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Natural Products Synthesis

Enantioselective Total Synthesis of (−)-Cephalotanin B

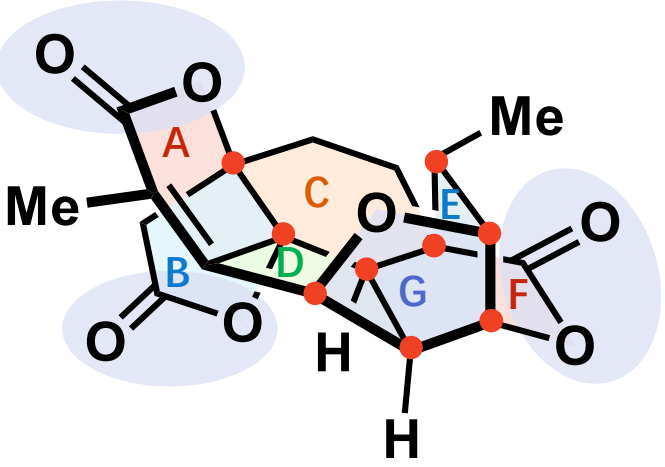
*Zezhong Sun[+], Shuang Jin[+], Jianing Song, Lihua Niu, Fan Zhang, Han Gong, Xin Shu, Yunxia Wang, and Xiangdong Hu**

Cephalotaxus Diterpenoids

Intriguing Biological Properties

Discovered in 2016

No Report on Its Synthesis



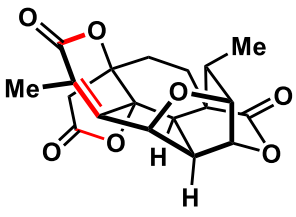
(−)-cephalotanin B

Congested Heptacyclic Skeleton

9 Consecutive Stereocenters

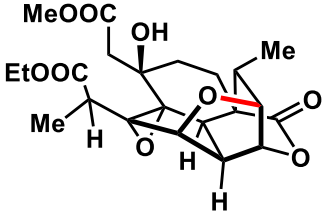
3 Lactone Units

Retrosynthetic Analysis



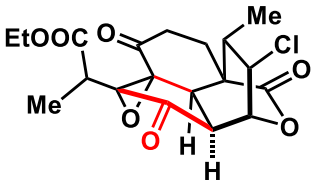
(−)-cephalotanin B (**1**)

epoxide-opening /elimination/ lactonization



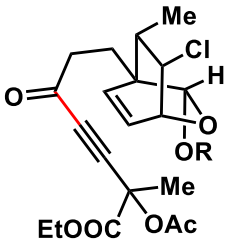
6

formation of ring G



7

stereoselective Pauson-Khand /deacyloxylation



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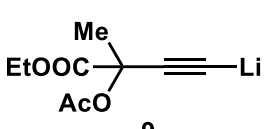
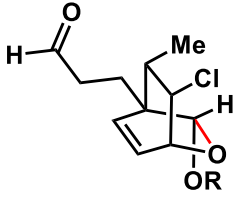


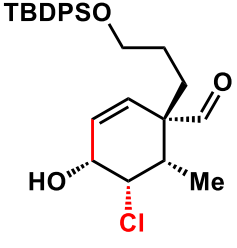
9

bridged acetalization



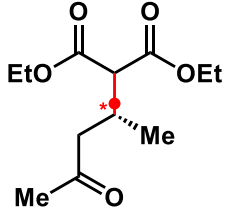
10

Dieckmann condensation /C3-chlorination



11

asymmetric Michael addition



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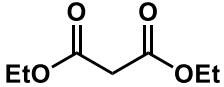
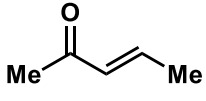


13

+



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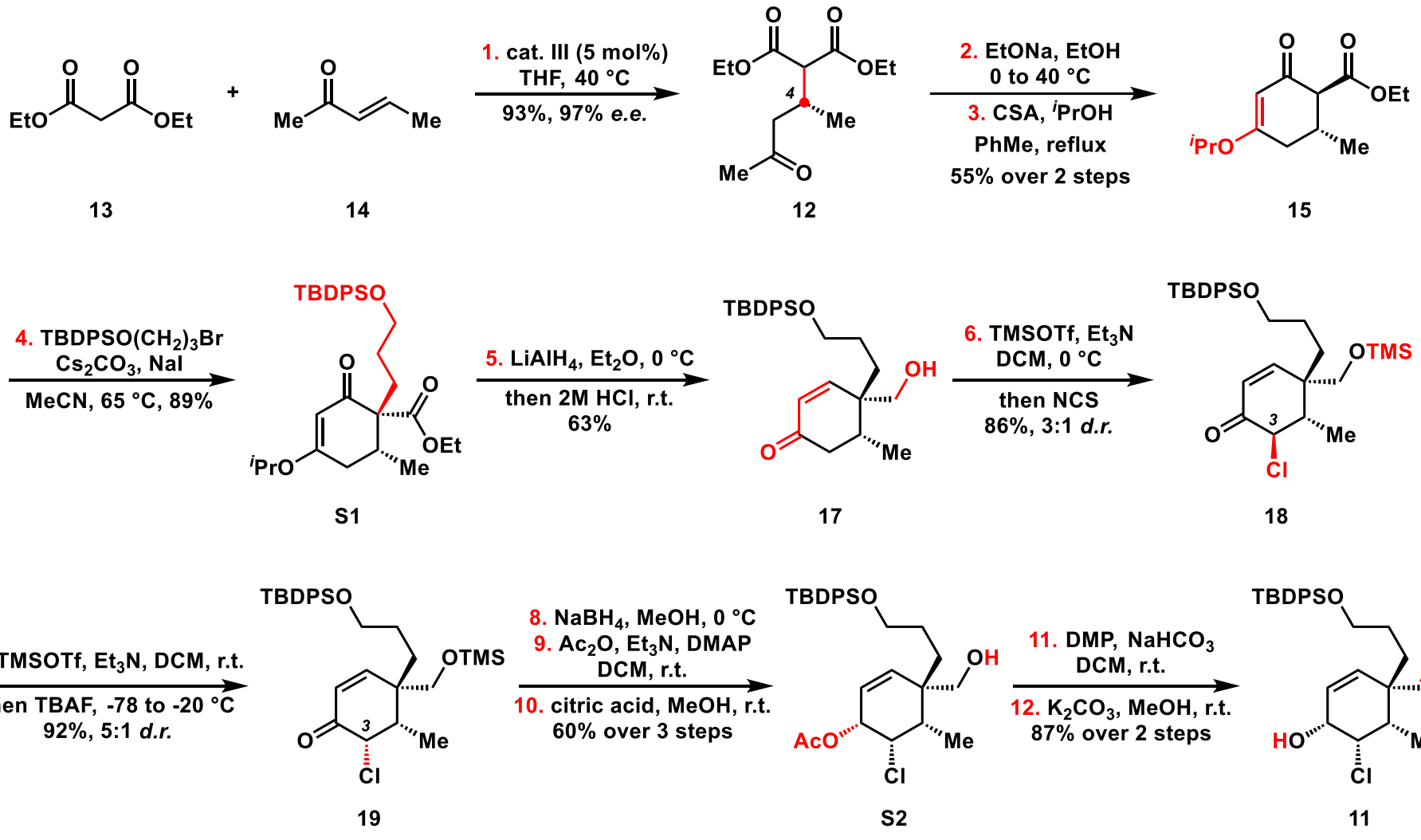
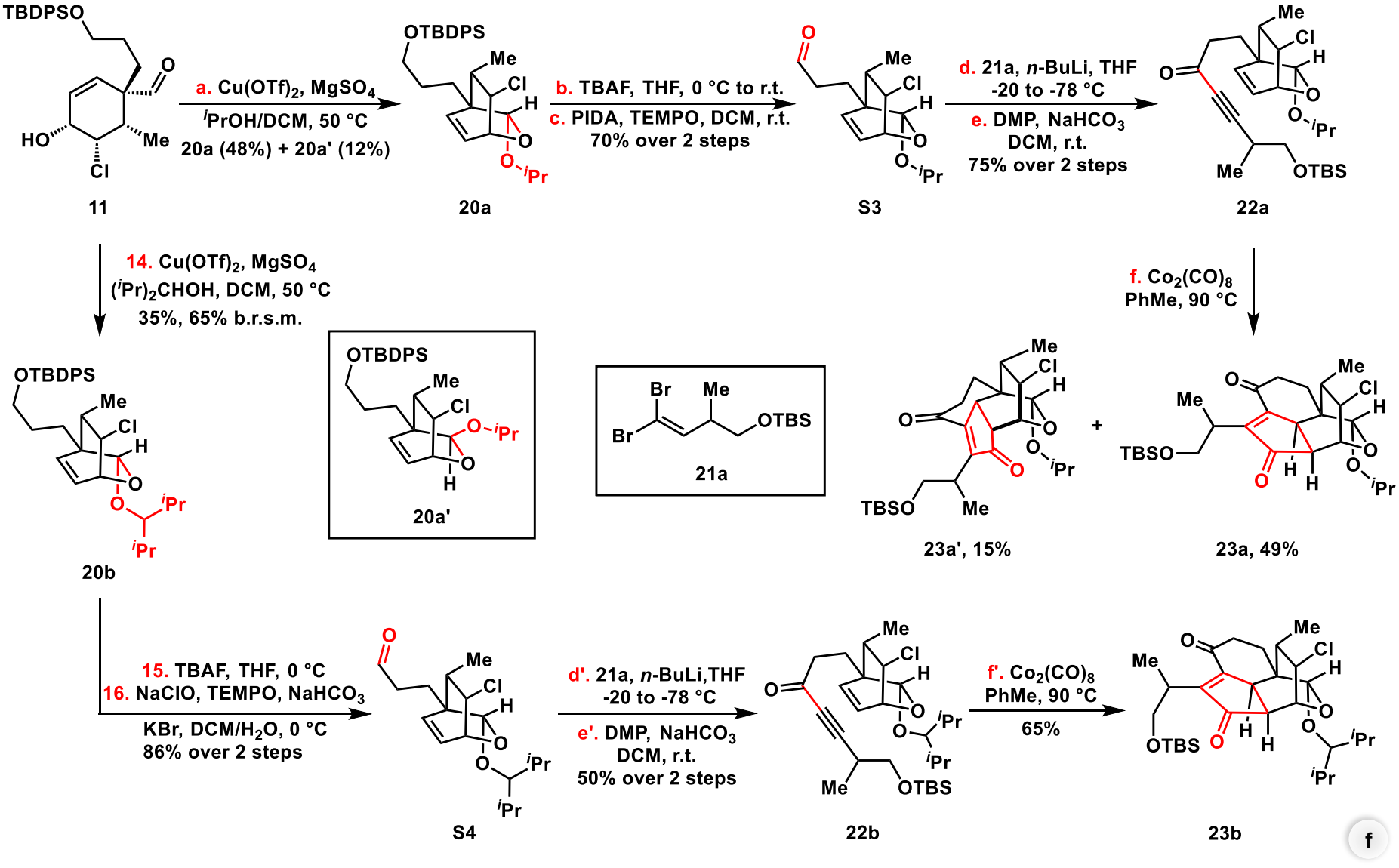
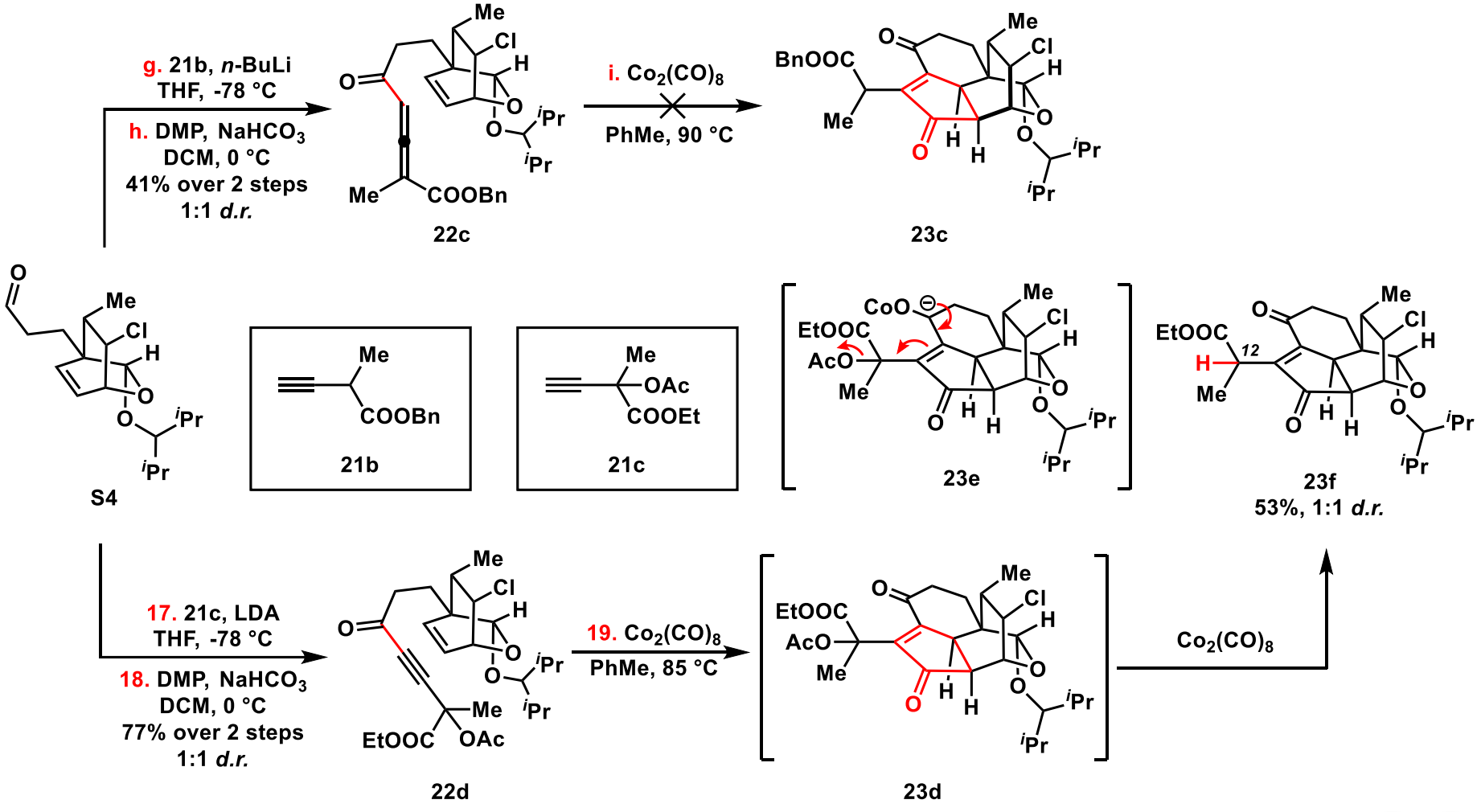
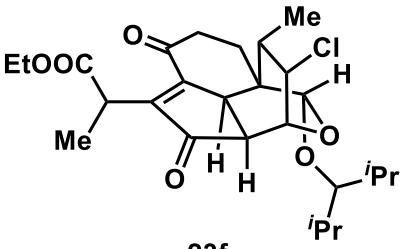

13
14
1. cat. III (5 mol%)
THF, 40 °C
93%, 97% e.e.
12
2. EtONa, EtOH
0 to 40 °C
3. CSA, iPrOH
PhMe, reflux
55% over 2 steps
15
4. TBDPSO(CH2)3Br
Cs2CO3, NaI
MeCN, 65 °C, 89%
S1
5. LiAlH4, Et2O, 0 °C
then 2M HCl, r.t.
63%
17
6. TMSOTf, Et3N
DCM, 0 °C
then NCS
86%, 3:1 d.r.
18
7. TMSOTf, Et3N, DCM, r.t.
then TBAF, -78 to -20 °C
92%, 5:1 d.r.
19
8. NaBH4, MeOH, 0 °C
9. Ac2O, Et3N, DMAP
DCM, r.t.
10. citric acid, MeOH, r.t.
60% over 3 steps
S2
11. DMP, NaHCO3
DCM, r.t.
12. K2CO3, MeOH, r.t.
87% over 2 steps
11

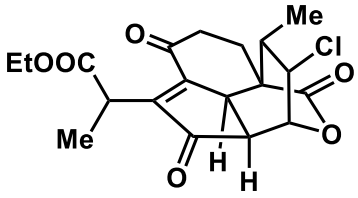

TBDPSO
HO
Me
Cl
O
11
a. Cu(OTf)2, MgSO4
iPrOH/DCM, 50 °C
20a (48%) + 20a' (12%)
OTBDPS
Me
Cl
H
O
O
iPr
20a
b. TBAF, THF, 0 °C to r.t.
c. PIDA, TEMPO, DCM, r.t.
70% over 2 steps
S3
d. 21a, n-BuLi, THF
-20 to -78 °C
e. DMP, NaHCO3
DCM, r.t.
75% over 2 steps
22a
14. Cu(OTf)2, MgSO4
(iPr)2CHOH, DCM, 50 °C
35%, 65% b.r.s.m.
20b
20a'
Br
Me
OTBS
21a
f. Co2(CO)8
PhMe, 90 °C
TBSO
23a', 15%
+
23a, 49%
15. TBAF, THF, 0 °C
16. NaClO, TEMPO, NaHCO3
KBr, DCM/H2O, 0 °C
86% over 2 steps
S4
d'. 21a, n-BuLi,THF
-20 to -78 °C
e'. DMP, NaHCO3
DCM, r.t.
50% over 2 steps
22b
f'. Co2(CO)8
PhMe, 90 °C
65%
23b
f


g. 21b, n-BuLi
THF, -78 °C
h. DMP, NaHCO3
DCM, 0 °C
41% over 2 steps
1:1 d.r.
22c
i. Co2(CO)8
PhMe, 90 °C
23c
S4
21b
21c
23e
23f
53%, 1:1 d.r.
17. 21c, LDA
THF, -78 °C
18. DMP, NaHCO3
DCM, 0 °C
77% over 2 steps
1:1 d.r.
22d
19. Co2(CO)8
PhMe, 85 °C
23d
Co2(CO)8



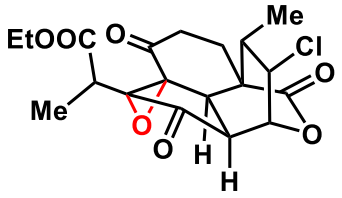
23f

20. $TiCl_4$, DCM
0 °C to r.t.
21. DMP, $NaHCO_3$
DCM, r.t.
80% over 2 steps



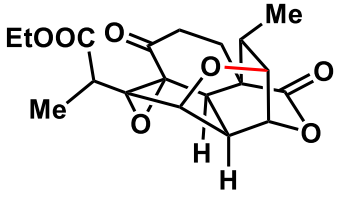
25

21. H_2O_2, Na_2HPO_4
MeOH/H_2O, 0 °C, 72%



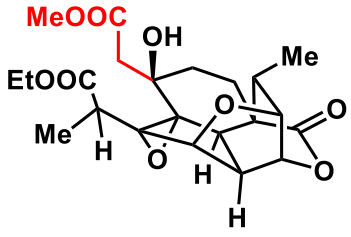
7

22. $NaBH_4$, MeOH/DCM, 0 °C
23. $AgBF_4$, DCM, r.t.
then DMP
79% over 2 steps



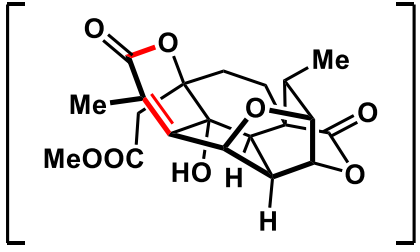
26

24. LiTMP, MeOAc
PhMe, -78 to 0 °C
69%, 2.5:1 *d.r.*

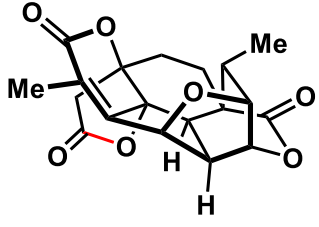


6

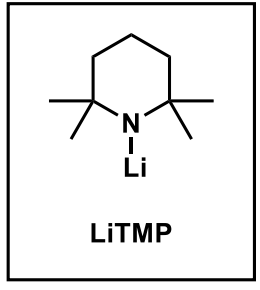
25. *p*-TSA, benzene
65 °C
50% over 2 steps



27

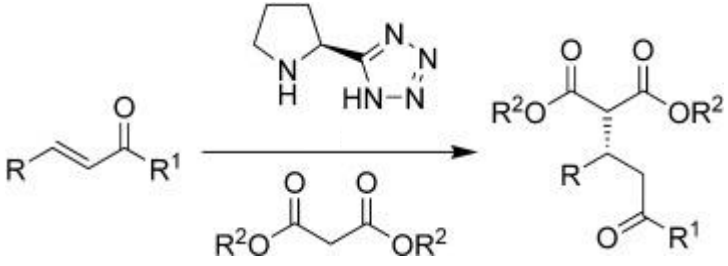


(−)-cephalotanin B (**1**)



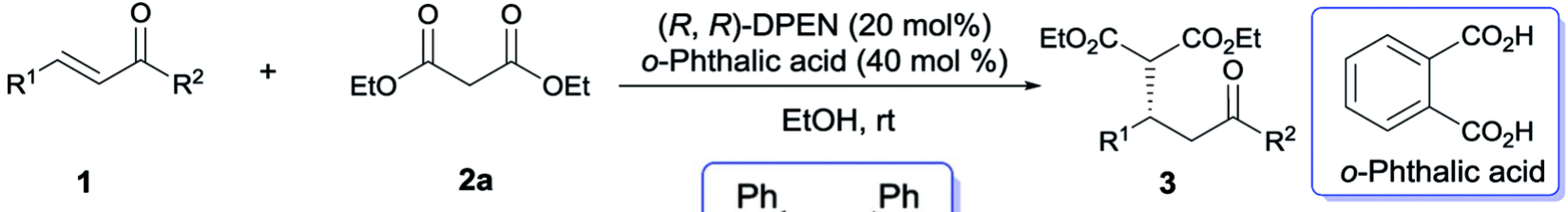
LiTMP

Step 1 Asymmetric Michael Addition



R = R_1 = Me
R_2 = Et
82% yield, -64% *ee*

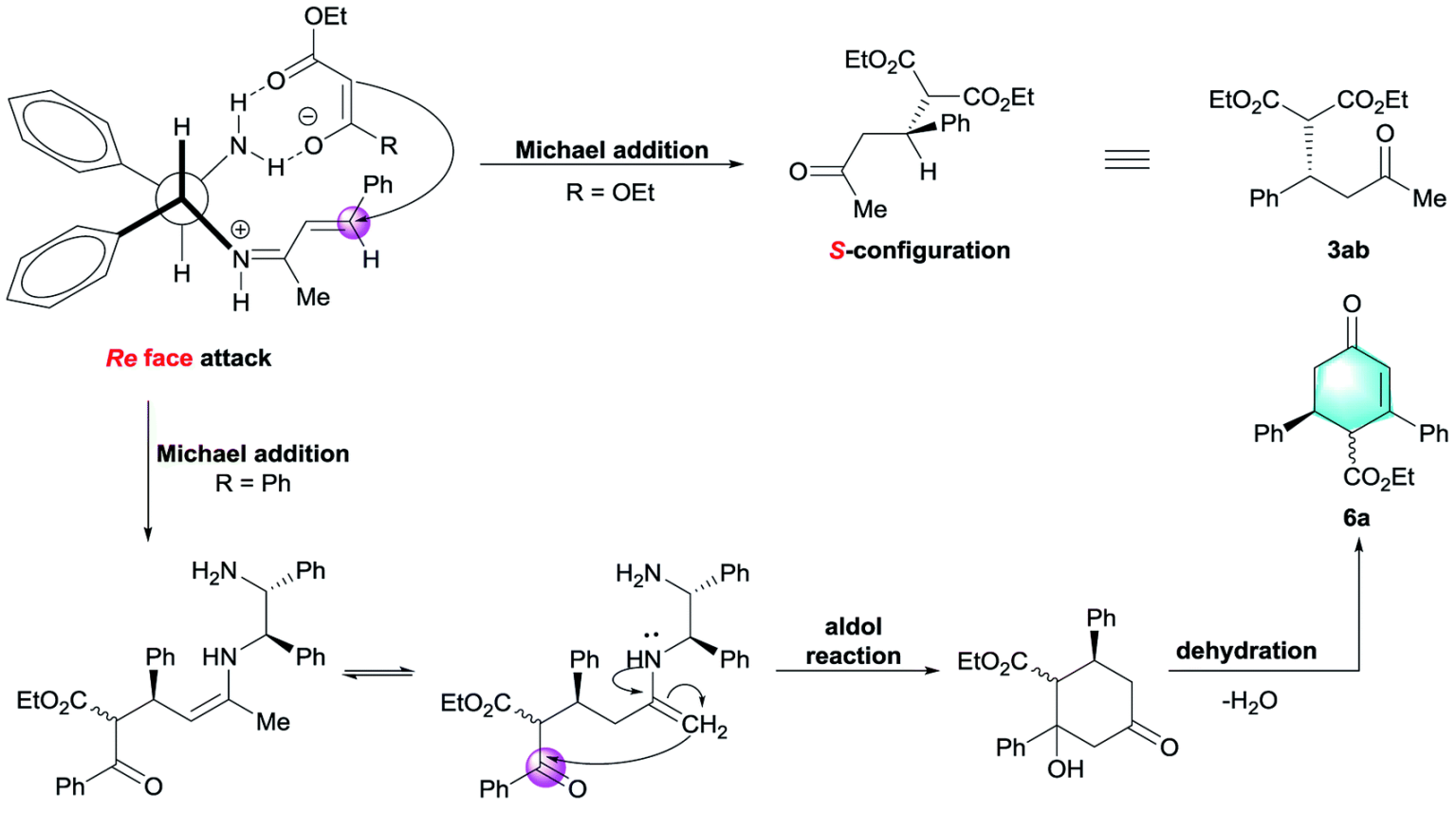
Chem. Eur. J., **2008**, *14*, 6155.



R_1 = R_2 = Me
70% yield, -86% *ee*

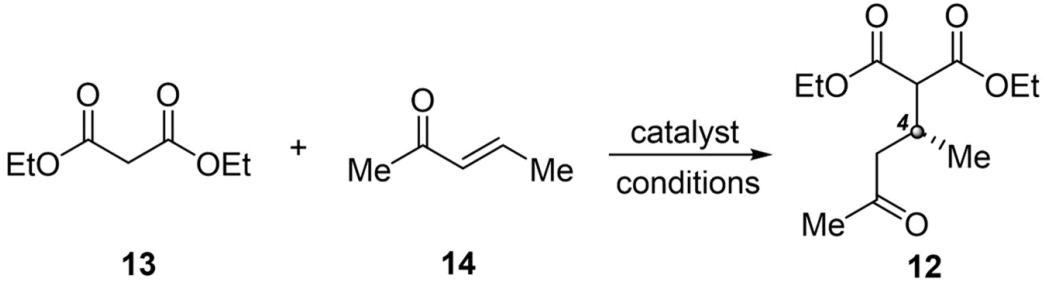
RSC Adv., **2018**, *8*, 41699.

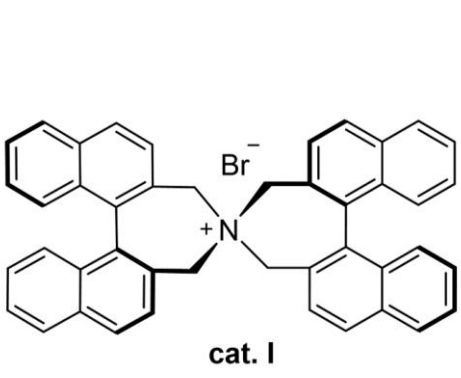
Step 1 Asymmetric Michael Addition

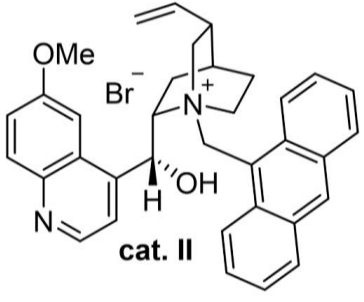


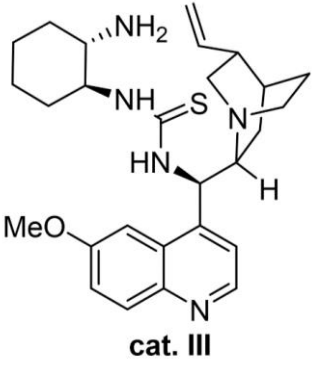
RSC Adv., **2018**, *8*, 41699.

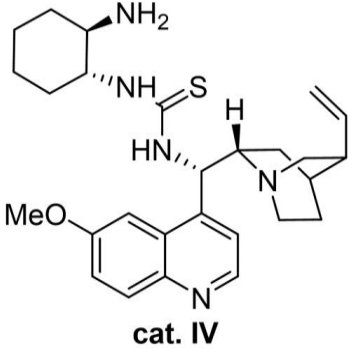
Step 1 Asymmetric Michael Addition

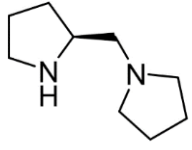






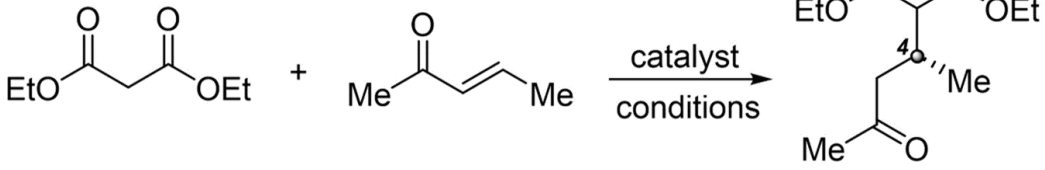




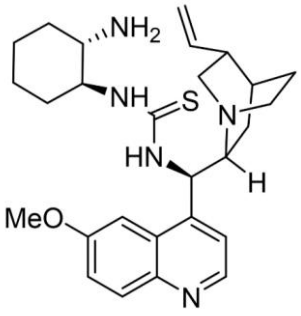


Entry[a]	Catalyst	Conditions	Yield [%][b]	ee [%]
1[c]	cat. I	PhMe, 5% NaOH, rt	4	-9
2[c]	cat. II	PhMe, 5% NaOH, rt	0	no reaction
3	cat. III	PhMe, 40 °C	69	98
4	cat. IV	PhMe, 40 °C	83	-94
5	cat. V	THF, 40 °C	17	-29

Step 1 Asymmetric Michael Addition



13 14 12



cat. III

Entry[a]	Catalyst	Conditions	Yield [%][b]	ee [%]
6	**cat. III**	**THF, 40 °C**	**95**	**98**
7	cat. III	1,4-dioxane, 40 °C	40	97
8	cat. III	Et_2O, 40 °C	78	97
9	cat. III	DCM, 40 °C	44	93
10	cat. III	acetone, 40 °C	65	96
11[d]	cat. III	THF, 40 °C	93	97

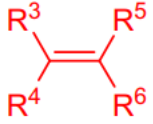
[a] Unless otherwise noted, all reactions were performed with 0.25 mmol of **13**, 0.275 mmol of **14** and 5 mol% catalyst in 2 mL solvent.
[b] Yield of the isolated product.
[c] 0.038 mmol of NaOH (5 % aq.) was added after the dissolution of the catalyst.
[d] The reaction was performed on a 20 g scale with respect to **13**.

Step f&19 Pauson-Khand Reaction

Pauson & Khand (1973):

terminal or internal alkyne

+

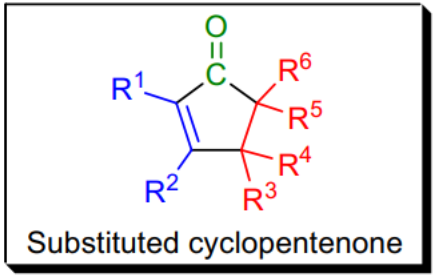


mono-, di- or trisubstituted alkene

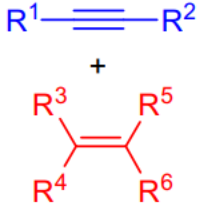
$Co_2(CO)_8$ (1 equiv)

solvent / heat

$R^1 > R^2$



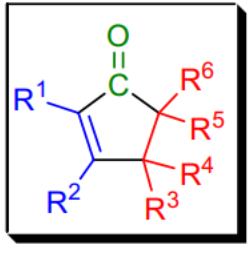
Modified P-K reaction:



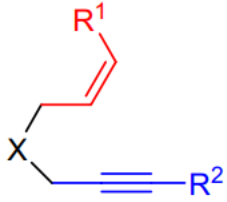
transition metal complex (1 equiv)

promoter / solvent

CO atmosphere



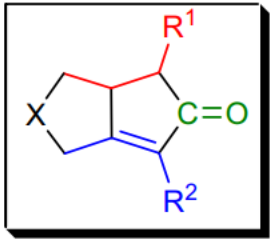
Intramolecular variant:



$Co_2(CO)_8$ (1 equiv)

promoter / solvent

X = CH_2, CHR, CR_2, O, NHR, S

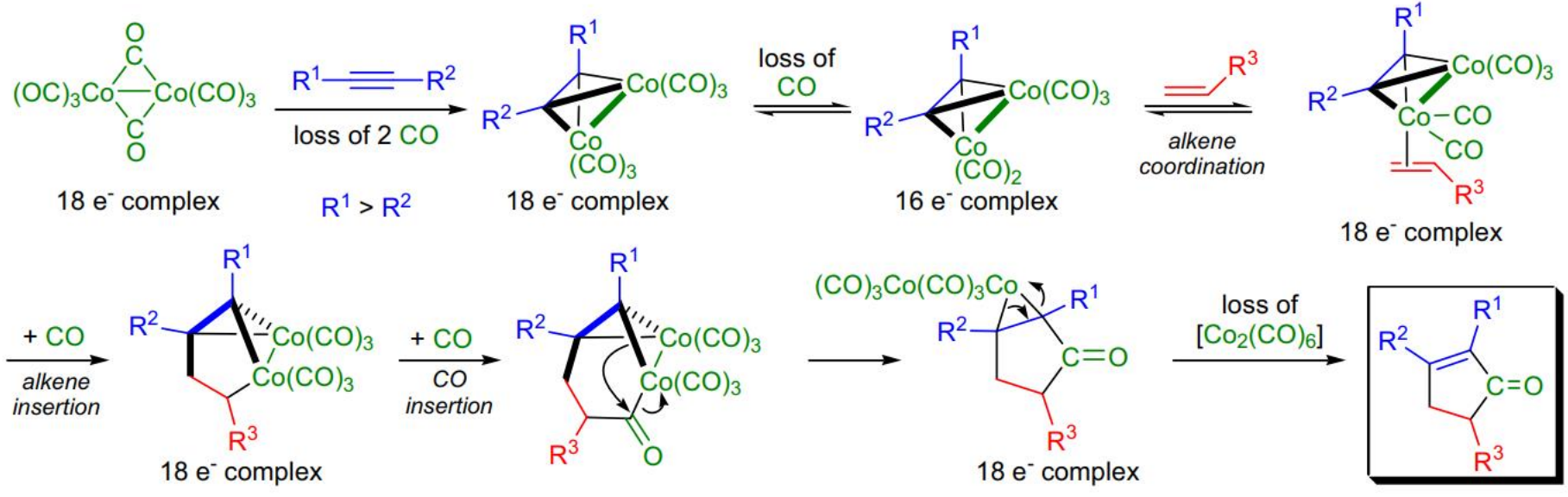


R^{1-6} = H, alkyl, aryl, substituted alkyl and aryl; transition metal complex: $Co_2(CO)_8$, $Fe(CO)_5$, $Ru_2(CO)_{12}$, Cp_2TiR_2, $Ni(COD)_2$, $W(CO)_6$, $Mo(CO)_6$, $[RhCl(CO)_2]_2$; promoter: NMO, TMAO, $RSCH_3$, high-intensity light/photolysis, "hard" Lewis base

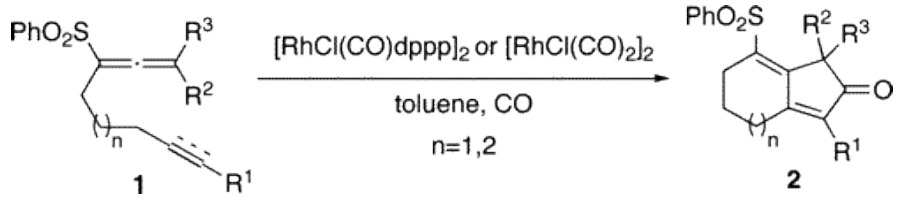
Step f&19 Pauson-Khand Reaction

Mechanism: [48-62]

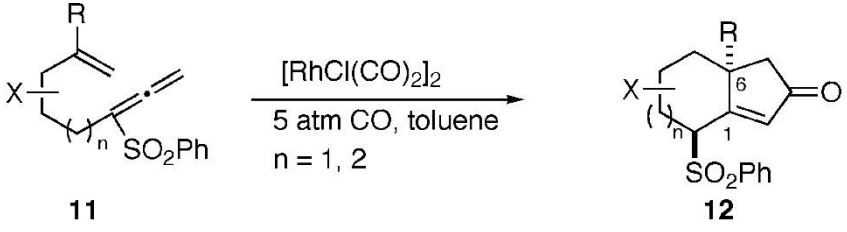
The mechanism of the *Pauson-Khand reaction* has not been fully elucidated. However, based on the regio- and stereochemical outcome in a large number of examples, a reasonable hypothesis has been inferred.

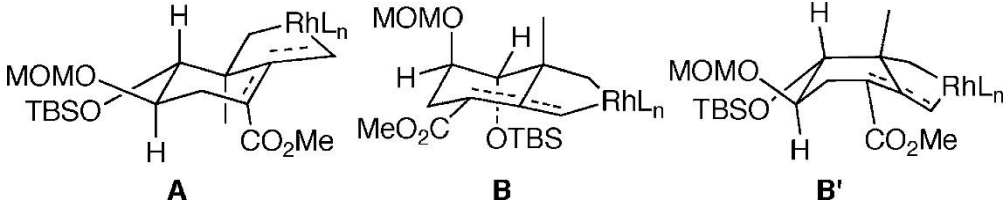


Step i Pauson–Khand Cycloaddition of Allenenes



Org. Lett., **2006**, *8*, 1217.

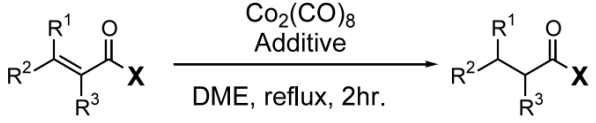




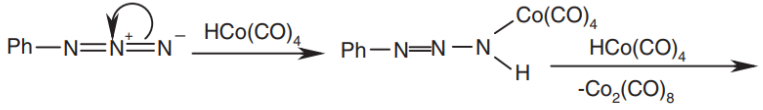
Org. Lett., **2008**, *10*, 2385.

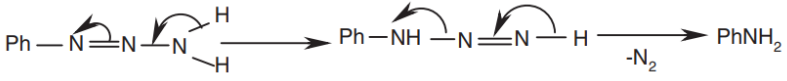
Step 19 Reductive Capability of $Co_2(CO)_8$

- $CoH(CO)_4$ as a Reductant



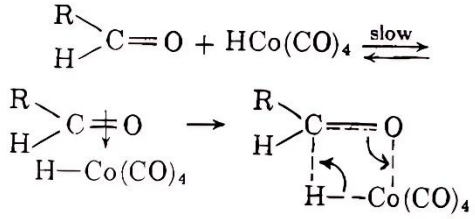
Tetrahedron Lett., **2003**, *44*, 2775.





Chem. Lett., **2005**, *34*, 340.

$$RCHO + 2HCo(CO)_4 \longrightarrow RCH_2OH + Co_2(CO)_8 \quad (1)$$



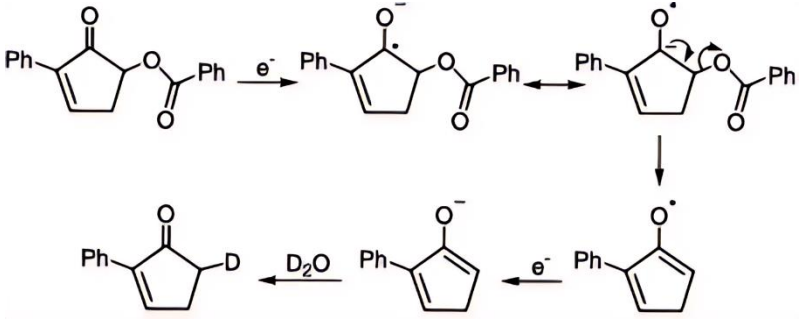
II

$$II \longrightarrow R{-}CH_2OCo(CO)_4\ (III) \quad (3)$$

$$III + HCo(CO)_4 \xrightarrow{fast} RCH_2OH + Co_2(CO)_8 \quad (4)$$

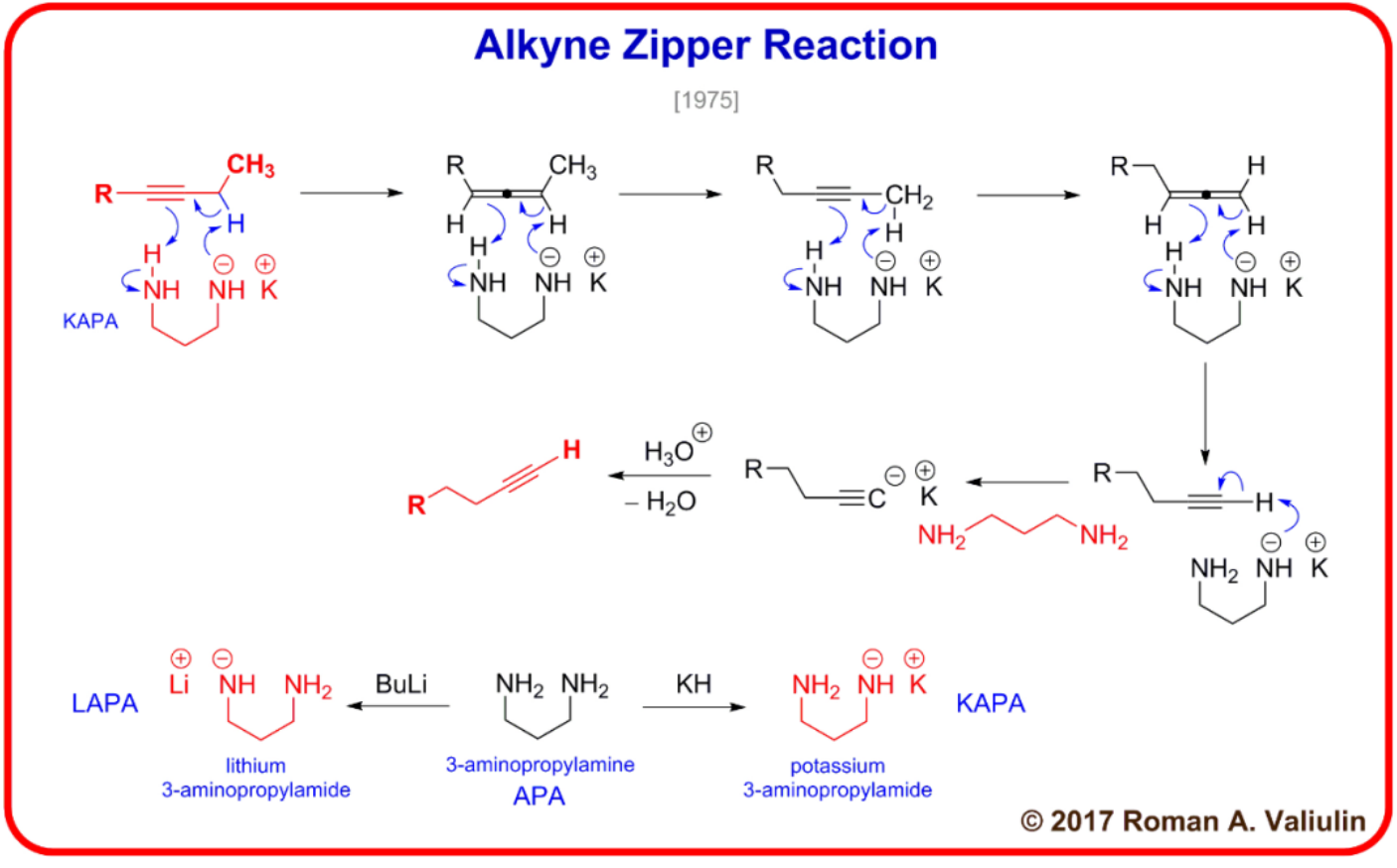
J. Org. Chem., **1962**, *27*, 3698.

- Reductive Deacyloxylation: Similar to SmI_2



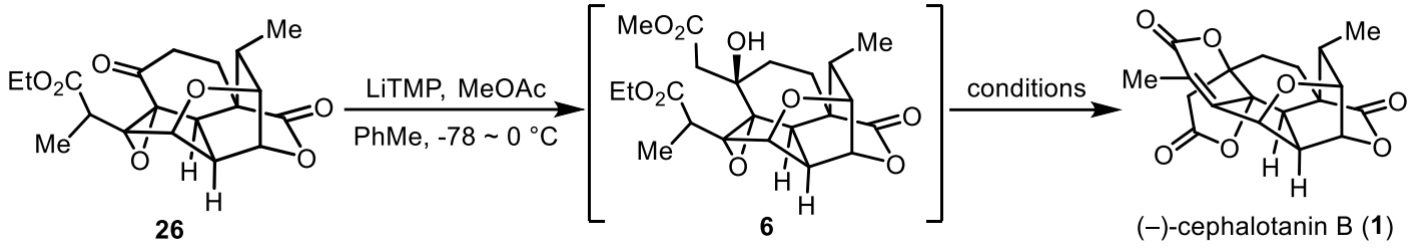
Org. Lett., **2008**, *10*, 2385.

Step g Alkyne Zipper Reaciton



J. Am. Chem. Soc., **1975**, *97*, 891.

Step 25 Epoxide-opening/Elimination/Dual-Lactonization Cascade



Conditions	Yield of **1** (from **26**)
$TiCl_4$, DCM, 0 °C	decomposition
TMSOTf, DCM, 0 °C	decomposition
$HNTf_2$, DCE, 0 °C	decomposition
TFA, DCE, 90 °C	15%
PTSA, DCE, 90 °C	23%
PTSA, DCE, 65 °C	42%
PTSA, PhMe, 65 °C	13%
PTSA, PhH, 65 °C	**51%**
LDA, THF, -78 °C	decomposition
LiOH, THF, 40 °C	no reaction
Na_2CO_3, THF, 40 °C	no reaction