COMMUNICATION

Chemoenzymatic synthesis of (+)-(4*E*,15*E*)-docosa-4,15-dien-1-yn-3-ol, a component of the marine sponge *Cribrochalina vasculum*

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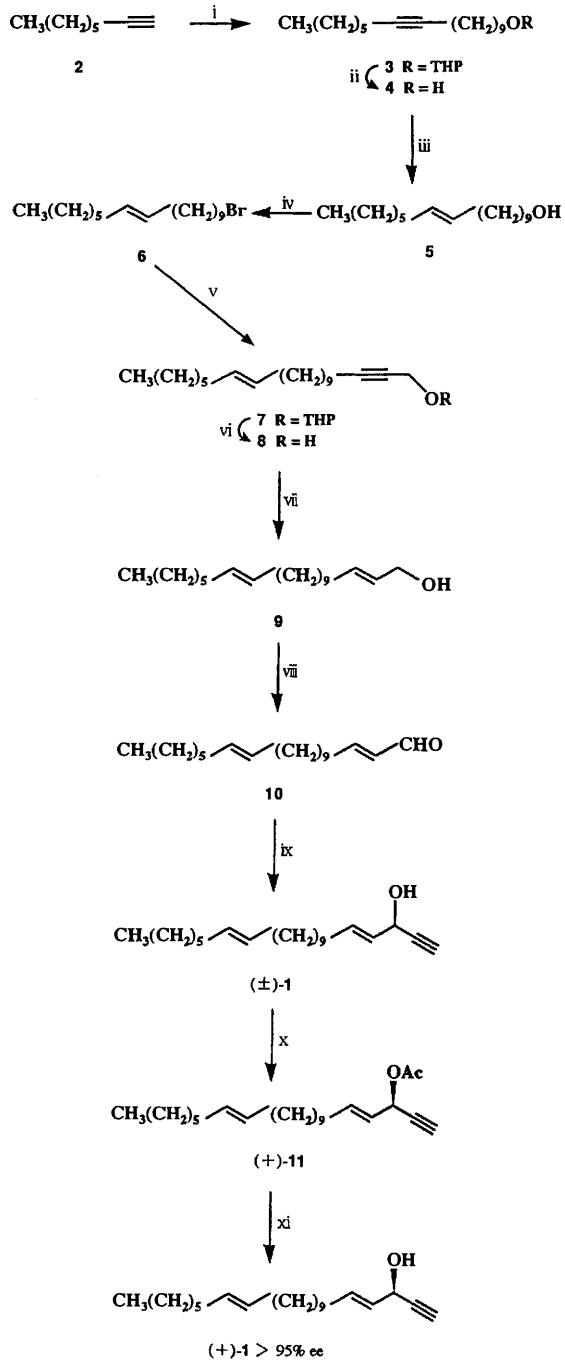
An acetylenic alcohol, (+)-(4*E*,15*E*)-docosa-4,15-dien-1-yn-3-ol 1, isolated from the marine sponge *Cribrochalina vasculum*, was synthesized in highly enantiomerically pure form by lipase-catalysed transesterification with Novozym 435 (*Candida antarctica*).

In conjunction with our efforts to develop the chemoenzymatic synthesis of optically active natural products utilizing lipases,[1,2] we required an efficient method for preparing the chiral 4-en-1-yn-3-ol skeleton in enantiomerically pure form. This work, to our knowledge, constitutes the first synthesis of the enantiomer of (4*E*,15*E*)-docosa-4,15-dien-1-yn-3-ol **1**; compound **1** is one of the five new acetylenic alcohols possessing a characteristic 4-en-1-yn-3-ol skeleton isolated from the marine sponge *Cribrochalina vasculum* and shows *in vitro* immunosuppressive and antitumour activities.[3–5] The key step in this synthesis is the lipase-catalysed transesterification of (±)-**1** with Novozym 435 (*Candida antarctica*, Novo Nordisk Bioindustrial A/S, Denmark) to give the corresponding chiral acetate **11** in a highly enantioselective manner.

Oct-1-yne **2** was alkylated with BuLi and the tetrahydropyran-2-yl (THP) ether derived from 9-bromononan-1-ol in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU), followed by treatment with toluene-*p*-sulfonic acid (*p*-TsOH) to give acetylenic alcohol **4** in 76% yield from **2**. Alcohol **4** was reduced with LAH in diglyme, and the resulting (*E*)-olefinic alcohol **5** (91% yield) was converted into the bromide **6** in 84% yield. Coupling of **6** with the THP ether of prop-2-yn-1-ol and subsequent treatment with *p*-TsOH produced enyne alcohol **8** in 75% yield from **6**, which was transformed in the usual manner into the *trans* diene alcohol **9** in 90% yield. The alcohol was oxidized with active MnO_2 to the aldehyde **10**, and the latter was treated with lithium acetylide–ethylenediamine to yield (±)-**1** in 33–40% yield based on **9**.

To complete the chemoenzymatic synthesis of the enantiomer of **1**, the lipase-catalysed enantioselective acylation of racemic **1** with Novozym 435 and vinyl acetate† was carried out in diethyl ether (30 min, 43% conversion). Chiral acetylenic acetate **11** thus obtained was then subjected to alkaline hydrolysis to give the expected chiral alcohol **1** with an enantiomeric purity of >95% ee {$[\alpha]_D^{25}$ +18.43 (*c* 1.69, MeOH), $[\alpha]_D^{25}$ +12.75 (*c* 3.49, pentane)}.



Scheme 1 *Reagents and conditions:* i, $Br(CH_2)_9OTHP$, BuLi, THF–DMPU; ii, *p*-TsOH, MeOH; iii, LAH, diglyme; iv, $Ph_3P{\cdot}Br_2$, CH_2Cl_2; v, $HC{\equiv}CCH_2OTHP$, BuLi, THF–DMPU; vi, *p*-TsOH, MeOH; vii, LAH, Et_2O; viii, MnO_2, CH_2Cl_2; ix, $HC{\equiv}CLi{\cdot}H_2N(CH_2)_2NH_2$, THF–DMSO; x, lipase Novozym 435, vinyl acetate, Et_2O; xi, KOH, MeOH

† Enzymatic transformations of (±)-**1** or (±)-**11** with other lipases, such as lipases PS, AK and LIP (*Pseudomonas* sp.) and lipases MY and AY (*Candida* sp.), showed low enantioselectivities; lipases LIP- and AK-catalysed hydrolysis of (±)-**11** yielded (+)-**1** of 67% ee {3.5 h, 40% conversion, $[\alpha]_D^{25}$ +13.3 (*c* 1.30, MeOH)} and 42% ee {21.5 h, 43% conversion, $[\alpha]_D^{25}$ +6.12 (*c* 2.43, MeOH)}, respectively. Lipase PS gave low enantioselectivities for certain unsaturated secondary alcohols.[2] Norin et al. have carried out lipase Novozym-catalysed transesterification by using *S*-ethyl thiooctanoate as acyl donor and observed high enantioselectivity for simple secondary alcohols including octan-2-ol and undec-1-yn-3-ol.[7,10]

The absolute stereochemistry at C-3 of the natural **1** has been suggested to be *R* on the basis of the CD profile of the *p*-bromobenzoate of **1**[5] and of the ^{1}H NMR spectra of the chiral MTPA esters of **1**;[6] the stereochemistry at C-3 of the two analogous alcohols (4*E*)-16-methylicos-4-en-1-yn-3-ol and (4*E*)-19-methylicos-4-en-1-yn-3-ol, was also assigned as *R*.[5] The value $[\alpha]_D^{25}$ +4.9 (*c* 4.5, MeOH) has been reported to be the specific rotation of the natural **1**.[3] The absolute configuration of some chiral acetylenic alcohols (+)-oct-1-yn-3-ol,[2] (+)-undec-1-yn-3-ol,[7] (−)-tetradec-1-yn-3-ol[8] and (+)-(5*Z*)-undec-5-en-1-yn-3-ol,[9] possessing an alk-1-yn-3-ol function similar to **1**, has been shown to be *R*, *R*, *S* and *R*, respectively.

In conclusion, we have described the first enantioselective synthesis of chiral acetylenic alcohol **1** in 11 steps from oct-1-yne **2** by biochemical transformation with lipase Novozym 435.

Experimental

Compounds (±)-**1** and (+)- and (−)-**1** were fully characterized by comparing their spectral data with those reported for the natural **1**[3] and for the racemic **1** prepared by Kulkarni *et al.*[4] All new compounds gave satisfactory microanalytical and/or IR and NMR spectral data. The enantiomeric purity of the chiral alcohols (+)- and (−)-**1** was determined on HPLC analysis of the corresponding 3,5-dinitrophenylurethane derivatives prepared by treatment with 3,5-dinitrophenyl isocyanate, using a Waters 510 liquid chromatograph equipped with a UV detector (254 nm). A Sumichiral OA 2100I 4.0 × 250 mm column (Sumica Chemical Analysis Service, Osaka) was used at a flow rate of 1.0 cm^3 min^{-1} [hexane–1,2-dichloroethane–EtOH (80:10:0.4)]. The ee of (+)-acetate **11** was based on that of the corresponding (+)-alcohol **1**.

Enantioselective acylation of (±)-1 with Novozym 435

Racemic acetylenic alcohol **1** (0.5 g, 1.57 mmol) was treated with vinyl acetate (0.41 g, 4.76 mmol) in diethyl ether (15 cm^3) in the presence of Novozym 435 (0.5 g). The mixture was stirred for 30 min at 30 °C; GC analysis showed that the conversion was about 43%. After filtration through Celite, the filtrate was worked up in the usual way. Purification by column chromatography on silica gel with hexane–ethyl acetate (30:1) gave (+)-acetate **11** (0.21 g, 37%) with 95% ee $[\alpha]_D^{25}$ +16.31 (*c* 1.60, MeOH) and (−)-alcohol **1** (0.28 g, 56%) with 66% ee $[\alpha]_D^{25}$ −15.78 (*c* 5.13, MeOH). The enantiomeric ratio for this biotransformation (*E* value), $E = 78$, was calculated according to Chen *et al.*[11]

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