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Asymmetric cis - Hydroxylation via Epoxidation-Carboxylation: A Formal Synthesis of (+)-Citreoviral

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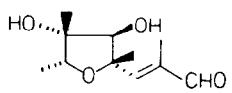
Summary: Asymmetric epoxidation of tiglyl alcohol combined with Pd(0) catalyzed conversion to the vicinal diol with retention of configuration provides an efficient asymmetric synthesis of a key intermediate to (+)-citreoviral and related compounds.

Citreoviral (1) and citreodiol (2),[1] co-metabolites with and the former being a synthetic intermediate for citreoviridin,[2] a potent neurotoxic mycotoxin which acts as an inhibitor of ATP synthesis and hydrolysis catalyzed by mitochondrial enzyme systems, have been the subject of several recent synthetic endeavors.[3,4] A key intermediate in several syntheses has been the diol 3[3,4a] which requires only four straightforward steps to complete the synthesis. We wish to record a six step (seven reactions) asymmetric synthesis of this important intermediate which is more



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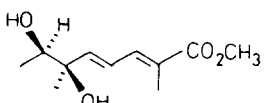

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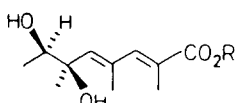
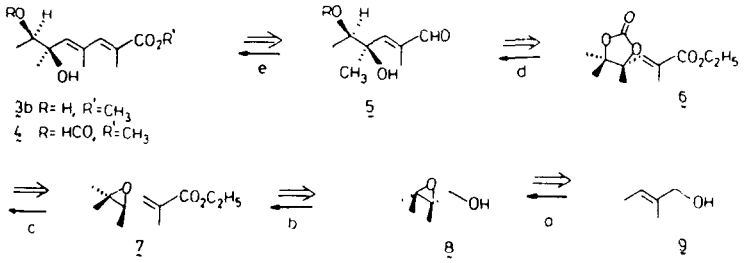


3

a) R=C_2H_5
b) R=CH_3

efficient than the earlier non-racemic synthesis by the recent development of a novel approach for the equivalent of cis-hydroxylation.[5] The same approach may be envisioned for the synthesis of citreodiol 2.

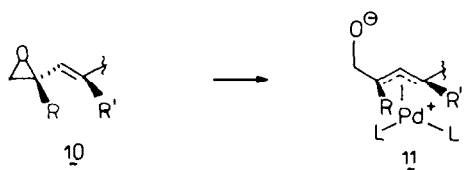
The Scheme outlines the retrosynthetic analysis. Olefination with stabilized Wittig reagents to produce E-enoates suggests the aldehyde 5 as the precursor. Using a carbonate as a precursor to the diol and an ester to the aldehyde as in 6 conceptually allows conversion of both functional groups to the required functionality of 5 in a single step. Based upon our newly developed Pd(0) chemistry,[5] a synthon for the carbonate 6 is the epoxide 7 which may arise by standard chain extension methods based upon olefination reagents from 8. Asymmetric epoxidation methodology[6] reveals tiglyl alcohol as a simple building block.



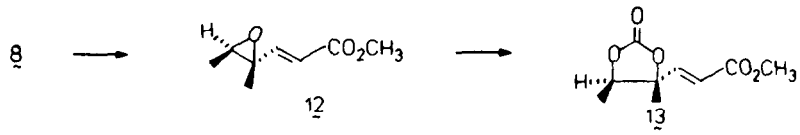
a) D(-)-DET, t-C_4H_9OOH, $Ti(OC_3H_7\text{-}i)_4$, CH_2Cl_2, -23° b) $(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2,-60°, then add Ph_3P $C(CH_3)$ $CO_2C_2H_5$, rt 49% overall from tiglyl alcohol c) $(dba)_3Pd_2$ $CHCl_3$, dppp, THF, 40 psi CO_2, rt, 55% d) DIBAL-H, CH_2Cl_2, -78°, 72% e) Ph_3P $C(CH_3)$ $CO_2C_2H_5$, CH_2Cl_2, rt, 81%

Catalytic asymmetric epoxidation[6] of tiglyl alcohol 9 using 7 mol% of D(-)-DET and 5 mol% titanium tetraisopropoxide gives the epoxy alcohol 8. The resultant alcohol 8 is directly subjected to a Swern oxidation in methylene chloride at -60°. After allowing the reaction to warm to 0°, the stabilized Wittig reagent, ethyl 2-(triphenylphosphoranylidene)propionate, is added and the reaction stirred at room temperature to give the epoxy ester 7[7] directly in 49% overall yield from tiglyl alcohol. This procedure of a one pot Swern oxidation stabilized Wittig condensation proves to be a very convenient and general approach from epoxyalcohols to enoates and by-passes handling of the sensitive epoxyaldehydes.

The Pd(0) catalyzed reaction of 7 with carbon dioxide proved particularly stubborn in our initial attempts using triisopropyl phosphite as a ligand. The reactions either did not proceed or did so very sluggishly. The unsatisfactory rate proved to be related to the purity of the vinyl epoxide and the choice of ligand. The high sensitivity of this substrate relative to our earlier cases may be associated with the high degree of substitution around both the olefin and the epoxide. In particular, a substitution pattern as depicted in 10 where R is alkyl and R' is

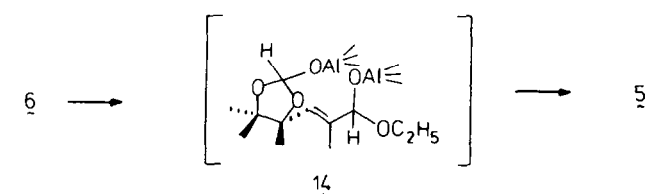


either H or alkyl appears to hinder formation of the preferred syn π-allylpalladium complex 11 by disfavoring the conformation of 10 required for ionization and/or by increasing non-bonded interactions between the substituents and the palladium template in 11. That changing R from hydrogen to methyl is more important than a similar change of R' is demonstrated in reaction of the epoxide 12[7]. Again, the reaction is very sensitive to the purity of the vinylepoxide but use of triisopropyl



phosphite ligand is satisfactory and the reaction does proceed in somwhat higher yield than the trimethyl analogue 7 to give carbonate 13.[7,8] The impurity that seems to poison the catalyst with sluggish substrates is not visible spectroscopically and we speculate, for the present, that it may emanate from the use of theSwern oxidation. Regardless, careful chromatography and/or distillation minimizes this effect. Reducing the effective steric bulk of the ligand by replacing triisopropyl phosphite with dppp is required for successful reaction with the vinylepoxide 7. With these modifications, a 55% yield of the desired carbonate 6[7,8] was obtained. Nmr chiral shift reagents establish the carbonate to be at least 93% enantiomerically pure.

DIBAL-H (3 eq.) at -78° produces selectively the aldehyde monoformate 5.[7,8] The location of the formate at the secondary alcohol is easily discerned by the downfield shift of the adjacent methine proton (δ 5.13, q, J=6.37 Hz). The selective reduction of carbonates to monoderivatized diols expands the scope of such synthetic intermediates. The ease by which formates are further reduced suggests that a tetrahedral intermediate such as 14 must be stable under the conditions of the



reduction and collapses only after protonation during work-up. The chemoselective formation of the secondary formate versus the tertiary formate may relate to steric factors.

Completion of the synthesis proceeded straightforwardly as outlined in the Scheme. Methanolysis ($NaOCH_3$, CH_3OH, rt, 92%) of 4 effects double trans-esterification to the diol ester 3b, $[\alpha]_D$=-15.4° ($CHCl_3$) (lit.[3] $[\alpha]_D$=-15.9° ($CHCl_3$), whose spectral properties correspond to those reported.[3] Using a similar sequence starting from carbonate 13, simple synthesis of citreodiol (2) can easily be envisioned.

The work reported herein demonstrates that the opening of epoxides with carbon dioxide in the presence of palladium can be achieved even in rather unfavorable cases. The reaction may be critically dependent upon the ligand and a broader choice of ligands, in particular both phosphines and phosphites, is possible than previously believed. The ability to achieve an equivalent of an enantioselective cis hydroxylation by asymmetric epoxidation and palladium catalyzed opening with retention of configuration significantly streamlines the synthesis of the optically active diol 3 and thus (+) citreoviral. While seven reactions are employed, the combination of the Swern oxidation and Wittig olefination of 8 into a single operation converts the sequence into six steps.

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7. All new compounds have been fully characterized spectrally.

8. 3b: Ir(CCl_4): 3540-3100, 1710 cm^{-1}. Nmr ($CDCl_3$, 200 MHz): δ 7.05 (bs, 1H), 5.50 (bs, 1H), 3.81 (q, J=6.4 Hz, 1H), 3.74 (s, 3H), 2.06 (d, J=1.22 Hz, 3H), 1.96 (d, J=1.36 Hz, 3H), 1.29 (s, 3H), 1.16 (d, J=6.34 Hz, 3H).
   5: Ir(CCl_4): 3514; 3300, 2906, 1732, 1700 cm^{-1}. Nmr ($CDCl_3$, 200 MHz): δ 9.36 (s, 1H), 8.06 (s, 1H), 6.34 (s, 1H), 5.28 (s, 1H), 5.13 (q, J=6.37 Hz, 1H) 1.98 (s, 3H), 1.40 (s, 3H), 1.32 (d, J=6.38 Hz, 3H).
   6: Ir (CCl_4): 1822, 1720 cm^{-1}. Nmr ($CDCl_3$, 200 M Hz): δ 6.61 (q, J=1.50 Hz, 1H), 4.64 (q, J=6.49 Hz, 1H), 4.22 (q, J=7.12 Hz, 2 H), 2.04 (d, J=1.50 Hz, 3H), 1.51 (s, 3H), 1.44 (d, J=6.49 Hz, 3H), 1.30 (t, J=7.18 Hz, 3H).
   13: Ir(CCl_4): 1825, 1730 cm^{-1}. Nmr ($CDCl_3$, 200 MHz): δ 6.87 (d, J=15.7 Hz, 1H), 6.16 (d, J=15.7, 1H) 4.54 (q, J=6.53 Hz, 1H), 3.77 (s, 3H), 1.48 (s, 3H), 1.41 (d, J=6.56, 3H).

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