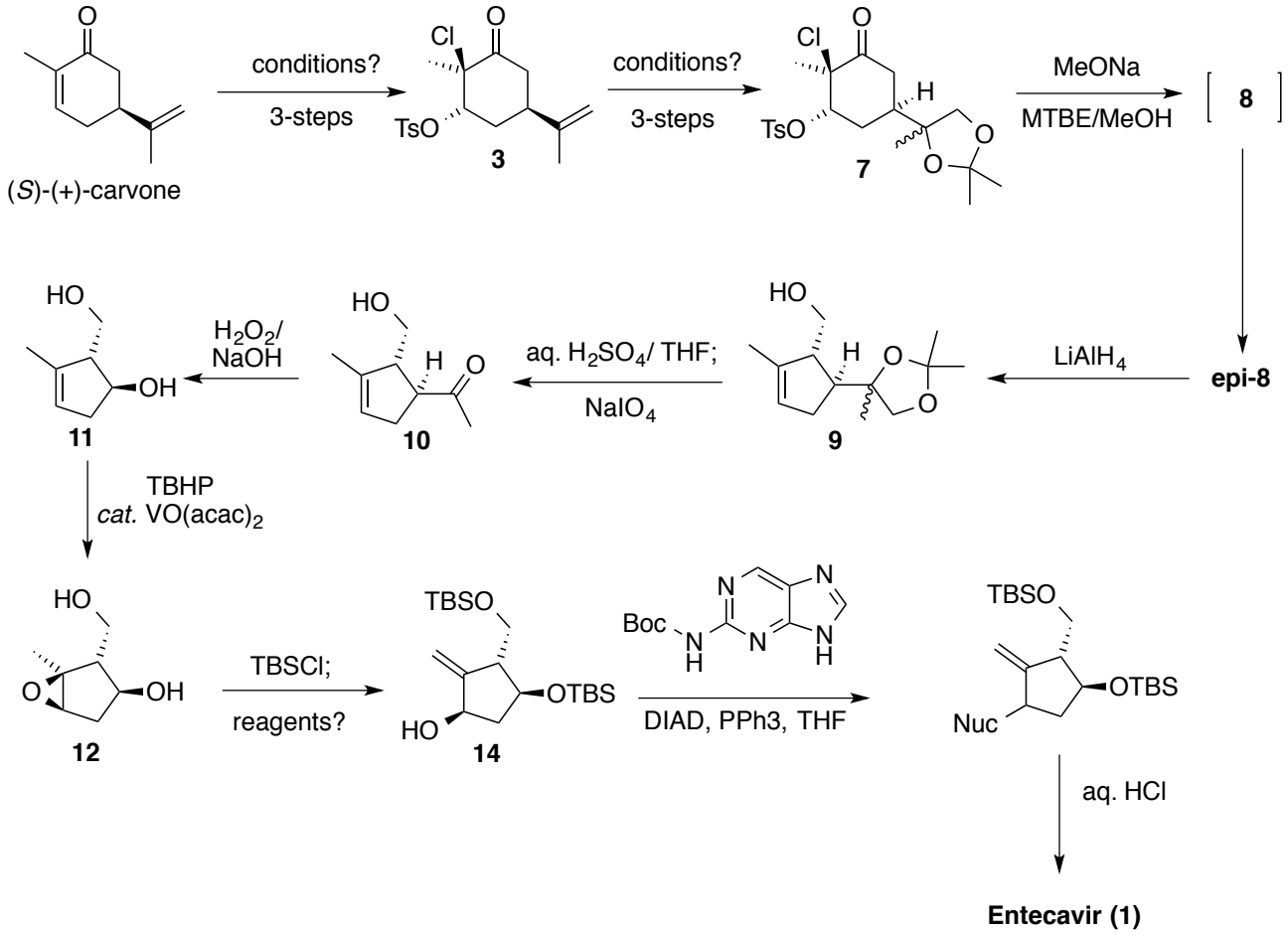
Pilot Production Total Synthesis of Entecavir

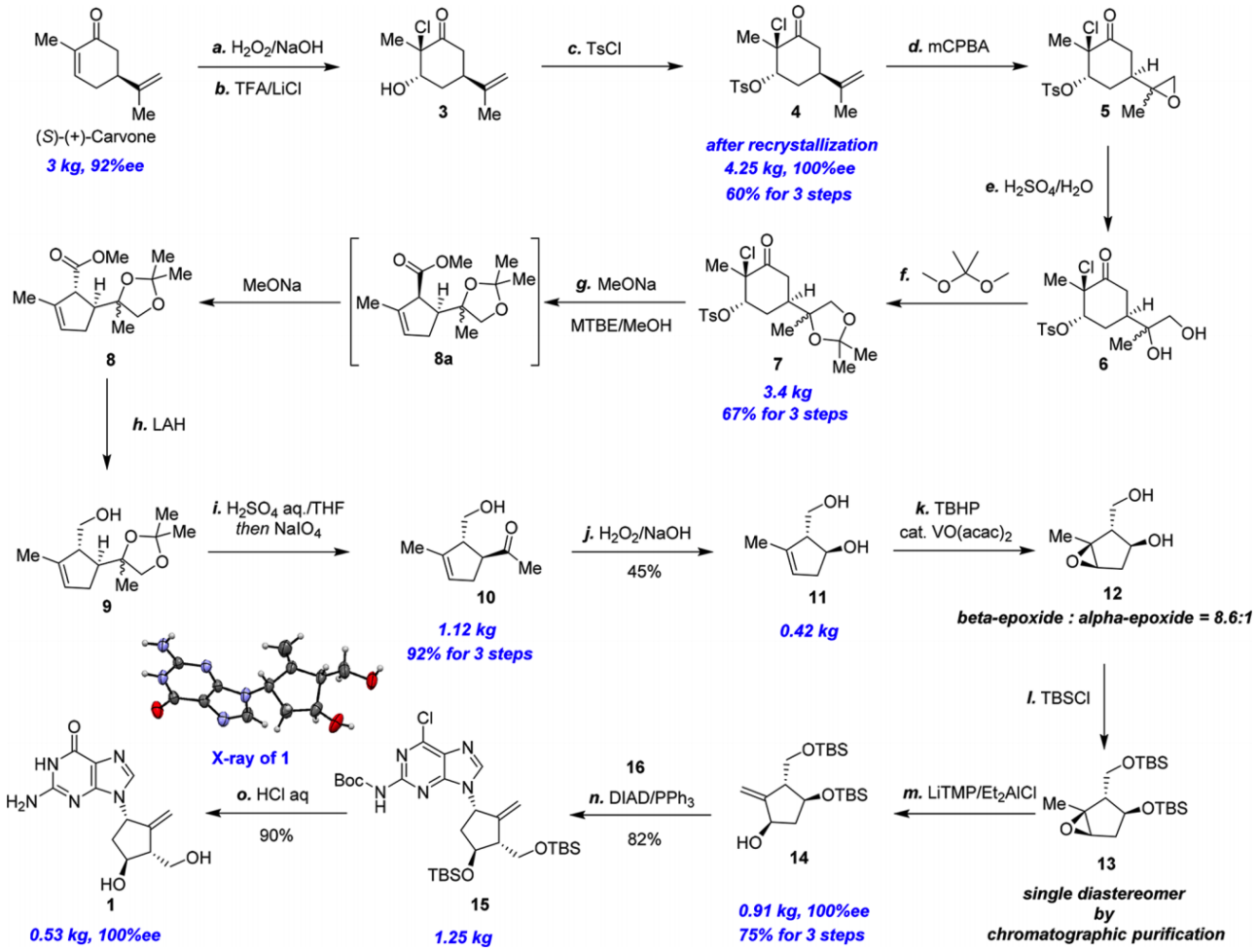
Group Renaud
Problem Set
08.03.18
submitted by NicholasTappin



1. Suggest conditions for the transformation of carvone into **3**. Don't forget to rationalize stereochemistry!
2. Suggest conditions for the transformation of **3** into **7**.
3. Provide a mechanism for **7** going to **epi-8** via **8**. Can you explain why **epi-8** is the thermodynamic sink, and why (with aide of a stereochemical model/ TS) it isn't initially formed? How is this named reaction called?
4. Give mechnism for the formation of **10**.
5. The two subsequent transformations are slightly unusual. Can you explain **10** to **11**, and **11** to **12** (usually what sort of double bonds are oxidized by $VO(acac)_2$? Why does the diastereoselectivity work well in this case?
6. Suggest reagents for the epoxide opening to yield **14**. Give a justification for your choice.
7. Give the name and mechanism for the substitution of alcohol **14**. Through which atom would nucleophile 16 react? What is the missing stereochemistry in **15**? Thereby provide the structure of Entecavir (1).

Yehua Jin et al. **OPR&D 2018** ASAP. doi: 10.1021/acs.oprd.8b00007

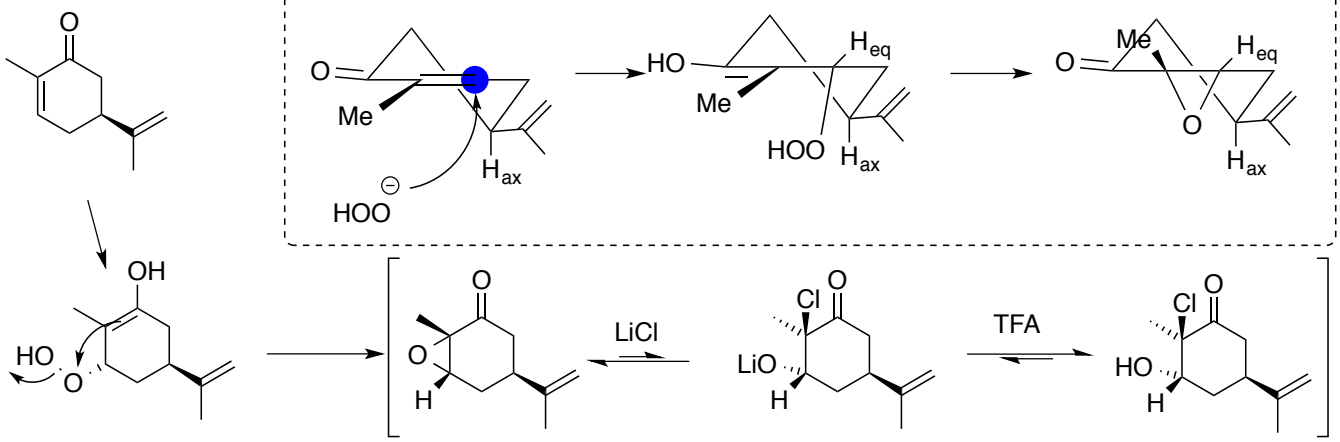
Scheme 2. Synthesis of Entecavir (1)[a]



[a]Reagents and conditions: (a) 30% $H_2O_{2(aq)}$, 4N $NaOH_{(aq)}$, MeOH, 0 °C; (b) TFA, LiCl, THF, 0–5 °C; (c) TsCl, DMAP, CH_2Cl_2, 25 °C (60% for 3 steps); (d) mCPBA, CH_2Cl_2, 25 °C; (e) H_2SO_4, H_2O, THF, 25 °C; (f) 2,2-dimethoxypropane, cat. PSA, CH_2Cl_2, 25 °C (67% for 3 steps); (g) MeONa, MTBE/MeOH, 0–25 °C; (h) LAH, THF, 5–10 °C; (i) 20% $H_2SO_{4(aq)}$, THF, 25 °C, then $NaIO_4$ 25 °C (92% for 3 steps); (j) 30% $H_2O_{2(aq)}$, 10% $NaOH_{(aq)}$, MeOH, 70 °C (45%); (k) cat. $VO(acac)_2$, TBHP, CH_2Cl_2, 0 ± 5 °C; (l) TBSCl, imidazole, cat. DMAP, DMF, 25 °C; (m) LiTMP, Et_2AlCl, toluene, 0 °C (75% for 3 steps); (n) **16**, DIAD, PPh_3, THF, 0 °C (82%); (o) 3 N $HCl_{(aq)}$, THF, 55 °C (90%).

Solutions

1. See scheme.



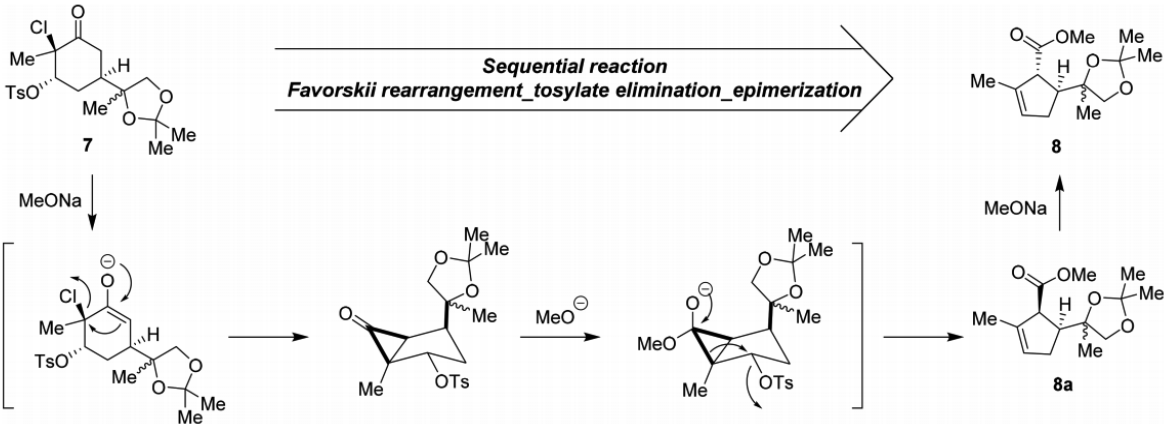
equilibirum displaced: Badjwa and Anderson **TL** 1991, *32*, 3021
carvone application: Ley **ACIE** 2003, *42*, 599; **Chem. - Eur. J.** 2007, *13*, 5688

2. See scheme.

in two steps with OsO4 (but this is presumably too toxic for a pilot synthesis of a pharmaceutical). mCPBA is well behaved and its sideproducts easily removed in the subsequent aqueous treatment.

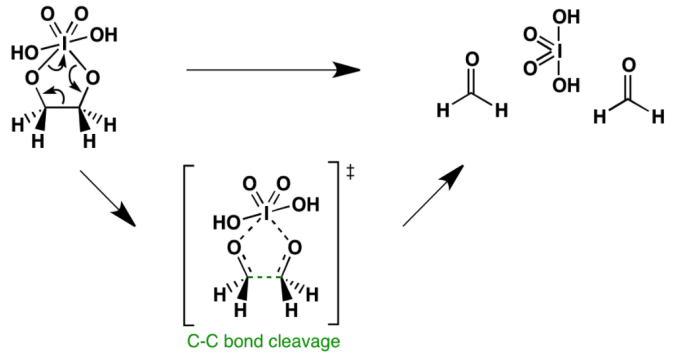
3.

Scheme 3. Proposed Mechanism of the Tandem Reaction Sequence from 7 to 8

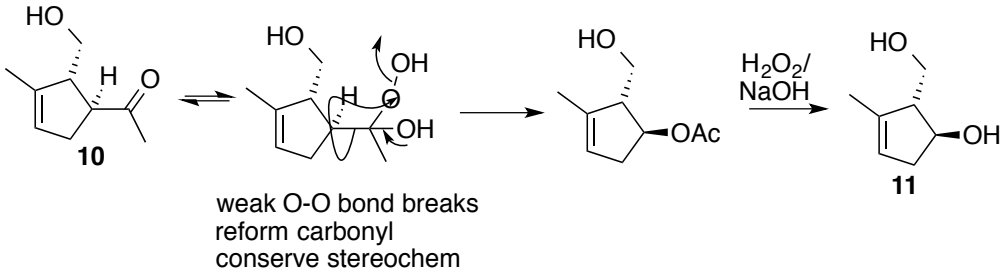


epimerization puts two groups in cyclopentene ring in a trans relationship

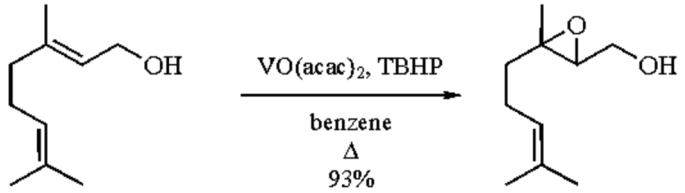
4. hypervalent iodine oxidation/ glycol cleavage



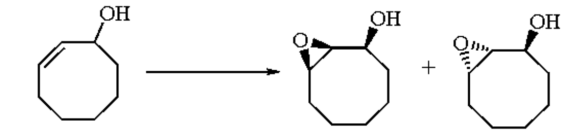
5. Baeyer-Villiger oxidation (slightly unusual conditions - usually a peracid is used).



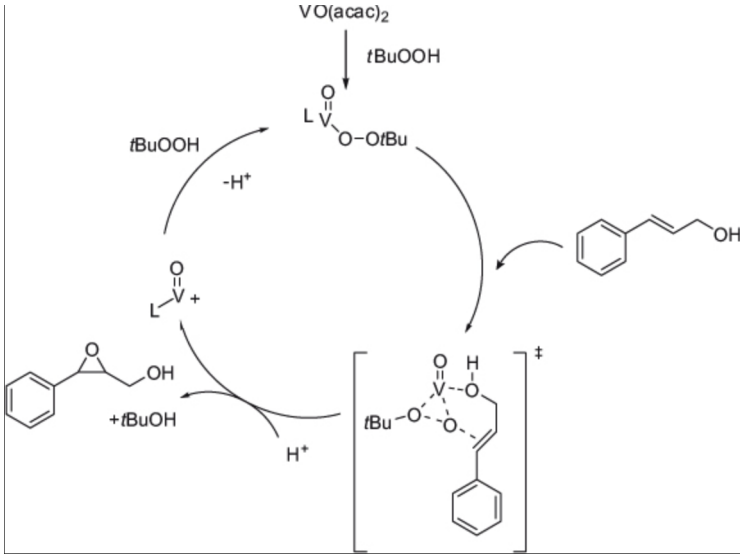
"vanadium acac" is selective for allylic alcohols:



it is also stereoselective. This is important for understanding the mechanism/ TS:



	% *cis*	% *cis*
$VO(acac)_2$, TBHP	97	3
m-CPBA	0.2	99.8
$MoO_2(acac)_2$	42	58

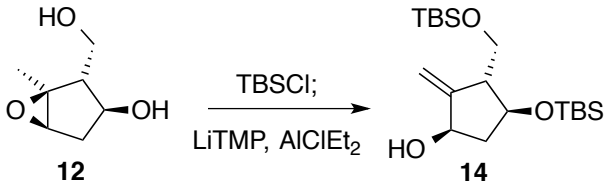


standard mech.

Our alcohol is homoallylic but there are other examples in literature of stereoselectivity in these cases (see citations in original article). We have a cyclic system so the directing ability of the alcohol should be very high. The secondary alchol appears to be the directing alchol rather than the primary one. I assume this is due to proximal effects...?

For a more in depth discussion of the epoxidation with TBHP, see: Journal of Catalysis 294 (2012) 1–18

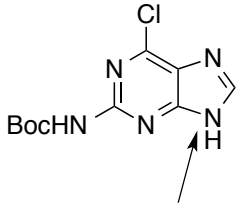
6. See Scheme.



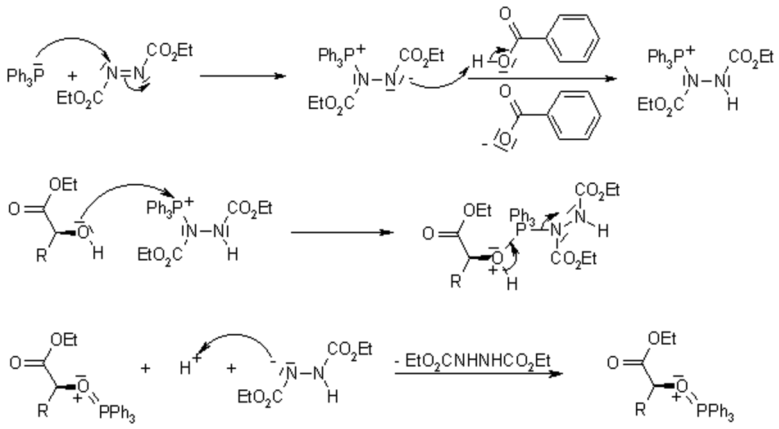
12 **14**

need to complex epoxide with a LA and thereby lengthen one of the C-O bonds before deprotonation. Otherwise another isomer could result.

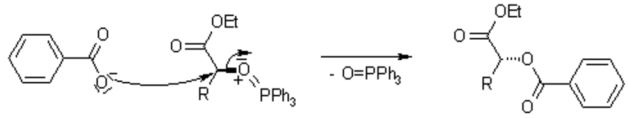
7. Mitsunobu reaction. Inversion since SN2. NucH not Nuc!!!



least nucleophilic N because it's lone pair are used for the armoatic ring. (At least until it is deprotonted).
But, all other positions will substitute reversibly, and without possibility for futher reaction.
Remeber that we need a NucH not a Nuc.



The reaction proceeds with clean inversion, which makes the Mitsunobu Reaction with secondary alcohols a stereogenic centers in natural product synthesis.



Side Reaction: