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# Rearrangement of a Hindered Allylic Alcohol During Vanadium-Catalyzed Epoxidation. A Short Synthesis of Uvidin-C.[1]

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**Abstract:** A study on the hydroxyl-directed epoxidation of allylic alcohols **3b** and **3c** is provided, leading to a synthesis of uvidin-C (**1**).

Uvidin-C **1**[2] and forskolin **2**[3] are examples of terpenes which bear $C_6$-β, $C_7$-β oxygen functionality. As part of a program directed toward the synthesis of the latter substance,[4] we chose to explore a method for the introduction of such oxygen functionality into a pre-existing hydrocarbon framework.[5] This Letter details our approach and reveals a unique solvent dependent rearrangement during a $VO(acac)_2$-catalyzed epoxidation of a hindered allylic alcohol.

Epoxidation of methyl bicyclofarnesate **3**[6] (m-CpBA, $CH_2Cl_2$, 5h) produced the crystalline α-epoxide **4a** (mp 62.5-63.5°C) in 78% yield.[7] Exposure of the epoxide to lithium diisopropylamide (LDA) (1.20 equiv., THF, -78°C → 25°C, 38h) provided a 4:1 mixture (NMR) of the known esters **5** (mp 97-98.5°C, lit.[8] mp 100°C) and **6** (mp 104-105.5°C, lit.[8] mp 108°C), previously prepared by singlet oxygen oxidation of **3a**. Exocyclic olefin **6** does not appear to arise via elimination through the methyl group of **4**, but rather, it is derived from kinetic protonation of the enolate of **5** which is formed with the excess base. Thus, treatment of ester **5** with 2 equiv. of LDA followed by kinetic protonation gave a 1:1 mixture (~75%, NMR) of **5** and **6**, in addition to other by-products. Isomer **6** was converted to the conjugated isomer **5** (KOH, dioxane, reflux) as described by Kitahara,[8] raising the overall yield of **5** to 79%.

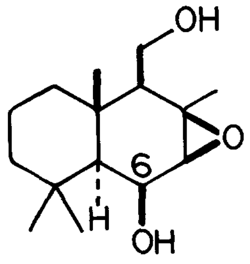
Dehydration of hydroxy ester **5** (methanesulfonic anhydride, $Et_3N$, DMAP, $CH_2Cl_2$, reflux, 15h) afforded the dienoate in 84% yield. The 6,7-double bond of unsaturated ester **7** was selectively epoxidized (m-CpBA, 99% purity, $CH_2Cl_2$, 25°C, 35h)[9] to provide a single epoxide (81%) which was assigned the α-configuration in analogy with the previous epoxidation.[10] Reductive elimination (Li/$NH_3$, THF, -78°C, 0.5h)[11] of epoxy ester **8** provided allylic alcohol **3b** (mp 70-71.5°C) in 52% yield after chromatography. The NMR spectrum of **3b** (250 MHz, $CDCl_3/D_2O$) revealed the $C_6$-H (δ 4.27) as a doublet ($J_{5,6}$ = 9.5 Hz). Irradiation of the $C_5$-H at δ 1.18 collapsed the $C_6$-H signal to a broad singlet. The magnitude of $J_{5,6}$ confirmed the equatorial configuration of the $C_6$-OH. Oxidation (PCC, $CH_2Cl_2$, 2h, 25°C) of **3b** to enone **3d** (mp 80-81°C; IR 1739, 1679 $cm^{-1}$) followed by reduction (DIBAL, THF/hexane, 0.75h, -5°C) provided axial allylic alcohol **3c** (mp 113.5-115.5°C) in 91% overall yield.

A study of the ability of the hydroxyl group of allylic alcohols **3b** and **3c** to direct epoxidation with m-CpBA[12] or VO(acac)$_2$/*tert*-BuOOH[13] was undertaken. The epoxidation of α-alcohol **3b** (m-CpBA, $CH_2Cl_2$, 25°C, 5h) or (*tert*-BuOOH, 16 mol % VO(acac)$_2$, $CH_2Cl_2$, 25°C, 4h) gave exclusively the α-epoxide **4b**. This epoxidation sheds little knowledge on hydroxyl participation, given the inherent propensity for α-face epoxidation of non-hydroxylic olefins **3a** and **7**. Oxidation of epoxide **4b** (PCC/NaOAc, $CH_2Cl_2$, 25°C) produced a single epoxy ketone **4d**. Epoxidation of the hindered β-alcohol proved more interesting. Treatment of **3c** with m-CpBA yielded a 1:1 mixture of two alcohols which were distinctly different (NMR) from epoxide **4b**. Oxidation of the mixture of epoxy alcohols gave rise to a 1:1 mixture of epoxy ketones. One of these proved to be **4d**; the other isomer was assigned as the β-epoxy ketone **9d**. Accordingly, the epoxidation provided the isomeric β-hydroxy epoxides **4c** and **9c**. The dihedral angle (molecular models) between the $C_6$-H and $C_7$-H in **4c** is nearly 90° (δ 3.03, d, J=1.5 Hz, $C_{7\beta}$-H) while in **9c** $C_6$-H and $C_7$-H bonds are almost eclipsed (δ 3.26, d, J=5.7 Hz, $C_{7\alpha}$-H). In the seemingly less polar solvents hexane, benzene, and ether,[14] the ratio of **4c**/**9c** was 9:1.

Hydroxyl-directed epoxidation of axial alcohol **3c** (benzene, 2 equiv. *tert*-BuOOH) under several sets of conditions of temperature and catalyst concentration [12 mol % VO(acac)$_2$, (80°C (5h), 40°C (13h), 25°C (66h)); 25 mol % VO(acac)$_2$, 25°C (68h)] consistently provided a ~ 60/35 mixture of epoxy alcohol **9c** and enone **3d**.[15] The NMR spectrum of the mixture revealed the presence of <5% of epoxy alcohol **4b**. When the epoxidation was performed with $CH_2Cl_2$ as the solvent (20-25 mol % VO(acac)$_2$, 22-29h) β-hydroxy, β-epoxide **9c** and α-hydroxy-α-epoxide **4b** were formed in a 65/20 ratio along with 15% of enone **3d**. Reduction of the amount of catalyst to 9%, increased the **9c**/**4b** ratio to 80/5, while the amount of enone **3d** remained constant at 15%. Oxidation (PCC) of the 65/20 mixture of epoxy alcohols gave the same ratio of epoxy ketones **9d** and **4d**.

In $CH_2Cl_2$ solution, the amount of isomerized epoxy alcohol **4b** increases relative to epoxy alcohol **9c** as the concentration of the catalyst increases, while the amount of enone **3d** remains constant. The dependence of the ratio upon catalyst concentration implies that the vanadium complex of axial alcohol **3c**, which is sterically hindered and has the $C_6$-oxygen bond overlapping with the p-orbitals of the double bond, undergoes displacement with catalyst from the α-face followed by epoxidation.

Reduction ($LiAlH_4$, ether) of hydroxyester **3c** gave the corresponding diol, which was exclusively epoxidized from the β-face with either m-CpBA or VO(acac)$_2$/TBHP (3 mol %, $CH_2Cl_2$) to afford **1**, whose NMR spectrum was identical with that of a naturally occurring sample of uvidin-C.



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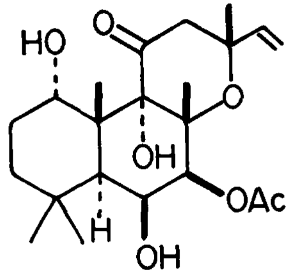

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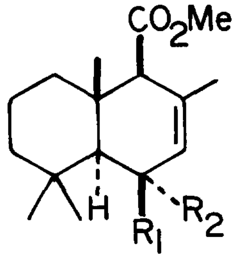

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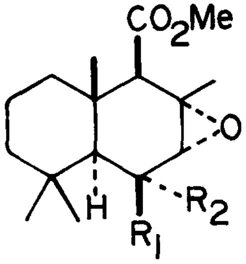

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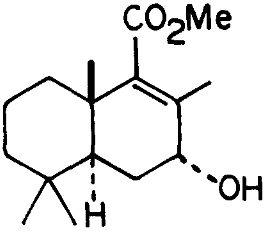

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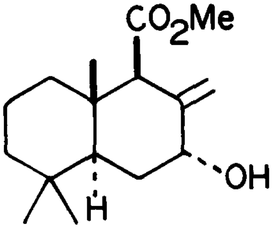

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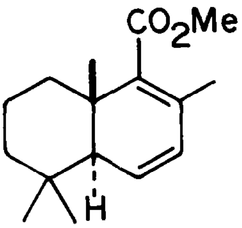

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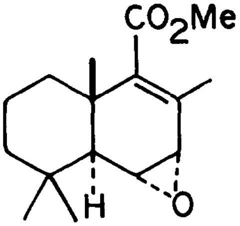

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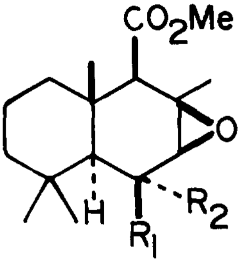

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a, $R_1 = R_2 = H$; b, $R_1 = H, R_2 = OH$; c, $R_1 = OH, R_2 = H$; d, $R_1 = R_2 = O$

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**References and Notes:**

1. We dedicate this Letter to Professor Harry H. Wasserman on the occasion of his sixty-fifth birthday. His many talents as a chemist, teacher, and artist have contributed to his high-caliber editorship of Tetrahedron Letters.
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