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TOTAL SYNTHESIS OF VENUSTATRIOL

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Summary: Venustatriol (**1**) has been synthesized by an enantioselective and convergent route via key intermediates **9** and **15**.

Venustatriol (**1**), a tetraoxacyclic squalenoid from *Laurencia venusta*, has been found to display promising antiviral activity.[1] This fact coupled with the interesting structural features of **1** and the availability of only very small amounts of **1** from *L. venusta* suggested the desirability of research on the synthesis of **1**. This note reports a successful enantioselective total synthesis of venustatriol.[2]

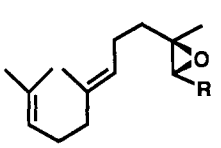
The (2*R*,3*R*)-epoxide **2** was synthesized in 92% yield from *E,E*-farnesol, (-)-diethyl (2*R*,3*R*)-tartrate, $Ti(OiPr)_4$, and t-BuOOH in the presence of molecular sieves (as described for geraniol[4]).[5] Oxidation of **2** with 6 equiv of CrO_3•2py in CH_2Cl_2 at 23° for 8 h gave the corresponding epoxy aldehyde (90%) which was converted to the 2-carbon homologated aldehyde **4** by the sequence (1) Wittig reaction with methoxycarbonylmethylenetriphenylphosphorane (1 equiv in CH_2Cl_2 at 23° for 5 h) to give epoxy ester **3** (90%); (2) selective reduction of the α,β-double bond of **3** (1 atm H_2, 5% Rh-Al_2O_3, 10 equiv of py,[6] THF, 23° for 5 h, 91% yield); (3) ester reduction with 1.08 equiv of diisobutylaluminum hydride in toluene at -78° for 2 h to form **4** (89%). Reaction of **4** with 2 equiv of sodium cyanide and 1.5 equiv of acetic acid in 3 : 1 THF-H_2O at 23° for 10 min gave a mixture of diasteriomeric cyanohydrins (1 : 1) which upon treatment with 5 mole % of tosic acid in acetonitrile at 23° for 3 h underwent cyclization to give after chromatography on SG[6] (4 : 1 hexane-EtOAc) cyano ether **5** (40%) and the 14-epimer (39%) as colorless oils (SG-TLC R_f values of **5** and 14-epi-**5** were 0.44 and 0.31 with 2 : 1 hexane-EtOAc).[7] Additional amounts of **5** could be obtained from the 14-epimer by reaction with 2.2 equiv of potassium hexamethyldisilazane in THF at -23° for 5 h, cooling to -78° and quenching with propionic acid.

The 6,7-double bond of **5** was epoxidized stereoselectively to form **6** by reaction with 1.3 equiv of (-)-diethyl tartrate, 1.1 equiv of titanium isopropoxide and 3 equiv of trityl hydroperoxide in CH_2Cl_2 in the presence of molecular sieves at 0° initially and then at 23° for 15 h (62% conversion, 74% yield).[8] Cyclization of **6** to form **7** was effected by reaction with 5 mole % of methanesulfonic acid in CH_2Cl_2 at 0° for 2 h (61%). Reaction of **7**

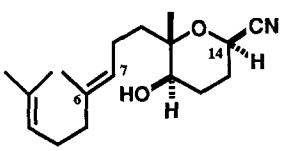
with 1.1 equiv of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD) in CH_3NO_2 at 23° for 1 h afforded the desired *(R)*-3-bromotetrahydropyran **8** (26%) along with the 3-epimer (5%) and a mixture of the isomeric 2-bromo-2-propyltetrahydrofurans (61%). The desired **8**, mp 158-160°, $[\alpha]_D^{23}$ + 9.82° (c=1 in $CHCl_3$), was separated from the other products of brominative cyclization by SG chromatography and recrystallization, and the by-products were combined and treated with powdered zinc (30 equiv) and acetic acid (5 equiv) in ether at 23° for 24 h to regenerate **7** in 94% yield. A number of other conditions for the brominative cyclization involving TBCD in different solvents (CH_3CN, THF, DMF, and py) and other brominating agents (e.g. $Br_2C(CN)_2$) were no more effective for the conversion of **7** to **8**. Reduction of **8** using 2 equiv of diisobutylaluminum hydride in CH_2Cl_2 (0.05 M) at -23° for 2 h and subsequent exposure of the resulting product to 0.5 M hydrochloric acid provided aldehyde **9** (54%).

The (2*R*, 3*R*)-epoxide of geraniol (prepared analogously to **2**[4]) was treated with 1 equiv of NaH and 1.1 equiv of benzyl bromide in THF (0.3 M) at 23° for 14 h to form the corresponding benzyl ether **10** (82%). Epoxide cleavage using 0.18 M perchloric acid in 6 : 1 THF-H_2O at 23° for 14 h converted **10** to the diol **11** in 85% yield. Oxidation of **11** with 1.05 equiv of powdered pyridinium chlorochromate (in CH_2Cl_2 at 23° for 10 h with stirring followed by filtration through Celite, stirring of the filtrate with SG for 10 h, elution of the product from SG with ethyl acetate, and chromatography on SG (1 : 1 hexane-EtOAc)) afforded stereospecifically the tetrahydrofuran **12** (43%).[9] Reaction of **12** with 3 equiv of sodium hydride in THF followed by 5 equiv of chloromethyl ether in CH_2Cl_2 at 0° for 10 min, 23° for 24 h, and 55° for 48 h provided the formal derivative **13** (79%). The bicyclic formal **13** was homologated to **14** by the sequence (1) debenzylation (1 atm H_2, 10% Pd-C catalyst in EtOH at 23° for 3 h, 98%); (2) oxidation to the corresponding aldehyde (1.1 equiv of oxalyl chloride, 1.3 equiv of Me_2SO in CH_2Cl_2 (30 min, -78°) followed by addition of 3 equiv of Et_3N and warming from -78° to 0° over 5 min, 93%); (3) Wittig reaction with methylenetriphenylphosphorane (1.1 equiv in THF at -78° for 10 min and 23° for 3 h, 86%). The olefin **14** was transformed into primary bromide **15** by the sequence (1) hydroboration with 3 equiv of 9-BBN (0.5 M in THF, 23° for 10 h) followed by treatment with 7 equiv of sodium hydroxide and 25 equiv of hydrogen peroxide at 23° for 10 h to form the primary alcohol (88%); and (2) replacement of primary OH by Br (1.1 equiv of Ph_3P and 1.3 equiv of CBr_4 in CH_2Cl_2 at 23° for 3 h) to give **15**, $[\alpha]_D^{23}$ + 79.8° (c=2.5 in $CHCl_3$), in 96% yield.

The skeleton of venustatriol was assembled from aldehyde **9** and bromide **15** by the sequence (1) bromine-lithium exchange by reaction of **15** with 2.1 equiv of tert-BuLi in ether at -78° for 15 min; (2) conversion of the resulting lithium reagent to the corresponding cerium reagent by stirring with 1.5 equiv of powdered anhydrous $CeCl_3$ at -78° for 10 min and 0° for 2 h; and (3) reaction of the cerium reagent[10] from **15** with aldehyde **9** (0.1 M in the reaction) at -78° for 10 min and 0° for 2 h to give after quenching with aq NH_4Cl and SG chromatography the coupling product **16** stereoselectively (85%). Reaction of **16** with 1.1 equiv of oxalyl chloride, 1.3 equiv of Me_2SO at -78° for 30 min and subsequently with 5 equiv of Et_3N (initially at -78° and then at -78° to 0° over 5 min) produced ketone **17** (85%) which upon treatment with 3 equiv of methylmagnesium bromide in THF at -78° for 30 min and -78° to 0° over 30 min provided stereoselectively tertiary alcohol **18** in



2 R = CH_2OH
3 R = (*E*)-CH=CHCOOCH$_3$
4 R = CH_2CH_2CHO



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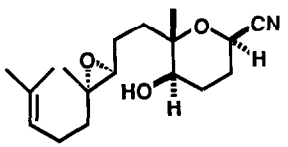

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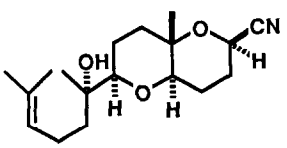

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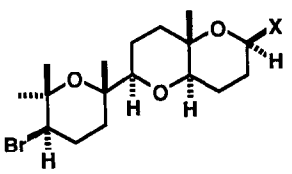
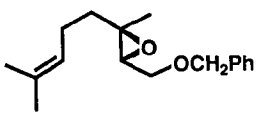


8 X = CN
9 X = CHO



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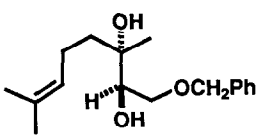

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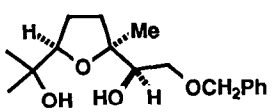
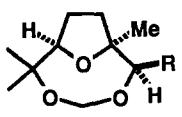
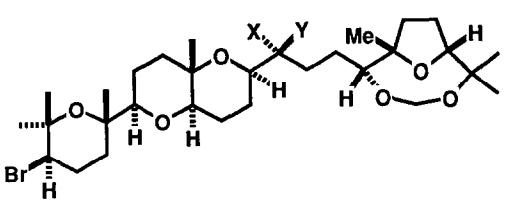


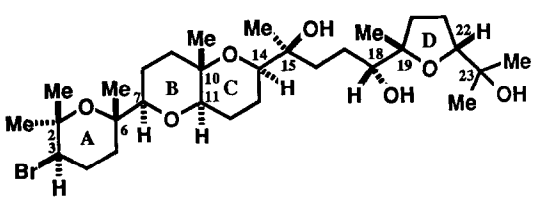
12



13 R = CH_2OCH_2Ph
14 R = $CH{=}CH_2$
15 R = CH_2CH_2Br



16 X = OH, Y = H
17 X, Y = O
18 X = CH_3, Y = OH



1

98% yield. The formation of both **16** and **18** is highly stereocontrolled in the manner predicted for addition of the organometallic reagent to a metal chelate between the C-ring oxygen and the C(15) carbonyl at the less screened face of C(15).

Deprotection of the formal derivative **18** using 0.02 M tosic acid in 5 : 1 THF-H_2O at 40° for 9 h generated venustatriol (**1**) in 83% yield. Synthetic venustatriol, mp 160-161°, $[\alpha]_D^{23}$ + 9.32° (c=0.6 in $CHCl_3$)[1], was shown to be identical with a naturally derived sample by 500 MHz ^1H NMR, ^{13}C NMR, MS (EI, DEI, CI, FAB), FT-IR, and TLC (3 solvent systems) comparison.[11]

Although the above described synthesis of venustatriol involves a number of highly stereoselective steps, the *trishomoallylic* epoxidation **5** → **6** and the conversion of **11** → **12** by PCC are especially noteworthy. Complete control over the course of the brominative cyclization **7** → **8** is an interesting challenge for further research.[12]

REFERENCES AND NOTES

1. S. Sakemi, T. Higa, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Letters*, **27**, 4287 (1986).
2. For other synthetic studies on venustatriol and related oxacyclic squalenoids such as thyrsiferol[3] see (a) M. Hashimoto, T. Kan, K. Nozaki, M. Yanagiya, H. Shirahama, and T. Matsumoto, *Tetrahedron Letters*, **29**, 1143 (1988) and the *in press* reference cited therein; and (b) C. A. Broka, L. Hu, W. J. Lee, and T. Shen, *Tetrahedron Letters*, **28**, 4993 (1987).
3. (a) J. W. Blunt, M. P. Hartshorn, T. J. McLennan, M. H. G. Munro, W. T. Robinson, and S. C. Yorke, *Tetrahedron Letters*, 69 (1978); (b) T. Suzuki, M. Suzuki, A. Furasaki, T. Matsumoto, A. Kato, Y. Imanaka, and E. Kurosawa, *Tetrahedron Letters*, **26** 1329 (1985); and (c) T. Suzuki, S. Takeda, M. Suzuki, E. Kurosawa, A. Kato, and Y. Imanaka, *Chem. Lett.*, 361 (1987).
4. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y.Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).
5. Satisfactory FT-IR, 500 MHz ^1H NMR, and mass spectral data were obtained for each synthetic intermediate using chromatographically purified and homogeneous samples.
6. Abbreviations used herein: pyridine, py; tetrahydrofuran, THF; silica gel, S.G.; 2,4,4,6-tetrabromocyclohexa-2,5-dienone, TBCD. All reactions involving air or moisture sensitive substances were conducted under an inert atmosphere.
7. Carbon numbering as for **1**.
8. This interesting stereoselective epoxidation of a *trishomoallylic* alcohol did not produce appreciable amounts of the diastereomeric 6,7-epoxide. With the (+)-diethyl (2*S*,3*S*)-tartrate-derived catalyst for this epoxidation **5** was transformed into a mixture of **6** and the diastereomeric 6,7-epoxide in a ratio of 3 : 4 by ^1H NMR analysis. The stereoselective synthesis of **5** could not be achieved using t-BuOOH as oxidant. For a related example of stereoselective oxidation of a bishomoallylic alcohol see T. Fukuyama, B. Vranesic, D. P. Negri and Y. Kishi, *Tetrahedron Letters*, 2741 (1978).
9. For precedent see D. M. Walba and G. S. Stout, *Tetrahedron Letters*, **23**, 727 (1982).
10. T. Imamoto, Y. Sugiura, and N. Takiyama, *Tetrahedron Letters*, **25**, 4233 (1984).
11. We are grateful to Dr. S. Sakemi and the Sea Pharm. Co. for a sample of naturally derived venustatriol. The mp of **1** is reported[1] as 161.5°. We were not able to take a mixture mp of synthetic **1** with the reference sample (*ca.* 1 mg) because the latter was an oil.
12. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

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