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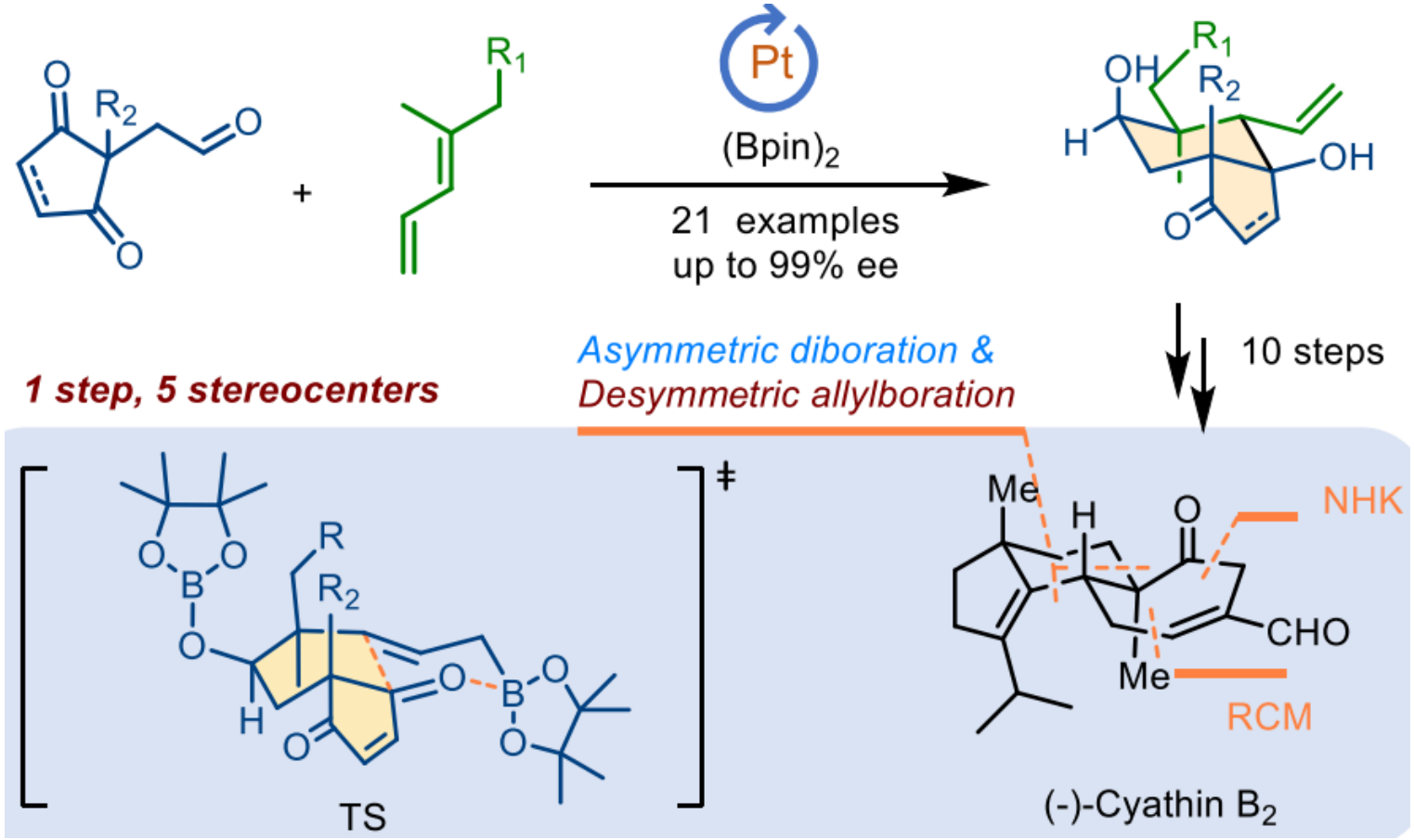
Article

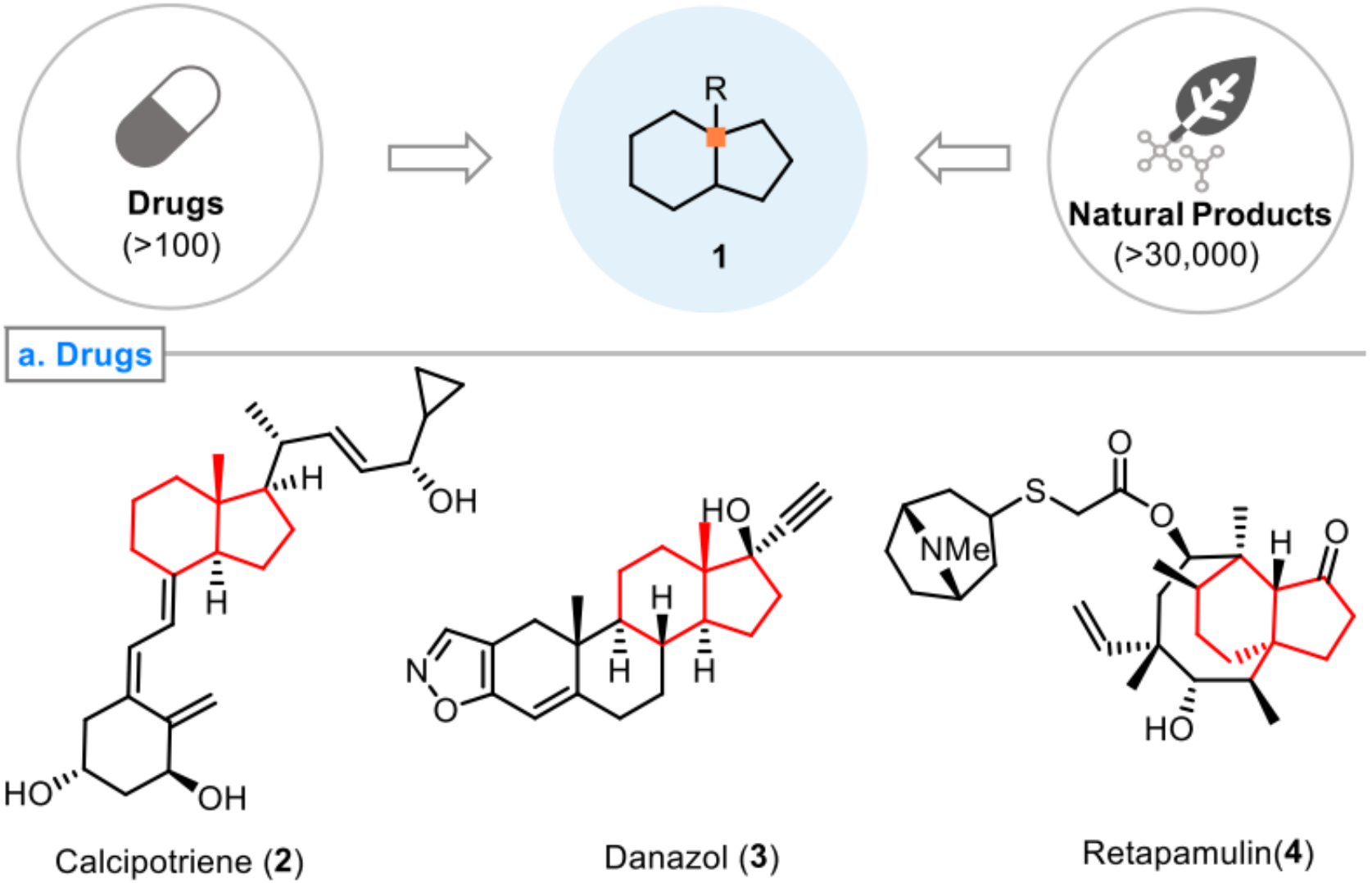
Enantioselective Total Synthesis of (−)-Cyathin B_2: A Desymmetric Double-Allylboration Approach

Jianping Wang, Jiacheng Yin, Hayatullah Imtiaz, Hongyu Wang, and Yun Li*



J. Am. Chem. Soc., **2024**, *146*, 25078.

Representative Examples of Hydrindane Contained Drugs and Natural Products Including Cyathane Diterpenoids



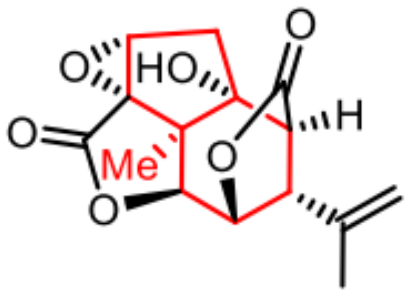
Calcipotriene (**2**)

Danazol (**3**)

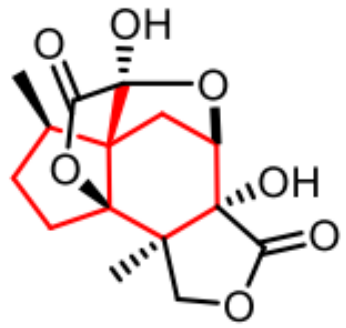
Retapamulin(**4**)

Representative Examples of Hydrindane Contained Drugs and Natural Products Including Cyathane Diterpenoids

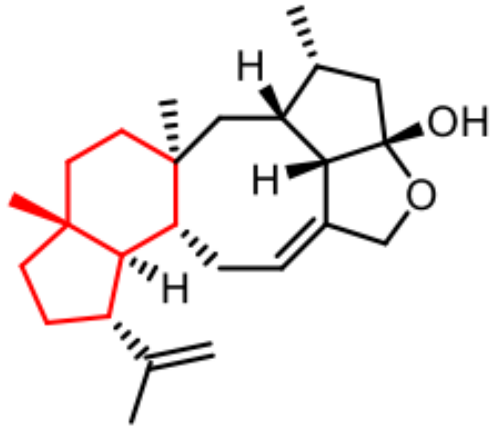
b. Natural products



picrotoxinin (**5**)

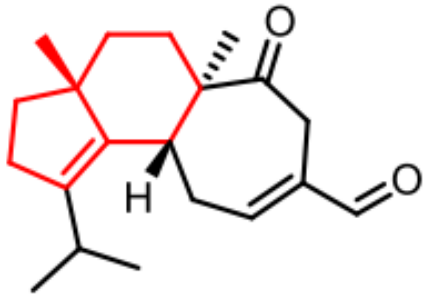


jiadifenolide (**6**)

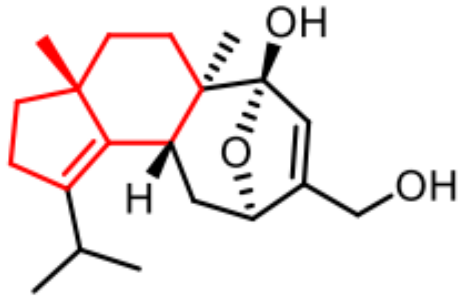


variecolol (**8**)

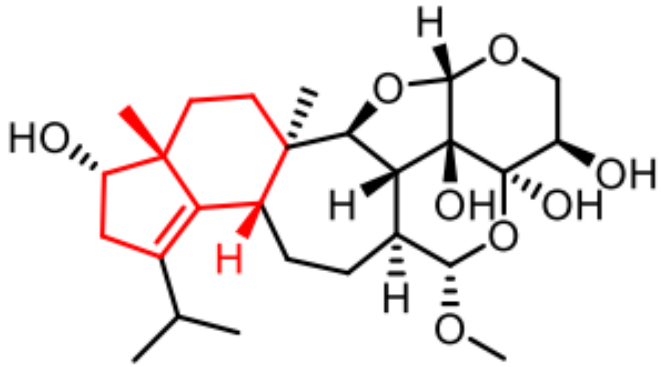
Cyathane



Cyathin B_2 (**9a**)



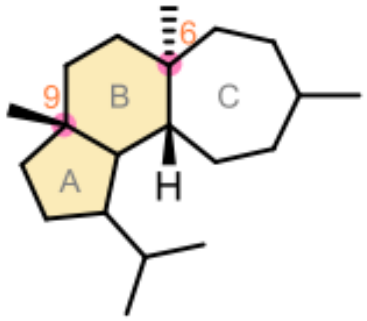
Cyathin A_3 (**9b**)



striatoid A (**9c**)

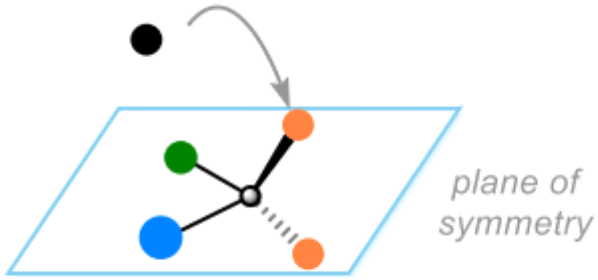
Strategy on the Asymmetric Synthesis of Cyathane

- **Previous asymmetric approach:**



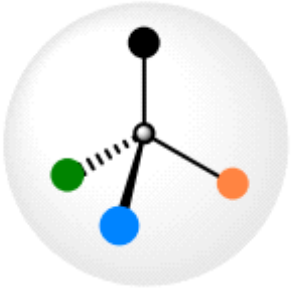
cyathane

- [4+2],[2+2] & ring-expansion
  Ward 2000, 2007
- yeast reduction & IM-aldol
  Nakada 2007, 2008
- AAA & Ru-cycloisomerization
  Trost 2005
- Robinson & Nazarov
  Danishefsky 2005
- DA & ROM/RCM
  Phillips 2005
- allylation & radical cyclization
  Stoltz 2008
- Hydrogenation & Friedel-Craft
  Xie 2017
- yeast reduction & Friedel-Craft
  Han 2018



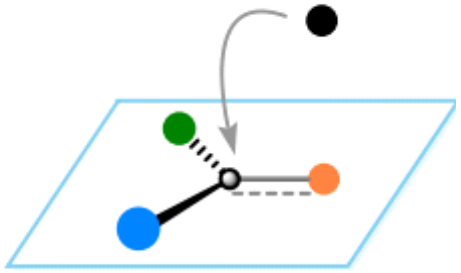
Desymmetrization

The desymmetrization strategy to introduce quaternary carben centers from simple precursors



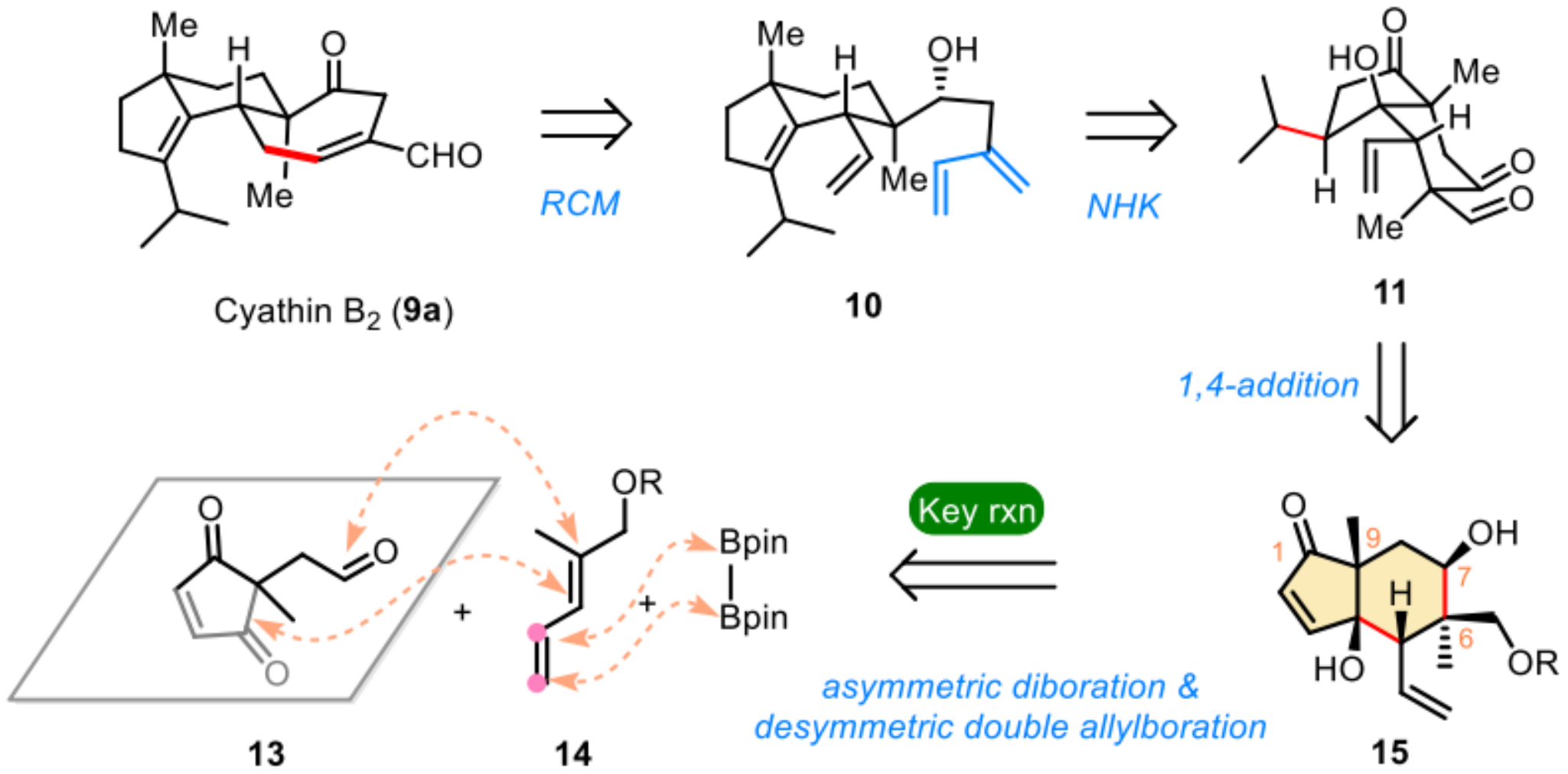
Quaternary stereocentres

Enantiofacial selection

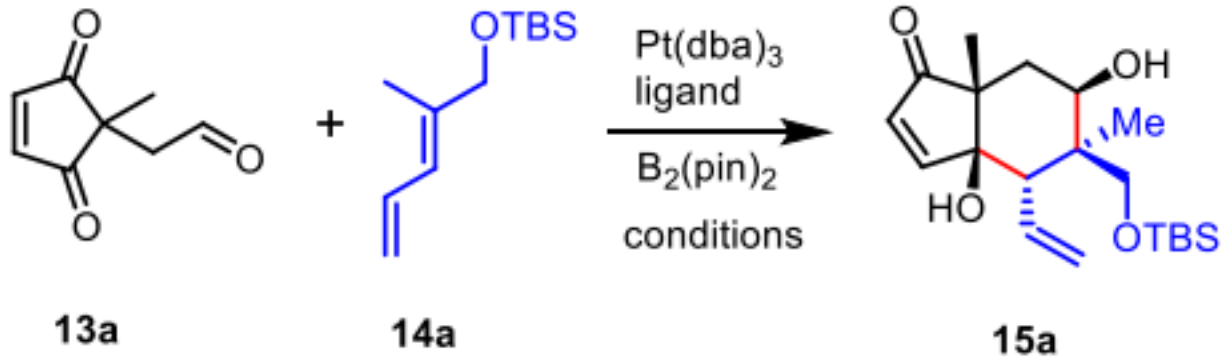


Retrosynthetic Analysis of (-)-Cyathin B_2

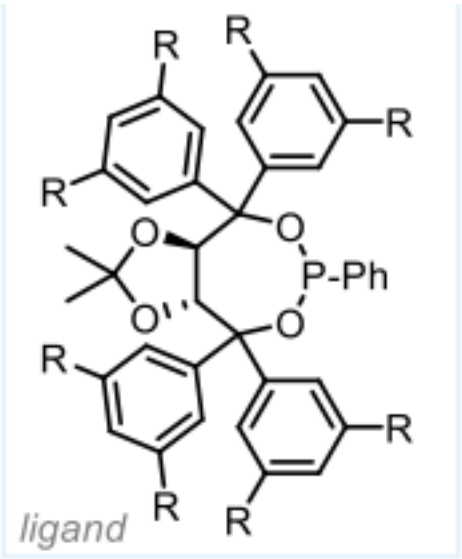
- **This work** (enantioselective desymmetrization approach):



Studies on the Synthesis of Functionalized Hydrindane via Asymmetric Diboration/Double-Allylboration Cascade



13a 14a 15a

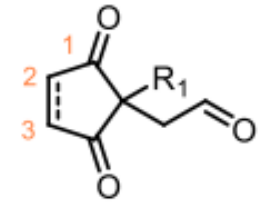


entry	ligand	-R	solvent	temp. (°C)	yield[c] (%)	ee (%)
1	none	-	toluene	100	0	N.D.
2	PPh_3	-	toluene	100	0	N.D.
3	$P(OEt)_3$	-	toluene	100	0	N.D.
4	L1	H	toluene	100	trace	1
5	L2	Me	toluene	100	21	25
6	L3	Et	toluene	100	32	37

7	L4	CF_3	toluene	100	0	N.D.
8	**L5**	***i*-Pr**	**toluene**	**100**	**75**	**90**
9	L6	*t*-Bu	toluene	100	52	90
10	L5	*i*-Pr	xylene	100	25	69
11	L5	*i*-Pr	THF	100	60	83
12	L5	*i*-Pr	PhCl	100	18	67
13	L5	*i*-Pr	toluene	80	27	90
14	L5	*i*-Pr	toluene	120	72	90
15	L5	*i*-Pr	toluene	160	64	86

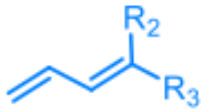
[a]The reactions were conducted by combining a catalyst (2.0 mol %), ligand (2.4 mol %), and $B_2(pin)_2$ (1.05 equiv) with a solution of **14a** (1.0 equiv) under an argon atmosphere in a solvent (1.0 M) at 60 °C. The mixture was stirred until TLC indicated a complete consumption of **14a**. Subsequently, **13a** (1.0 equiv) was introduced into the reaction mixture and stirred for an additional 24 h at the specified temperature. [b]$B_2(pin)_2$ = Bis(pinacolato)diboron.

Substrate Scope



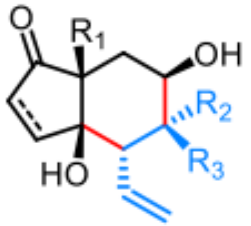
13a: R_1=Me; C_2=C_3
13b: R_1= Et; C_2=C_3
13c: R_1= Bn; C_2=C_3
13d: R_1= allyl; C_2=C_3
13e: R_1= Me; C_2-C_3

+



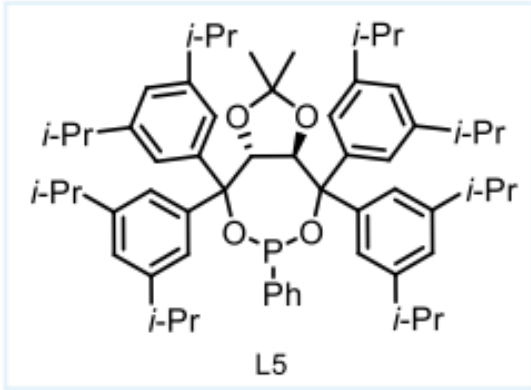
14a: R_2= Me, R_3= CH_2OTBS
14b: R_2= Me, R_3= $CH_2OTBDPS$
14c: R_2= Me, R_3= CH_2OPMB
14d: R_2= Me, R_3= $(CH_2)_3OTBS$
14e: R_2= Me, R_3= (CH_2)prenyl
14f: R_2= Me, R_3= $(CH_2)_2Ph$
14g: R_2= Me, R_3=Ph(4-OMe)
14h: R_2= Me, R_3= Ph(3-OMe)

$Pt(dba)_3$
L5
$B_2(pin)_2$
toluene

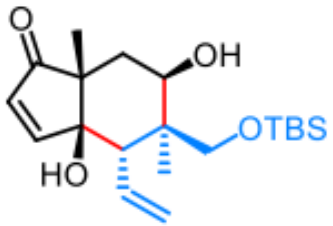


15

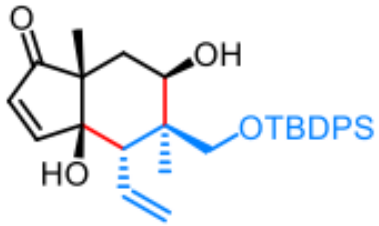
14i: R_2= Me, R_3= Ph
14j: R_2= (CH_2)prenyl, R_3= Me
14k: R_2= Me, R_3= CH_2OBn
14l: R_2= Me, R_3= furanyl



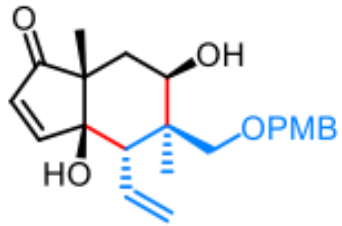
L5



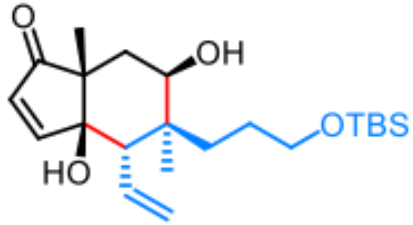
15a
(13a + 14a)
Y: 75%, d.r. = 15 : 1
ee: 90%



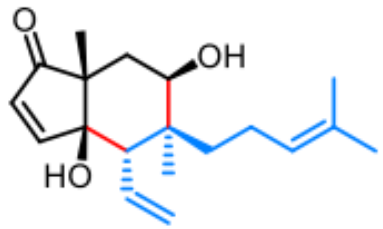
15b
(13a + 14b)
Y: 65%, d.r. > 20 : 1
ee: 93%



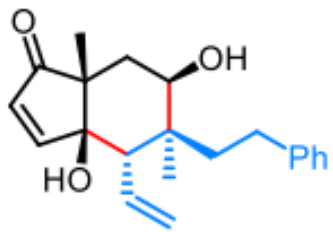
15c
(13a + 14c)
Y: 65%, d.r. = 15 : 1
ee: 73%



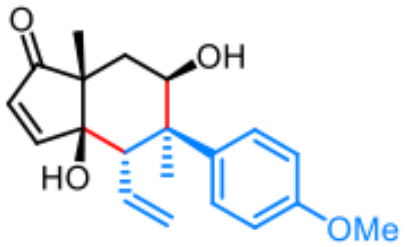
15d
(13a + 14d)
Y: 62%, d.r. > 20:1
ee: 90%



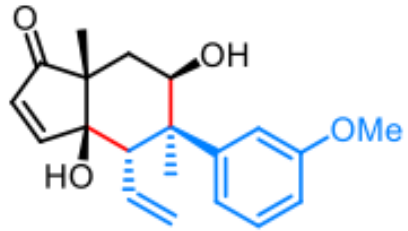
15e
(13a + 14e)
Y: 51%, d.r. = 4 : 1
ee: 90%
(x-ray)



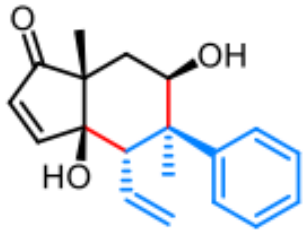
15f
(13a + 14f)
Y: 57%, d.r.> 20 : 1
ee: 71%



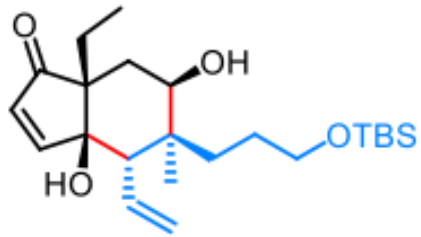
15g
(13a + 14g)
Y: 50%, d.r. > 20 : 1
ee: 90%
(x-ray)



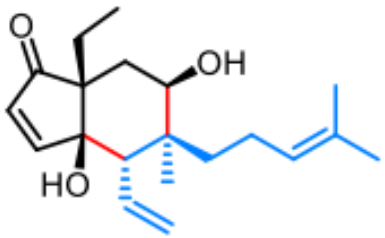
15h
(13a + 14h)
Y: 44%, d.r. = 15 : 1
ee: 86%
(x-ray)



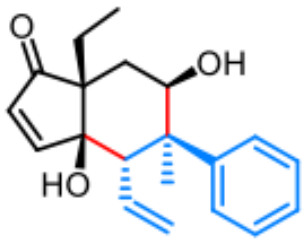
15i
(13a + 14i)
Y: 47%, d.r. = 12 :1
ee: 88%



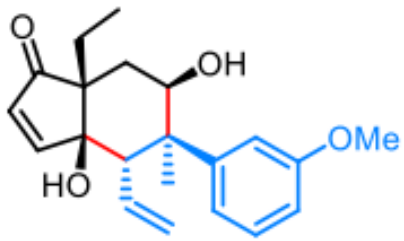
15j
(13b + 14d)
Y: 47%, d.r. > 20:1
ee: 95%



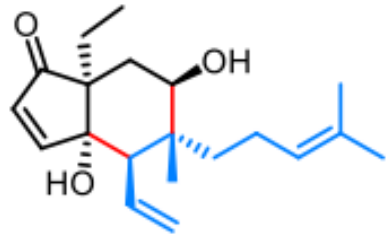
15k
(13b + 14e)
Y: 51%, d.r. = 12 : 1
ee: 86%



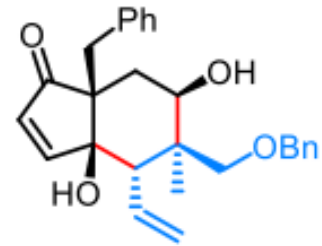
15l
(13b + 14i)
Y: 40%, d.r. > 20 : 1
ee: 90%



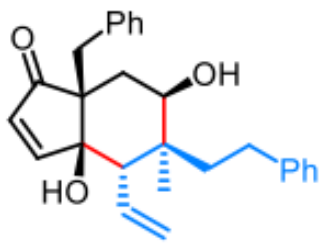
15m
(13b + 14h)
Y: 48%, d.r. > 20 : 1
ee: 94%



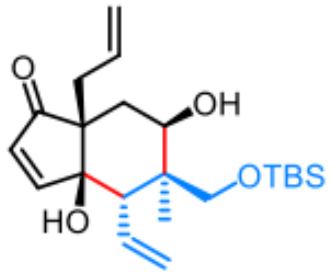
15n
(13b + 14j)
Y: 56%, d.r. > 20 : 1
ee: 77%
(x-ray)



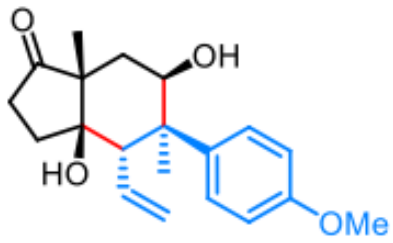
15o
(13c + 14k)
Y: 57%, d.r. > 20:1
ee: 84%
(x-ray)



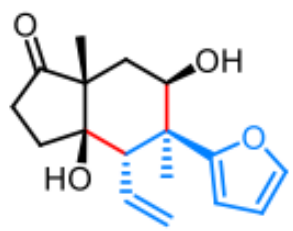
15p
(13c + 14f)
Y: 55%, d.r.> 20 : 1
ee: 67%



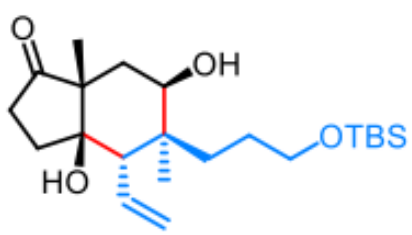
15q
(13d + 14a)
Y: 41%, d.r.> 20 : 1
ee: 90%



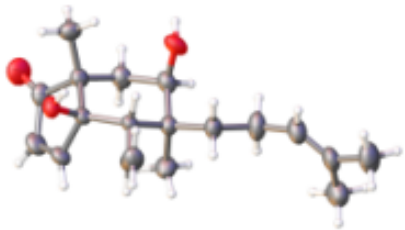
15r
(13e + 14g)
Y: 31%, d.r. > 20 : 1
ee: 92%
(x-ray)



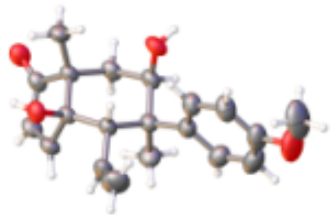
15s
(13e + 14l)
Y: 42%, d.r. = 8 : 1
ee: 92%



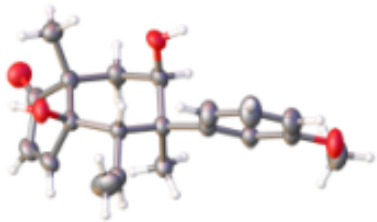
15t
(13e + 14d)
Y: 32%, d.r. = 4 : 1
ee: 92%



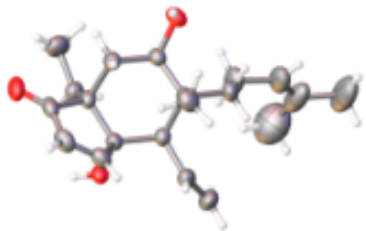
x-ray of **15e**



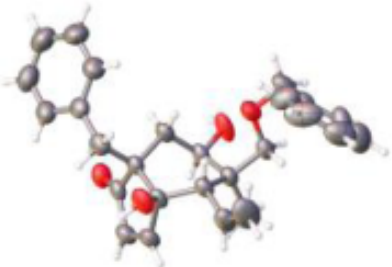
x-ray of **15g**



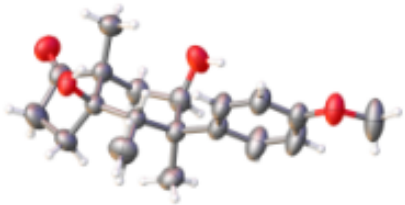
x-ray of **15h**



x-ray of **15n**



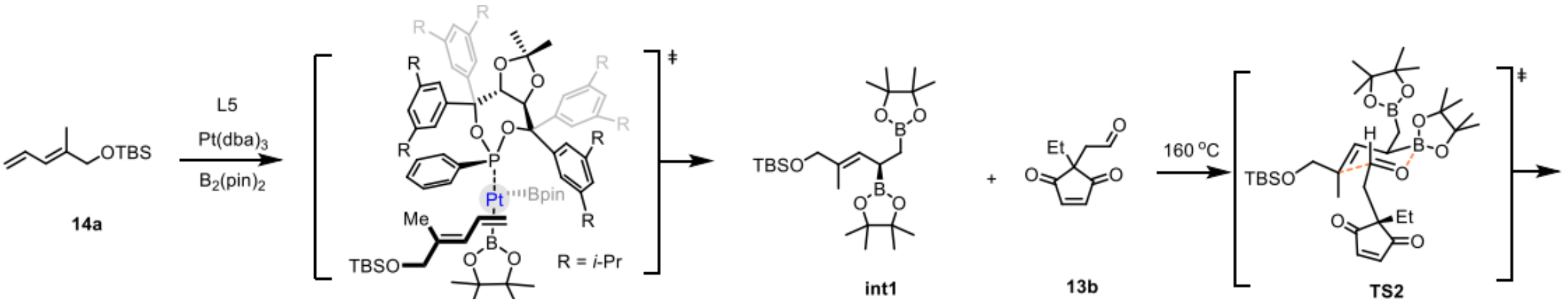
x-ray of **15o**



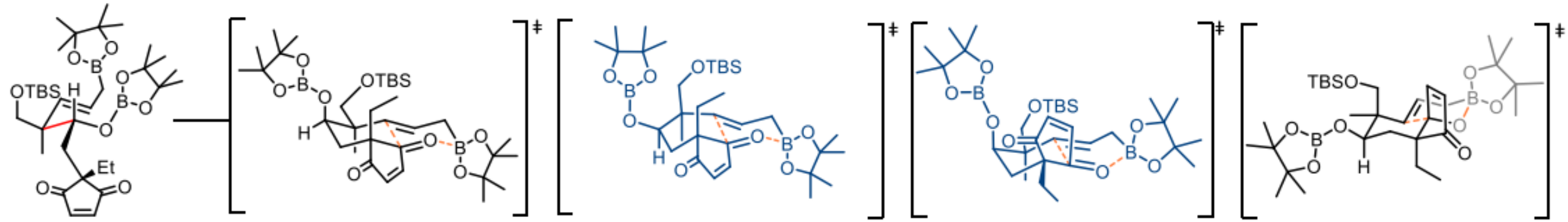
x-ray of **15r**

[a]The reactions were conducted by combining a catalyst (2.0 mol %), ligand (2.4 mol %), and $B_2(pin)_2$ (1.05 equiv) with a solution of **14** (1.0 equiv) under an argon atmosphere in toluene (1.0 M) at 60 °C. The mixture was stirred until TLC indicated complete consumption of **14**, then compound **13** (1.0 equiv) was introduced into the reaction mixture and stirred for an additional 24 h at 100 °C. The yields refer to isolated products, dr values were determined by ^{1}H NMR and enantiomeric excess (ee values) were determined by HPLC analysis by using a chiral stationary phase. For details, see the Supporting Information.

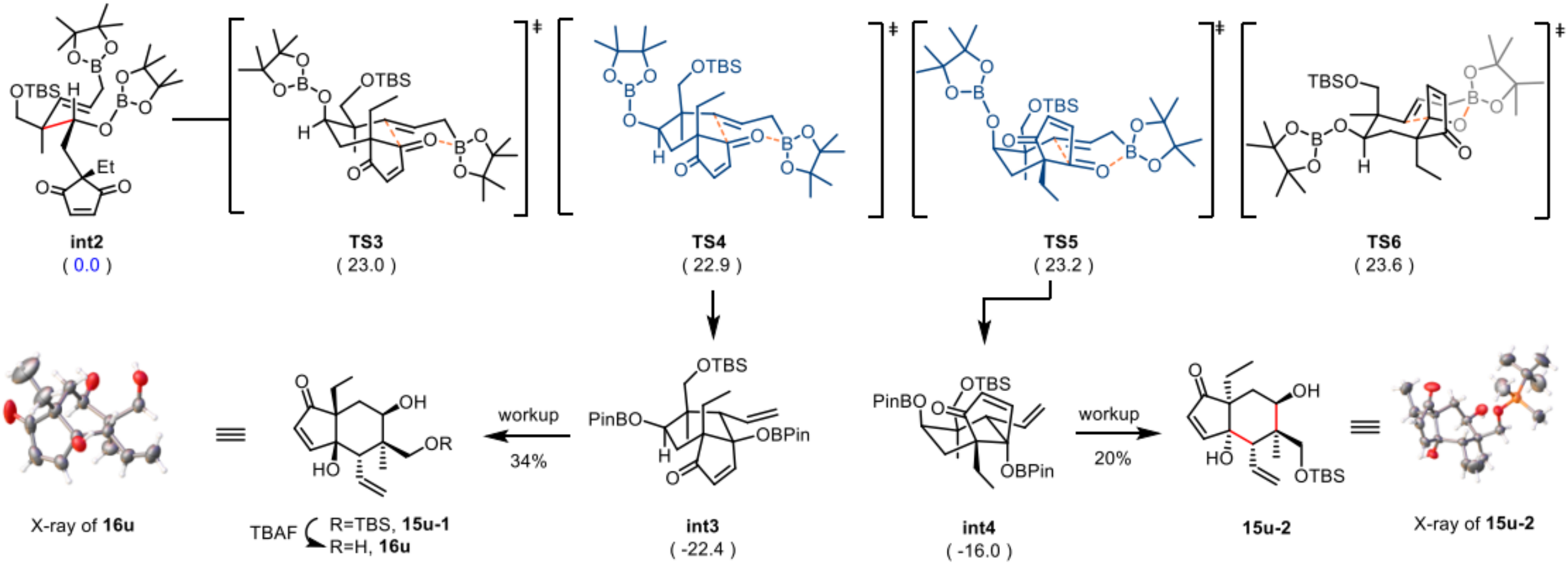
Stereochemical Model for the Double-Allylbaration Step



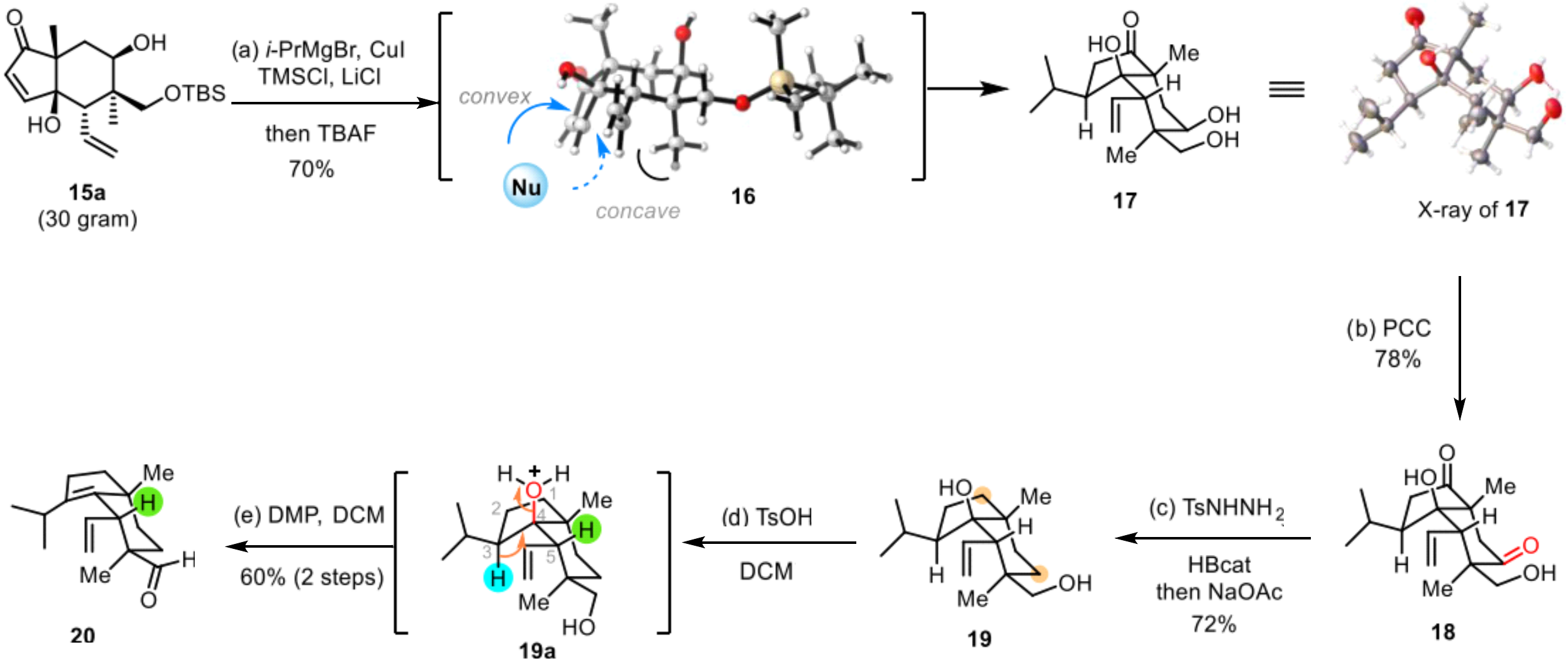
Stereochemical Model for the Double-Allylboration Step[a]



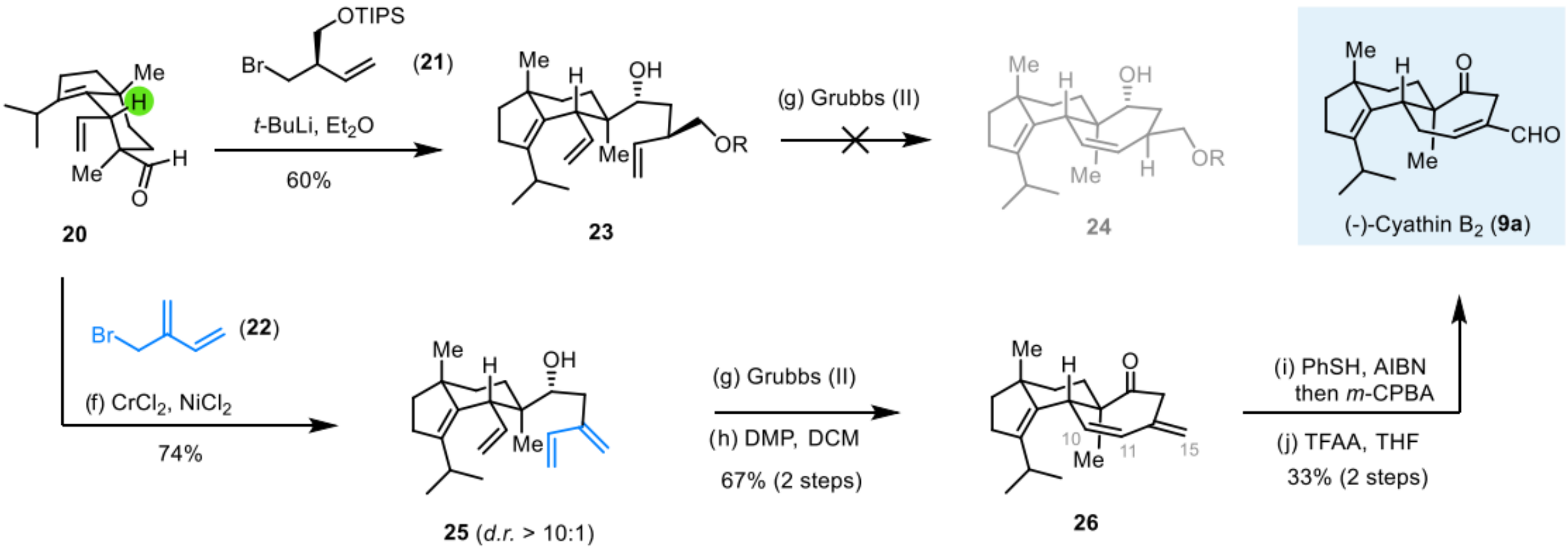
Stereochemical Model for the Double-Allylbaration Step



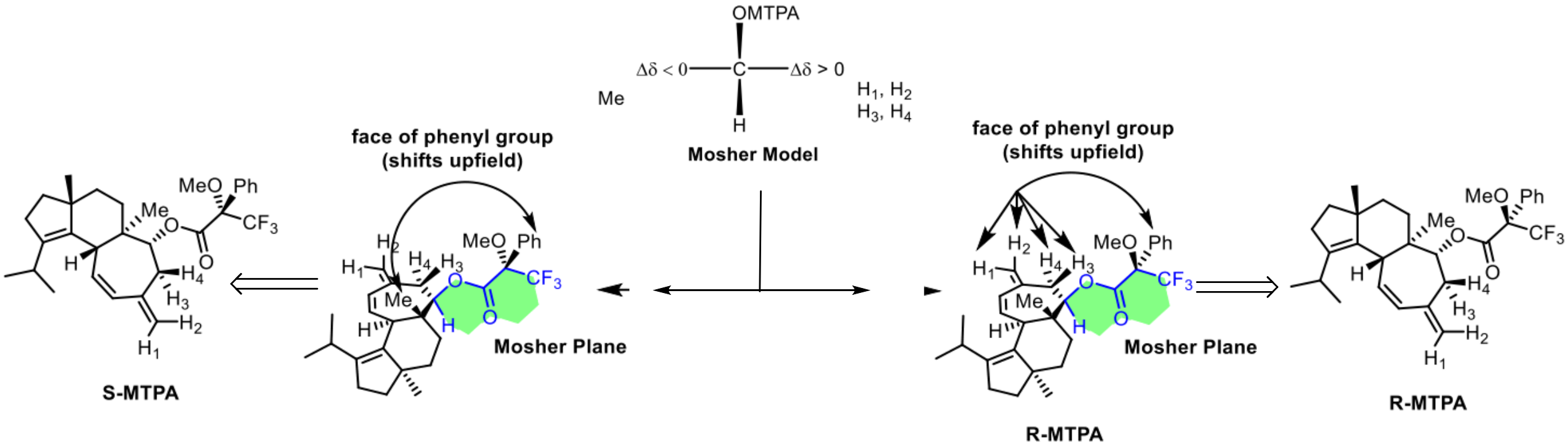
Enantioselective Total Synthesis of (-)-Cyathin B_2



Enantioselective Total Synthesis of (-)-Cyathin B_2



The Mosher Method for Determining the Configuration of Hydroxy Group



$\Delta\delta(\delta_S - \delta_R)$ of compounds 30b and 30a

Porton	Chemical shift of S-MTPA (600 M)	Chemical shift of R-MTPA (600 M)	$\Delta\delta(\delta_S - \delta_R)$
H_1	4.97	4.92	> 0
H_2	4.95	4.87	> 0
H_3	2.72, 2.71, 2.69, 2.69	2.66, 2.65, 2.63, 2.63	> 0
H_4	2.87, 2.86, 2.85, 2.85	2.79, 2.78, 2.77, 2.75	> 0
Me	1.03	1.04	< 0