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PII: S0040-4039(14)01438-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.08.085
Reference: TETL 45052

To appear in: *Tetrahedron Letters*

Received Date: 8 May 2014
Revised Date: 5 August 2014
Accepted Date: 25 August 2014

Please cite this article as: Lee, H., Lee, Y-K., Kim, D-G., Son, M-S., Nam, T-g., Jeong, B-S., Tocopherol side chain synthesis via asymmetric organocatalytic transfer hydrogenation and convenient measurement of stereoselectivity, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.08.085

Tetrahedron Letters
journal homepage: www.elsevier.com

Tocopherol side chain synthesis via asymmetric organocatalytic transfer hydrogenation and convenient measurement of stereoselectivity

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
tocopherol
asymmetric synthesis
organocatalyst
stereoselectivity
UV-HPLC

ABSTRACT

An asymmetric synthetic route for 1-iodofarnesane, a key intermediate for tocopherol side chain synthesis, starting from (+)-(*R*)-citronellal was developed. 1-Iodofarnesane was prepared through eight steps in about 50% overall yield, and asymmetric transfer hydrogenation of the enal with a chiral organocatalyst was conducted as a stereoinduction step. To measure the stereoinduction level and optical purity of the product, a convenient analytical method was developed in which a phenylcarbamate derivative of the C_{15} alcohol was found to be suitable to give proper polarity and UV-activity for chiral UV-HPLC analysis.

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α-Tocopherol (**1**, α-TOH) has been known as nature's best lipophilic chain-breaking antioxidant.[1] Its antioxidant activity is attributed to the ability to donate hydrogen atom from its O–H bond to chain propagating lipid peroxyl radical.[2] Therefore, many synthetic versions of α-TOH derivatives have been prepared to show better hydrogen atom donating characteristics and air-stability.[2,3] Among them, 6-aminopyridin-3-ol analogues have much better antioxidant activities (better H-atom donation) and air-stabilities (higher ionization potential of aromatic ring tethering –OH group) than α-TOH.[4] One of the best examples is the N-tocopherol (N-TOH, **2**), which has the same side chain as α-TOH. N-TOH showed excellent antioxidant activity in bulk solvent as well as in the LDL oxidation system.[4d] In addition, it does not promote tocopherol-mediated peroxidation (TMP) even at increased concentration. Interestingly, N-TOH showed much better binding affinity to human tocopherol transfer protein (hTTP).[4d] TTP is responsible for the transportation of tocopherols to VLDL particle.[5] Differential uptake of (*R,R,R*)-tocopherol over (*S,R,R*)-tocopherol by TTP is attributed to the specific interaction between tocopherol and the protein.[6] The stereochemistry of the tocopherol side chain is responsible for the uptake and therefore the *in vivo* antioxidant activity.[6] Mechanically, the tocopherol side chain has biological implications such that its lipophilicity renders the tocopherol head group to be incorporated at proper depth inside the LDL particle where the lipid peroxyl radical resides.[6a,7] The C_{16} isoprenoid side chain of α-TOH is biosynthesized through the mevalonate pathway where a farnesyl moiety is formed as a crucial precursor. Chemically, this chain can be synthesized in different ways.[8]

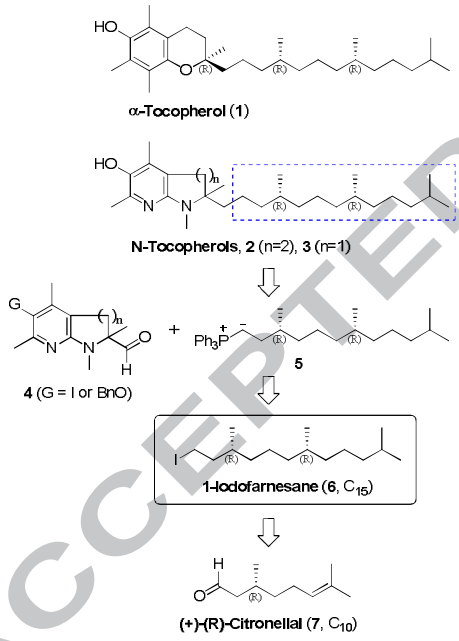
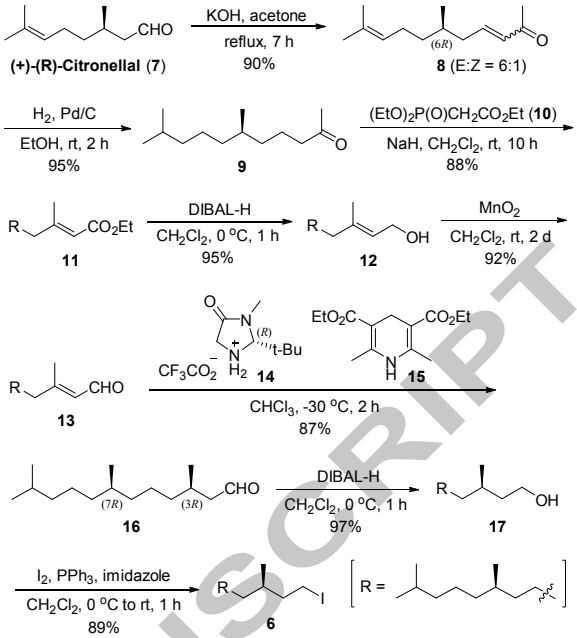


Figure 1. Tocopherol side chain and its synthesis.

In this letter, we report a synthetic route for 1-iodofarnesane (**6**), a key intermediate for tocopherol side chain synthesis, from commercially available (+)-(*R*)-citronellal (**7**) via asymmetric transfer hydrogenation as a key step utilizing a Hantzsch ester and a chiral imidazolidinone organocatalyst. We also present derivatization of an intermediate by which stereoselectivity of asymmetric transfer hydrogenation can be measured using UV-HPLC.

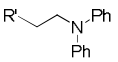
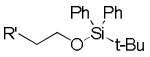
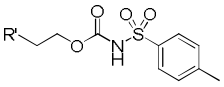
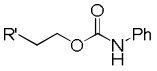
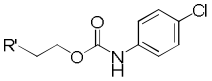


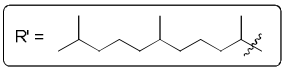
Scheme 1. Synthesis of 1-iodofarnesane (**6**) from (+)-(*R*)-citronellal (**7**) using organocatalytic transfer hydrogenation as a key step.

As shown in Scheme 1, synthesis began with a Claisen-Schmidt reaction of commercially available (+)-(*R*)-citronellal (**7**) with acetone to give C_{13} α,β-unsaturated ketone **8** in 90% yield.[8f] Subsequent hydrogenation of the two olefins afforded saturated C_{13} ketone **9** in 95% yield which was then subject to a Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate (**10**) to give C_{15} α,β-unsaturated ester **11** in 88% yield. **11** was then smoothly reduced to allyl alcohol **12** with DIBAL-H in 95% yield. Mild oxidation of the allyl alcohol of **12** with manganese(IV) oxide afforded C_{15} α,β-unsaturated aldehyde **13**, a substrate for asymmetric transfer hydrogenation reaction. The origin of stereoselectivity is suggested to be transient formation of a chiral iminium function between an α,β-unsaturated aldehyde substrate and a chiral secondary amine catalyst.[9] Then, hydride from Hantzsch ester is delivered in a stereoselective manner as NAD(P)H or $FADH_2$.[9] In this study, for asymmetric transfer hydrogenation of the enal **13**, we employed MacMillan's imidazolidinone **14** as a chiral organocatalyst[10] and diludine (**15**), a commercially available Hantzsch ester, as a hydride source, which afforded saturated aldehyde **16** in 87% yield. The aldehyde **16** was reduced to primary alcohol **17** in 97% yield, followed by iodination of the alcohol to give 1-iodofarnesane (**6**), the final goal of this synthesis. Synthesis is highly efficient so that the overall yield was about 50% in eight steps from (+)-(*R*)-citronellal (**7**).

Next, we wanted to check the optical purity of the newly formed C(3)-methine group in the aldehyde **16** or the alcohol **17** using chiral UV-HPLC analysis, one of the most widely used analytical tools for determination of stereoselectivity. However, they were difficult to analyze in UV-HPLC due to their extremely low polarity and UV-inactivity. Therefore, we prepared racemic versions of **16** and **17** in order to identify retention times in HPLC traces of each stereoisomer and to conduct derivatization for improved UV detection and suitable polarity. Racemic versions of **16** (aldehyde) and **17** (alcohol) were prepared according to the literature procedure,[8l,11] and then several derivatives were prepared as shown in Table 1.

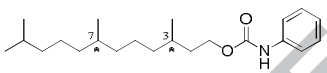
Table 1. Compounds for chiral UV-HPLC analysis.

Entry	Substrate	Conditions	Derivative
1	***rac*-16**	Ph_2NH, $NaBH(OAc)_3$	
2	***rac*-17**	TBDPSCl, Et_3N, DMAP	
3	***rac*-17**	TsNCO, Et_3N	
4	***rac*-17**	PhNCO, Et_3N, DMAP	
5	***rac*-17**	*p*-ClPhNCO, Et_3N	



The derivatives were screened about their polarity and UV-sensitivity. Diphenylamino analogue (entry 1) and *tert*-butyldiphenylsilyl ether (entry 2) were still too non-polar for HPLC separation. Carbamate derivatives (entries 3–5) of the alcohol generally showed proper polarities; however, the tosylcarbamate (entry 3) and the *p*-chlorophenylcarbamate (entry 5) were still troublesome in a clear separation of the four stereoisomers. On the other hand, the phenylcarbamate derivative (entry 4) was a suitable compound for good resolution in chiral UV-HPLC. Four different stereoisomers of the phenylcarbamate (***rac*-18**) of the racemic C_{15} alcohol (***rac*-17**) were clearly separated, and the data and optimal analytical conditions are described in Table 2.

Table 2. Chiral UV-HPLC analysis of **18**[a]



18

Peak	RT (min)[b]	Area %		Abs. config.[c]
		***rac*-18**	**18** from **17**	
P^1	28.2	25%	7%	3*R*,7*S*
P^2	31.3	25%	63%	3*R*,7*R*
P^3	39.1	25%	27%	3*S*,7*R*
P^4	48.5	25%	3%	3*S*,7*S*

[a] HPLC conditions; • Column: Chiralpak AD-H chiral column (4.6×250 mm), • Eluent: 0.2 v/v% 2-propanol in hexanes, • Temperature: 23 °C, • Detection: 233 nm, • Flow rate: 1.0 mL/min.

[b] Retention time.

[c] Absolute configuration.

Before the determination of stereoinduction level of the key step (**13**→**16**), we had to check the exact optical purity of the starting material, (+)-(*R*)-citronellal (**7**) because it is known that commercially available (+)-(*R*)-citronellal is not entirely optically pure. The optical purity of **7** was determined by chiral UV-HPLC analysis of the Claisen-Schmidt product **8**. To this end, racemic version of **8**, ***rac*-8**, was prepared from racemic citronellal. Two enantiomers in ***rac*-8** were separated in good resolution in chiral HPLC analysis under the following conditions: i) chiral column: Chiralcel OD-H (4.6×250 mm), ii) eluent: 0.2 v/v% 2-propanol in hexanes, iii) temperature: 23 °C, iv) detection: 254 nm, v) flow rate: 0.6 mL/min, and vi) retention times: 13.7 min (6*S*-isomer), 14.6 min (6*R*-isomer). The (+)-(*R*)-citronellal used in this study was a 9:1 enantiomeric mixture based on this chiral HPLC analysis. With this analytical information in hand, we finally determined the stereoselectivity of the organocatalytic transfer hydrogenation of the enal **13** by a chiral HPLC analysis of **18** prepared from **17**. As shown in Table 2, relative area %'s of the four stereoisomers were observed in approximate ratio of $7(P^1):63(P^2):27(P^3):3(P^4)$. From this data, we envisioned that P^1 and P^4 peaks originated from the minor enantiomer, (–)-(*S*)-citronellal, while P^2 and P^3 peaks represented (+)-(*R*)-citronellal (**7**), the major enantiomer, because the ratio between the sum of area of P^2 and P^3 and that of P^1 and P^4 was about 9:1. Therefore, P^2 and P^3 peaks contain (7*R*)-configuration while the other peaks have (7*S*)-configuration. The chiral imidazolidinone catalyst **14** we used is well known to promote asymmetric transfer hydrogenation of acyclic enal systems to corresponding aldehydes with a single stereochemical outcome in a very consistent manner.[10a] Or, (*R*)-configured imidazolidinone catalyst afforded only one stereochemical outcome in 90-97% ee starting from various enal substrates. Furthermore, the (*S*)-configured MacMillan's imidazolidinone catalyst, the opposite enantiomer of our catalyst **14**, asymmetrically reduces (*E*)-citral, an isoprenoid enal which contains the identical local substitution environment to our substrate, to (*R*)-configured aldehydes as major product (enantiomeric ratio = 70:30).[10b] Thus, we believe the major peaks, P^1 and P^2, are favored products that contain the (3*R*)-configuration in the asymmetric transfer hydrogenation over the (3*S*)-minor isomers, P^4 and P^3, respectively. Taken together, we were able to identify the absolute configuration of the four peaks (i.e., P^1: 3*R*,7*S*, P^2: 3*R*,7*R*, P^3: 3*S*,7*R*, P^4: 3*S*,7*S*) as shown in Table 2.

From the above assignment, stereoselectivity of the asymmetric transfer hydrogenation was calculated to be 40% ee Although the catalyst did show much better stereoselectivity in the other types of substrate,[10a] this moderate stereoselectivity is not an outlier in the chemistry of this catalyst, but, in fact, is in line with literature value. The catalyst is reported to give only 40% ee as well when the substrate is (*E*)-citral which contains very high degree of homology in local substitution patterns as our substrate.[10b] Interestingly, there exists a chiral phosphoric acid catalyst which seems to be much more stereoselective in transfer hydrogenation of this type of substrate. It showed very efficient asymmetric transfer hydrogenation of C_{10}-(*E*)-citral and C_{15}-farnesal to the corresponding aldehyde in 90% ee and 92% ee, respectively.[10b] Since their local substitution patterns are virtually identical to that of our substrate, the compound **13**, it is highly likely that the chiral phosphoric acid catalyst would have afforded much better stereoselectivity than the catalyst used in this work.

In summary, we developed an eight-step synthetic route for a chiral C_{15} isoprenoidal tocopherol side chain starting from (+)-(*R*)-citronellal in which asymmetric organocatalytic transfer hydrogenation was employed as the key step. We also developed a convenient chiral UV-HPLC analysis method for measuring the optical purity of the tocopherol side chain. A facile derivatization of the C_{15} alcohol **17** to the corresponding phenylcarbamate **18** provided proper polarity and UV-sensitivity, which led to clear separation of the four stereoisomers in HPLC.

Acknowledgement

This work was supported by the Yeungnam University Research Grant (Grant No.: 212-A-380-222).

Supplementary Data

Supplementary data associated with this article can be found in the online version, at http://

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Graphical Abstract

Tocopherol side chain synthesis via asymmetric organocatalytic transfer hydrogenation and convenient measurement of stereoselectivity

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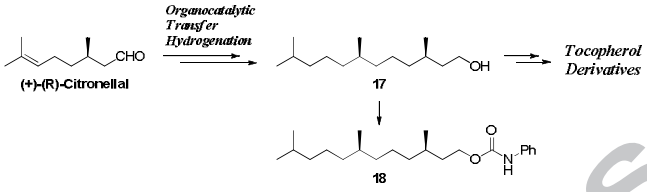

Highlights

- An asymmetric synthetic route for 1-iodofarnesane from citronellal was developed.
- An asymmetric organocatalytic transfer hydrogenation was employed as the key step.
- A convenient chiral UV-HPLC analysis for measuring stereoselectivity was developed.
- A phenylcarbamate analog provided proper polarity and UV-sensitivity for analysis.