reaction[23] between iodide **4** and isopentylmagnesium bromide proceeded efficiently in the presence of 1-phenylpropyne as an additive, followed by desilylation with TBAF, providing C_{10} alcohol intermediate **10** in 93% yield, which was further transformed to the corresponding bromide **11** in 96% yield using Ph_3P/NBS. The desired C_{15} vitamin E side-chain **1** was prepared in 70% yield via another round of $CuCl_2$/1-phenylpropyne-catalyzed alkyl–alkyl cross-coupling reaction[23] between C_5 iodide **4** and the Grignard reagent derived from C_{10} bromide **11**, followed by desilylation with TBAF.



Scheme 3. The synthesis of C_{15} vitamin E side-chain **1**.

We then wanted to determine the enantiomeric purity of the C_{15} vitamin E side-chain **1**. Mosher ester analysis of γ-chiral alcohol **1** proved to be ineffective for determining the optical purity of **1**. We recently demonstrated that 2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid)[26] ester analysis is a widely applicable and powerful method for chiral discrimination of various β- and more-remotely chiral primary alcohols including those of isotopomers.[20,21] As expected, two diastereomeric MαNP esters **12a** and **12b** derived from γ-chiral alcohol **1** showed significantly different chemical shifts. In particular, the γ-methyl groups of these two diastereomers **12** showed completely separate ^{1}H NMR signals (Figure 3), which indicated that the enantiomeric excess of alcohol **1** is greater than 99%. In addition, the diastereomeric purity of alcohol **1** was also confirmed to be greater than 99% by ^{13}C NMR analysis.

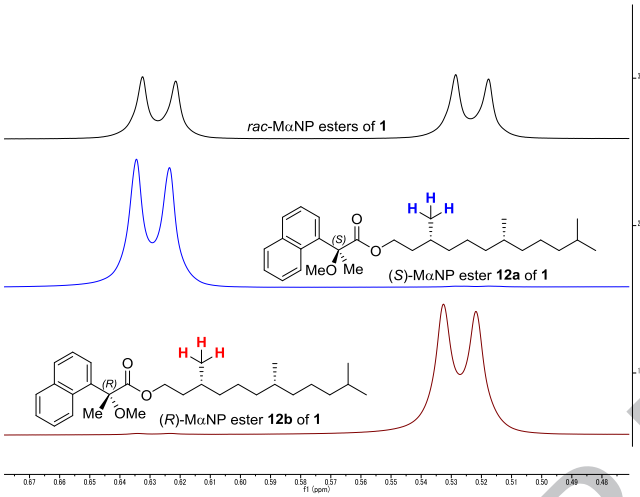


Figure 3. ^{1}H NMR spectra of diastereomeric MαNP esters of γ-chiral alcohol **1** ($CDCl_3$, 600MHz).

In summary, we have developed a highly enantioselective (>99% ee) and diastereoselective (>98% de) route to chiral C_{15} vitamin E side-chain **1** via ZACA–Cu-catalyzed cross-coupling from 3-buten-1-ol. The key *α,ω*-dioxyfunctional C_5 synthon **6** (≥99% ee) was readily prepared by ZACA–LICA protocol, which can be further functionalized at both ends. Two sequential Cu-catalyzed alkyl–alkyl cross-coupling reactions of the enantiomerically pure C_5 iodide **4** were employed as the key steps for preparing the C_{15} vitamin E side-chain **1**. In addition, we demonstrated that ^{1}H NMR analysis of MαNP ester is a convenient method for measuring the optical purity of the C_{15} vitamin E side-chain **1**. It should be noted that various (*R*)- and (*S*)-*α,ω*-difunctional compounds have been successfully prepared as enantiomerically pure (≥99% ee) substances by ZACA–LICA protocol.[19-21] This novel approach promises to provide a reliable method for highly enantioselective and diastereoselective syntheses of various possible stereoisomers of chiral isoprenoid natural products and analogues. Further studies along this line are currently ongoing in our laboratories.

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