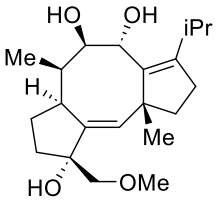
Synthesisof (−)-Cotylenol,a 14-3-3 Molecular Glue Component, Ryan A. Shenvi

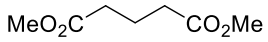
J. Am. Chem. Soc. 2023, 145, 37, 20634–20645



(-)cotylenol

- Molecular glue between 14-3-3 proteins and phosphoprotein clients
- Potential anti cancer drugs
- producer organism Cladosporium species has lost the ability to proliferate in culture

Synthesis of A



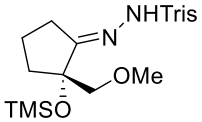
Na,TMSCl

1

1. $(MeO)_2CH_2$
   $Zn(OTf)_2$
   Name
2. K10,MeOH
   40% over 3 steps

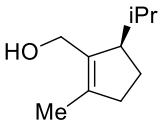
2

1. Chiral SFC (42%)
2. $TrisNHNH_2$ (87%)
   (4:1 E/Z)
3. TMSCl, imidazole
   (48%)



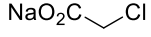
A

Synthesis of C



3
4 steps from
(S)-limonene

NaH



HMPA/THF
60 °C

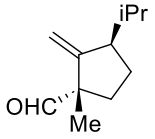
4

LiTMPS, THF
-78 °C to 0 °C

5

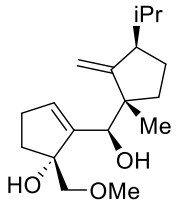
$NaIO_4$

MeOH, 45 °C
66% over 2 steps



C

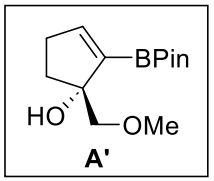
A + C n-BuLi (3 equiv.) ✕



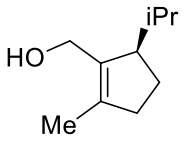
What's the name reaction of the intempted reaction?
Rearrangement occurs when A is protected with TMS, mechanism?

Change of strategy

Asymmetric synthesis of **A'** instead of fragment A



A'



3

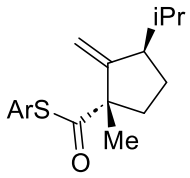
ArSH
$BF_3 \cdot OEt_2$

DCM, -10 °C
(91%)

6

$CHCl_3$
NaO*t*-Bu
H_2O/SiO_2

THF, -46 °C to rt
Mechanism?



C'

5 mol% $Pd_2(dba)_3$
15 mol% P(2-furyl)$_3$
1.6 equiv CuTC
2 equiv $B(OH)_3$
A'

4:1 acetone/EtOAc
rt, 16 h (54%)

7

$NaBH_4$
$CeCl_3 \cdot 7H_2O$
MeOH, -78 °C

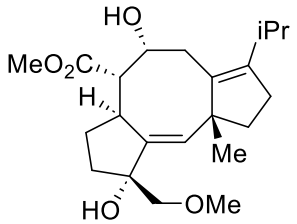
8

CO_2Me
NMM, DCM, 0 °C

68% over 2 steps,
>20:1 E:Z

9

160 °C
mesitylene

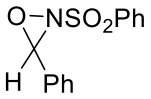


10

1. DMP
2. KOH, aq CH_2O

3. $MsCl$, Et_3N
then DBU
69% over 3 steps

11



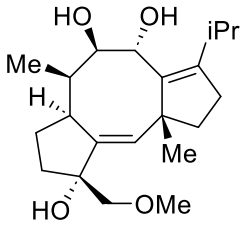
1.KHDMS, -78 °C,

(94%, > 20:1 dr)

12

1. TrisNHNH2, NaHCO3,
MeOH, (49, 7:1 dr)

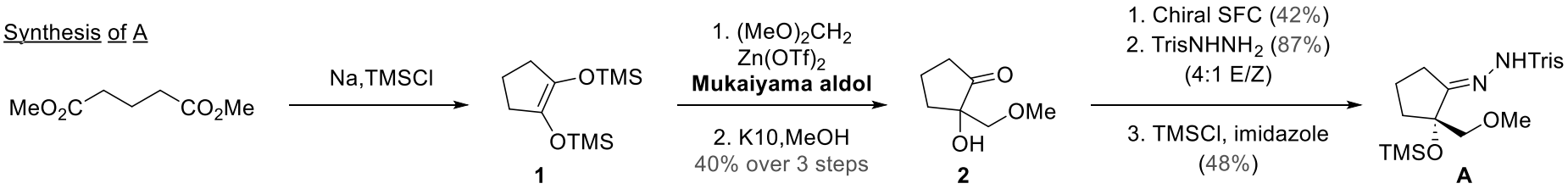
2. $[BH(O_2CiPr)_3]^-$ $[Me_4N]^+$
MeCN, (83%, >20:1 dr)



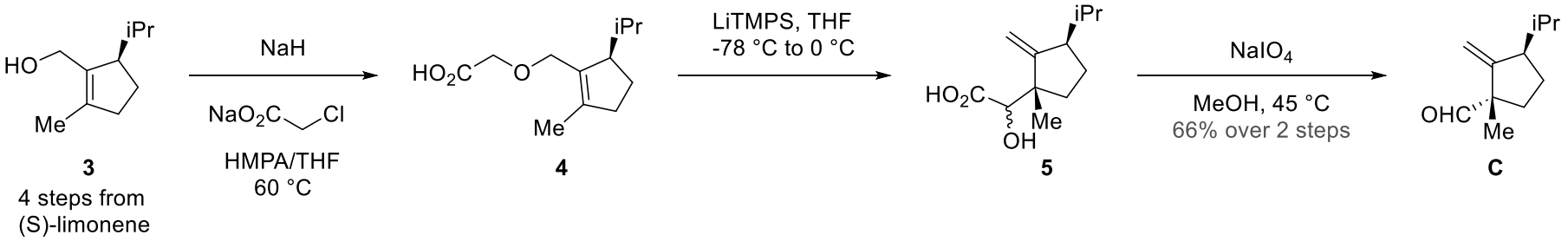
cotylenol

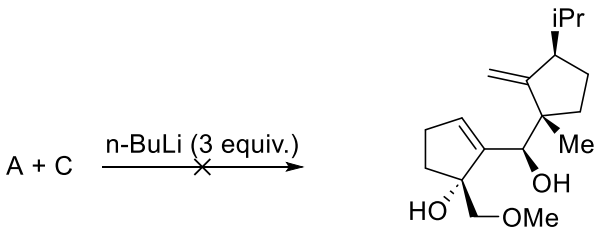
Solutions

Synthesis of A



Synthesis of C





What's the name reaction of the intempted reaction? **Shapiro**
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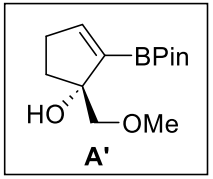
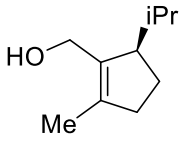
Retro [1,4] Brook

Change of strategy

Also referees noted the limitations of using SFC, instead asymmetric synthesis of **A'**



A'



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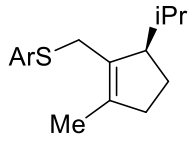
$BF_3 \cdot OEt_2$

DCM, -10 °C
(91%)



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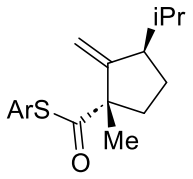

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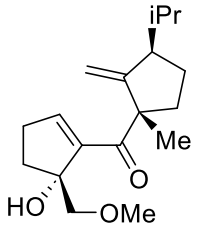

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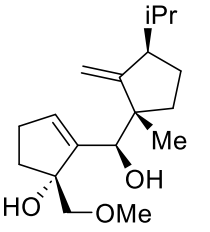

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CO_2Me
NMM, DCM, 0 °C

68% over 2 steps,
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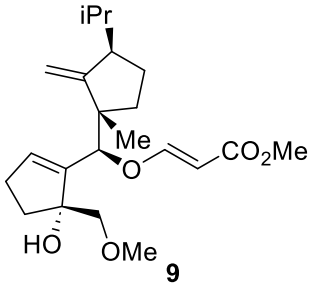
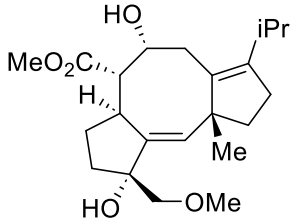


9

160 °C
mesitylene

tandem Claisen-ene



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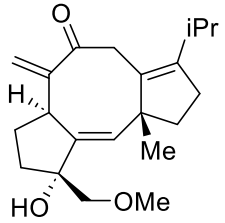
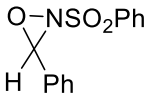


11



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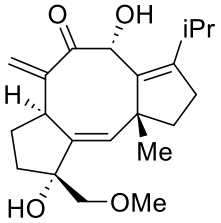

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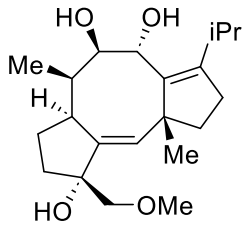

cotylenol