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09. 07. 01

Siteselective C-H Oxidation

-Contents-

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2. Siteselective C-H oxidation
3. Application to total synthesis of eudesmane terpenes
4. Summary

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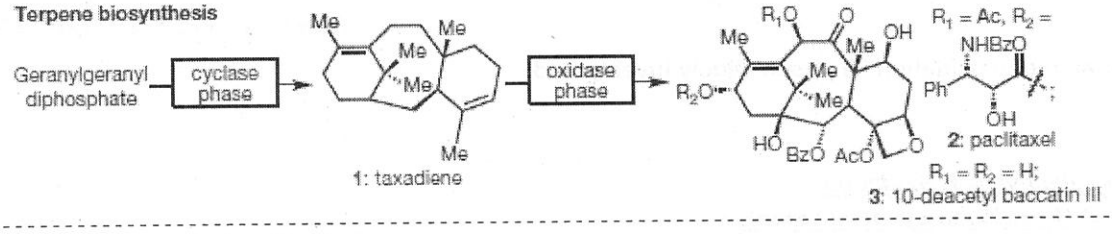
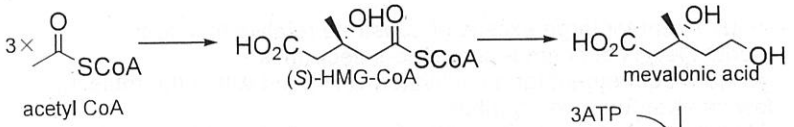
1. Introduction

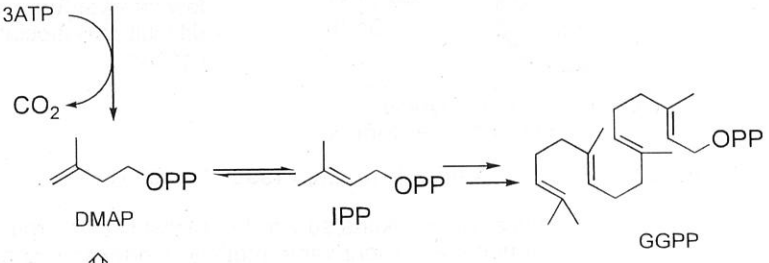
• About terpene biosynthesis

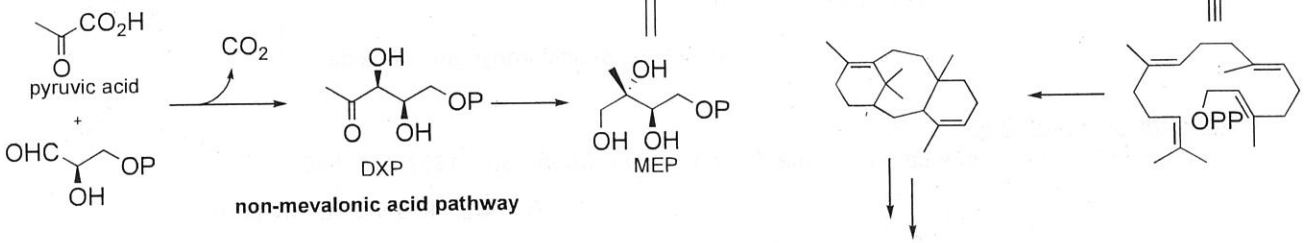
Terepene biosynthesis
(cyclase phase + oxidase phase)



mevalonic acid pathway

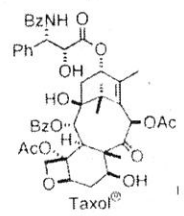






non-mevalonic acid pathway

Oxyfunctionalized by cytochrome P450



• Oxidation of carbon framework by cytochromeP450

X-ray structure of CytchromeP450

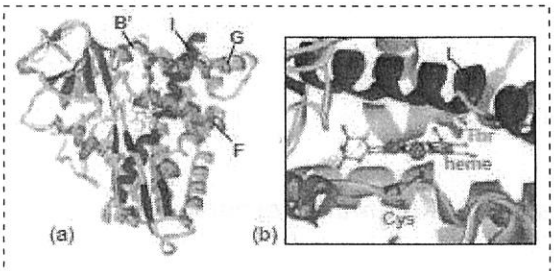


Figure 3. (a) Schematic representation of P450cam. (b) The views of the heme-binding region.

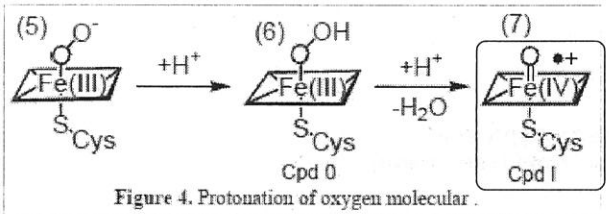


Figure 4. Protonation of oxygen molecular .

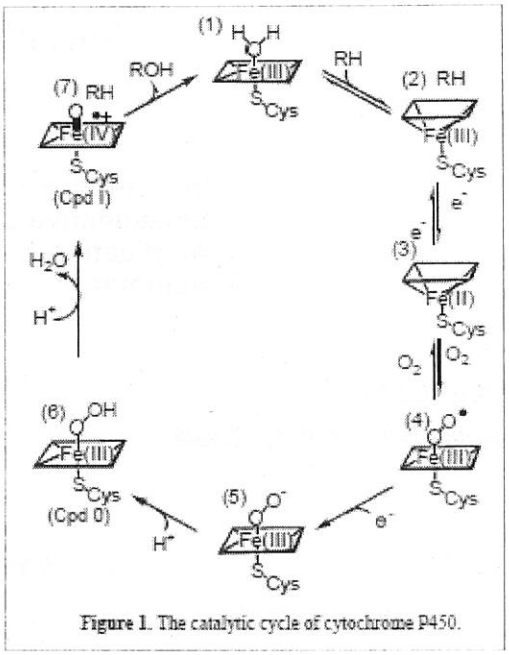


Figure 1. The catalytic cycle of cytochrome P450.

Biomimetic oxidation has been widely investgated.

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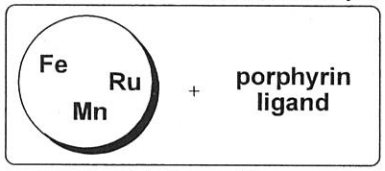
2. Siteselective C-H oxidation

2-1. C-H oxidation by metal complex.

• Heme-type catalyst

traditional C-H oxidation catalyst



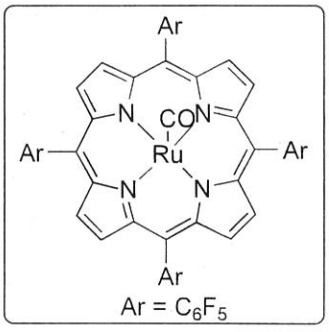
oxidant : PhI=O, pyridine, *N*-oxide, peroxide, etc.

- requirement for large excess of substrate relative to oxidant.
- modest levels of chemo- and regio-selectivities.
- general requirement for an activated C-H bond within the molecule.
- low catalyst turn over number
- difficulties associated with synthesis and modification of porphyrin ligands.

Groves, J. T. *et al. J. Am. Chem. Soc.* **1996**, *118,* 8961.

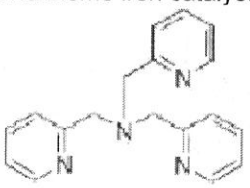
- In this system, alkane substrate : oxidant = 1 : 1 ratio. (adamantane, cyclohexane, methylcyclohexane, or decaline)
- yield : 70 ~ 90%, TON : up to 120,000.

oxidant : 2, 6-dichloropyridine *N*-oxide



• Nonheme-type catalyst

First example of nonheme iron catalyst : Que, L. *et al. J. Am. Chem. Soc.* **1997**,*119*, 5964.



TPA

1 amine, 3 pyridine

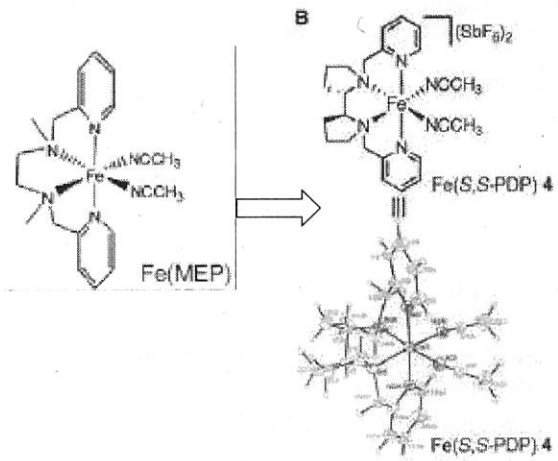
☞ See Suzuki-san's lit. (M2 part)

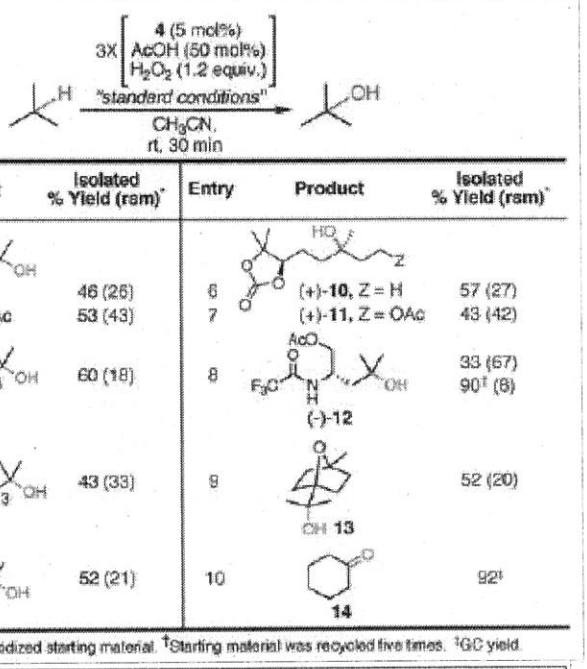
$[Fe(TPA)(CH_3CN)_2](ClO_4)_2$ was used.

- only simple substrate. (cyclohexane, *cis*- or *trans*- dimethylcyclohexane, etc.)
- selectivity is modest.

• *Predictable C-H oxidation by Fe Catalyst*

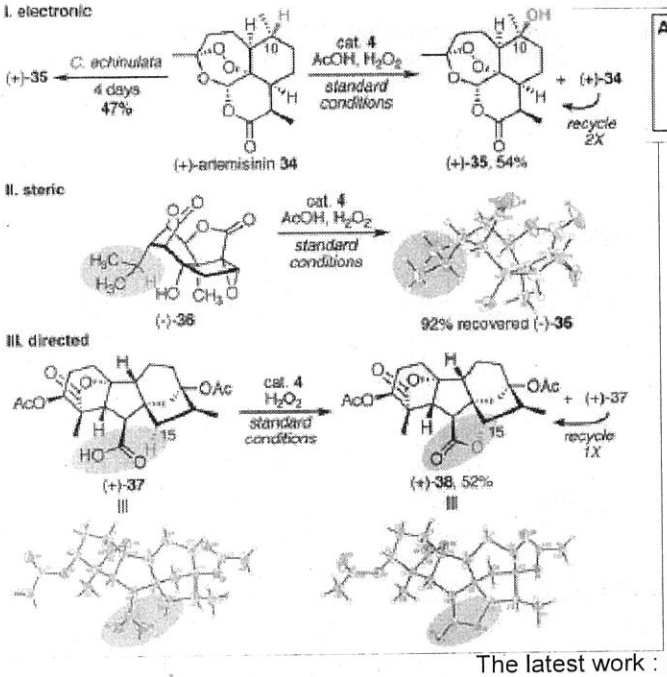
White, C. M. *et al. Science* **2007**, *318*, 783.

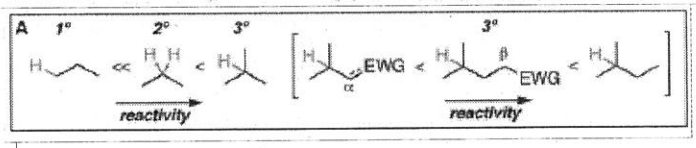




Entry	Product	Isolated % Yield (rsm)*	Entry	Product	Isolated % Yield (rsm)*
1	**5**, X = Br	46 (25)	6	(+)-**10**, Z = H	57 (27)
2	**6**, X = OAc	53 (43)	7	(+)-**11**, Z = OAc	43 (42)
3	**7**	60 (18)	8	(-)-**12**	33 (67) 90† (8)
4	**8**	43 (33)	9	**13**	52 (20)
5	**9**	52 (21)	10	**14**	92‡

*rsm = % recovered unoxidized starting material. †Starting material was recycled five times. ‡GC yield.





- No cleavage of endoperoxide. (Fe(II)-mediated cleavage of endoperoxide was known.)
- Sterically-hindered tertiary C-H bond was not oxidized.
- In case of III, secondary C-H bond was oxidized. (The corresponding methyl ester of **37** didn't gave **38**.)

The latest work : Ribas, X., Costas, M. *et al. Angew. Chem. Int. Ed.* Early View.

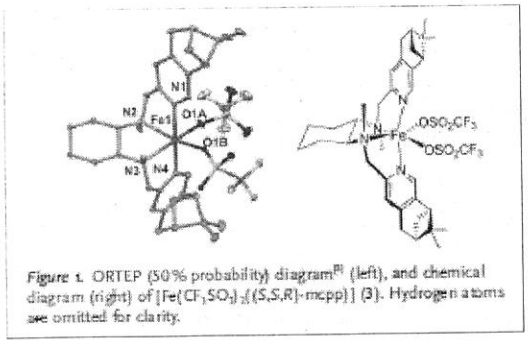
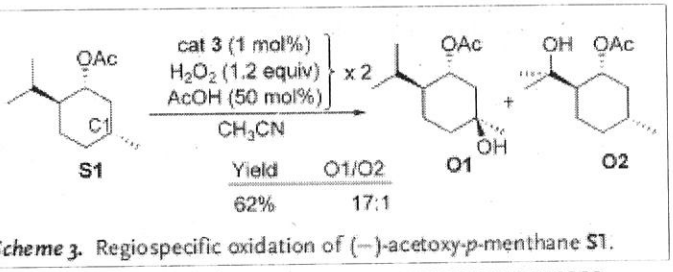


Figure 1. ORTEP (50% probability) diagram[81] (left), and chemical diagram (right) of $[Fe(CF_3SO_3)_2((S,S,R)\text{-mcpp})]$ (3). Hydrogen atoms are omitted for clarity.



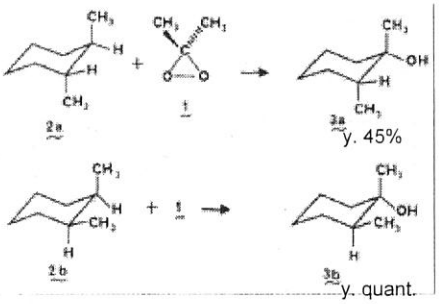
Scheme 3. Regiospecific oxidation of (−)-acetoxy-*p*-menthane **S1**.

- Catalyst loading was 1 mol%.
- In case of White's catalyst : **O1/O2** = 11:1, **O1** = 50%

2-2. Metal-free siteselective C-H oxidation

• DMDO

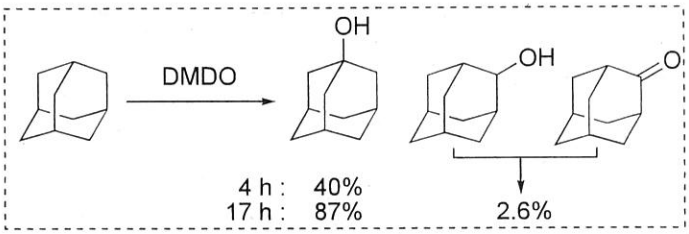
Murray, R. W. *et al. J. Am. Chem. Soc.* **1986**, *108*, 2470.



In a typical reaction a solution of **1** in acetone (25 mL, 0.052 M) was added to a solution of adamantane (0.321 g; 2.35 mmol) in 25 mL of acetone. The solution was stirred at 22 °C while protected from light. Progress of the reaction was followed by periodic sampling and capillary GC analysis (DB-1701 fused silica

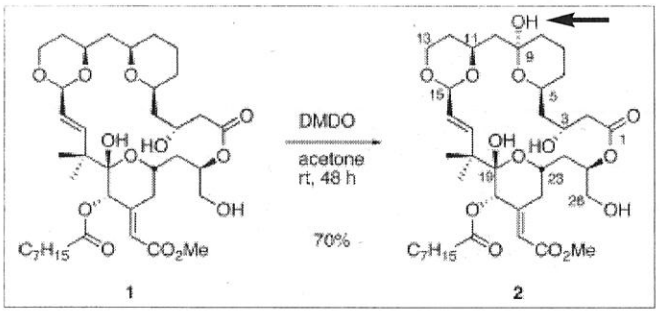
⟹ • Stereospecific (retention)
• Equatorial C-H is selectively oxidized.

☞ In case of adamantane



- secondary alcohol was further oxidized to the correspondingketone.

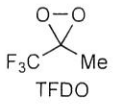
• Application to oxifunctionalization of bryostatin analogue. : Wender, P. A. *et al. Org. Lett.* **2005**, *7*, 79.



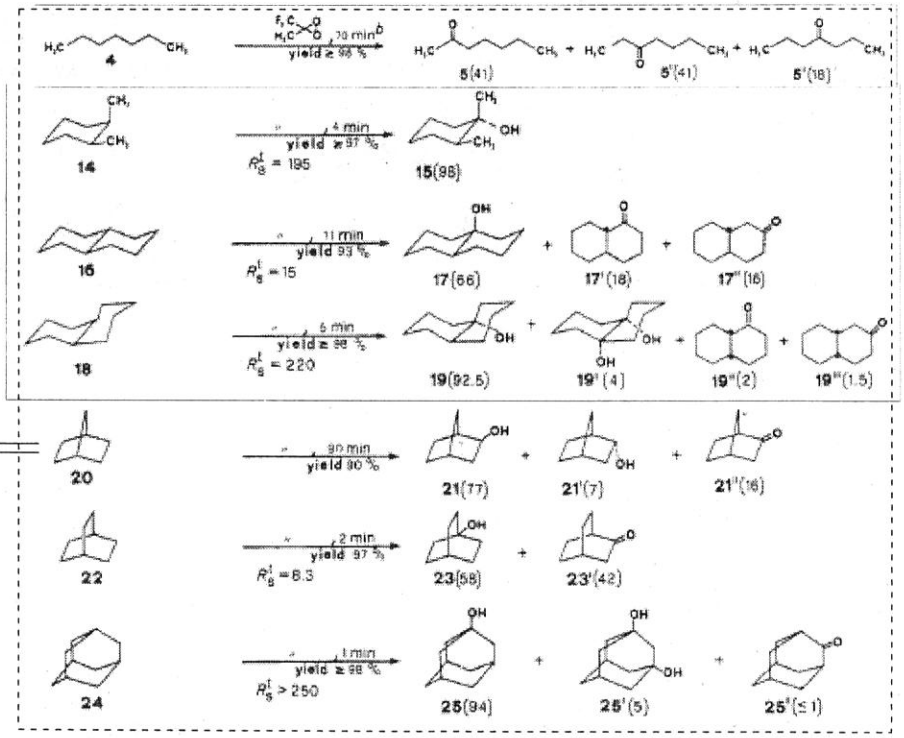
- completeconversion of **1** to a single new product in 70% yield.

• TFDO

Methyl(trifluoromethyl)dioxirane : Curci, R. *et al. J. Am. Chem. Soc.* **1989**, *111*, 6749.



reactivity : TFDO > DMDO
selectivity : unchanged.



- exceptional case
no tertiary alcohol

[a] In CH_2Cl_2/TFA (from 9:1 to 7:3) mixed solvent, at −22 °C; yields and product distributions (parenthetic values) determined with hydrocarbon to dioxirane ratios of initial concentration (ca. 0.1 M) close to unity (unless noted otherwise), at hydrocarbon conversion ≥50%. [b] Ratio of hydrocarbon to dioxirane initial concentration ca. 0.5.

• *Mechanism of dioxirane O-insertion into a C-H bond*

- Possible mechanism.
  - ×1. S_N2-like pathway. ⟶ including C-H bond cleavage in the hydrocarbon fragment.
  - ○2. Concerted pathway.
  - ○3. Free-radical pathway.

- High stereoselectivity.
- No halogenated product was obtained. (In case of TFDO, reactions were conducted in CH_2Cl_2/TFP media) ⟹ Concerted pathway?

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experimental evidence of radical pathway

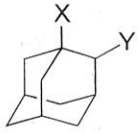
Minisci, F. *et al, Tetrahedron Lett.* **1995**, *36*, 1697.

Table 1. Oxidation and Halogenation of Adamantane (1 mmol) by DMD (0.5 mmol) and $CBrCl_3$[a].

conversion (%)[b]	$CBrCl_3$ (mmol)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	3 / 4
62	0.25	60.0	2.6	29.6	5.6	0.7	1.5	5.3
68	0.50	47.1	3.6	40.2	7.4	0.5	0.8	5.4
76	1.00	34.1	4.8	50.9	9.2	0.6	0.4	5.5
79	2.50	19.2	4.1	57.1	19.0	0.4	0.2	3.0
80	4.00	16.3	4.4	55.7	23.6	traces	--	2.4

[a] the reagents are dissolved in acetone (5 mL) and analyzed by GLC after 1h at room temperature; [b] conversion of adamantane based on DMD.

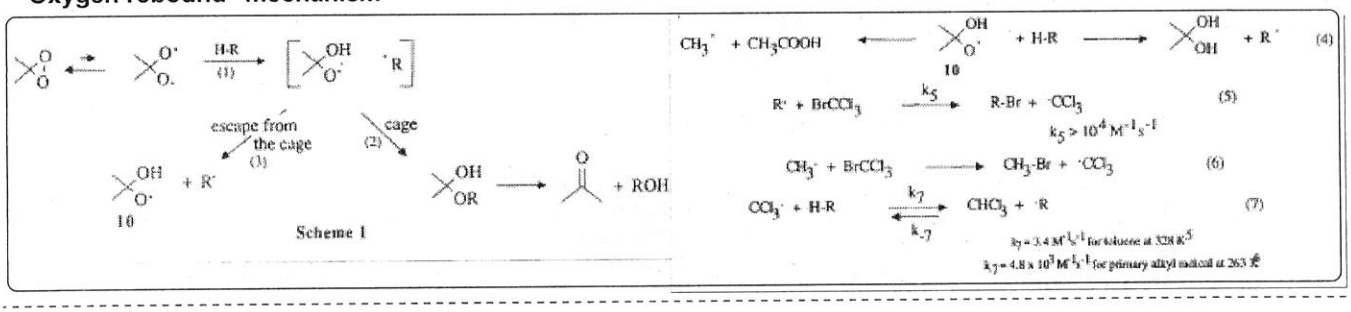
1. X = OH, Y = H
2. X = Cl, Y = H
3. X = Br, Y = H
4. X = H, Y = Br
5. X = H, Y = OH
6. X = H, Y = ketone



- Halogenated product was obtained by reaction of DMDO and $CBrCl_3$ system.
- No halgenated product in the absence of DMDO.

radicalic pathway?

"Oxygen rebound" mechanism



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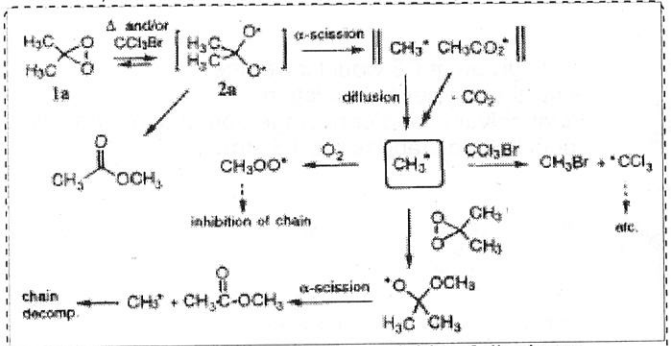
experimental evidence of concerted pathway

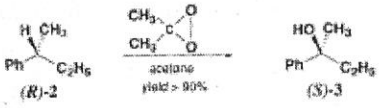
Curci, R. *et al. Tetrahedron Lett.* **1996**, *37*, 249.



CCl_3Br induced the radical reactivitiy of dioxirane.

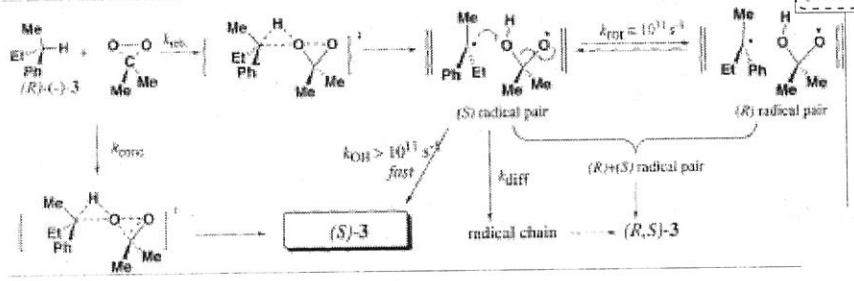
Curci, R. *et al. Chem. Eur. J.* **1997**, *3*, 105.

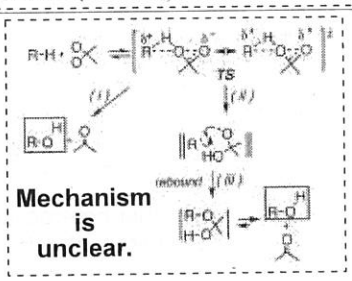
Table 2. Enantioselective oxidation of (*R*)-2-phenylbutane by DMD.



Entry	DMD/equiv [a]	T/°C	t/h	Conv./% [b]	ee(2)/% [c]	ee(3)/%
1	7	8	60	58	70.9	31.0 [d]
2	10	25	40	85	61.6	62.2 [e]

[a] Relative to (*R*)-2. DMD added over 10 min. [b] Determined by GC (DB1 column, 30 m × 0.53 mm, 1.5 mm i.d.; *T* prog.: 100 °C (0.5 min), 100 to 280 °C (10 °C min^{-1})] and/or ^{1}H NMR spectroscopy of the crude reaction mixture. [c] As determined (±1%) by high-resolution chiral HRGC employing a Megadex-5 column (30% 2,3-dimethyl-6-pentyl-β-cyclodextrin, 0.20–0.25 mm film, 25 m × 0.25 mm i.d., FID detector, He c.g.) and peak fitting analysis (corr. coeff. 0.999), standardized versus racemic alkane **2**. [d] Determined (±2%) by ^{1}H NMR spectroscopy (500 or 400 MHz, $CDCl_3$) using (+)-Eu(hfc)$_3$. [e] As determined by chiral GC analysis (permethylated β-cyclodextrin, 30 m × 0.25 mm; *T* prog.: 50 °C (3.0 min), 50 to 95 °C (5.0 °C min^{-1})].

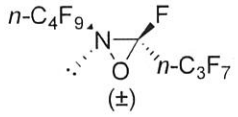




すばやい再結合 or concerted) まだまだ、わからない。

• *Perfluorodialkyl oxaziridine*

Resnati, G. *et al. J. Am. Chem. Soc.* **1993**, *115*, 4897.



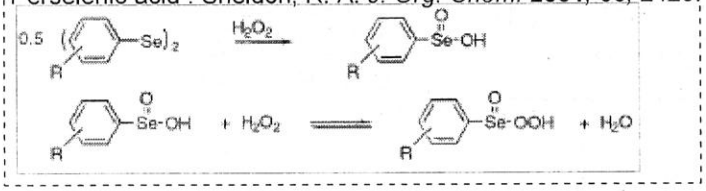
(±)

- Similar reactivity and selectivity of dioxirane.
- Reaction mechanism may be also similar to that of dioxiranes.
- Stable at rt.

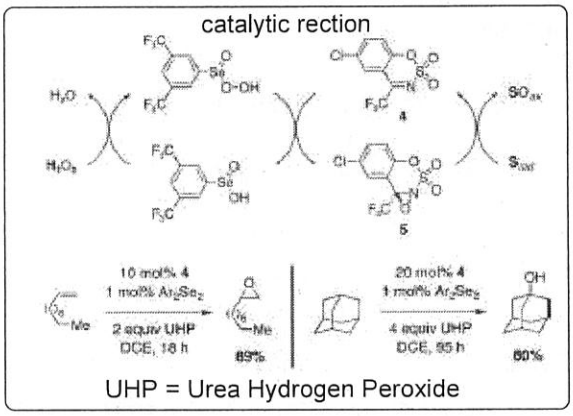
• *Oxaziridine-mediated catalytic hydroxylation*

J. Du Bois *et al. J. Am. Chem. Soc.* **2005**, 127, 15391.

Perselenic acid : Sheldon, R. A. *J. Org. Chem.* **2001**, *66*, 2429.



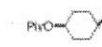
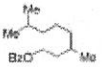
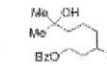
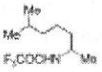
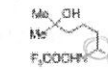
catalytic rection



UHP = Urea Hydrogen Peroxide

- Ar_2Se_2 and UHP gave < 10% conversion to epoxide.

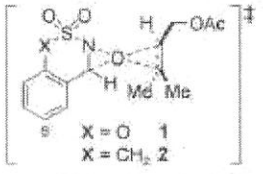
Table 1. Catalytic Oxidations with UHP, Ar_2Se_2, and 4

Entry	Substrate	Product	mol% 4	Time (h)	Yield[a]
1			20	48	63[b]
2			20	72	36[c]
3			20	96	43[c]
4			20	72	39[c]
5			20	72	70
6			10	36	92
7			10	12	94
8			20	45	96

[a] Reactions conducted at 22–50 °C using 1 mol % of Ar_2Se_2 and 2–4 equiv of UHP, 0.5–1.0 M in substrate; see Supporting Information for experimental details. [b] Reaction performed at 35 °C. [c] Reaction performed at 50 °C.

• *Improved catalyst*

J. Du Bois *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 1.



$\Delta E_{act}(TS^1)$ = 16.0 kcal mol^{-1}

$\Delta E_{act}(TS^2)$ = 19.4

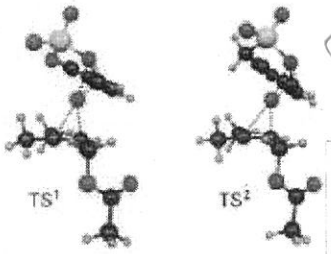
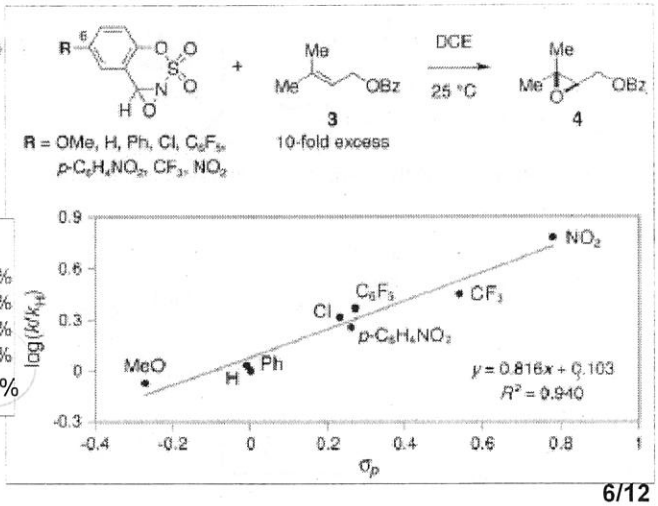
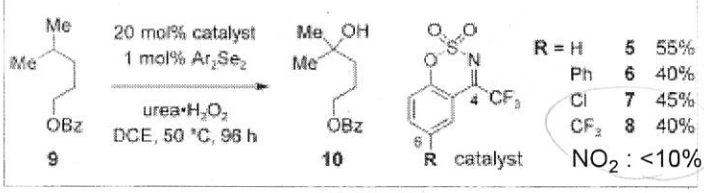


Figure 1. Calculated transition structures (B3LYP/6-31G*, CPCM (DCE)) for alkene epoxidation by oxaziridines **1** and **2**.

- EWG group at C6 would lower the activation barrier for oxidation.
- Polar solvents and/or hydrogen-bond donor additives could help to stabilize the TS structure.

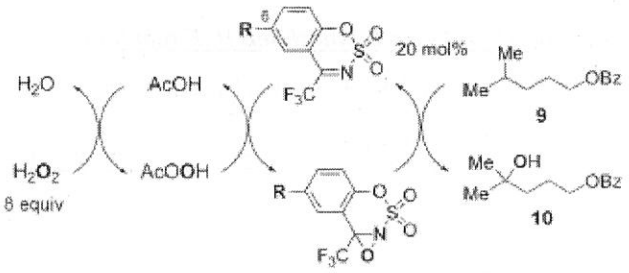




R = H	5	55%
Ph	6	40%
Cl	7	45%
CF_3	8	40%
NO_2		<10%

- No other heterocycle outperformed the parent structure **5**.

- Acetic acid is also as a co-solvent to help solubilize apolar substrates.

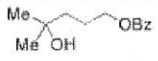
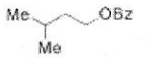
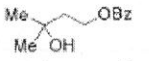
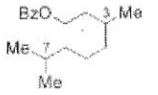
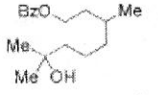
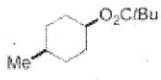
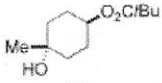
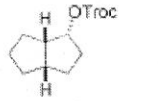
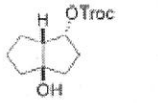
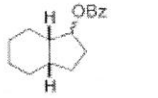
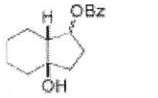
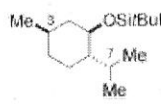
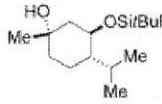
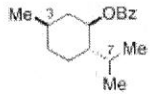
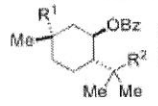
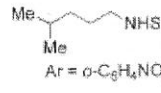
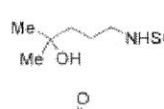
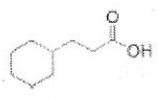
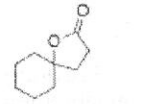


Catalyst shape is important? ←

Entry	R	Cat.	σ_p	Conversion [%][a]
1	H	5	0	40
2	Ph	6	0	50
3	Cl	7	0.23	70
4	CF_3	8	0.54	60
5	C_6F_5	11	0.27	95
6	p-$C_6H_4NO_2$	12	0.26	20

[a] Conversion determined by ^{1}H NMR integration of the unpurified reaction mixture. Reaction conditions: 20 mol% catalyst, 8 equiv 50% H_2O_2, 0.25 M 1:1 AcOH/H_2O, 50°C, 96 h.

Table 2: Substrate profile for reactions catalyzed by **11**.[a]

Entry	Substrate	Product	Yield [%][b]
1			75
2			44
3			70[c]
4			61
5			38
6			82
7			34
8		 R^1 = H, R^2 = OH; R^1 = OH, R^2 = H	47[d]
9	 Ar = o-$C_6H_4NO_2$		66
10			40[e]

[a] Troc = trichloroethoxycarbonyl; Bz = benzoyl. [b] Optimized reaction conditions: 20 mol% catalyst 11, 8 equiv 50% H_2O_2, 0.25 M 1:1 AcOH/H_2O, 50 °C, 96 h. [c] Yield of isolated product after 48 h. [d] The ratio of C3/C7 hydroxylation products is ca. 1:1. An additional 10–15% of the product resulting from benzoate migration to the C7-OH is also obtained. [e] Product volatility accounts for some diminution in yield.

- more electron-rich C-H bonds were oxidized. (Entry 3, 5, 6)

stereogenic center = retention

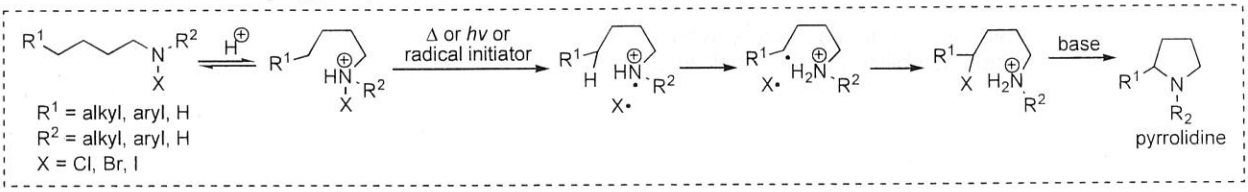
positional selectivity can be controlled by protecting groups.

The reaction conditions are tolerant to a number of common functional groups. (esters, silyl ethers, sulfonylated amines, carboxylic acids.)

• 1,3-diol synthesis by modified HLF reaction.

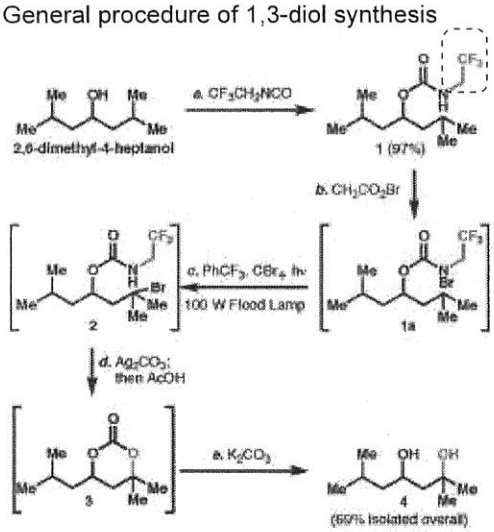
Baran, P. S. *et al. J. Am. Chem. Soc.* **2008**, *130*, 7247.

☞ Hofmann-Löffler-Freytag(HLF) reaction



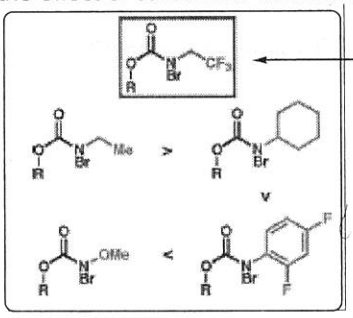
R^1 = alkyl, aryl, H
R^2 = alkyl, aryl, H
X = Cl, Br, I

General procedure of 1,3-diol synthesis



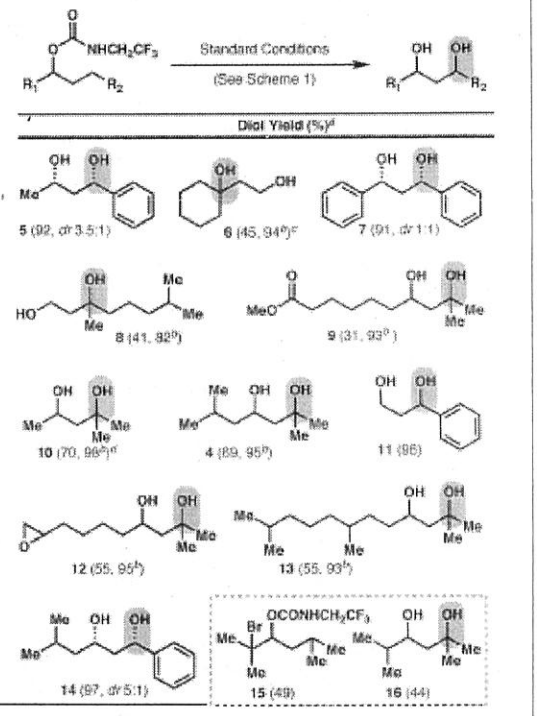
[a] Reagents and conditions: (a) CF_3CH_2NCO (1.0 equiv), DCM, Pyr (1.0 equiv), 23 °C, 2 h, 97%; (b) CH_2CO_2Br (1.0 equiv), DCM, 0 °C, 5 min; (c) $PhCF_3$ (0.05 M), CBr_4 (1.0 equiv), 23 °C, hv, 7 min; (d) Ag_2CO_3 (1.25 equiv), DCM, 23 °C, 1 h; then AcOH, 15 min; (e) K_2CO_3 (5.0 equiv), MeOH, 23 °C, 2 h, 69% overall. DCM = dichloromethane, Pyr = pyridine.

the effect of carbamate structure



the best carbamate.

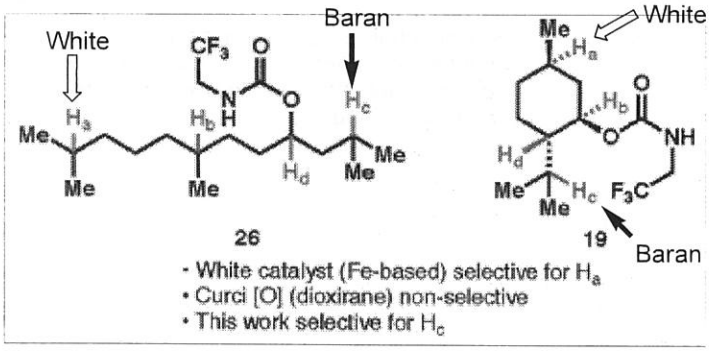
Table 1. Scope of Directed C–H Oxidation



[a] Isolated yield. [b] Yield brsm. [c] CBr_4 is not necessary. [d] A 56% isolated yield on gram scale; 88% yield brsm.

- 1,3-diols are selectively obtained. (**8**, **13**, **20**)
- esters and epoxides are tolerated. (**9**, **12**)
- tertiary center < benzylic center (**14** is the sole product)

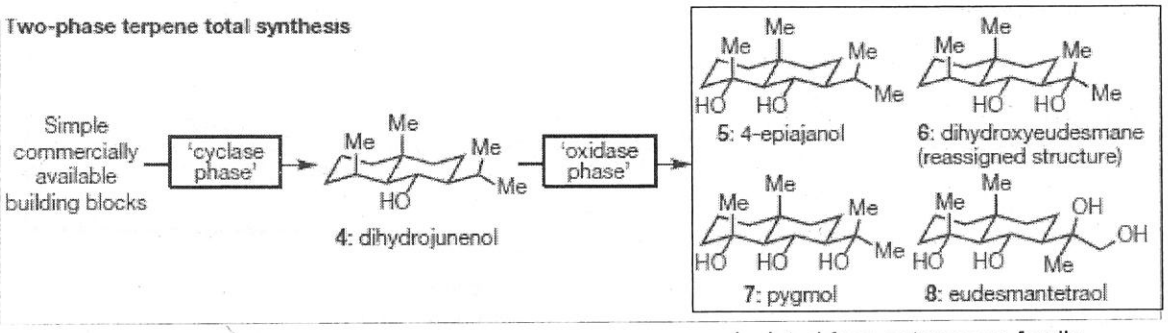
no selectivity. (**15** cannot be cyclized under these conditions)



Problematic point.
stoichiometric of Ag_2CO_3.
d.r. (including radical path)
5 steps is necessary.

3. Application to total synthesis of eudesmane terpenes

Baran, P. S. *et al. Nature*, **2009**, *459*, 824.



- Isolated from asteraceae family.
- No total synthesis have been reported.
- Wide range of biological actvities. (antifungals, anti-tumor etc.)

• Synthesis of carbon framework (Cyclase phase)

- Gellman, S. H. *et al. Org. Lett.* **2005**, *7*, 4253.

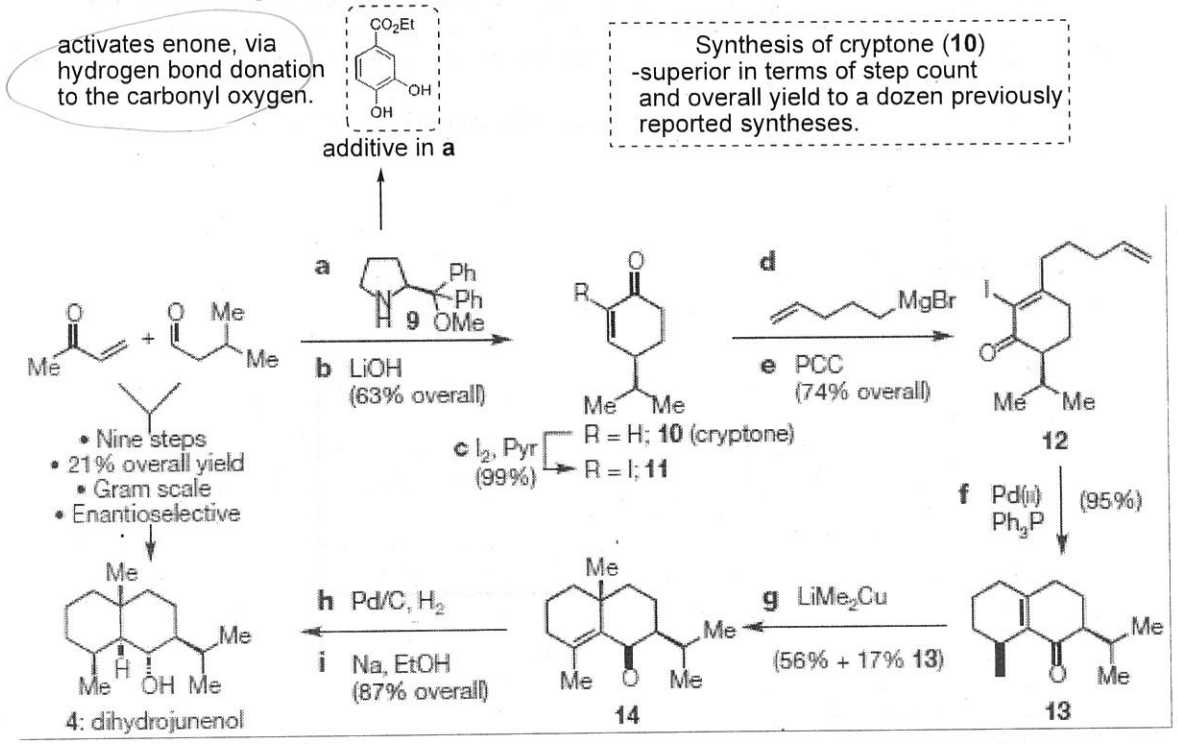
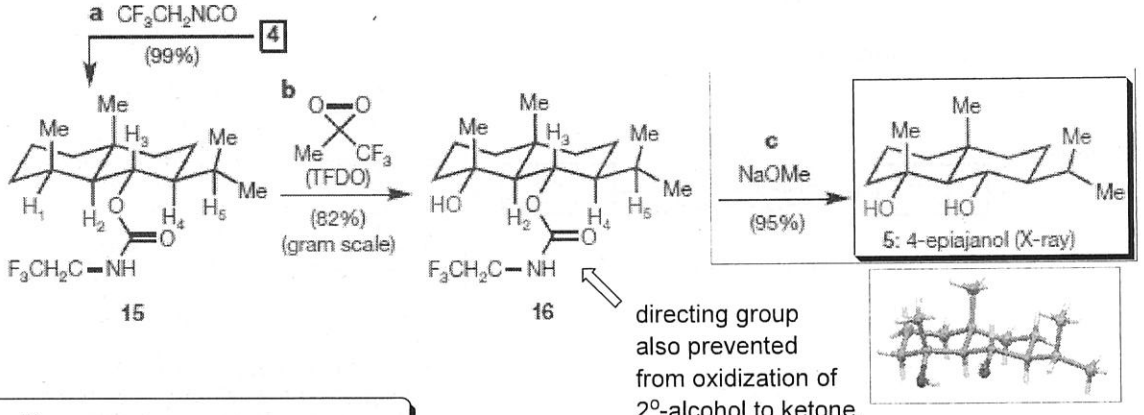
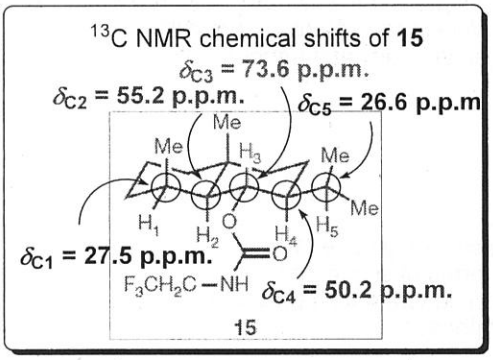


Figure 2 | Simple, enantioselective total synthesis of dihydrojunenol (4). Reagents and conditions as follows. **a**, Methyl vinyl ketone (1.5 equiv.), 3-methyl butyraldehyde (1.0 equiv.), prolinol catalyst (0.05 equiv.), ethyl 3,4-dihydroxybenzoate (0.20 equiv.), neat, 4 °C, 36 h, 89%. **b**, LiOH (0.1 equiv.), *i*-PrOH, room temperature (RT, 23 °C), 24 h, 63% over two steps, 89% enantiomeric excess. **c**, I_2 (1.2 equiv.), Pyr/DCM, RT, 12 h, 99%. **d**, $(CH_2CHCH_2CH_2CH_2)MgBr$ (1.5 equiv.), toluene, −78 °C, 30 min; then 0 °C, 30 min. **e**, PCC (1.2 equiv.), 3 Å MS, DCM, RT, 6 h, 74% over two steps. **f**, $Pd(OAc)_2$ (0.1 equiv.), Ph_3P (0.3 equiv.), Et_3N (1.2 equiv.), Ag_2CO_3 (1.0 equiv.), CH_3CN, 70 °C, 3 h, 95%. **g**, $LiMe_2Cu$ (1.5 equiv.), DCM, 0 °C, 4 h, 56% (17% recovered starting material). **h**, H_2 (1 atm), Pd/C (0.1 equiv.), EtOAc, RT, 30 min. **i**, Na (5 equiv.), EtOH, RT, 30 min, 87% over two steps. Et_3N, triethylamine; DCM, dichloromethane; I_2, iodine; Pyr, pyridine; PCC, pyridinium chlorochromate; MS, molecular sieves; Ph_3P, triphenylphosphine; CH_3CN, acetonitrile; $LiMe_2Cu$, lithium dimethylcuprate; EtOAc, ethyl acetate. For selected physical data for compounds **11**, **12**, **13**, **14** and **4**, see the Supplementary Information.

• ***Siteselective oxidation (Oxidase phase)***

Oxidation level 1 → 2





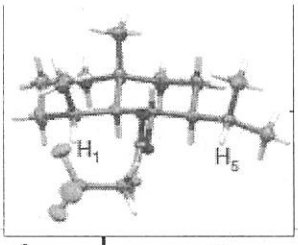
$\delta_{C3} > \delta_{C2} \approx \delta_{C4} > \delta_{C1} \approx \delta_{C5}$

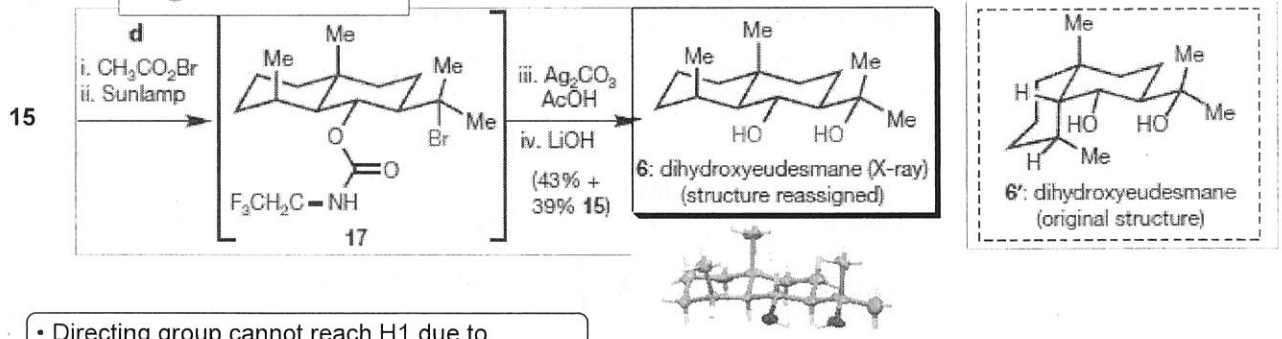
- H1 and H5 are the most likely tertiary C-H bonds to be oxidized with an electrophilic oxidant.
- TFDO selectively oxidized equatorially oriented C-H bonds in preference to those adopting an axial configuration.
  (H1 : equatorial, H5 : multiple conformation)

☞ See page **4**.

‖

selective $\mathbf{H_1}$ oxidation by TFDO





- Directing group cannot reach H1 due to its geometric constraints.

↓

sitespecific oxidation at $\mathbf{H_5}$ by modified HLF rxn.

Figure 3 | Total syntheses of 4-epiajanol (5) and dihydroxyeudesmane (6) through site-specific C–H oxidations of dihydrojunenol (4). Reagents and conditions as follows. **a**, CF_3CH_2NCO (1.0 equiv.), Pyr (4.0 equiv.), DMAP (catalytic), DCM, RT, 1 h, 99%. **b**, TFDO (1.0 equiv.), DCM, −20 °C, portion-wise addition of TFDO over 30 min, then additional 30 min, 82%. **c**, NaOMe (5.0 equiv.), MeOH, 70 °C, 2 h, 95%. **d**, CH_3CO_2Br (1.0 equiv.), DCM, 0 °C, 5 min; $PhCF_3$, 100-W sunlamp, 10 min; Ag_2CO_3 (1.2 equiv.), DCM, RT, 30 min, then aqueous acetic acid, RT, 30 min; LiOH (10 equiv.), THF/H_2O, RT, 10 min, 43% (39% recovered **15**). DMAP, 4-dimethylaminopyridine; TFDO, methyl(trifluoromethyl)dioxirane; NaOMe, sodium methoxide; THF, tetrahydrofuran. For selected physical data for compounds **5**, **6**, **15** and **16**, see the Supplementary Information. Compounds **5**, **6** and **15** were verified by X-ray crystallography.

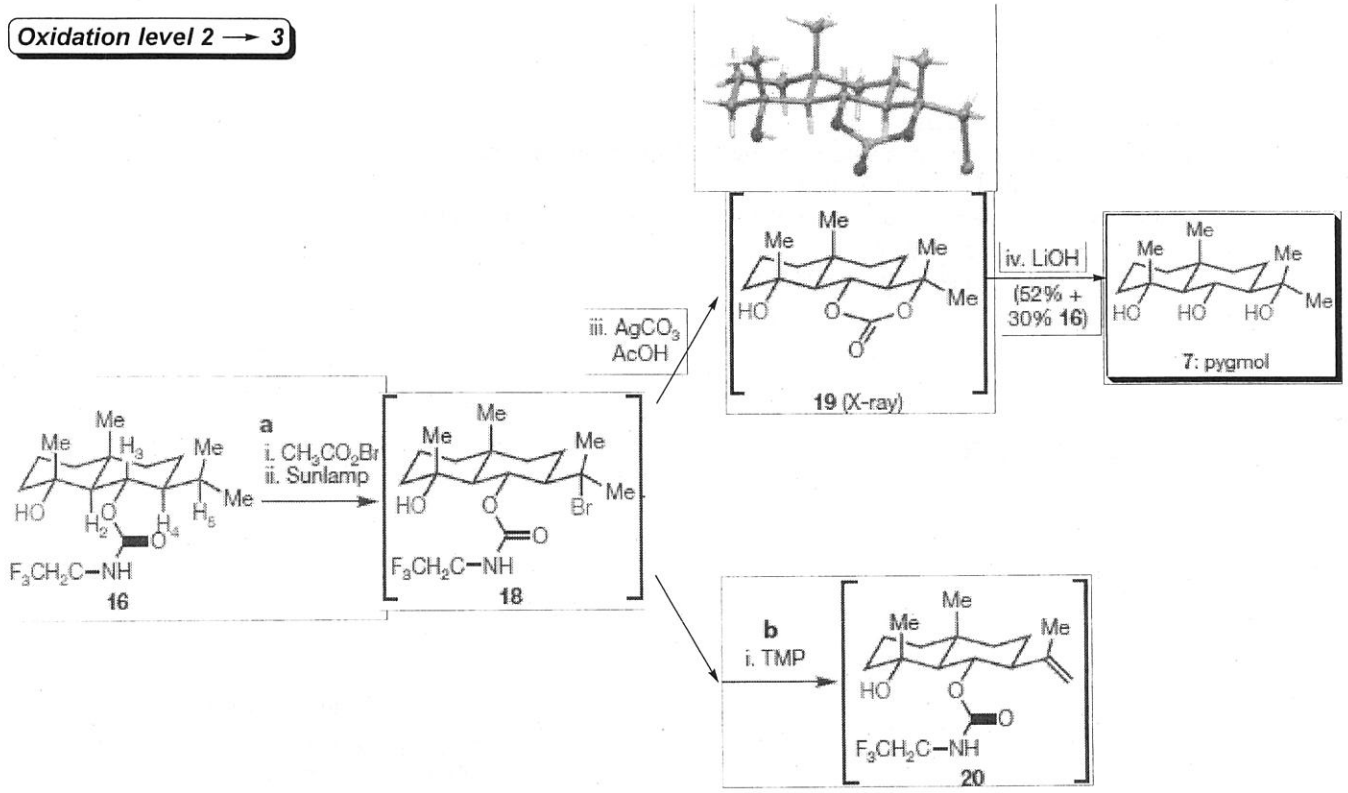
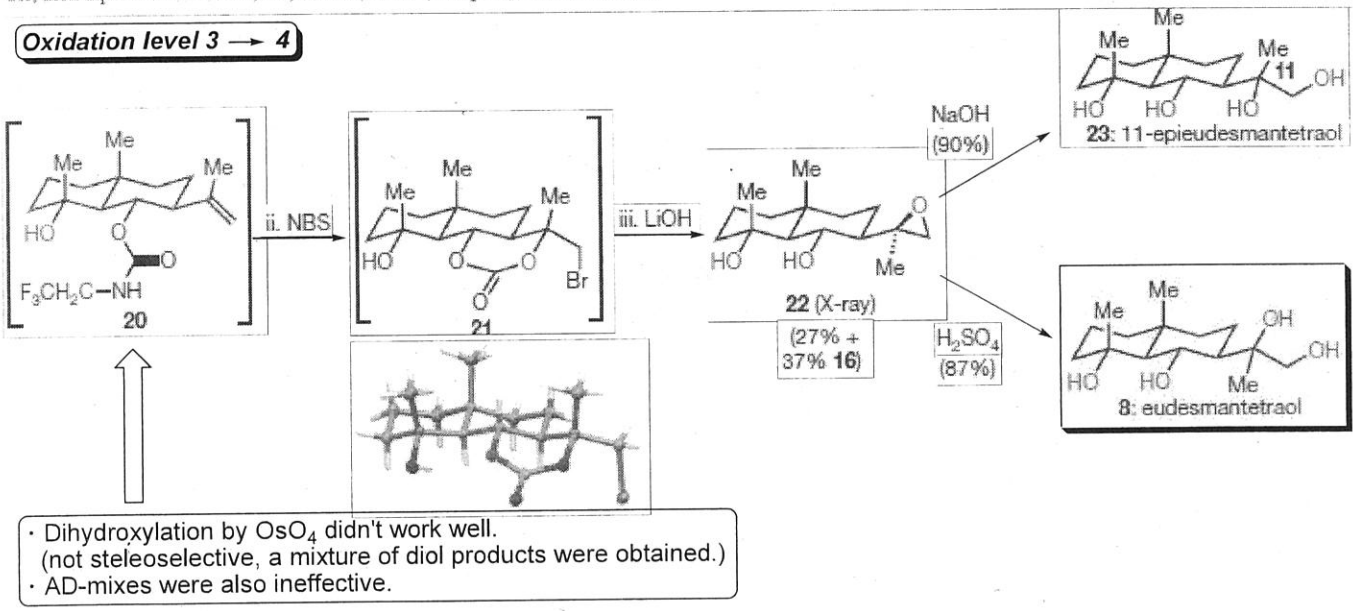


Figure 4 | Total syntheses of pygmol (7) and eudesmantetraol (8) through site-specific C–H oxidations of 16. Reagents and conditions as follows. a, CH_3CO_2Br (1.0 equiv.), DCM, 0 °C, 5 min; $PhCF_3$, 100-W sunlamp, 20 min; Ag_2CO_3 (1.2 equiv.), DCM, RT, 30 min, then aqueous acetic acid, RT, 30 min; LiOH (10 equiv.), THF/H_2O, RT, 10 min, 52% (30% recovered **16**). b, TMP (2.0 equiv.), toluene, 80 °C, 12 h; NBS (2.0 equiv.), DCM, RT, 6 h, then aqueous acetic acid, RT, 30 min; LiOH (10 equiv.), THF/H_2O, RT, 10 min, 27% (37% recovered **16**). c, 3 M NaOH, DMSO, 80 °C, 2 h, 90%. d, 0.1 M H_2SO_4, DME/H_2O, RT, 1 h, 87%. TMP, 2,2,6,6-tetramethylpiperidine; NBS, *N*-bromosuccinimide; DMSO, dimethylsulphoxide; DME, 1,2-dimethoxyethane. For selected physical data for compounds **7**, **8**, **19**, **21**, **22** and **23**, see the Supplementary Information. Compounds **19**, **21** and **22** were verified by X-ray crystallography.



- Dihydroxylation by OsO_4 didn't work well.
  (not steleoselective, a mixture of diol products were obtained.)
- AD-mixes were also ineffective.

compound	dihydrojunenol (**4**)	4-epiajanol (**5**)	dihydroxyeudesmane (**6**)	pygmol (**7**)	eudesmanetetraol (**8**)
steps	9	12	12	13	15
overall yield (%)	21	17	9	9	4

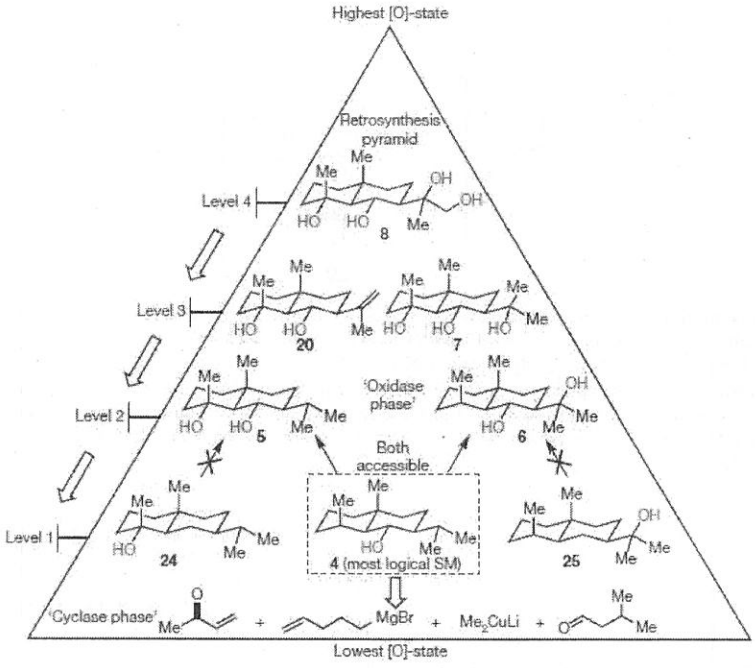
4. Summary

• Siteselective C-H oxidation

Siteselective C-H oxidation is a powerful method for organic synthesis, but there is room for further improvement.

For example : selective oxidation of 1^{o}-, 2^{o}- unactivated C-H bonds.
moderate yield.
substrate generality etc.

• Baran's total synthesis



Baran's 8 rules

- less redox reaction.
- more C-C formation
- convergency
- linear escalation of oxidation state.
- cascade reaction.
- no protecting group.
- new methodology
- biomimetic reaction