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THE SYNTHESIS OF (3*R*)-NEROLIDOL

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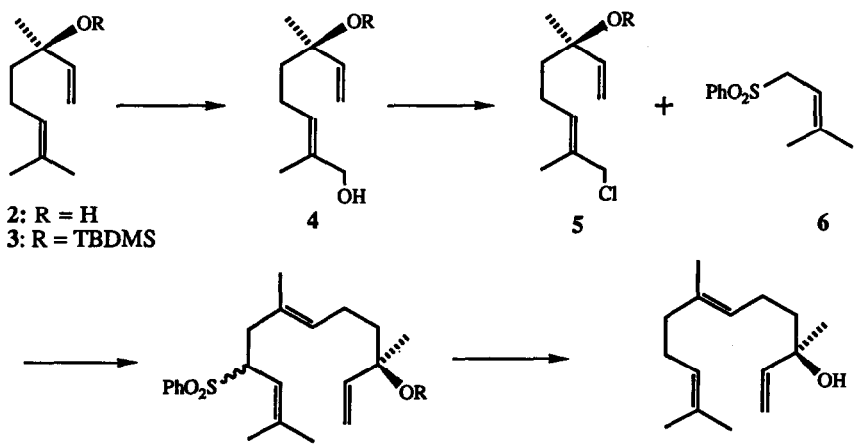
Summary: The sesquiterpene natural product (3R)-nerolidol has been prepared in six steps starting from (3R)-linalool.

Extensive experiments have established the intermediacy of the tertiary allylic esters, linalyl pyrophosphate and nerolidyl pyrophosphate (NPP) in the enzymatic formation of cyclic monoterpenes and sesquiterpenes from the respective acyclic precursors, geranyl and farnesyl pyrophosphate.[1] Based on these results we have proposed a comprehensive stereochemical scheme for terpenoid cyclizations which correlates the conformation and absolute configuration of linalyl and nerolidyl pyrophosphate with the configuration of the eventually formed monoterpene or sesquiterpene product.[2] For example, the enzymatic cyclization of farnesyl pyrophosphate to trichodiene has been shown to proceed exclusively by way of (3*R*)-NPP[3a] while formation of β-*trans*-bergamotene is believed to involve the exclusive intermediacy of the corresponding (3*S*)-NPP.[3b] Experimental testing of such proposals requires samples of the individual enantiomers of the relevant tertiary allylic pyrophosphate esters. Unfortunately, although both antipodes of linalool are readily available,[4] only (3*S*)-nerolidol is conveniently obtained from natural sources.[5] To overcome this difficulty, we have developed a short and efficient synthesis of (3*R*)-nerolidol (**1**) starting with the lower homolog (3*R*)-linalool (**2**).



Scheme 1

We have previously prepared samples of labeled farnesol, using the Julia coupling of allylic sulfones[6] with derivatives of geranyl benzyl ether to effect construction of the farnesyl skeleton.[7] The last step in this procedure involves the simultaneous removal of the phenylsulfonyl and benzyl residues by reductive elimination with Li/EtNH$_2$. Unfortunately, application of the analogous sequence to the corresponding benzyl ether of linalool

failed due to predominant cleavage of the allylic ether C-O bond during the reduction of the derived nerolidol benzyl ether. On the other hand, further experimentation revealed that the lithium salt of nerolidol itself was stable under the usual reducing conditions. We therefore turned to the use of the *t*-butyldimethylsilyl (TBDMS) protecting group. It was expected that the TBDMS group would be compatible with the functionalization and coupling of the linalool moiety, yet could be selectively removed prior to the eventual reductive cleavage of the phenylsulfonyl group. Accordingly, (3R)-linalool, **2**, $[\alpha]^{23}_D$ -13.5 (c 0.44, $CHCL_3$),[4] was converted to the corresponding TBDMS ether **3** (1.2 equiv. TBDMSOTf, 2 equiv. 2,6-lutidine, CH_2Cl_2, rt, 30 min, 97 %).[8] (Scheme 1) Oxidation of **3** with SeO_2 (0.5 equiv., EtOH, reflux, 4 h) followed by $NaBH_4$ reduction of the resulting mixture of aldehyde and alcohol gave the trans allylic alcohol **4** (23 %). Reaction of **4** with triphenylphosphine (2 equiv.) in refluxing carbon tetrachloride[9] (4 h) afforded the allylic chloride **5** (48 %) which was coupled (THF, -78 °C, 0.5 h) with the sulfonyl-stabilized anion generated by treatment of dimethylallyl phenyl sulfone (**6**) (1.2 equiv) with *n*-butyl lithium (1.1 equiv, -78 °C, 0.5 h and rt, 0.5 h) to produce the (3*R*)-9-phenylsulfonyl nerolidol TBDMS ether (**7**) in 78 % purified yield. Deprotection with $(n\text{-Bu})_4NF$ (2 equiv) in refluxing THF (18 h) gave 9-phenylsulfonyl nerolidol (**8**) (82 %, mp 93-94 °C). Finally, reaction of **8** with 2 equiv of *n*-BuLi in THF generated the corresponding lithio alkoxide which underwent smooth reductive elimination of the phenylsulfonyl group by treatment with excess Li in $EtNH_2$ (-78 °C, 20 min) to afford, after chromatographic purification, a 72 % yield of (3*R*)-nerolidol (**5**), $[\alpha]^{23}_D$ -12.5 (c 0.022, $CHCl_3$).[5]

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References and Notes

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8. All new compounds exhibited spectroscopic data(^1H and ^{13}C NMR, ir, and ms) consistent with the assigned structure and gave satisfactory elemental analysis or high resolution ms data. **3**: ^1H NMR ($CDCL_3$): 5.84 (1H, dd, J = 10.7, 17 Hz), 5.38 (1H, m), 5.14 (1H, dd, J = 1.6, 17.3 Hz), 4.99 (1H, dd, J = 1.6, 10.7 Hz), 3.98 (2H, s), 2.05 (2H, m), 1.65 (3H, s), 1.47 - 1.52 (2H, m), 1.30 (3H, s), 0.87 - 0.90 (9H, m), 0.05 - 0.08 (6H, m). **7**: ^1H NMR ($CDCL_3$): 7.81 (2H, m), 7.59 (1H, m), 7.51 (2H, m), 5.86 (1H, ddd, J = 2, 10.7, 17.3 Hz), 5.17 (2H, m), 5.03 (1H, dt, J = 1.08, 10.7 Hz), 4.87 (1H, dd, J = 1.2, 10.7 Hz), 3.85 (1H, dddd, J = 2.7, 3.06, 3.10, 10.7 Hz), 2.83 (1H, bd, J = 13 Hz), 2.27 (1H, dd, J = 2.6, 12.3 Hz), 1.97 (2H, m), 1.63 (3H, m), 1.48 (5H, m), 1.24 (3H, d, J = 2.7 Hz), 1.14 (3H, s). **1**: ^1H NMR ($CDCL_3$): 5.9 (1H, dd, J = 10.7, 17 Hz), 5.18 - 5.23 (1H, dd, J = 1.3, 17 Hz), 5.04 - 5.16 (3H, m), 1.95 - 2.07 (6H, m), 1.53 - 1.67 (11H, m), 1.28 (3H, s)
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