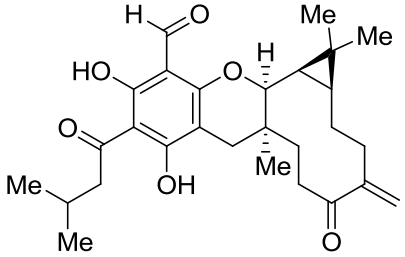
SnAZzy Synthesisers

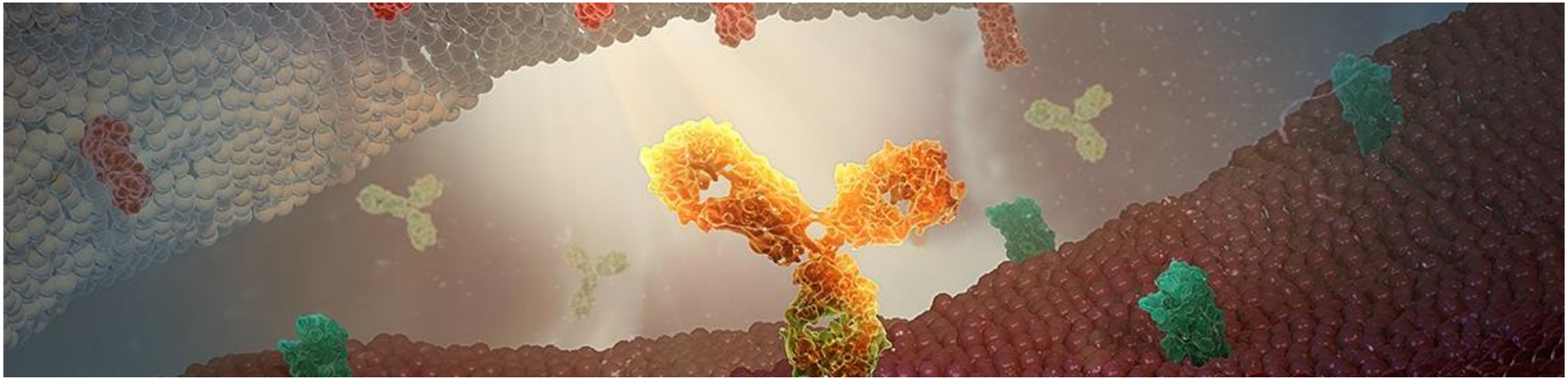
4th National Retrosynthesis Competition, 10th March 2017

AstraZeneca, IMED Oncology, Cambridge, UK

Nicolas Cheval, Charlene Fallan, Robert Foster, Lindsay McMurray, Olga Moleva, Thomas Moss, Daniel O'Donovan



Eucalrobusone D



The SnAZzy Synthesisers

‘ChAZzy Synthesiser’
Charlene Fallan

‘Capt. Lindlar’
Lindsay McMurray

‘Ms. Molymods’
Olga Moleva

‘The Photosynthesiser’
Nico Cheval

‘Cope Commander’
Robert Foster

‘D-dog’
Daniel O’ Donovan

‘Half-Marathon Man’
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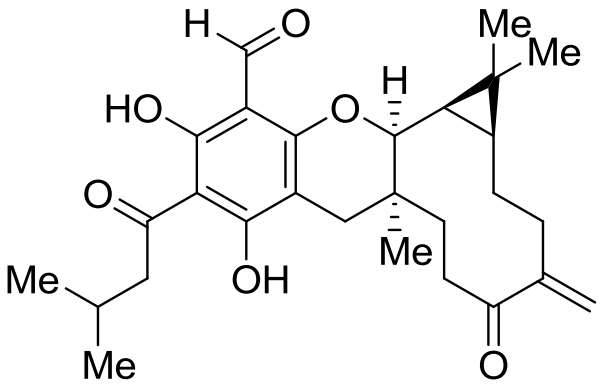
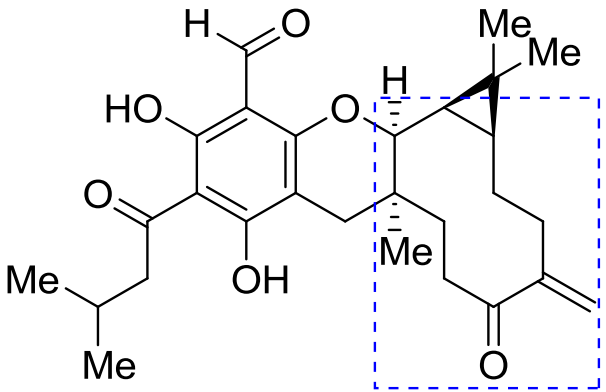
“When life gives you lemons, make limonene”

Possible routes to the synthesis of eucalrobusone D



Possible routes to the synthesis of eucalrobusone D

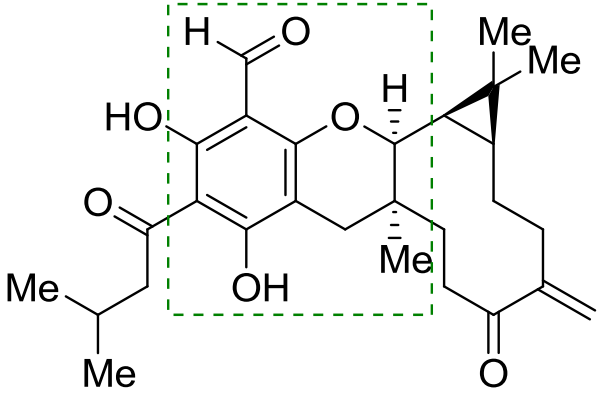


Cyclodecane

- Pd-catalysed allylation (**Baran**, *germacranes*)
- Pinacol coupling (**Nicolaou**, *taxol*)
- Ring closing metathesis (**Takao**, *clavilactone D*)
- ***Anionic oxy-Cope*** (**Still**, *germacranes*)

1. *Angew. Chem. Int. Ed.* **2012**, *51*, 11491; 2. *Nature* **1994**, *367*, 634;
3. *Chem. Eur. J.* **2017**, 10.1002/chem.201700483; 4. *J. Am. Chem. Soc.* **1977**, *99,* 4186.

Possible routes to the synthesis of eucalrobusone D



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Benzopyran

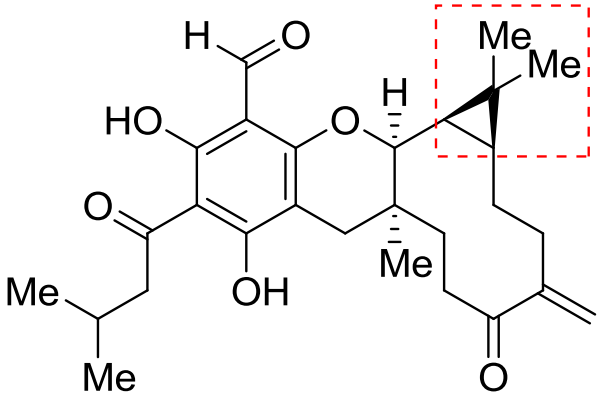
- [4+2]-Cycloaddition (**Cramer**, *psiguadial A, C, and D*)
- ***Intramolecular phenol ether synthesis*** (**Ohmori** and **Suzuki**, *rotenone*)

1. *Chem. Eur. J.* **2014**, *20,* 10654; 2. *Angew. Chem. Int. Ed*. **2017**, *56*,182.

Possible routes to the synthesis of eucalrobusone D

Gem dimethyl cyclopropyl

- Alkene cyclopropanation (**Morken**, *pumilaside aglycon*)
- ***Prepare from terpenoid*** (**Baran**, *ingenol*)



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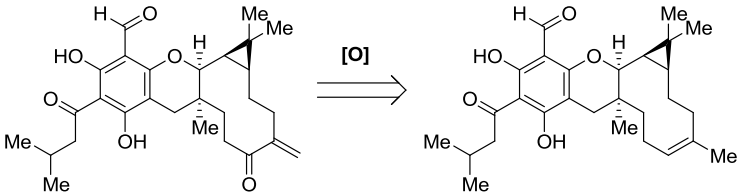
Retrosynthesis



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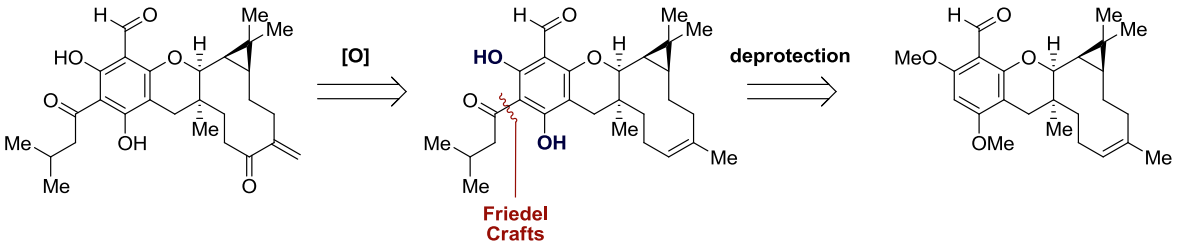
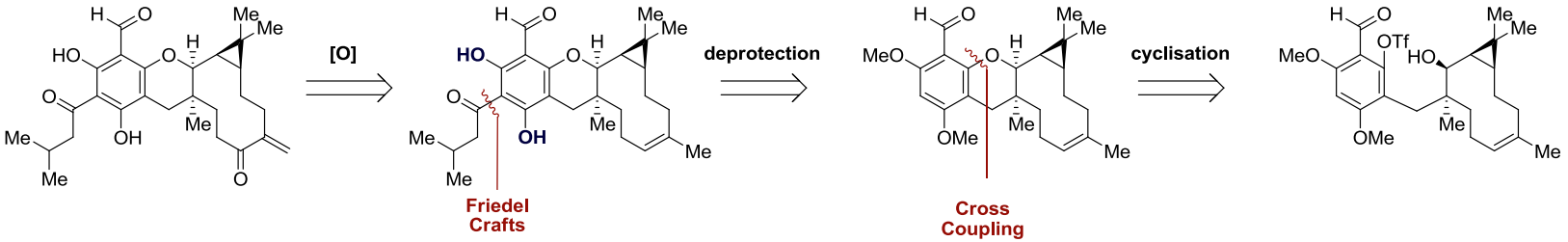


Retrosynthesis



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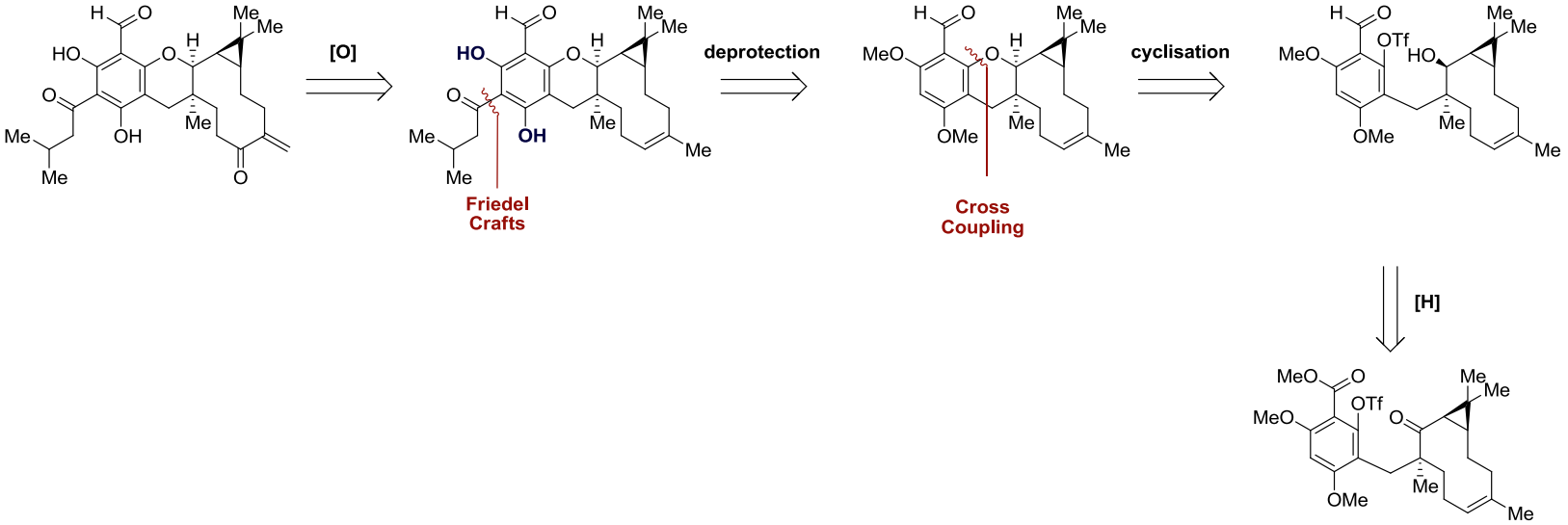

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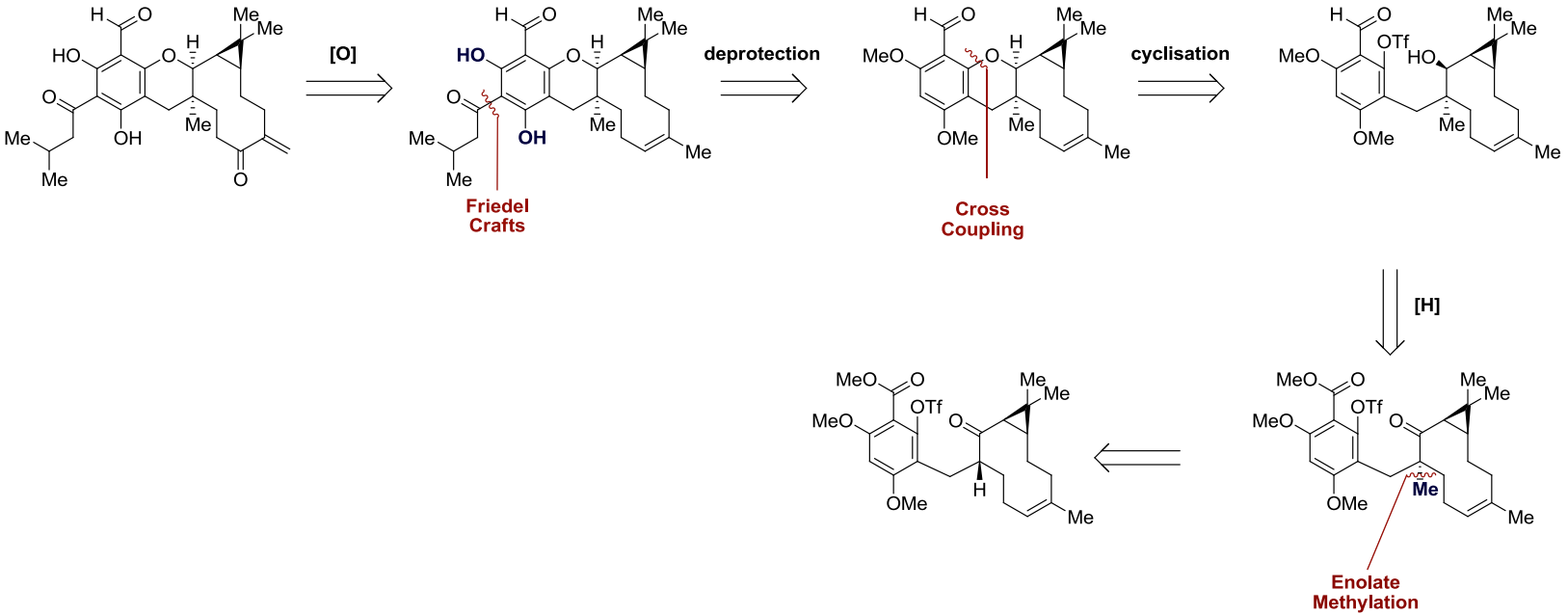
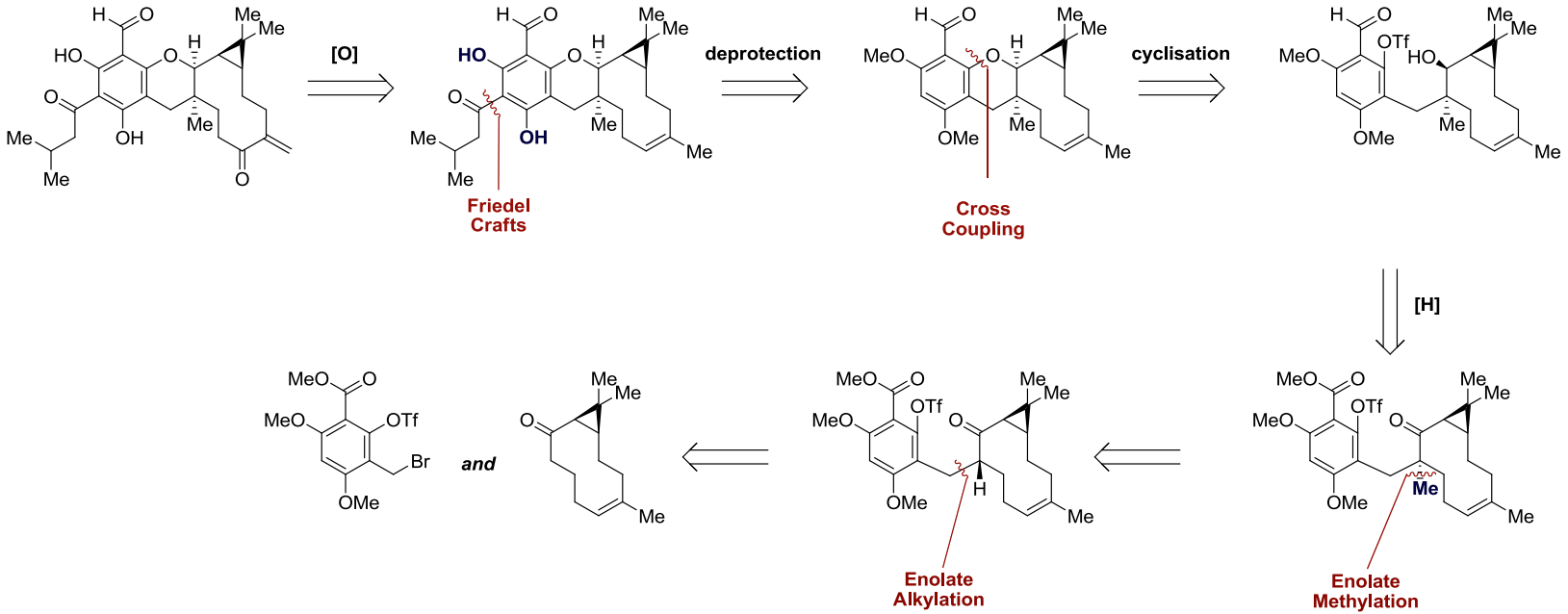


Retrosynthesis



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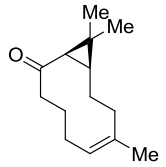

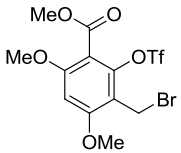

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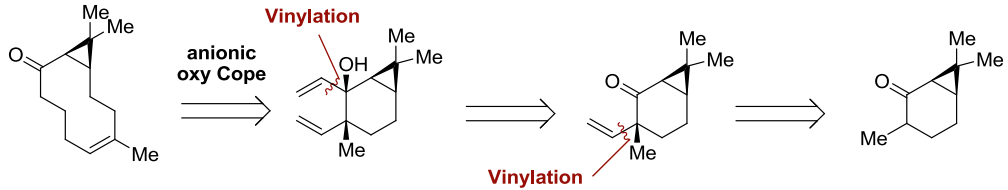

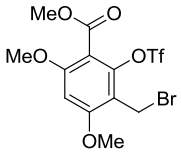

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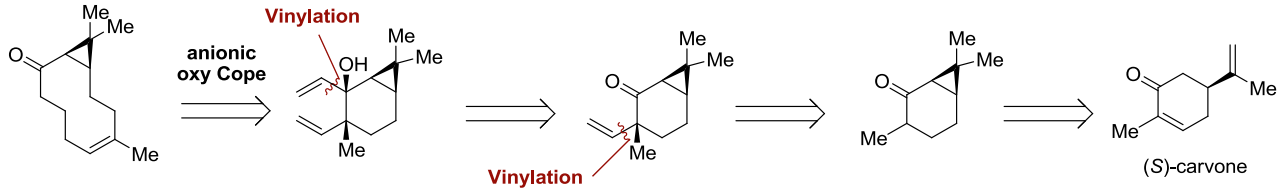

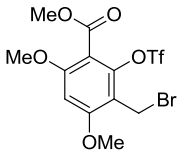

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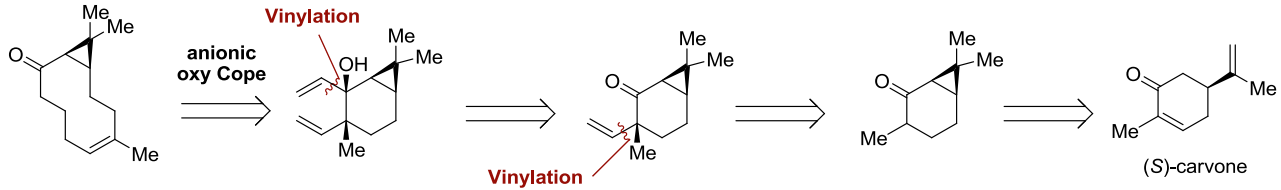

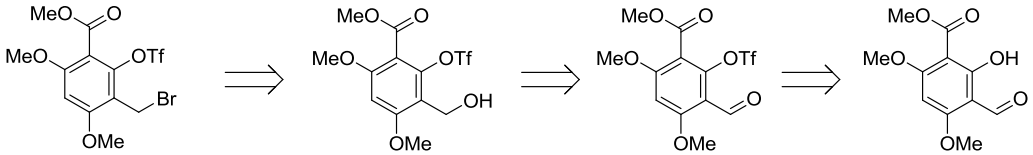

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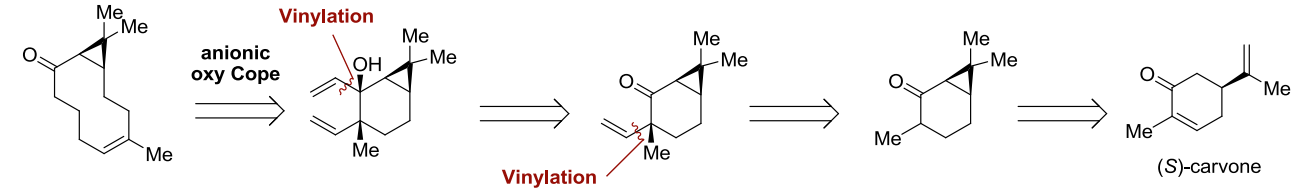
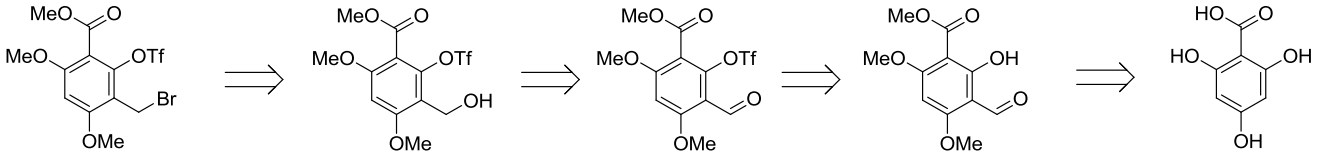
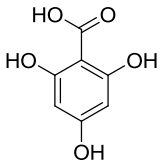




Forward synthesis

Synthesis of phenol intermediate:



£225 / 100g

1) Synthesis of phenol intermediate: *J. Org. Chem.* **2006**, *71*, 8151-8158; 2) synthesis of triflate *ortho* to aldehyde: *Bioorg. Med. Chem. Lett.* **2011**, *21*, 488-491; 3) reduction/bromination: *J. Org. Chem*. **2014**, *79*, 1529-1541.

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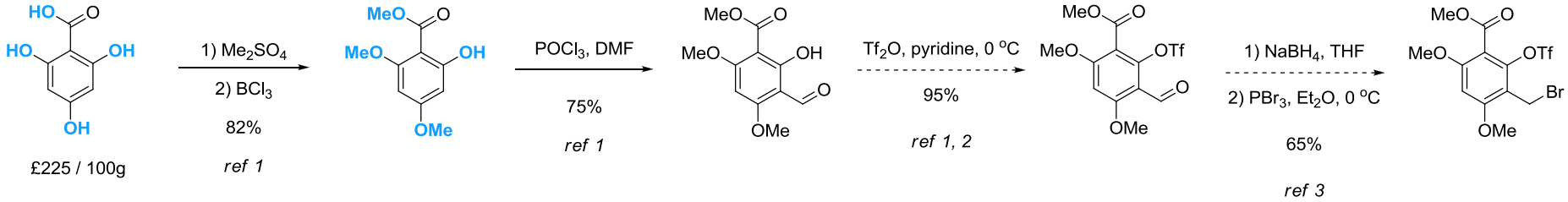

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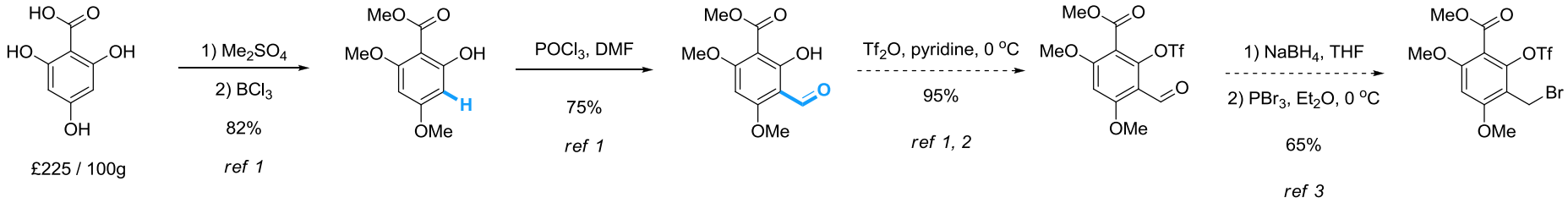

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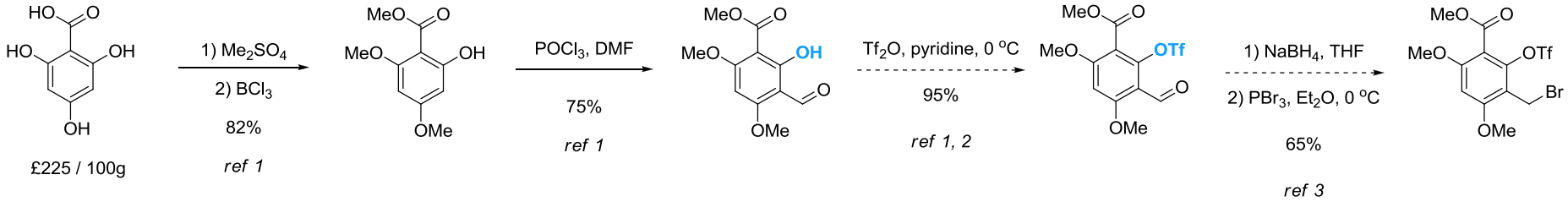

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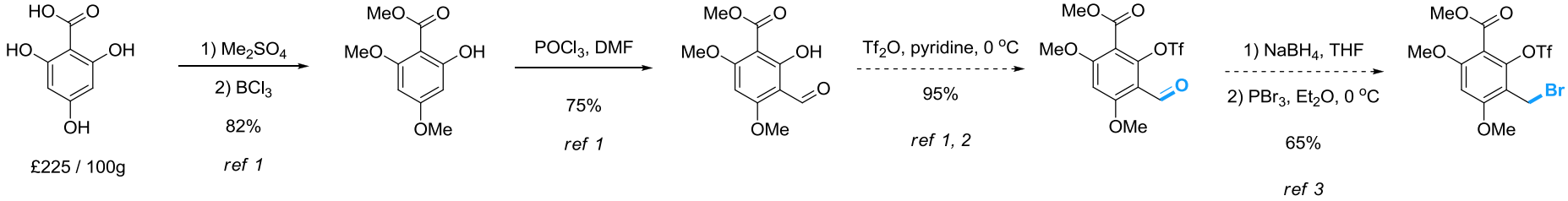

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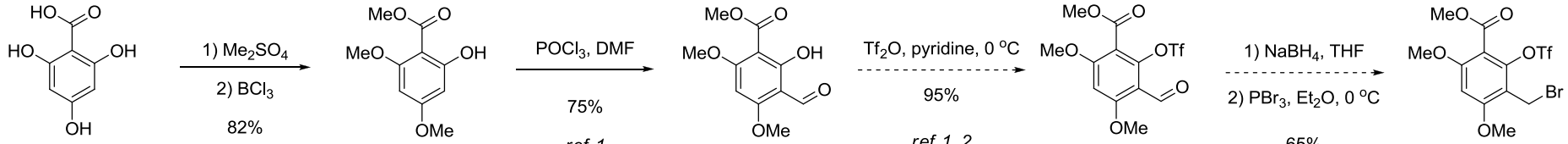

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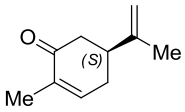
Synthesis of oxy-Cope precursor:



(*S*)-carvone
£107/kg

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Forward synthesis

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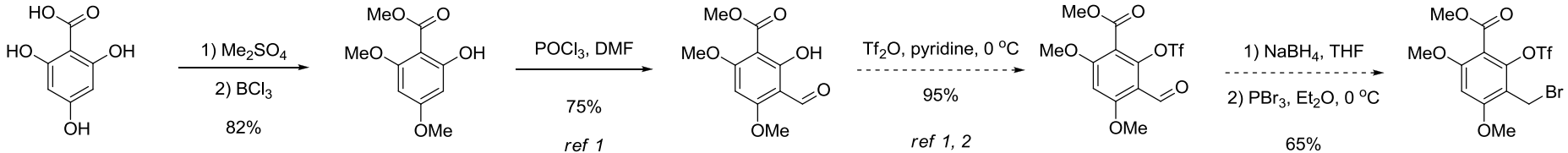

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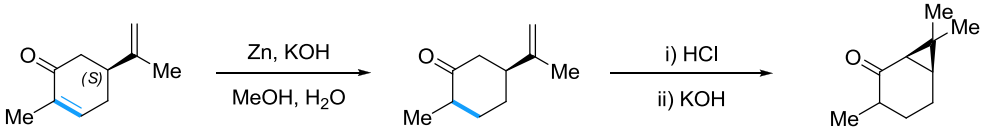

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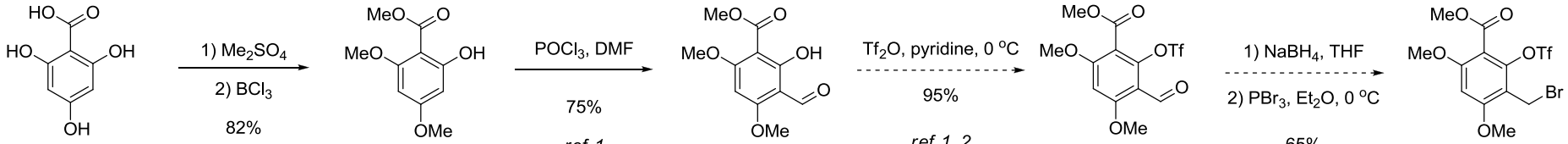

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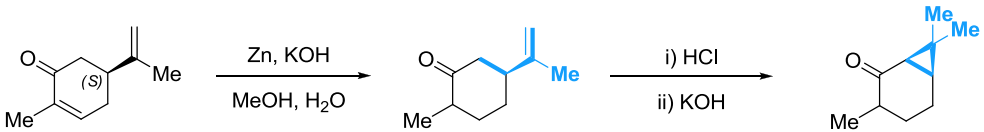

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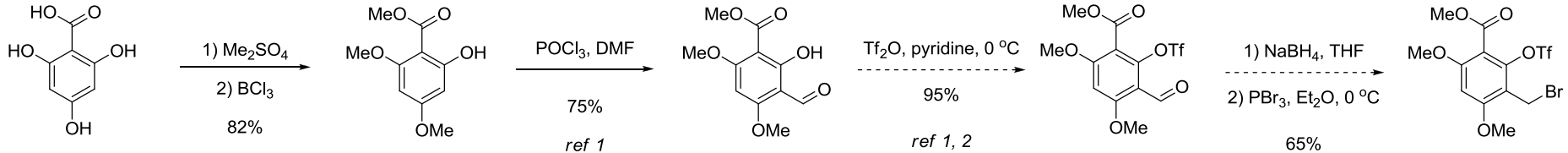

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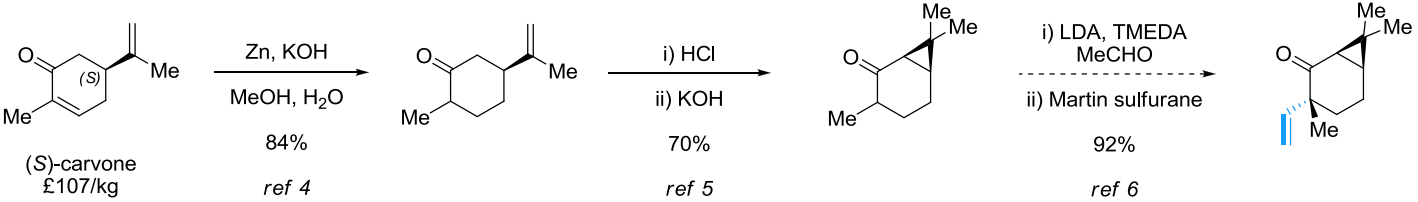

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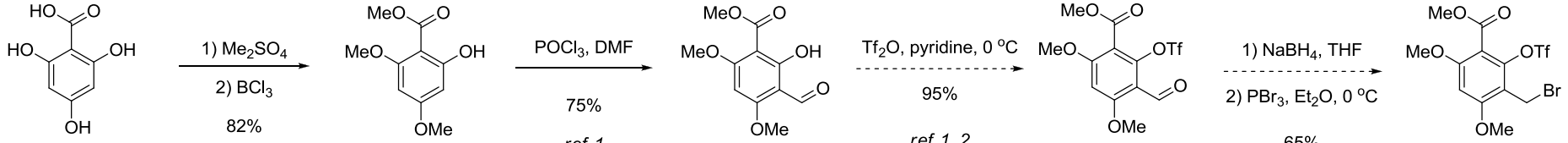
Forward synthesis

Synthesis of phenol intermediate:



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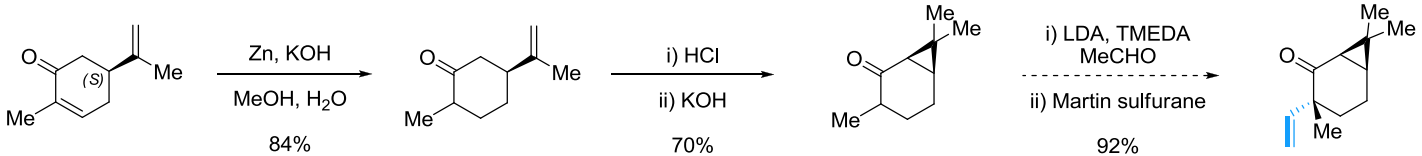

(*S*)-carvone
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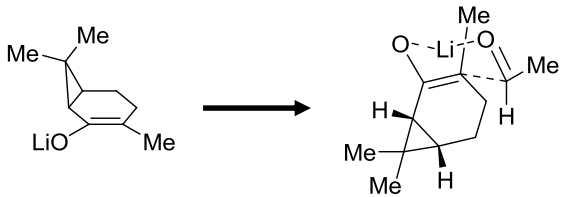
Cyclopropane blocks top face



Aldehyde adds to opposite face to cyclopropane

1) Synthesis of phenol intermediate: *J. Org. Chem.* **2006**, *71*, 8151-8158; 2) synthesis of triflate *ortho* to aldehyde: *Bioorg. Med. Chem. Lett.* **2011**, *21*, 488-491; 3) reduction/bromination: *J. Org. Chem*. **2014**, *79*, 1529-1541; 4) selective reduction of (R)-Carvone: *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103; 5) Cyclopropane formation: *Synlett*, **2001**, *9*, 1452-1454; 6) Two-step vinylation: *J. Am. Chem. Soc.*, **2005**, *127*, 14200-14201.

Forward synthesis

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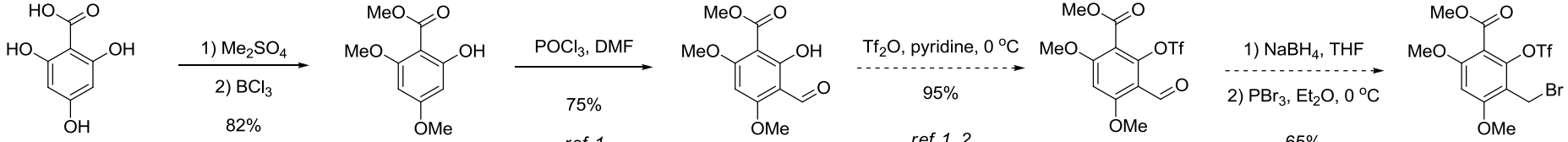

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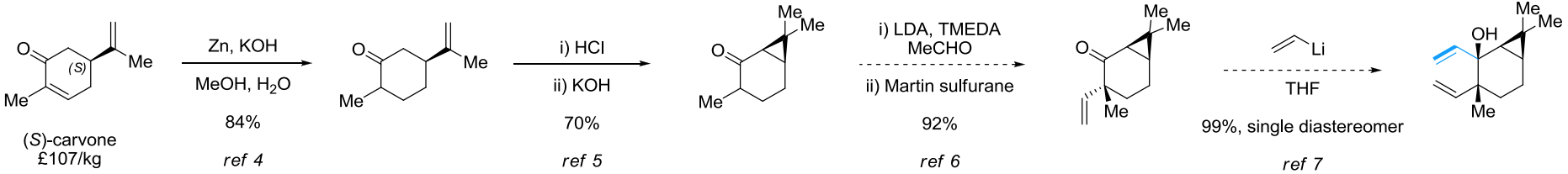

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Forward synthesis

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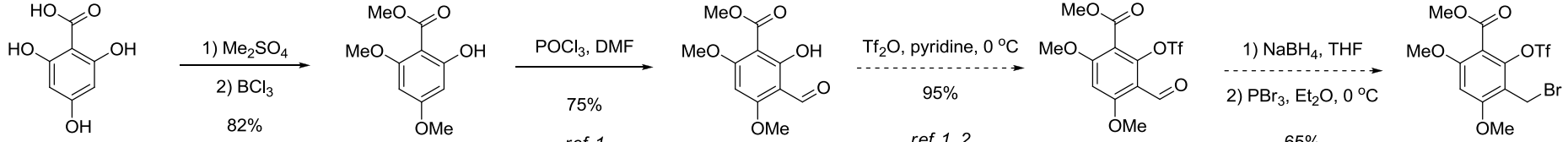
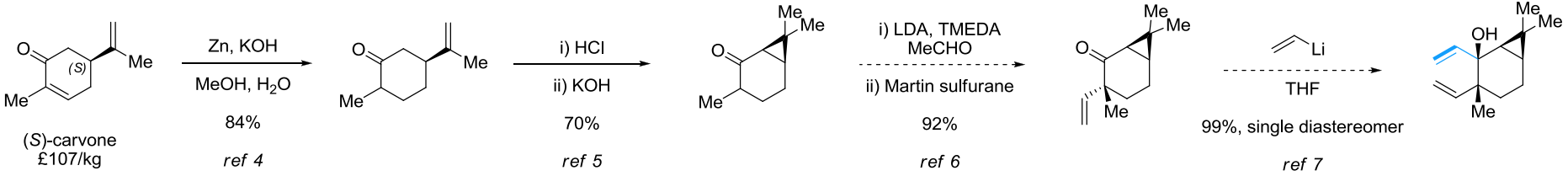


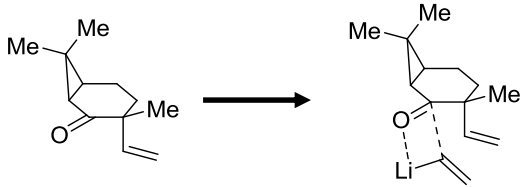
£225 / 100g

Synthesis of oxy-Cope precursor:



(*S*)-carvone
£107/kg

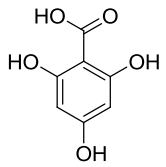
Cyclopropane blocks top face



Vinyl lithium attacks from opposite face to cyclopropane

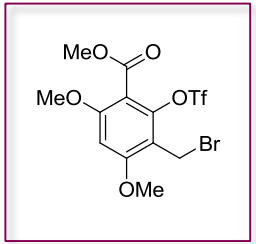
1) Synthesis of phenol intermediate: *J. Org. Chem.* **2006**, *71*, 8151-8158; 2) synthesis of triflate *ortho* to aldehyde: *Bioorg. Med. Chem. Lett.* **2011**, *21*, 488-491; 3) reduction/bromination: *J. Org. Chem*. **2014**, *79*, 1529-1541; 4) selective reduction of (*R*)-carvone: *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103; 5) Cyclopropane formation: *Synlett*, **2001**, *9*, 1452-1454; 6) Two-step vinylation: *J. Am. Chem. Soc.*, **2005**, *127*, 14200-14201; 7) vinyl lithium addition: *Tetrahedron*, **2016**, 72, 6634-6639.

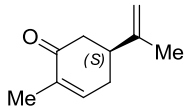
Forward synthesis



£225 / 100g

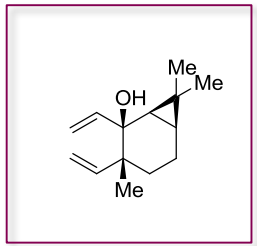
6 steps, 54% overall yield





(*S*)-carvone
£107/kg

4 steps, 54% overall yield



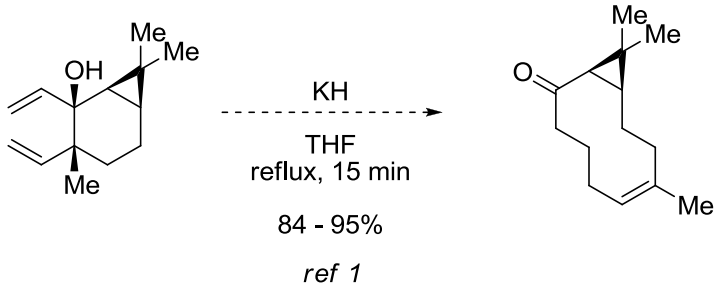
✓ Robust literature precedent for both fragments

✓ Stereoselective synthesis, controlled by readily available (*S*)-carvone

✓ Amenable to large scale syntheses

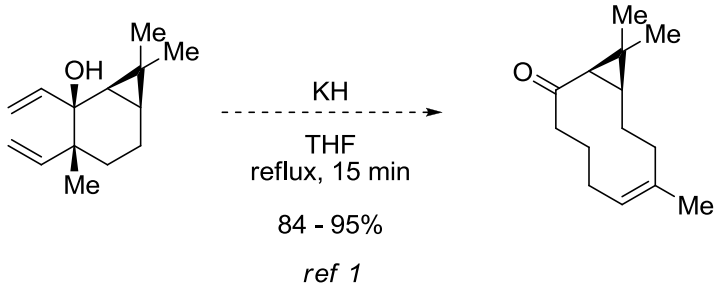
1) Synthesis of phenol intermediate: *J. Org. Chem.* **2006**, *71*, 8151-8158; 2) synthesis of triflate *ortho* to aldehyde: *Bioorg. Med. Chem. Lett.* **2011**, *21*, 488-491; 3) reduction/bromination: *J. Org. Chem*. **2014**, *79*, 1529-1541; 4) selective reduction of (*R*)-carvone: *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103; 5) Cyclopropane formation: *Synlett*, **2001**, *9*, 1452-1454; 6) Two-step vinylation: *J. Am. Chem. Soc.*, **2005**, *127*, 14200-14201; 7) vinyl lithium addition: *Tetrahedron*, **2016**, 72, 6634-6639.

Forward synthesis – anionic oxy-Cope

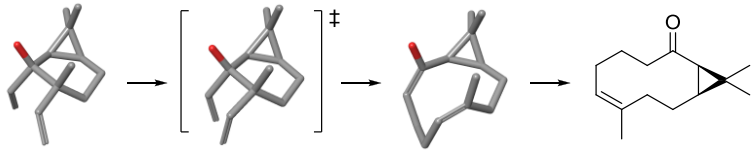


1) Oxy-Cope: *J. Org. Chem.* **1982**, *47*, 1632-1641

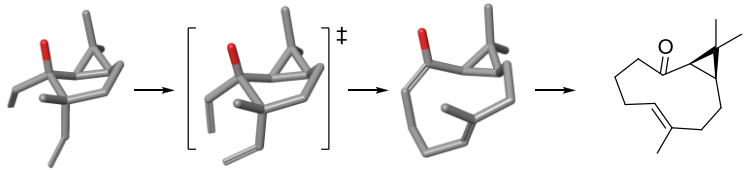
Forward synthesis – anionic oxy-Cope



PM3 Calculations:

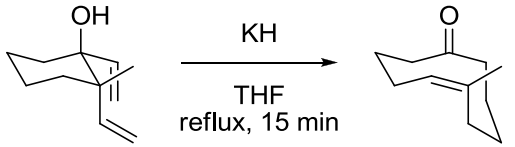


ΔE_{TS} = 21.7 kcal/mol



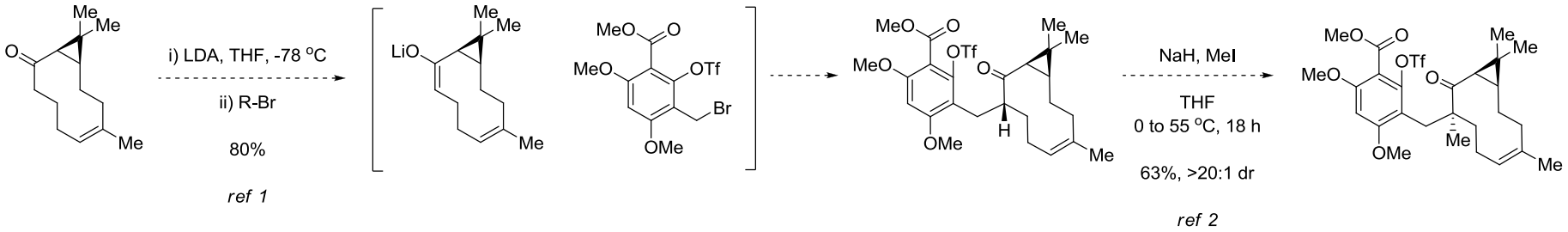
ΔE_{TS} = 31.6 kcal/mol

Anionic Oxy-Cope Stereoselectivity:



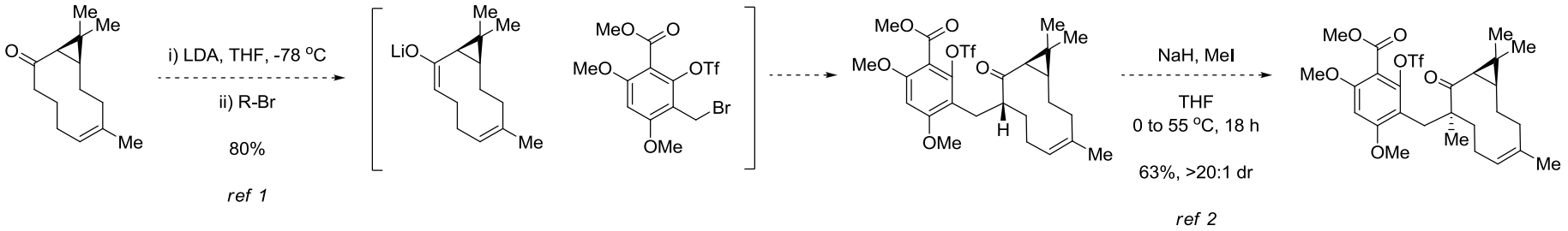
1) Oxy-Cope: *J. Org. Chem.* **1982**, *47*, 1632-1641

Forward synthesis - alkylation

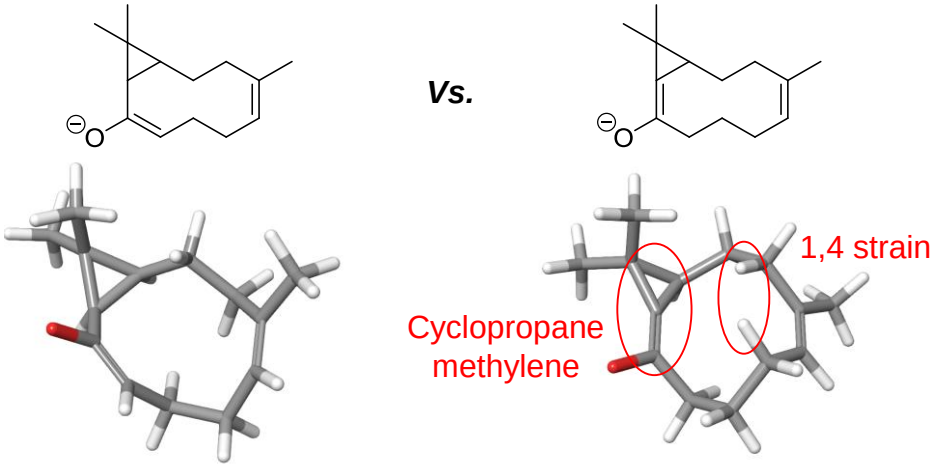


1) Regio/diastereoselectivity of alkylation: (a) *Tetrahedron*, **1998**, *54*, 2669-2682; (b) *J. Org. Chem.* **1999**, *64*, 7412-7418; precedent for selectivity over ester: *J. Org. Chem.* **2003**, 68, 5909–5916

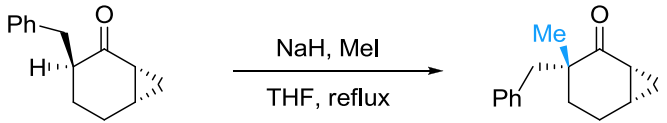
Forward synthesis - alkylation



Models for stereo/regioselectivity:

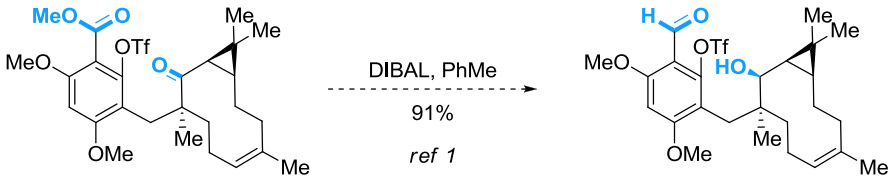


Example: *α'-alkylation of enolates (ref. 1b)*



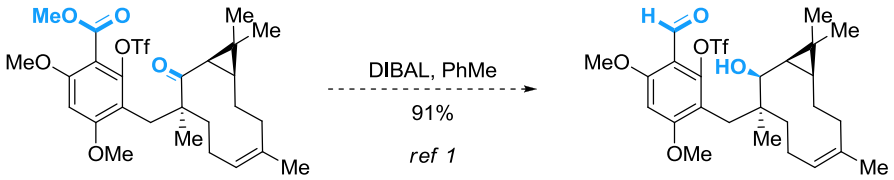
1) Regio/diastereoselectivity of alkylation: (a) *Tetrahedron*, **1998**, *54*, 2669-2682; (b) *J. Org. Chem.* **1999**, *64*, 7412-7418; precedent for selectivity over ester: *J. Org. Chem.* **2003**, 68, 5909–5916

Forward synthesis

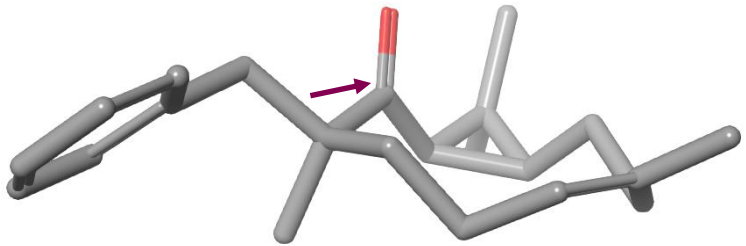


1) DIBAL ketone reduction: a) *Angew. Chem. Int. Ed.* **2011**, *50*, 6814–6818; b) *Angew. Chem. Int. Ed.* **2014**, *53*, 10970–10974; c) Ketone reduction controlled by cyclopropyl group:*Tetrahedron*, **2006**, *62*, 3266–3283.

Forward synthesis



Ketone Reduction Stereoselectivity

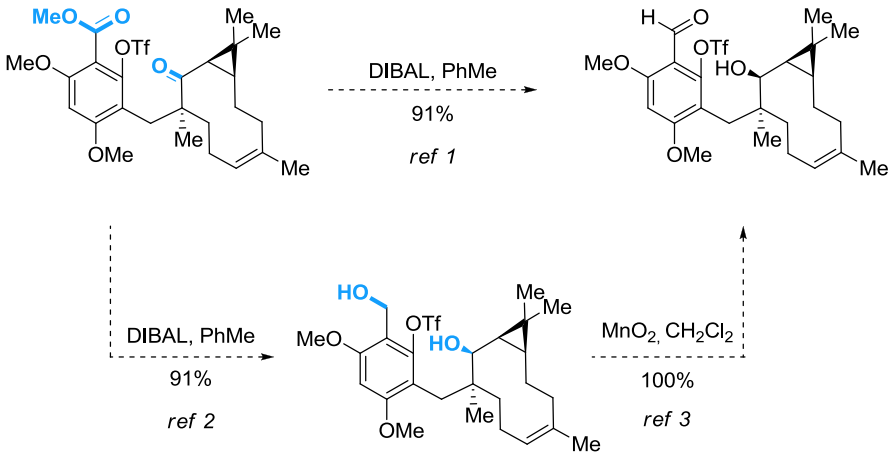


One face of the ketone is blocked by the cyclodecene

(Simplified benzyl group shown for clarity)

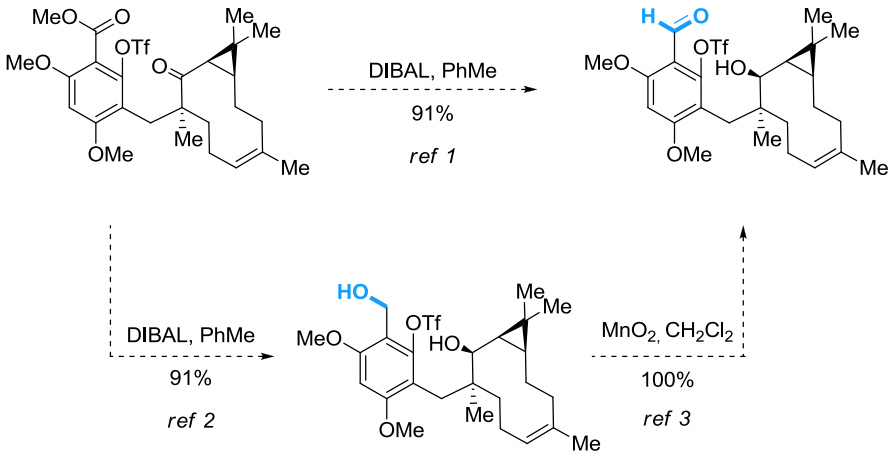
1) DIBAL ketone reduction: a) *Angew. Chem. Int. Ed.* **2011**, *50*, 6814–6818; b) *Angew. Chem. Int. Ed.* **2014**, *53*, 10970–10974; c) Ketone reduction controlled by cyclopropyl group: *Tetrahedron*, **2006**, *62*, 3266–3283.

Forward synthesis



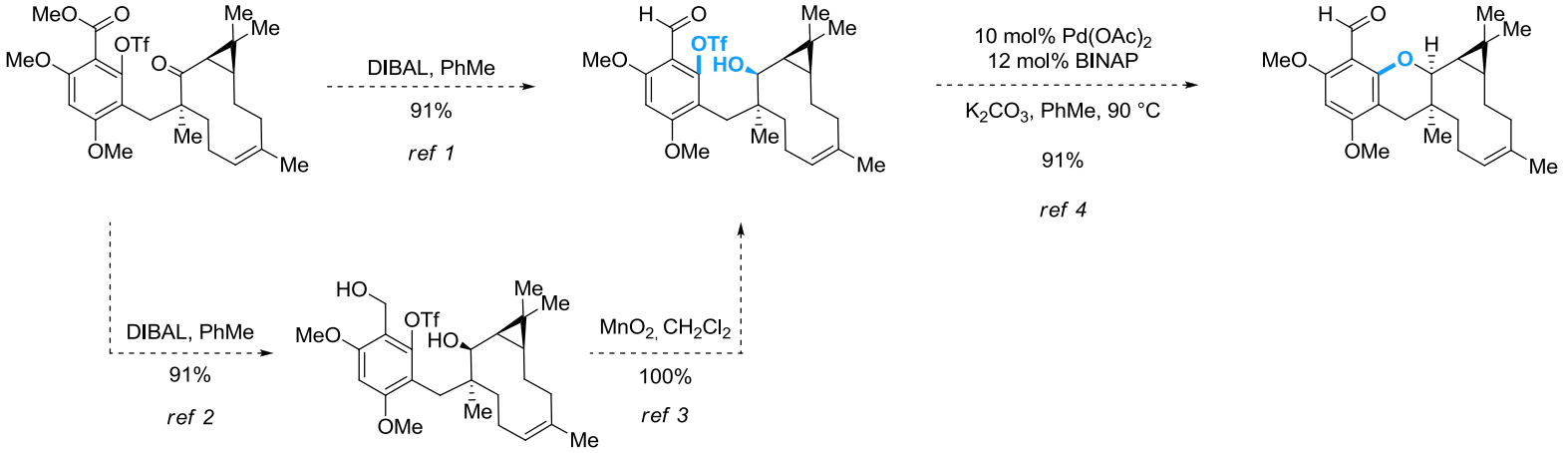
1) DIBAL ketone reduction: a) *Angew. Chem. Int. Ed.* **2011**, *50*, 6814–6818; b) *Angew. Chem. Int. Ed.* **2014**, *53*, 10970–10974; c) Ketone reduction controlled by cyclopropyl group: *Tetrahedron*, **2006**, *62*, 3266–3283. 2) DIBAL ester reduction: *J. Org. Chem.* **1988**, *53*, 3673–3680; 3) Oxidation: *Org. Lett.* **2004**, *6*, 3909–3912.

Forward synthesis



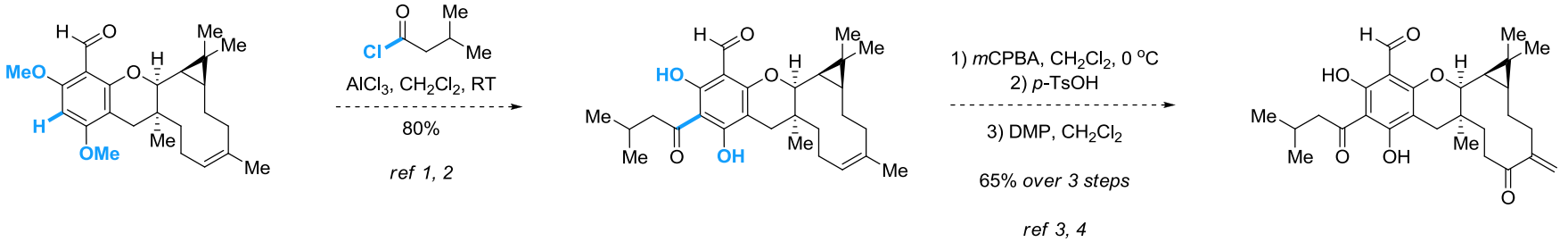
1) DIBAL ketone reduction: a) *Angew. Chem. Int. Ed.* **2011**, *50*, 6814–6818; b) *Angew. Chem. Int. Ed.* **2014**, *53*, 10970–10974; c) Ketone reduction controlled by cyclopropyl group: *Tetrahedron*, **2006**, *62*, 3266–3283. 2) DIBAL ester reduction: *J. Org. Chem.* **1988**, *53*, 3673–3680; 3) Oxidation: *Org. Lett.* **2004**, *6*, 3909–3912.

Forward synthesis



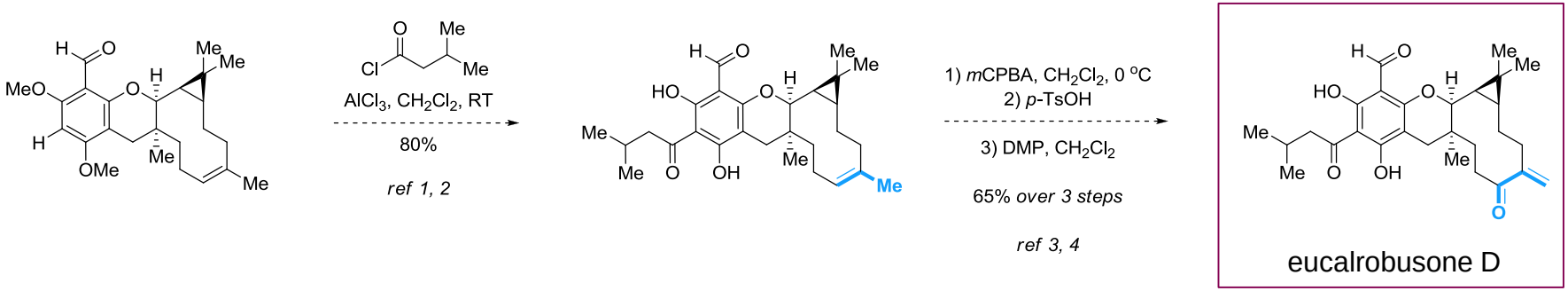
1) DIBAL ketone reduction: a) *Angew. Chem. Int. Ed.* **2011**, *50*, 6814–6818; b) *Angew. Chem. Int. Ed.* **2014**, *53*, 10970–10974; c) Ketone reduction controlled by cyclopropyl group: *Tetrahedron*, **2006**, *62*, 3266–3283. 2) DIBAL ester reduction: *J. Org. Chem.* **1988**, *53*, 3673–3680; 3) Oxidation: *Org. Lett.* **2004**, *6*, 3909–3912. 4) Cross-coupling: *Tetrahedron* **2003**, *59*, 6889–6897

Forward synthesis – end-game



1) Methyl deprotection with $AlCl_3$: *J. Org. Chem.* **2005**, *70*, 4585–4590; 2) Friedel Crafts in presence of phenol and aldehyde: *Eur. J. Org. Chem,* **1999**, *5*, 1011–1031;

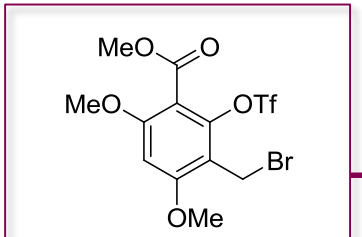
Forward synthesis – end-game



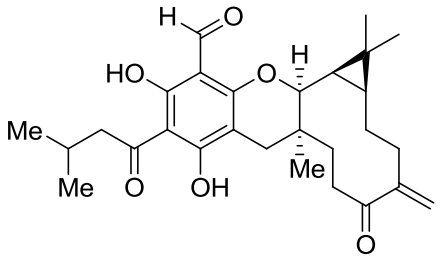
15 longest linear steps
12% overall yield

1) Methyl deprotection with $AlCl_3$: *J. Org. Chem.* **2005**, *70*, 4585–4590; 2) Friedel Crafts in presence of phenol and aldehyde: *Eur. J. Org. Chem*, **1999**, *5*, 1011–1031; 3) End-game: *Org. Lett.* **2014**, *16*, 4300-4303; 4) Use of pTsOH in epoxide ring-opening: *Tetrahedron*, **2015**, *71*, 2035-2045.

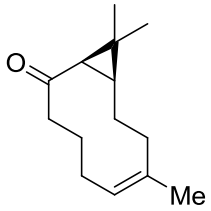
Summary



6 steps
54% overall yield



15 longest linear steps
12% overall yield

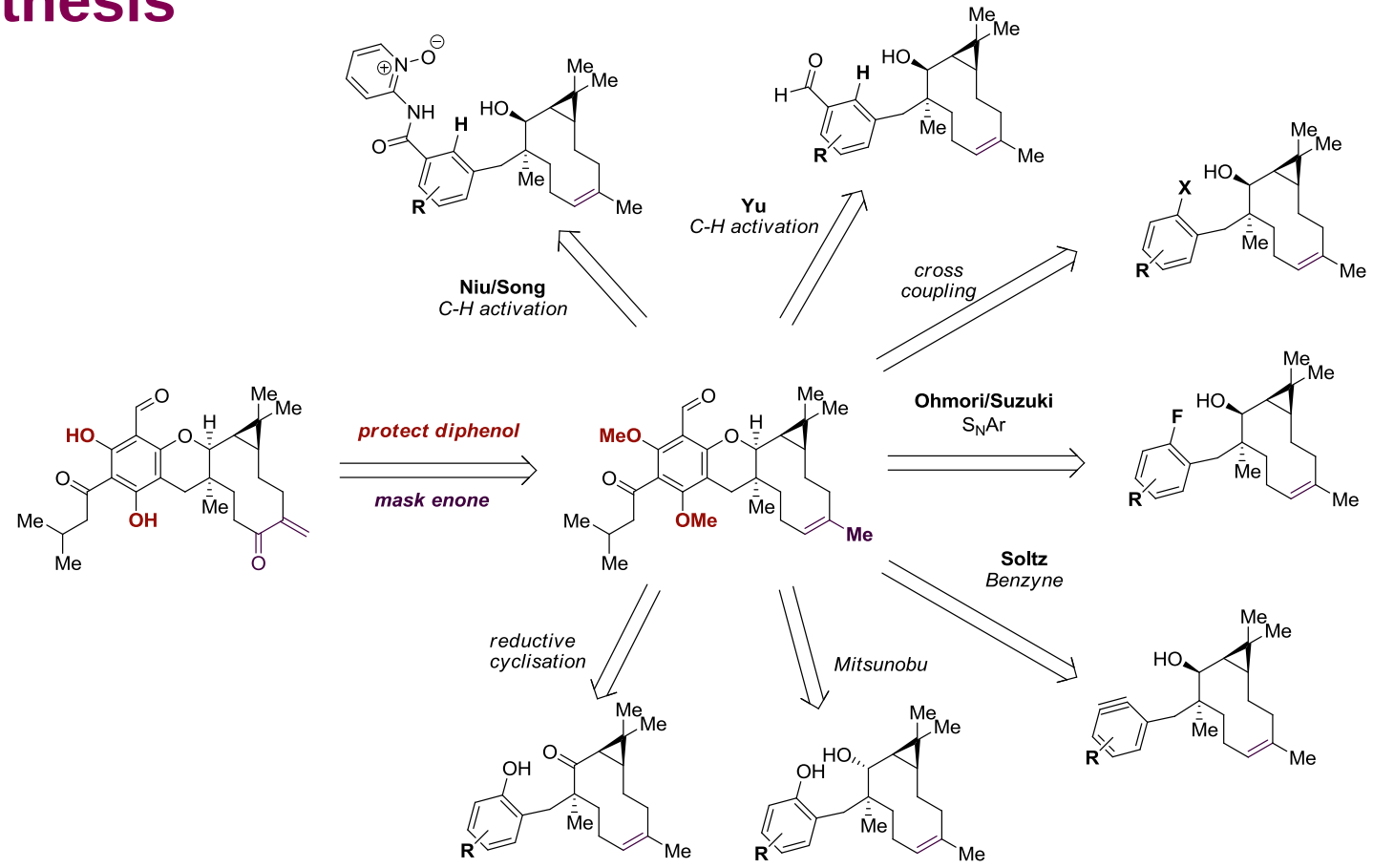


5 steps
50% overall yield

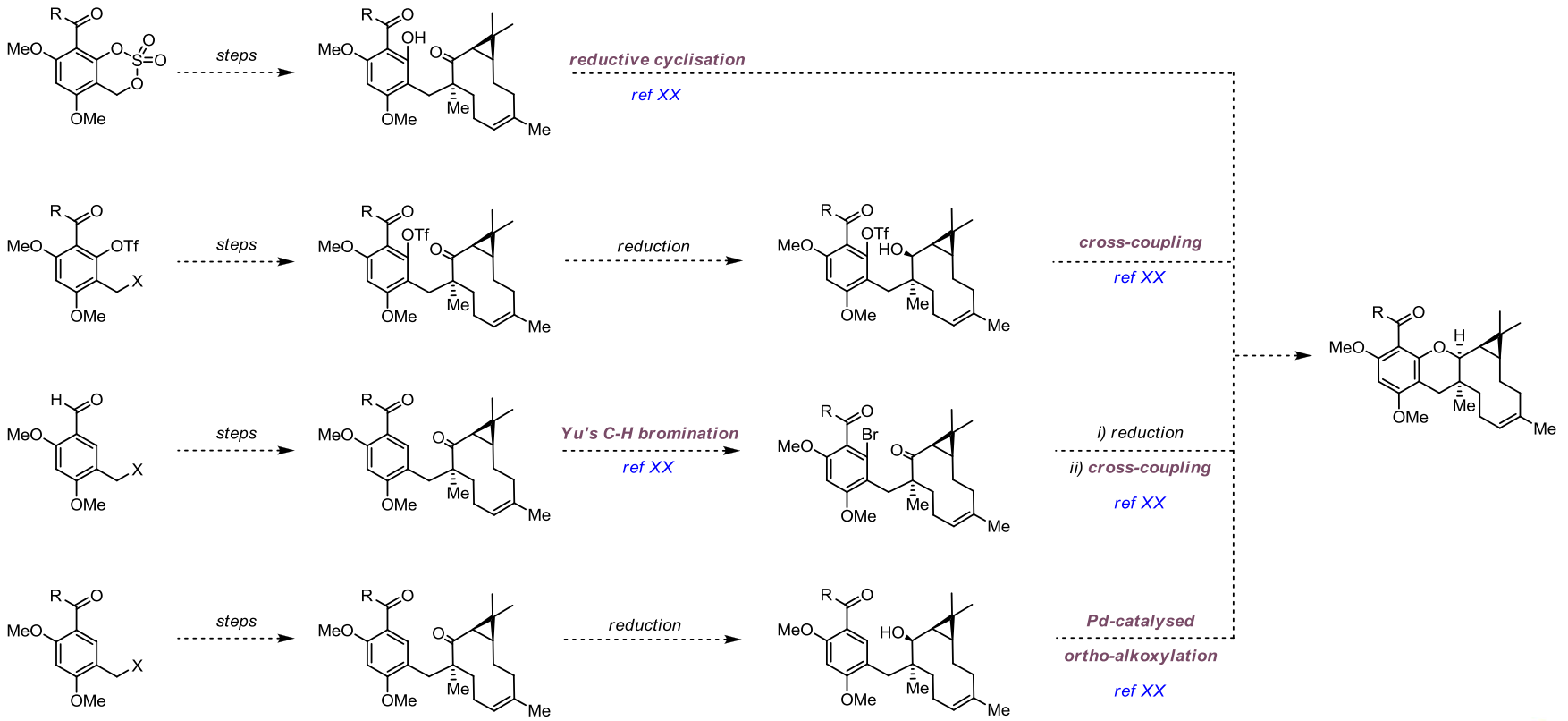
- Highly convergent synthesis of eucalrobusone D
- Key steps include anionic oxy-Cope rearrangement, alkylation, metal-catalysed cyclisation
- Stereochemistry controlled by cyclopropane, installed from readily available, enantiopure *S*-carvone

Back-up slides

Retrosynthesis

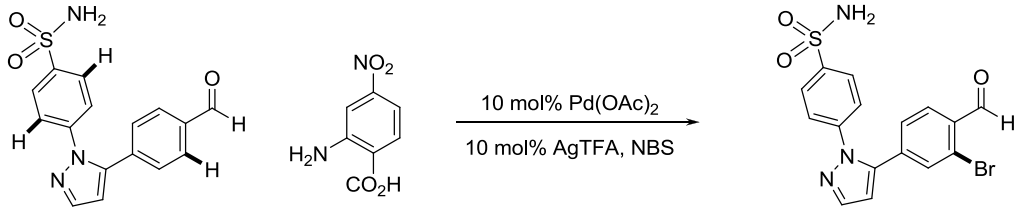


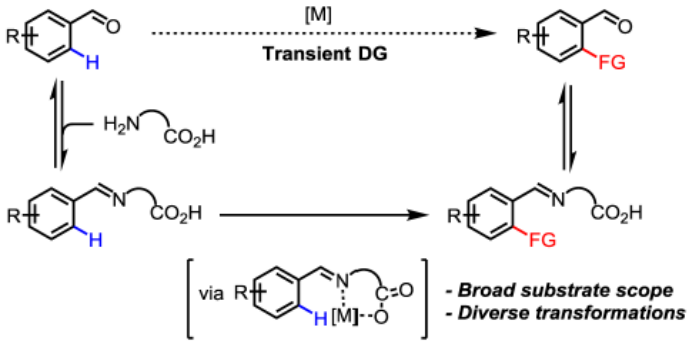
Ideas for cyclisation



1) reductive-cyclisation: Tetrahedron, **2015**, 71, 8187-8193, Chem. Eur. J. **2010**, *16*, 7586-7595 ; 2) cross-coupling with aryl triflates: *Tetrahedron* **2003**, *59*, 6889–6897; 3) Yu's directed-bromination: J. Am. Chem. Soc. **2017**, *139*, 888-896; 4) cross-coupling with aryl bromides: J. Am. Chem. Soc. **2000**, *122*, 12907-12908; 5) Pd-catalysed *ortho*-alkoxylation: Org. Lett. **2013**, *15*, 5842-5845; Chem. Eur. J. **2014**, *20*, 7507-7513; Angew. Chem. Int. Ed. **2015**, *54*, 272-275; J. Org. Chem. **2017**, *82*, 126-134

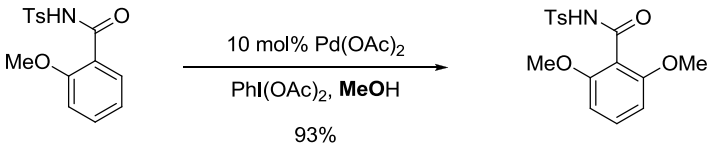
Yu's directed bromination





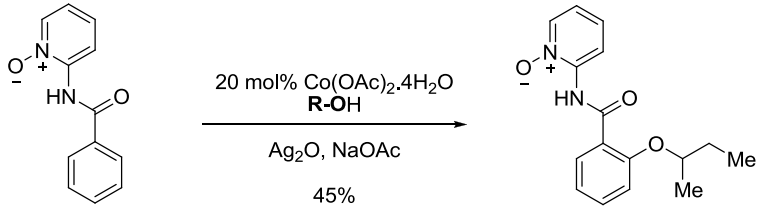
Ortho-directed C-H activation

Pd-catalysed *ortho*-alkoxylation of tosyl benzamides



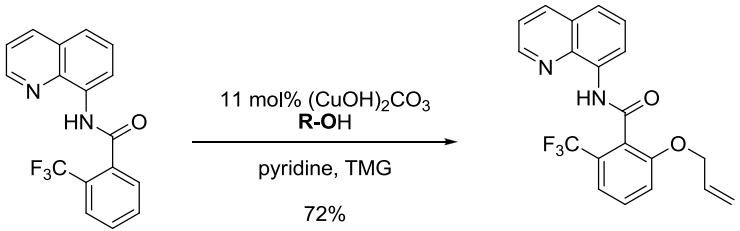
Chem. Eur. J. **2014**, *20*, 7507-7513

Co-catalysed *ortho*-alkoxylation of carboxamides



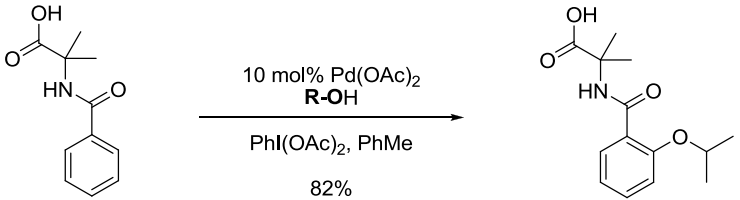
Angew. Chem. Int. Ed. **2015**, *54*, 272-275

Cu-catalysed *ortho*-alkoxylation of 8-amino-quinolone derivatives



Org. Lett. **2013**, *15*, 5842-5845

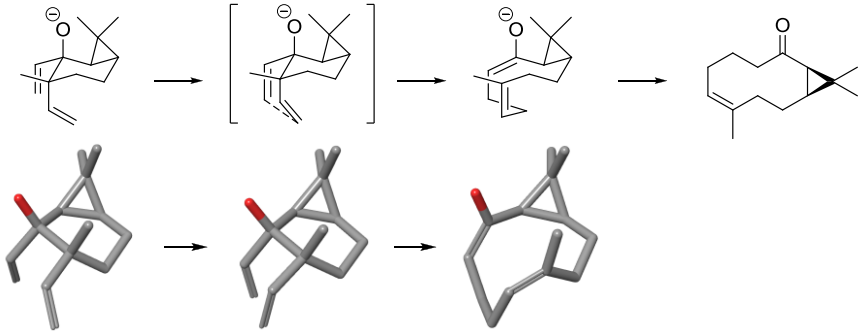
Pd-catalysed *ortho*-alkoxylation of *N*-benzoyl α-amino acids



J. Org. Chem. **2017**, *82*, 126-134

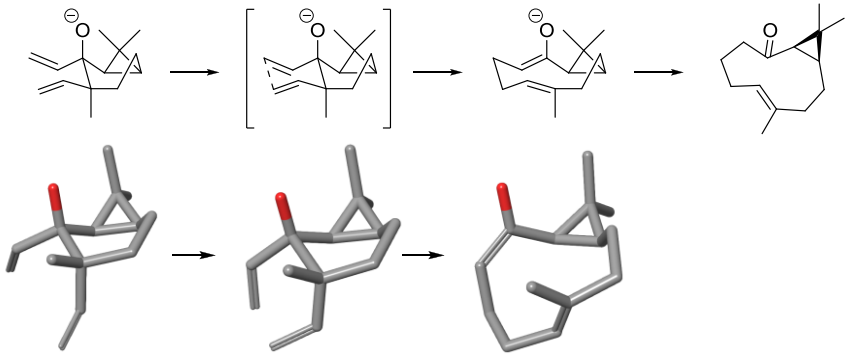
Oxy-Cope Stereochemistry

Boat TS
(*favoured*):



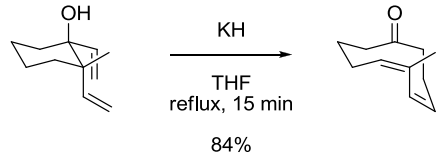
ΔE_{TS} = ***21.7*** *kcal/mol*

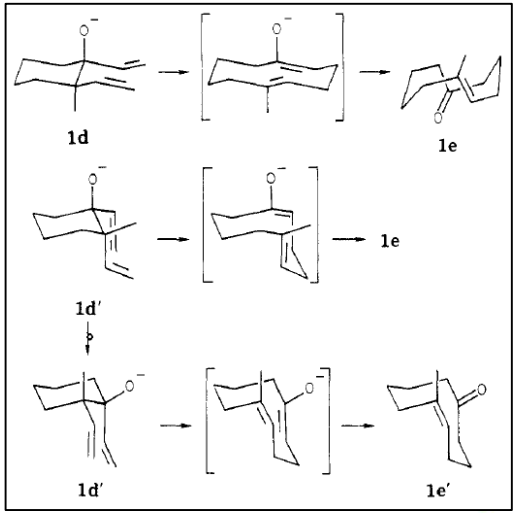
Chair TS
(*disfavoured*):



ΔE_{TS} = ***31.6*** *kcal/mol*

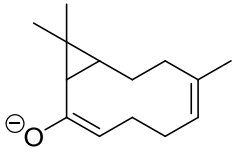
Experimental evidence:

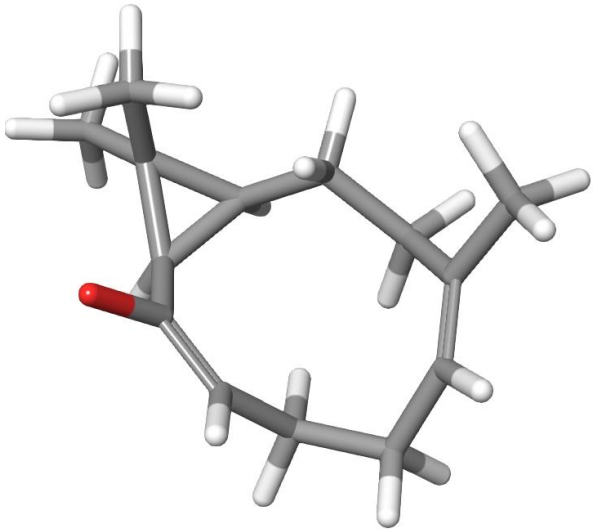




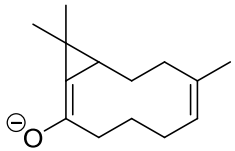
J. Org. Chem., **1982**, *47*, p. 1632 - 1641

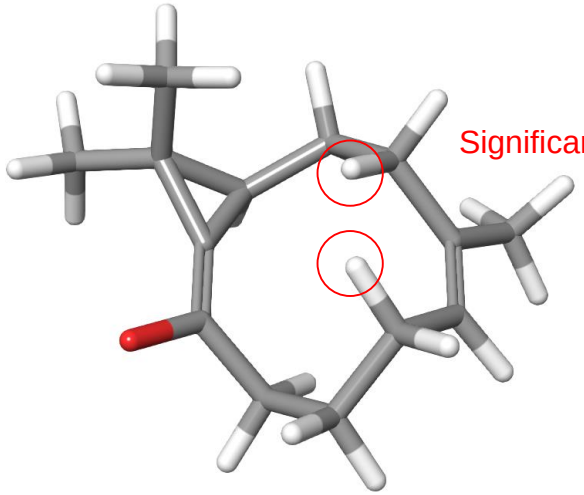
Thermodynamic control in enolate formation





E_{PM3} = -52844.3 kcal/mol





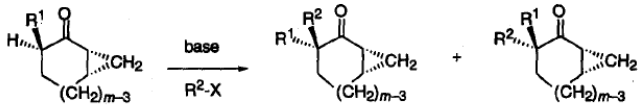
E_{PM3} = -52842.7 kcal/mol

Alkylation of cyclopropyl cyclic ketones

1) Alkylation of cyclopropyl ketones: *Tetrahedron* **1998**, *64*, 2669-2682

2) Methylation diasteroselectivity: *J. Org. Chem.* **1999**, *64*, 7412-7418

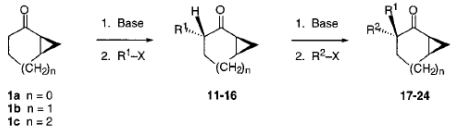
Table 2. α'–Alkylations of Enolates Derived from 3-Alkylbicyclo[*m*.1.0]alkan-2-ones.



Ketone	*m*	R^1	Base	R^2-X	Products	Yield, %	Diastereomer Ratio[a]
7a	3	$CH_2C_6H_5$	LDA	CH_3I	**20a**	32	>20:1
			NaH	CH_3I	**20a**	63	>20:1
			NaH	$C_6H_5CH_2Br$	**21**	43	na
8a	4	$CH_2C_6H_5$	LDA	CH_2=$CHCH_2Br$	**22a**	54	>20:1
			NaH	CH_2=$CHCH_2Br$	**22a**	80	>20:1
9a	4	CH_2=$CHCH_2$	LDA	$C_6H_5CH_2Br$	**24a,24b**	74	11:1
12a	5	$CH_2C_6H_5$	LDA	CH_3I	**25a**	44	>20:1
14a	5	CH_3	LDA	$C_6H_5CH_2Br$	**26a**	46	>20:1

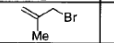
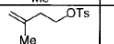
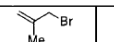
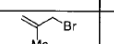
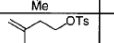
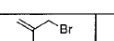
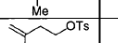
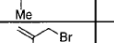
[a]Determined by NMR spectroscopy; limit of detection 20:1.

Table 1. Sequential Alkylations of Bicyclo[*m*.1.0]alkan-2-ones 1a–c



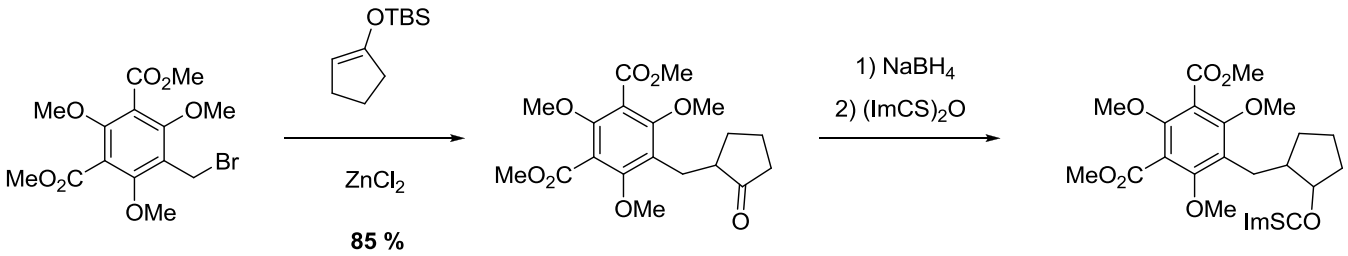
1a n = 0
1b n = 1
1c n = 2

11-16 **17-24**

	First Alkylation					Second Alkylation				
Ketone	Base	R_1–X	Product	Yield, %	DR[a]	Base	R_2–X	Product	Yield, %	DR[a]
1a	LDA	MeI	**11**	27	>20:1	NaH		**17**	56	>20:1
						NaH		**18**	38	>20:1
1a	LDA		**12**	58	>20:1	NaH	MeI	**19**	70	>20:1
1b	LDA	MeI	**13**[b]	68	10:1	NaH		**20**	78	>20:1
						NaH		**21**	75	>20:1
1b	LDA		**14**	90	4:1	NaH	MeI	**22**	88	>20:1
1b	NaH		**15**	34	2:1	NaH	MeI	**23**	93	>20:1
1c	LDA		**16**	61	>20:1	LDA	MeI	**24**	35	>20:1

[a] Diastereomer ratio determined by ^{13}C NMR analysis. [b] Preparation of this ketone was previously reported (see ref 5).

Evidence for alkylation in presence of methyl ester



1) *J. Org. Chem.* **2003**, 68, 5909–5916