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Synthesis of (+)-perillyl alcohol from (+)-limonene

Kimberly Geoghegan, Paul Evans *

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland

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ABSTRACT

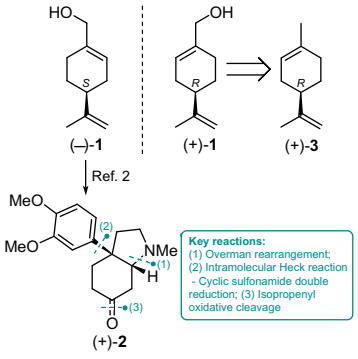
(+)-Perillyl alcohol (**1**) has been synthesised in four steps and 39% overall yield from commercially available limonene oxide (**4**). The sequence features, as its key step, a palladium(0)-mediated transformation of a secondary allylic acetate (**6**) into its primary isomer (**7**). An application of (+)-perillyl alcohol (**1**) in a formal synthesis of naturally occurring (−)-mesembrine (**2**) and (−)-mesembranol was demonstrated.

The naturally occurring monoterpene (−)-perillyl alcohol (**1**) represents a functionalised enantiopure molecule, which, along with its corresponding aldehyde, has been employed as a 'chiral-pool' starting material (Scheme 1).[1] We have recently used (−)-**1** to assemble (+)-**2**, the enantiomer of the naturally occurring *Sceletium* alkaloid, mesembrine.[2]

Since the enantiomer of perillyl alcohol is not currently commercially available, a chemical method to prepare (+)-**1** was considered. A means to isomerise selectively the endocyclic, trisubstituted alkene present in (−)-**1** is attractive in terms of efficiency but is without direct precedent.[3] Consequently, the inexpensive monoterpene limonene [(+)-**3**] was identified as a potential material to access (+)-**1**. Based on selectivity concerns the direct chemical allylic functionalisation of (+)-**3** was disregarded,[4] although it should be mentioned that a biotransformation using a modified organism has been reported to perform the necessary allylic oxidation converting (+)-**3** into (+)-**1**.[5]

In terms of converting (+)-**3** into (+)-**1** the aim was to take advantage of the differential reactivity between the endo- and the exocyclic alkene, which enables mono-epoxide **4** to be prepared.[6] This compound is in fact also commercially available as a mixture of *cis*- and *trans*-diastereoisomers[7] and based on literature precedent,[8,9] it was envisaged that a selective epoxide-allylic alcohol transposition would access a functionalised handle, ultimately facilitating the formation of (+)-**1**.

Thus, conversion of (+)-**3** into **4** was performed with 0.9 equiv of *meta*-chloroperbenzoic acid (*m*-CPBA) according to a literature procedure (*cis*-**4**/*trans*-**4**; 60:40).[6] This material was then treated with LDA[9] in THF at −78 °C, and following work-up, the allylic alcohol **5** was isolated as a mixture of diastereoisomers (Scheme 2). The secondary alcohol **5** was directly converted into acetate **6**, under standard conditions, which was isolated in good yield over the two steps. According to a literature report concerning a related compound, treatment of **6** with TMSBr was investigated.[8] However, in our hands, none of the hoped for primary allylic bromides (not shown) was formed. We therefore considered the use of π-allyl transition metal chemistry to isomerise the epimeric allylic acetoxy-functionality in **6** into its less-sterically encumbered primary isomer, **7**. Although the use of acetoxy groups as nucleophiles in π-allyl palladium chemistry does not feature frequently in the literature, several reports augured well for the success of the proposed formal Claisen rearrangement.[10] Pleasingly, after some



Scheme 1. Application of (−)-perillyl alcohol (**1**) in the synthesis of (+)-**2** and the proposed synthesis of (+)-**1** from limonene (+)-**3**.

* Corresponding author. Tel.: +353 17162291.
E-mail address: paul.evans@ucd.ie (P. Evans).

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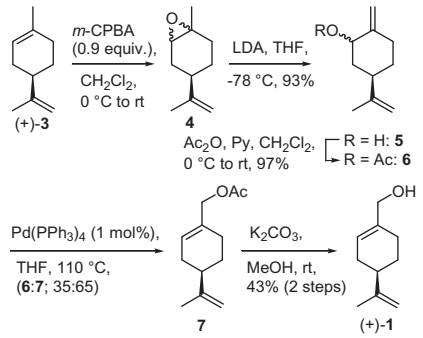
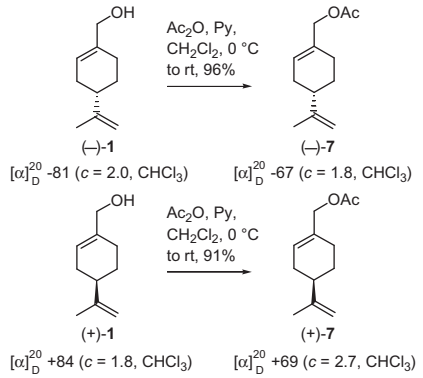


Scheme 2. Synthesis of (+)-perillyl alcohol (**1**) from (+)-limonene (**3**).



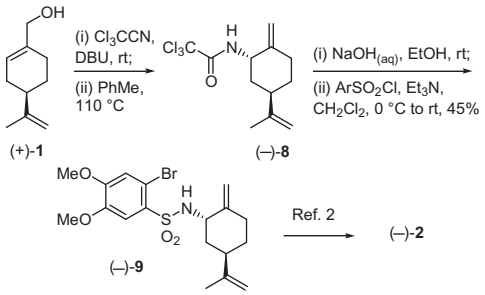
Scheme 3. Comparison of synthetic (+)-**1** and its acetate (+)-**7** with (−)-**1** and (−)-**7**.

optimisation, it was found that the use of 1 mol % of $Pd(PPh_3)_4$ in THF at 110 °C in a sealed tube led to the formation of **7** in 76% isolated yield as an inseparable mixture of **7** and **6** (65:35). Attempts to improve the isolated yield of **7**, and also to drive the process to completion with the inclusion of sodium acetate or tetra-*n*-butylammonium acetate (1–3 equiv), and by transferring the process to a microwave apparatus, were found neither to improve the isolated yield of **7** nor to alter dramatically the ratio between **7** and **6**.

Basic hydrolysis of the thus obtained mixture of **7** and **6** gave perillyl alcohol [(+)-**1**], which now proved separable from the corresponding secondary alcohol (**5**).[11] The material thus isolated was formed in 43% yield over the two steps, a figure reflecting that the allylic acetate rearrangement does not proceed to completion. Comparison between the specific rotation of commercial (*S*)-(−)-**1** and synthetic (*R*)-(+)-**1** demonstrated approximately equal and opposite values. Additionally, both enantiomers were converted into their corresponding acetates, (*S*)-(−)-**7** and (*R*)-(+)-**7**, and again polarimetry supported the stereochemical assignments (Scheme 3). Proton and carbon NMR spectra for both sets of enantiomers also matched, however, unfortunately we were unable to separate (−)-**7** and (+)-**7** by chiral GC (β-Dex column).

As shown in Scheme 4, synthetic (+)-perillyl alcohol (**1**) was subjected to an Overman rearrangement sequence, which initially gave (−)-**8**, that was subsequently converted into sulfonamide (−)-**9**. Since an identical strategy involving (+)-**9** was used for the synthesis of (+)-**2** and its related alcohol (+)-mesembranol, this sequence represents a formal synthesis of the naturally occurring alkaloids mesembrine [(−)-**2**] and (−)-mesembranol.[2]

Compound (−)-**9**, thus obtained from (+)-**1**, was compared with its enantiomer [(+)-**9**][2] by polarimetry and also chiral HPLC,[12] both of which served to further confirm the absolute stereochemistry of synthetic (+)-**1**.



Scheme 4. The Overman rearrangement of (+)-**1**: synthesis of (−)-**9**.

In summary, (*R*)-perillyl alcohol [(+)-**1**] was prepared in four steps (39% overall yield) from commercially available (+)-limonene oxide (**4**). The utility of (+)-**1** was demonstrated in a formal synthesis of natural mesembrine [(−)-**2**] by its four-step conversion into sulfonamide (−)-**9**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.039.

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11. *Synthetic procedure:* Under N_2, a mixture of acetate **6** (300 mg, 1.55 mmol, 1 equiv) and $Pd(PPh_3)_4$ (18 mg, 0.016 mmol, 1 mol %) in anhydrous THF (3.2 mL) was heated in a sealed glass pyrex tube for 15 h (oil bath temperature = 110 °C). Once cooled, Et_2O (10 mL) and H_2O (10 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined ethereal layers washed with brine (10 mL) and dried ($MgSO_4$). The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 9:1) to yield (*R*)-perillyl acetate [(+)-**7**] (228 mg, 76%) as a light orange oil which also contained **6** (**7**:**6**; 65:35). [R_f = 0.5 (*c*-Hex/EtOAc, 6:1); IR (KBr, neat): 2933, 1741, 1654, 1373, 1240, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.73 (s, 1H, CH), 4.73–4.70 (m, 2H, CH_2), 4.44 (s, 2H, CH_2), 2.19–2.02 (m, 4H, CH, CH_2), 2.06

(s, 3H, CH_3), 1.99–1.92 (m, 1H, CH_2), 1.87–1.81 (m, 1H, CH_2), 1.72 (s, 3H, CH_3), 1.53–1.45 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9 (CO), 149.6 (C), 132.6 (C), 126.1 (CH), 108.8 (CH_2), 68.6 (CH_2), 40.9 (CH), 30.5 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 21.1 (CH_3), 20.7 (CH_3)]. A solution of **7** (220 mg, 1.13 mmol, 1 equiv) in MeOH (10 mL) was treated with K_2CO_3 (156 mg, 1.7 mmol, 1.5 equiv) and the reaction mixture was stirred at room temperature and monitored by TLC. On completion, most of the MeOH was removed under reduced pressure before CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude alcohol, which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1) to yield (*R*)-perillyl alcohol [(+)-**1**] (100 mg, 43% from **6**) as a light yellow oil. $R_f = 0.2$ (*c*-Hex/EtOAc, 3:1); $[\alpha]_D^{20} + 84$ (*c* 1.8, $CHCl_3$) [(−)-**1**: $[\alpha]_D^{20} - 81$ (*c* 2.0, $CHCl_3$)]; IR (KBr, neat): 3332, 2923, 1646, 1451, 1436, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.70 (br s, 1H, CH), 4.78–4.67 (m, 2H, CH_2), 4.01 (s, 2H, CH_2), 2.23–2.03 (m, 4H, CH, CH_2), 1.99–1.89 (m, 1H, CH_2), 1.87–1.82 (m, 1H, CH_2), 1.74 (s, 3H, CH_3), 1.54–1.44 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.9 (C), 137.4 (C), 122.6 (CH), 108.8 (CH_2), 67.4 (CH_2), 41.3 (CH), 30.6 (CH_2), 27.6 (CH_2), 26.3 (CH_2), 20.9 (CH_3).

12. *HPLC analysis for (+)- and (−)-**9**:* (IC column), *n*-heptane/EtOH; gradient elution 90:10 to 50:50 (1.0 mL/min): (−)-**9** t_r = 22.95 min, (+)-**9** t_r = 24.62 min.