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Asymmetric Dihydroxylation of Geranyl, Neryl and *trans, trans*-Farnesyl Acetates

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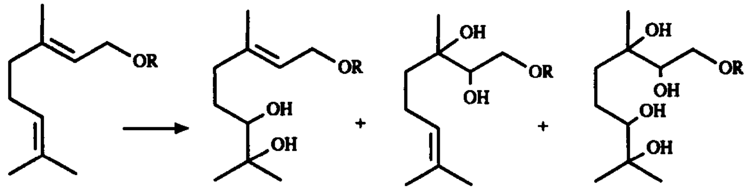
***Abstract*:** The asymmetric dihydroxylation of geranyl acetate, neryl acetate and *trans, trans* - farnesyl acetate was studied using the new Sharpless' ligands $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL. High enantioselectivity was always observed. High positional selectivity for the 6,7-olefin was observed in the case of the monoterpene acetates.

Exceptional progress has been made in the last years in the development of the catalytic asymmetric dihydroxylation (AD) of achiral olefins by means of OsO_4 and a variety of chiral ligands.[1-3] Sharpless has succeded recently in the regioselective mono-dihydroxylation of simple dienes, leading to ene diols with high enantiomeric purity.[1] This prompted us to investigate the AD of some important acyclic unsaturated monoterpene and sesquiterpene alcohols. We anticipated that the mono-dihydroxylation products would be valuable chiral synthons which can be used for the synthesis of various natural products in optically active forms. Some syntheses of these compounds have been previously published. However, these suffer from the fact that they either lead to racemic compounds or necessitate lengthy routes to introduce the new stereogenic centers with the desired absolute configuration.[4] For comparison with the AD reaction, we first selected geranyl acetate **1a** (Fluka, purity > 99%) as the test substrate in a non enantioselective catalytic OsO_4 oxidation. We followed the Van Rheenen osmilation procedure,[5] but using the quaternary mixture py - THF - ^tBuOH - H_2O (0.2 : 11 : 3.4 : 1.2) as a solvent. After stirring overnight at room temperature and 3 h at 35°C, the reaction proceeded to a 5 : 1 mixture of the 6,7-diol (**2a**) and 2,3-diol (**3a**) in 57% yield (84% on recovered **1a**) with the tetrol **4a** (mixture of diastereomers) found in traces.[6]



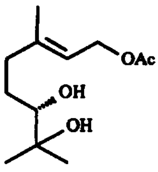
1a R = Ac
b R = H

2a R = Ac
b R = H

3a R = Ac
b R = H

4a R = Ac
b R = H

Positional selectivity in mono-dihydroxylation of the more electron-rich trisubstituted olefin[7] was expected to be improved substantially by using Sharpless' AD procedure with the new phtalazine cinchona class of ligands.[3,8] A dramatic evidence of the benefits of ligand-assisted catalysis was shown in the AD of geraniol (**1b**, Fluka, purity > 99.5%). The reaction of **1b** with AD-mix-α at 0°C gave in fact, after 24 h, the two olefins **2b** and **3b** in a 8 : 1 ratio and 52 % yield .[9] Even better results were obtained simply starting from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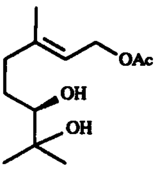
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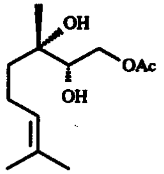
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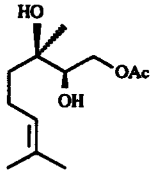
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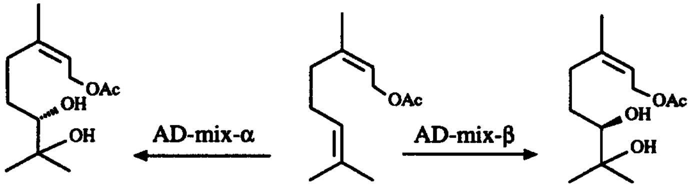
the corresponding acetate (**1a**). We anticipated that the more crowded steric environments and the reduced electron density should inhibit reaction at the allylic double bond of compound **1a**. In fact, when geranyl acetate (**1a**) was submitted to the AD reaction with AD-mix-α and AD-mix-β, the ratio **2a** : **3a** jumped to 92.5 : 7.5 and 95.5 : 4.5, respectively.[10] In either case the tetrol formation was negligible (≤ 3%). We observed a slightly faster reaction using the $(DHQD)_2$-PHAL ligand; however, both reactions were run at 0°C for 24 hours to give the major diol **2a** in 78% isolated yield in the former case and in 82% isolated yield in the latter case.[6] Compound **2a**, obtained with AD-mix-α, showed an optical rotation of $[\alpha]_D^{20}$ -22.9 (*c* 1.1, $CHCl_3$) and a 90% ee, and when AD-mix-β was used instead, an optical rotation of $[\alpha]_D^{20}$ + 25.2 (*c* 0.95, $CHCl_3$) and a 92 % ee.[11] According to the literature values[12] and the simple mnemonic device described in ref 3 the two enantiomeric 6,7-diols have the *S* and *R* absolute configuration at the stereogenic carbon atom C(6), respectively, and are thus represented by formulae **5** and **6**. Moreover, it is likely that the two minor 2,3-diols have structures **7** and **8**, respectively

Having established that an acetate group can effectively divert osmilation from the 2,3- double bond of geraniol, we submitted neryl acetate (**9**, Fluka, purity > 99%) to the same AD conditions. In principle, the osmilation preference for the distant double bond over the more encumbered *Z* allylic olefin should increase significantly compared to geranyl acetate (**1a**). According to our expectations, both the 2,3-diol and the tetrol products represented only trace amounts in the reaction mixtures with either ligand. The AD reaction with AD-mix-α gave the 6,7-diol, $[\alpha]^{D}_{20}$ - 18.7 (*c* 0.96, $CHCl_3$) and ≥ 98% ee, in 92% isolated yield, while the reaction with AD-mix-β afforded the corresponding enantiomer, $[\alpha]_D^{20}$ +18.8 (*c* 0.97, $CHCl_3$) and 97% ee, in 94 % yield.[11] As the sense of asymmetric induction should be the same as for **1a**, it thus appears that the two enantiomeric diols obtained from neryl acetate have *S* (formula **10**) and *R* (formula **11**) configuration, respectively.[6]



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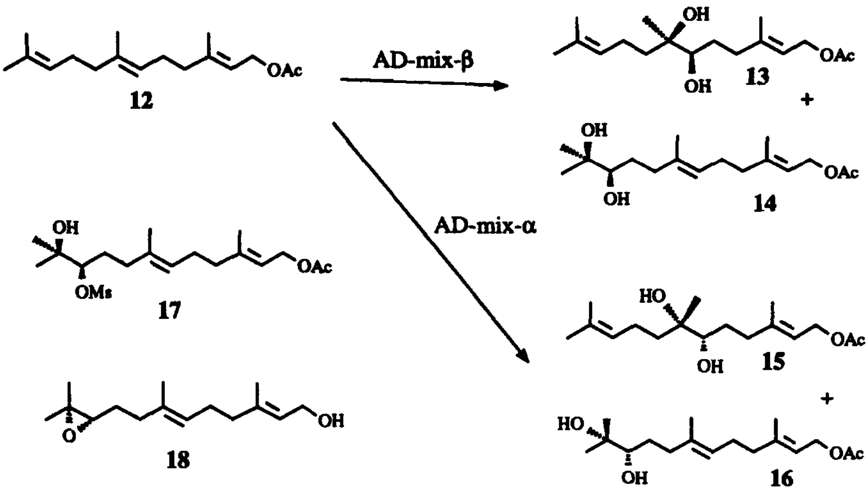
These encouraging results prompted us to investigate also the AD of *trans, trans*-farnesyl acetate (**12**, Aldrich, purity 96%) which contains an additional internal trisubstituted double bond. At 0° after 24 hours, the AD-mix-β reaction gave the 6,7- (**13**) and the 10,11- (**14**) diols[6,13] in 15.8% and 34.3% isolated yields respectively, along with the 6,7,10,11-tetrol (26.6%), recovered farnesyl acetate (20%) and traces of unidentified products (possibly the hexol and the 2,3-diols). Similar data were obtained using AD-mix-α, except that the sign of the optical rotation of the two monodihydroxy compounds **15** and **16** was opposite to that of the corresponding compounds **13** and **14**.[13] These results indicate that the osmium-ligand complexes



show a slight preference for the less encumbered olefin nearer the terminus; however, the modest regioselectivity makes this method impracticable for synthetic applications. The 10,11-diol acetate **14** was further converted to the corresponding 10-O-mesylate (**17**) by treatment of **14** with MsCl in py at -10° C for 1 hour. Reaction of **17** with K_2CO_3 in MeOH at r. t. for 2 hours afforded (*S*)-(-)-10,11-epoxyfarnesol (**18**),[6] oil, $[\alpha]_D^{20}$ - 2.0 (*c* 1, MeOH), with the inversion of configuration[14] at the chiral center of **14** (65 % from **14**). This result allows[14] the assignment of the *R* absolute configuration to the stereogenic carbon atom C(10) of **14** and indicates that the sense of asymmetric induction in the Sharpless AD of farnesyl acetate (**12**) is the same as for other trisubstituted olefins (see formulae **13-16**).[1,3,15]

In conclusion, the Sharpless asymmetric dihydroxylation of geranyl and neryl acetates allows the one-step synthesis of the very versatile chiral synthons **5**, **6**, **10** and **11** with high enantioselectivity; on the contrary, the AD of farnesyl acetate gave only modest regioselectivity for the 10,11-olefin, although with high ee.

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2. Corey, E. J., Noe, M. C., Sarshar, S., *J. Am. Chem. Soc.* **1993**, *115*, 3828-3829 and references 1 and 2 cited therein.
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4. Recently, R. Furstoss et al. have reported the stereoselective dihydroxylation of citronellol and the distant double bond of geraniol by means of the fungus *Aspergillus niger*. However, an unusual N-phenylcarbamate moiety is necessary in the substrate for its biooxygenation into the corresponding diol to proceed (Zhang, X.-M., Archelas, A., Furstoss, R., *J. Org. Chem.* **1991**, *56*, 3814-3817; Zhang, X.-M., Archelas, A., Furstoss, R., *Tetrahedron Asymmetry* **1992**, *3*, 1373-1376).
5. Van Rheenen, V., Kelly, R. C.,Cha, D. Y., *Tetrahedron Lett.* **1976**, 1973-1976.

6. Each compound was fully characterized by IR, HRMS, ^{1}H and ^{13}C NMR analysis.
7. The issues of the AD regioselectivity for olefins of the same class are largely unexplored. The AD reaction of squalene (Crispino, G. A., Sharpless, K. B., *Tetrahedron Lett.* **1992**, *33*, 4273-4274) suggests that the steric effects alone lead to modest positional selectivity for the more sterically accessible trisubsituted olefins.
8. Each AD reaction was run with 0.2 mol % of OsO_4 according to the general experimental procedure described by Sharpless in ref 3 . The two chiral ligands (dihydroquinidine)$_2$-1,4-dichlorophtalazine $(DHQD)_2$ - PHAL and (dihydroquinine)$_2$-1,4- dichlorophtalazine $(DHQ)_2$-PHAL,[3] in mixture with the other standard reactants ready for performing the AD of olefins, are now available from Aldrich as AD-mix-β and AD-mix-α formulation, respectively.
9. Neither the % ee nor the absolute configuration was determined for the oxidation products.
10. The ratio of the two diols was estimated by ^{1}H NMR spectroscopy and capillary GLC.
11. The % ee's were determined by ^{1}H NMR in the presence of $Eu(tfc)_3$ and by direct injection of the diols on a MEGADEX-1 (trimethyl-β-cyclodextrin 30% on OV1701) GLC column, 25 m long, 0.25 mm I. D., 0.25 μ film thickness. Chromatographic conditions: injector PTV (50°→ 260°C), detector 250°C, column oven program: 50°(1 min) to 180°(1 min), 10°/min; 180° to 200°, 4°/min; 200° to 215°, 10°/min; He as a carrier gas at 0.9 bar. Retention times of compounds **5**, **6**, **10**, **11**, **14** and **16** : 18.95, 19.14, 17.64, 17.76, 22.07 and 22.40 min, respectively.
12. a) Fourneron, J. D., Archelas, A., Furstoss, R., *J. Org. Chem.* **1989**, *54*, 4686-4689.
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    e) Yamada, S., Oh-Hashi, N., Achiva, K., *Tetrahedron Lett.* **1976**, 2557-2560.
13. **14**: $[\alpha]_D^{20}$ +12.3 (c 0.9, $CHCl_3$); 98% ee; **16**: $[\alpha]_D^{20}$ -11.4 (c 0.9 , $CHCl_3$), 94% ee.
14. a) Yamada, S., Oh-Hashi, N., Achiva, K., *Tetrahedron Lett.* **1976**, 2561-2564.
    b) Suzuki, Y., Marumo, S., *Tetrahedron Lett.* **1972**, 1887-1890.
    c) Suzuki, Y., Marumo, S., *J. Chem. Soc. Chem. Comm.* **1971**, 1199-1201.
15. Neither the absolute configuration nor the % ee was determined for the two 6,7-diols **13** and **15**; however, they are likely to have the *R,R* and *S,S* configuration, respectively.

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