

Asymmetric Total Synthesis of Aglacins A, B and E

Mengmeng Xu,^{a†} Min Hou,^{a†} Haibing He,^b Shuanhu Gao^{*a,b}

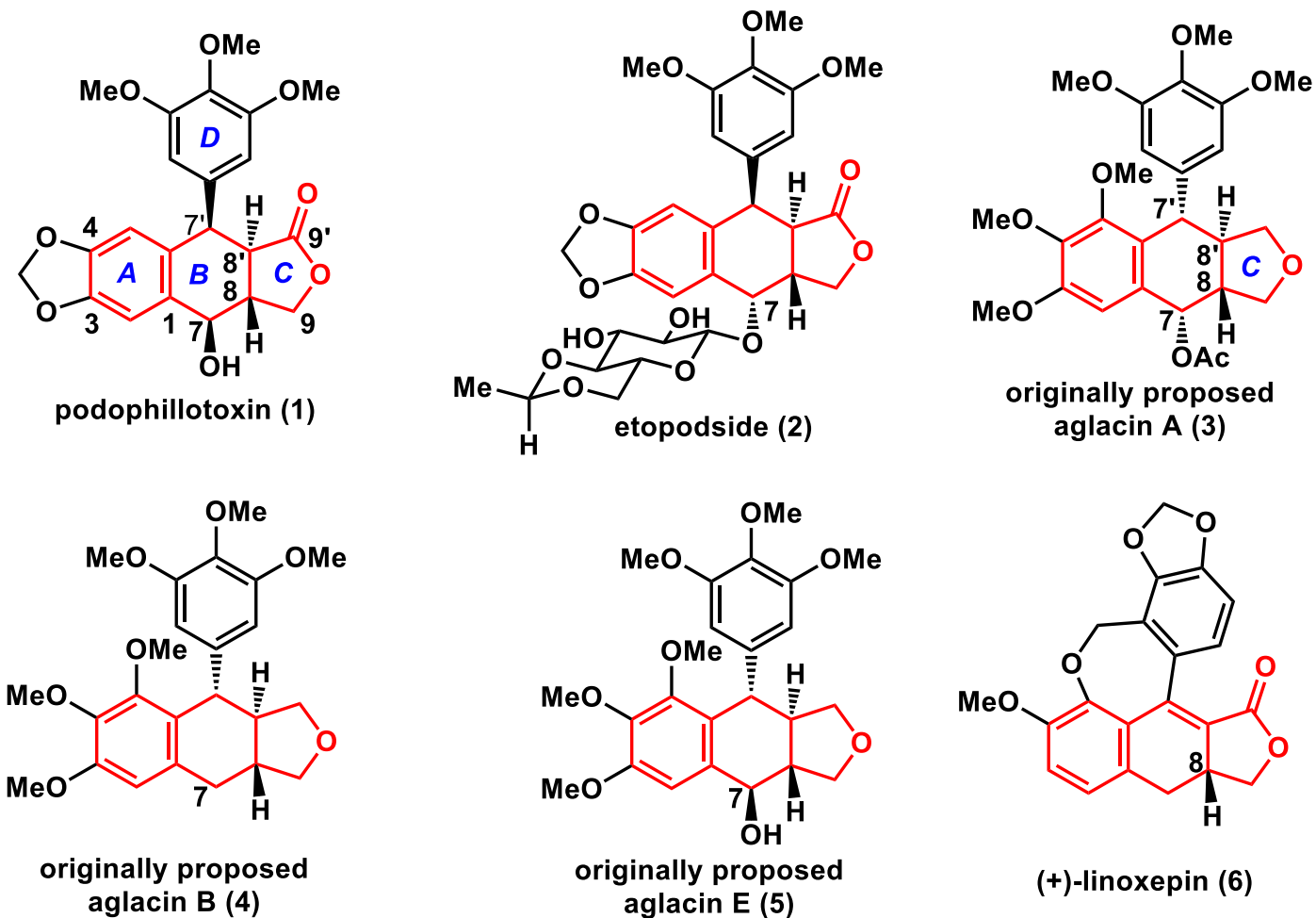
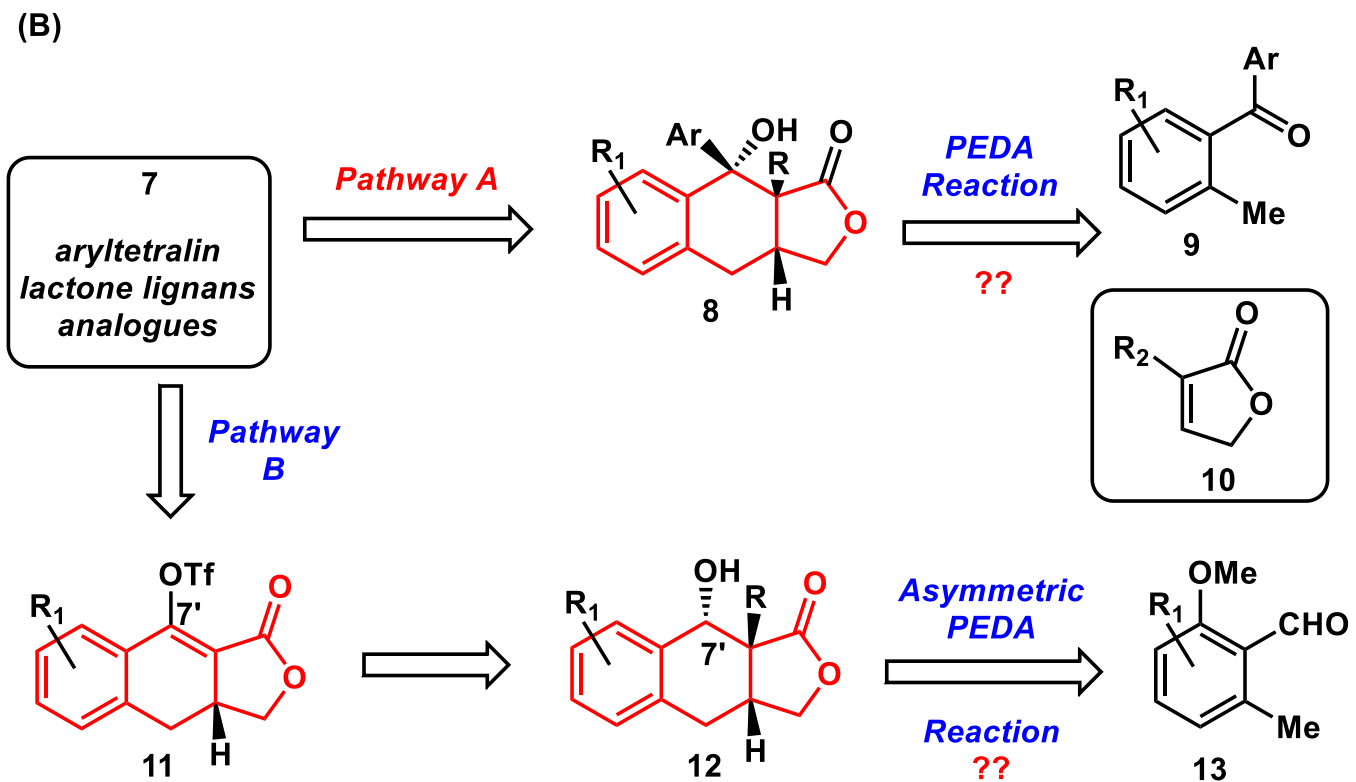
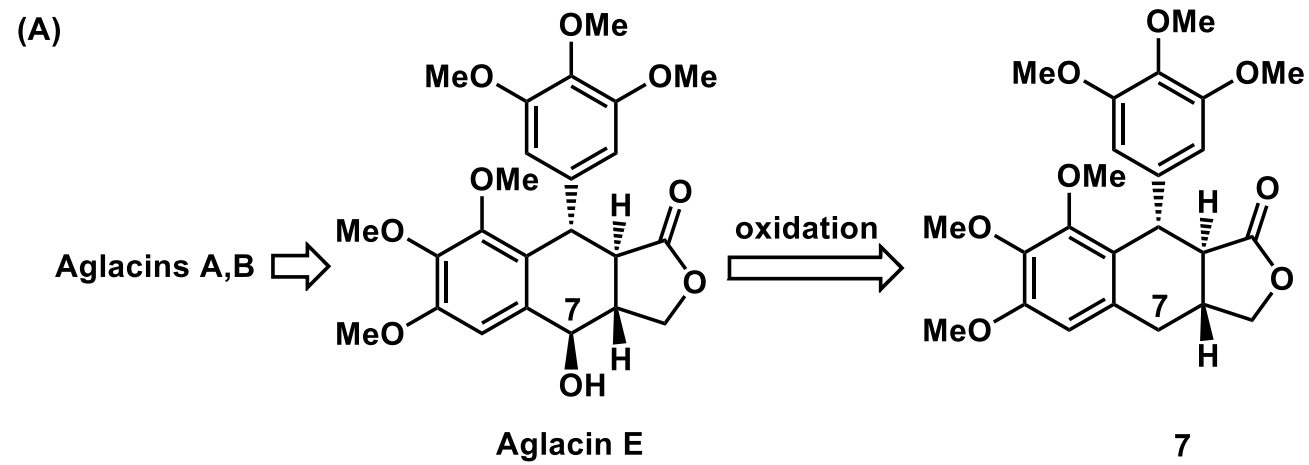
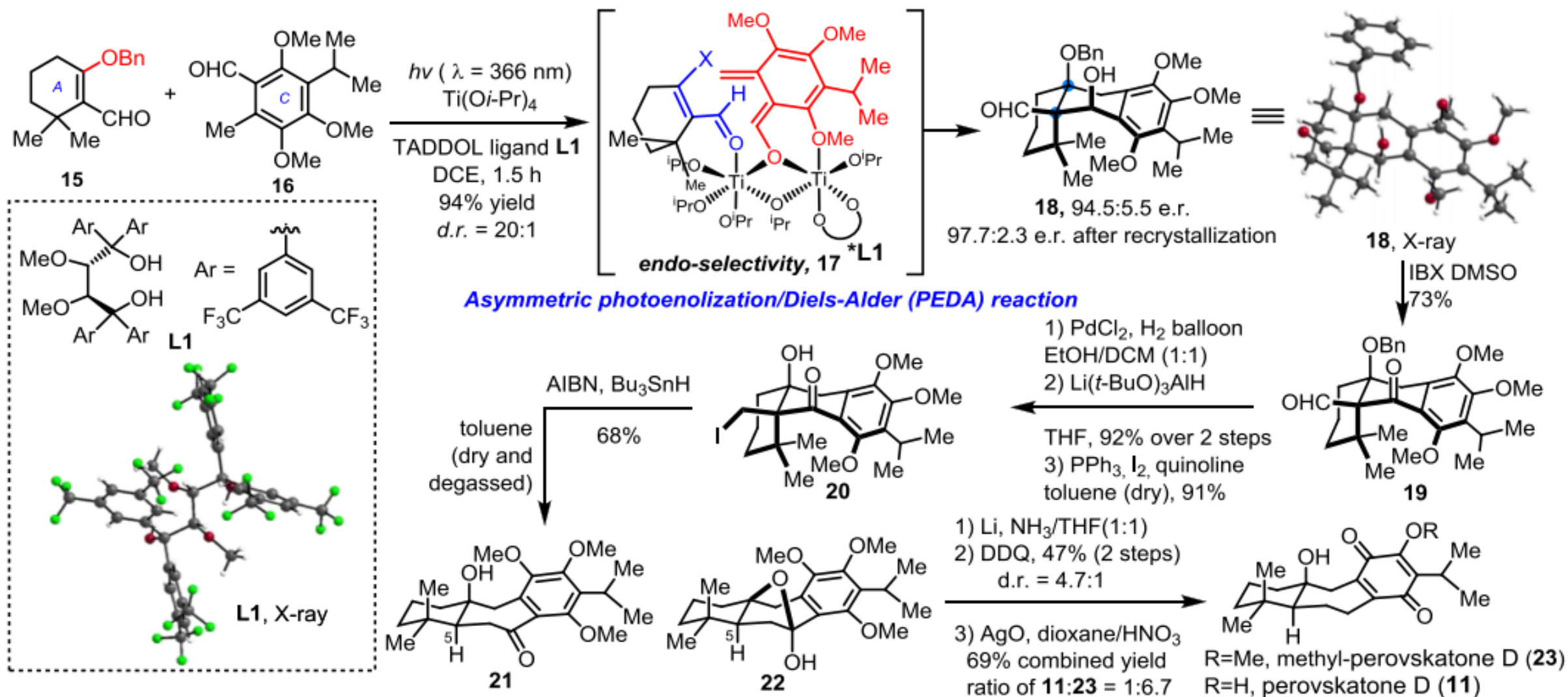


Figure 1. Podophyllotoxin, etoposide, originally proposed aglacins and (+)-linoxepin.

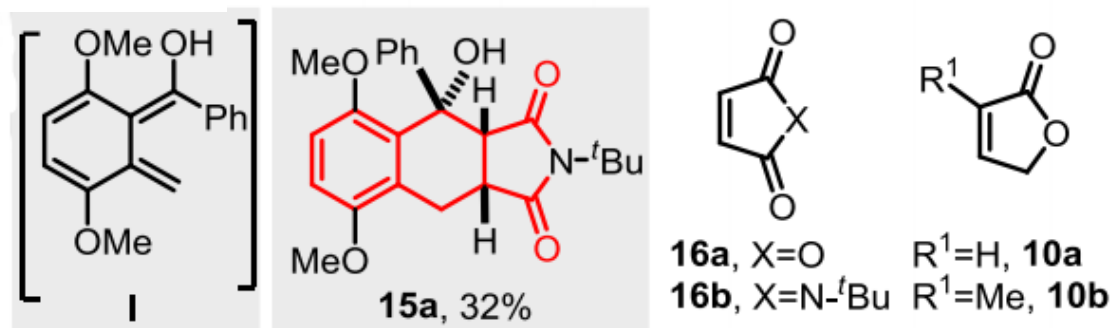
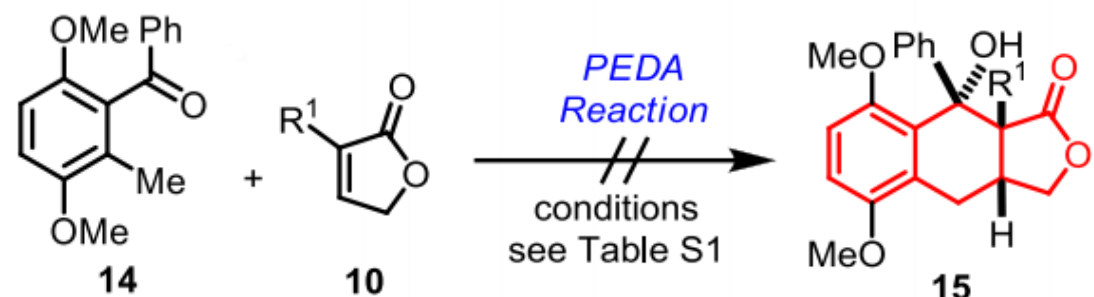


Scheme 1. Synthetic plan.

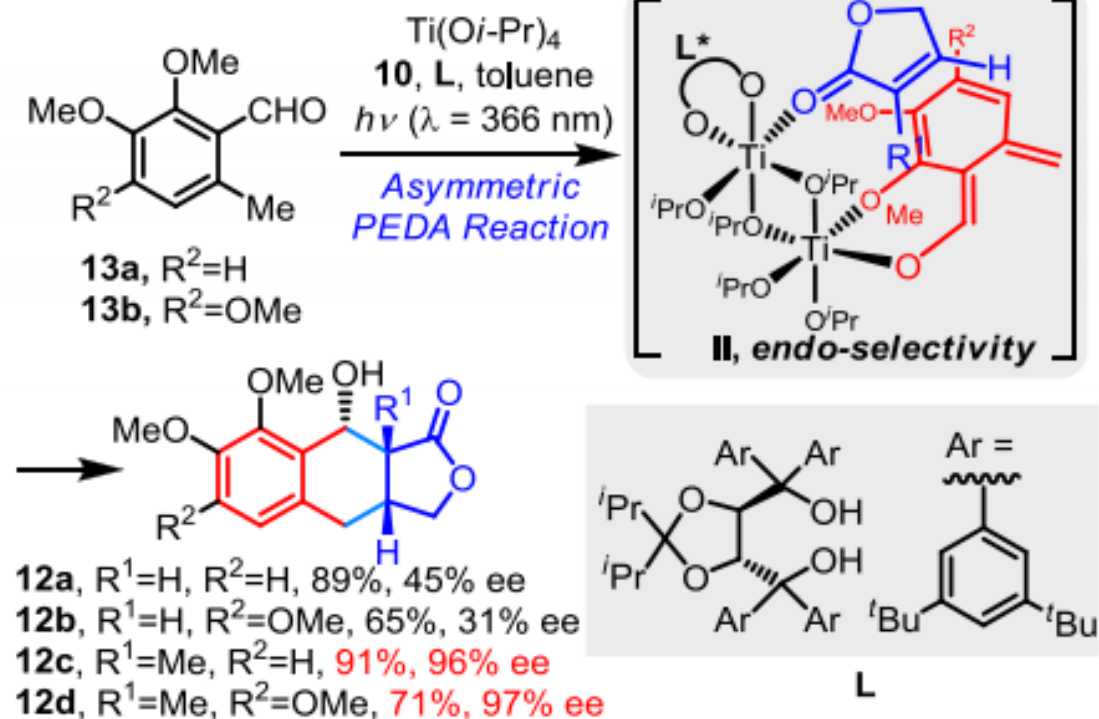
Scheme 2. Asymmetric Photoenolization/Diels–Alder (PEDA) Reaction and Total Synthesis of Perovskatone D



(A) Pathway A

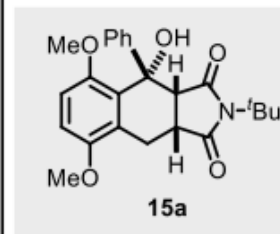
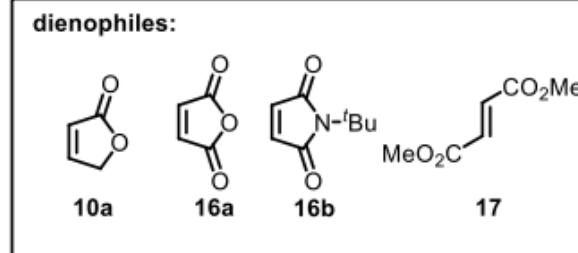
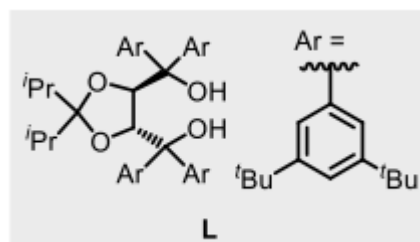
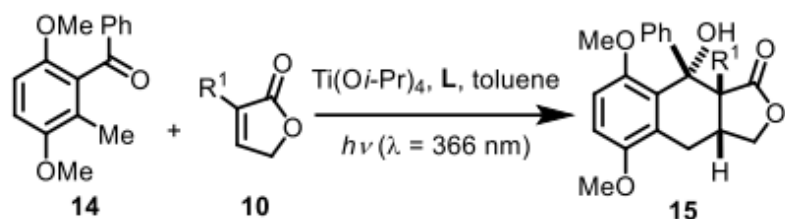


(B) Pathway B



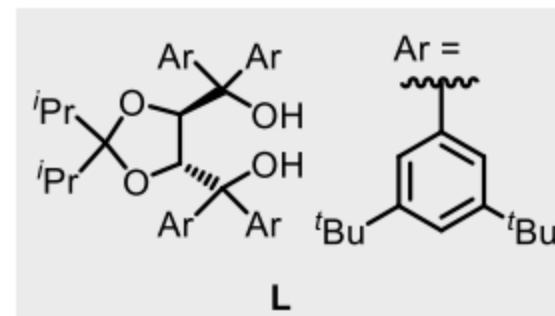
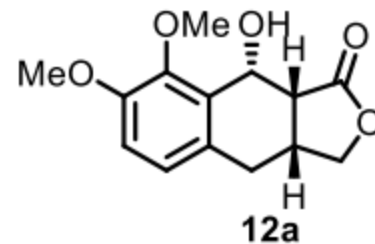
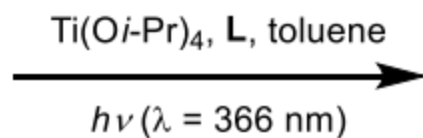
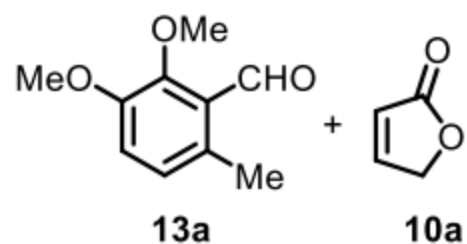
Scheme 2. Construction of tricyclic core of aryltetralin lactone lignans using asymmetric PEDA reactions.

Table S1. PEDA reaction: 14 as diene



entry	dienophile	Ti(O <i>i</i> -Pr) ₄	L	time	results
1	10a	none	none	4 h	N.R.
2	10a	1.0 equiv.	none	4 h	N.R.
3	10a	1.0 equiv.	0.5 equiv.	4 h	N.R.
4	16a	none	none	4 h	N.R.
5	16a	1.0 equiv.	none	4 h	N.R.
6	16a	0.4 equiv.	0.2 equiv.	4 h	N.R.
7	16b	none	none	4 h	15a , 9% yield
8	16b	1.0 equiv.	none	4 h	15a , 32% yield
9	16b	0.4 equiv.	0.2 equiv.	4 h	15a , 32% yield, 0% ee
10	17	none	none	4 h	ND, 17 almost decomposed
11	17	1.0 equiv.	none	4 h	ND, 17 almost decomposed
12	17	0.4 equiv.	0.2 equiv.	4 h	ND, 17 almost decomposed

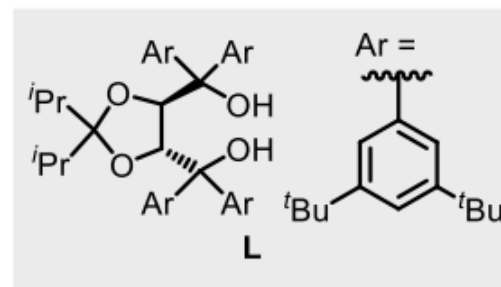
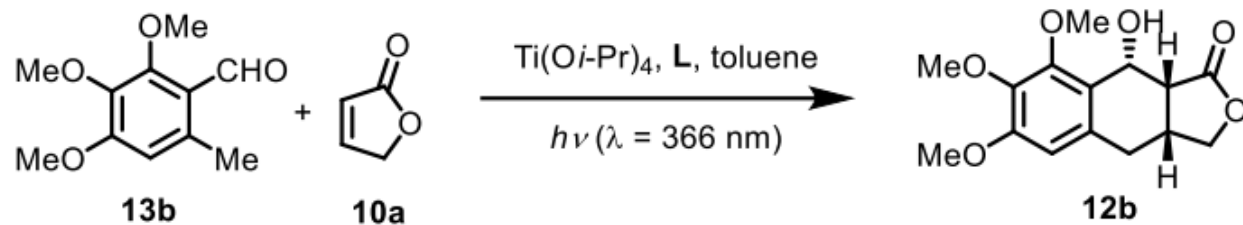
Standard reaction conditions: aromatic aldehyde (0.05 mmol, 1.0 equiv.), dienophile (0.75 mmol, 1.5 equiv.), toluene (5 mL, 0.01 M), 30 °C. yield was determined by ¹H NMR spectroscopic crude analysis using CH₂Br₂ as an internal standard; The ee values were determined by chiral HPLC analys.

Table S2. PEDAs reaction of **13a** and **10a**

entry	Ti(O <i>i</i> -Pr) ₄	L	time	Conv.	yield	ee
1	none	none	30 min	100%	33%	-
2	1.0 equiv.	none	30 min	100%	74%	-
3	1.0 equiv.	0.5 equiv.	30 min	100%	89%	45%
4	0.4 equiv.	0.2 equiv.	30 min	100%	90%	8%
5	0.2 equiv.	0.1 equiv.	30 min	100%	42%	0%

Standard reaction conditions: aromatic aldehyde (0.05 mmol, 1.0 equiv.), dienophile (0.75 mmol, 1.5 equiv.), toluene (5 mL, 0.01 M), 30 °C, Conversion and yield were determined by ¹H NMR spectroscopic crude analysis using CH₂Br₂ as an internal standard; The ee values were determined by chiral HPLC analysis

Table S3. PEDA reaction of **13b and **10a****

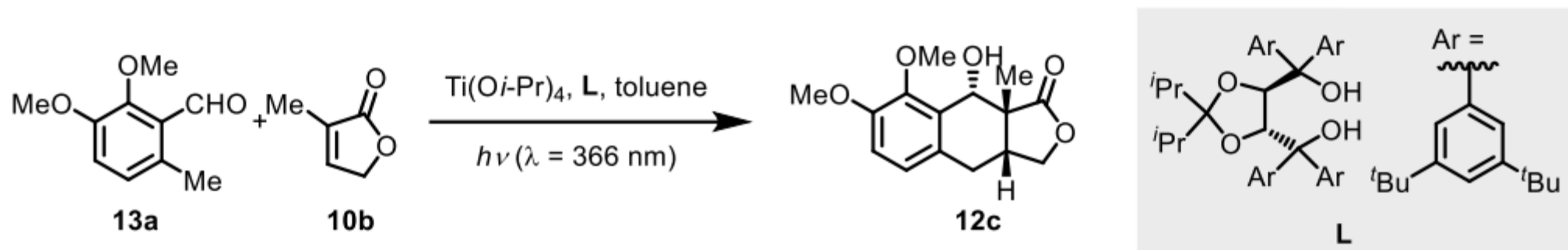


entry	Ti(O <i>i</i> -Pr) ₄	L	time	Conv.	yield	ee
1	none	none	30 min	89%	7%	-
2	1.0 equiv.	none	30 min	100%	65%	-
3	1.0 equiv.	0.5 equiv.	10 min	89%	65%	19%
4	1.0 equiv.	0.5 equiv.	20 min	99%	75%	17%
5	1.0 equiv.	0.5 equiv.	30 min	100%	65%	31%
6	0.4 equiv.	0.2 equiv.	30 min	86%	64%	19%
7	0.2 equiv.	0.1 equiv.	30 min	50%	trace	-
8 ^a	0.4 equiv.	0.2 equiv.	30 min	100%	64%	21%
9 ^a	0.2 equiv.	0.1 equiv.	30 min	100%	trace	-

Standard reaction conditions: aromatic aldehyde (0.05 mmol, 1.0 equiv.), dienophile (0.75 mmol, 1.5 equiv.), toluene (5 mL, 0.01 M), rt; Conversion and yield were determined by ¹H NMR spectroscopic crude analysis using CH₂Br₂ as an internal standard; The ee values were determined by chiral HPLC analysis.

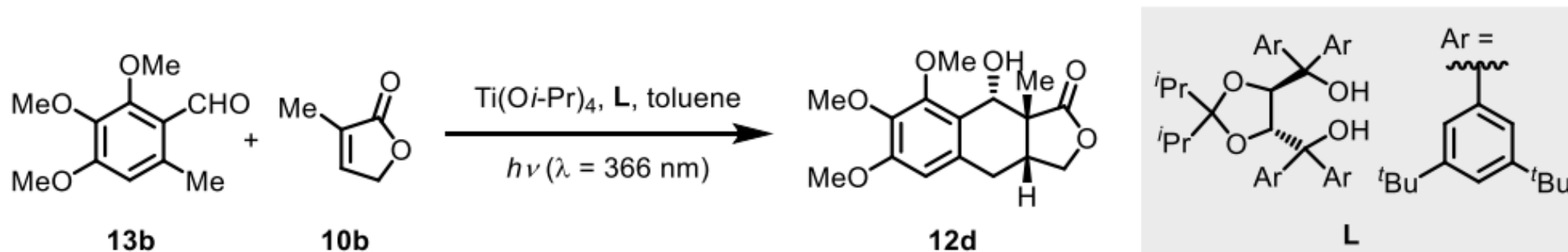
^aThe reaction was conducted in **13b** (0.075 mmol, 1.5 equiv.), **10a** (0.05 mmol, 1.0 equiv.)

Table S4. PEDA reaction of **13a** and **10b**



entry	$\text{Ti}(\text{O}i\text{-Pr})_4$	L	time	Conv.	yield	ee
1	1.0 equiv.	0.5 equiv.	30 min	100%	91%	96%
2	0.4 equiv.	0.2 equiv.	30 min	100%	60%	96%
3	0.2 equiv.	0.1 equiv.	30 min	-	decomposed	-

Standard reaction conditions: aromatic aldehyde (0.05 mmol, 1.0 equiv.), dienophile (0.75 mmol, 1.5 equiv.), toluene (5 mL, 0.01 M), 30 °C; Conversion and yield were determined by ^1H NMR spectroscopic crude analysis using CH_2Br_2 as an internal standard; The ee values were determined by chiral HPLC analysis.

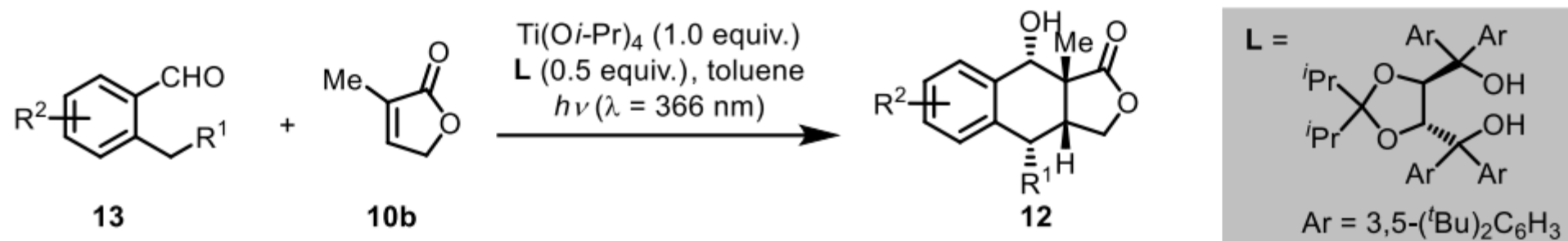
Table S5. PEDA reaction of **13a** and **10b**

entry	Ti(Oi-Pr) ₄	L	time	Conv.	yield	ee
1	1.0 equiv.	0.5 equiv.	10 min	83%	55%	98%
2	1.0 equiv.	0.5 equiv.	20 min	96%	74%	98%
3	1.0 equiv.	0.5 equiv.	30 min	100%	71%	97%
4	0.4 equiv.	0.2 equiv.	30 min	70%	8%	96%
5	0.2 equiv.	0.1 equiv.	30 min	-	N.R.	-
6 ^a	0.4 equiv.	0.2 equiv.	30 min	100%	12%	97%
7 ^a	0.2 equiv.	0.1 equiv.	30 min	-	decomposed	-

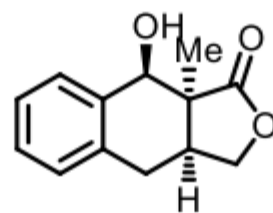
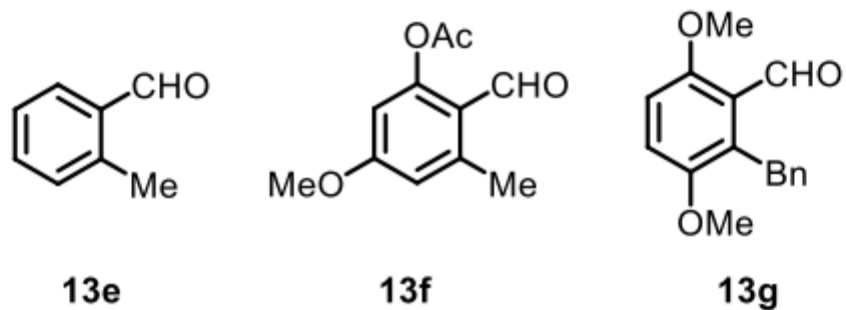
Standard reaction conditions: aromatic aldehyde (0.05 mmol, 1.0 equiv.), dienophile (0.75 mmol, 1.5 equiv.), toluene (5 mL, 0.01 M), 30 °C; Conversion and yield were determined by ¹H NMR spectroscopic crude analysis using CH₂Br₂ as an internal standard; The ee values were determined by chiral HPLC analysis.

^aThe reaction was conducted in **13b** (0.075 mmol, 1.5 equiv.), **10a** (0.05 mmol, 1.0 equiv.).

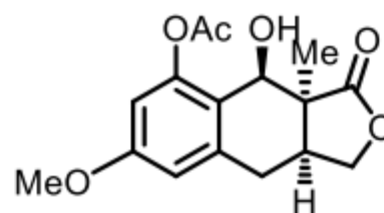
Table S6. Substrate scope of the APEDA reaction with electronic properties of aromatic aldehydes



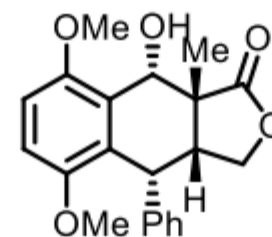
arylaldehyde:



12g, no reaction



12h, no reaction



12i, no reaction

Standard reaction conditions: aromatic aldehyde (0.05 mmol, 1.0 equiv.), dienophile (0.75 mmol, 1.5 equiv.), toluene (5 mL, 0.01 M), 30 °C.

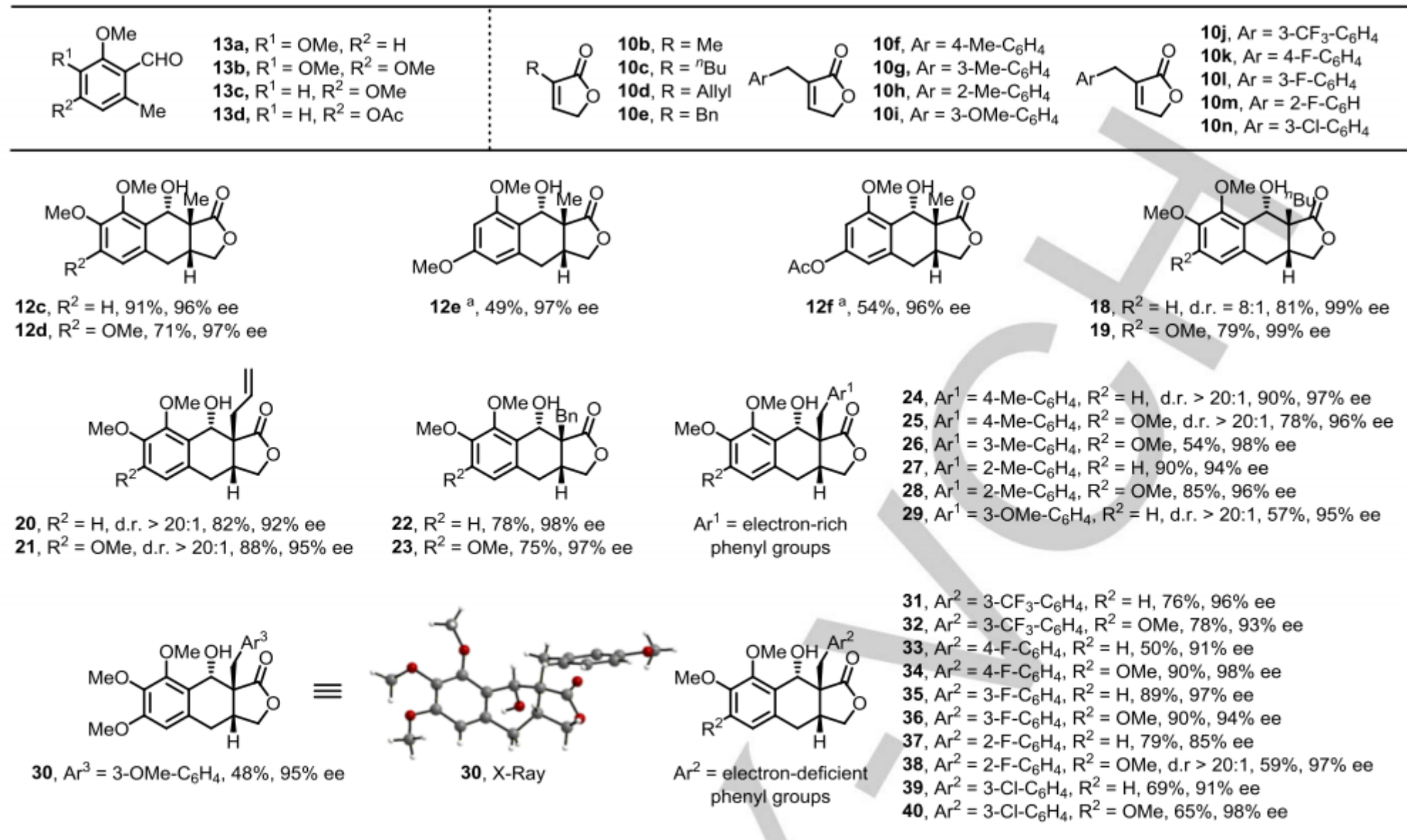
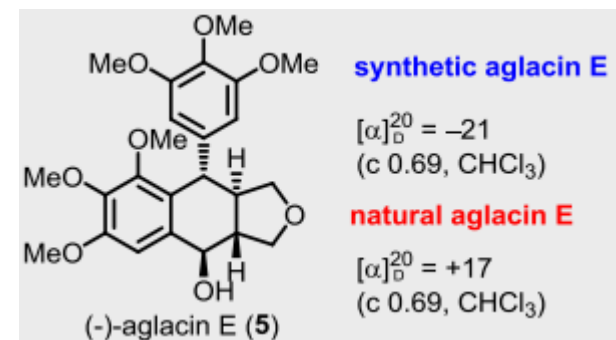
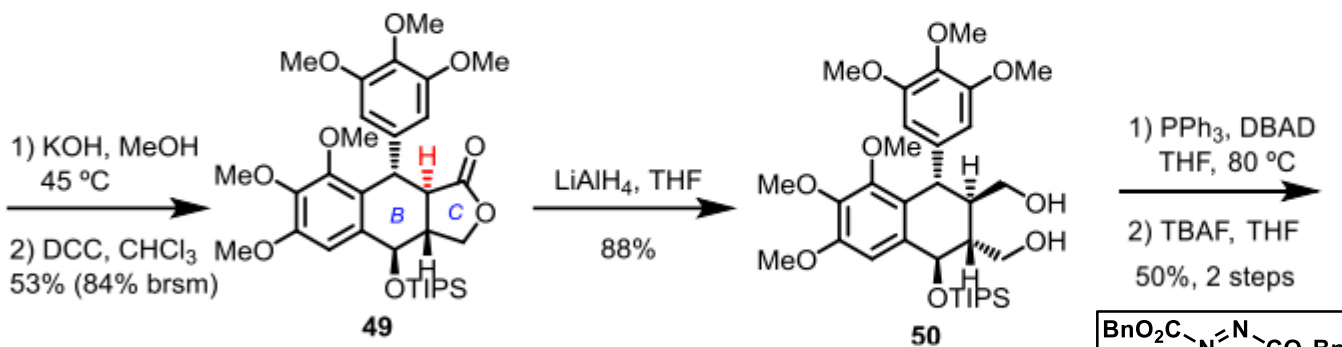
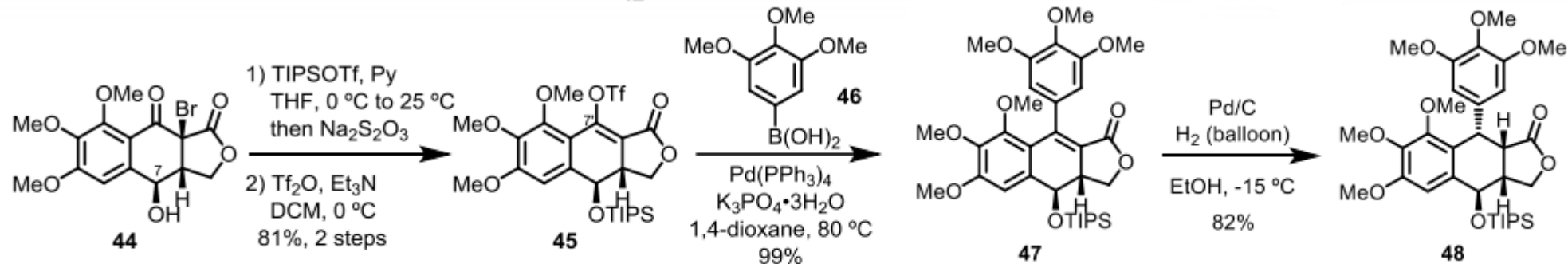
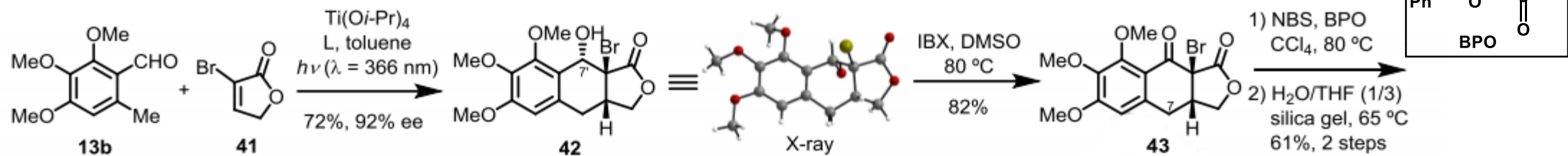


Table 1. Building a small library of aryltetralin lactones. Standard reaction conditions: aromatic aldehyde (0.30 mmol, 1.0 equiv.), dienophile (0.45 mmol, 1.5 equiv.), Ti(O*i*-Pr)₄ (0.30 mmol, 1.0 equiv.), **L** (0.15 mmol, 0.5 equiv.), toluene (30 mL, 0.01 M), 30 °C, 50 min. Isolated yields are shown. The ee values were determined by chiral HPLC analys, ^a 0.05 mmol scale.

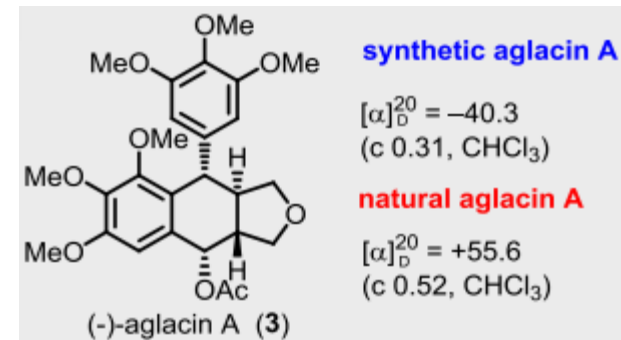
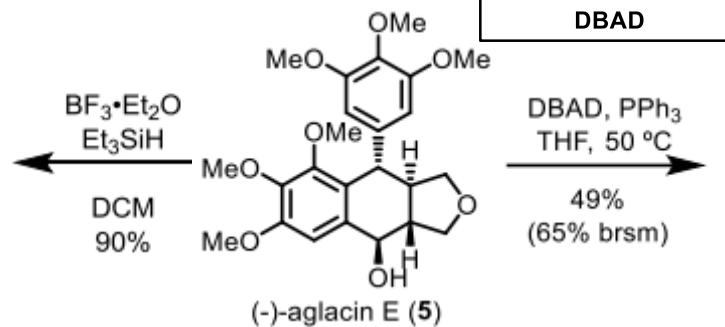
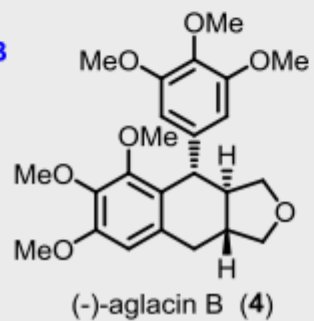


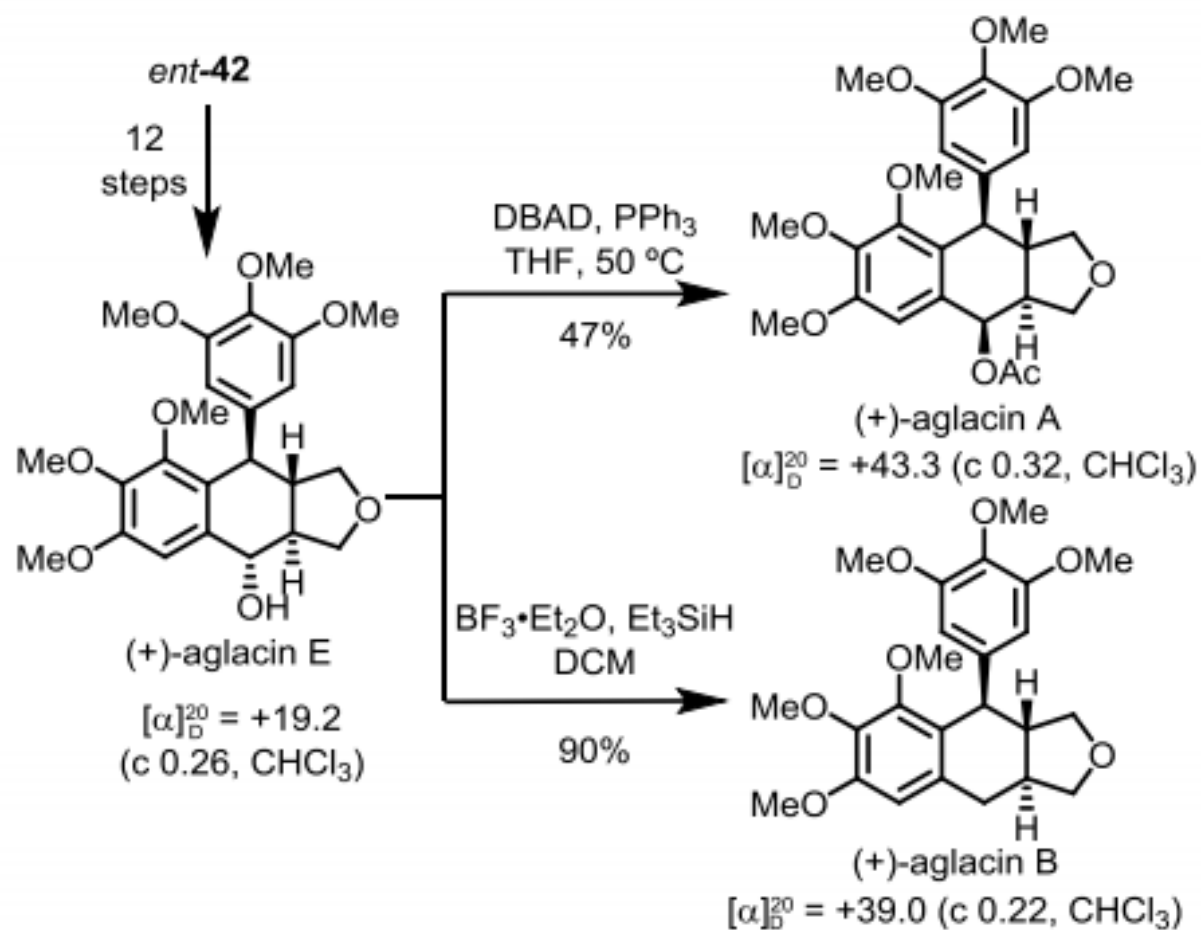
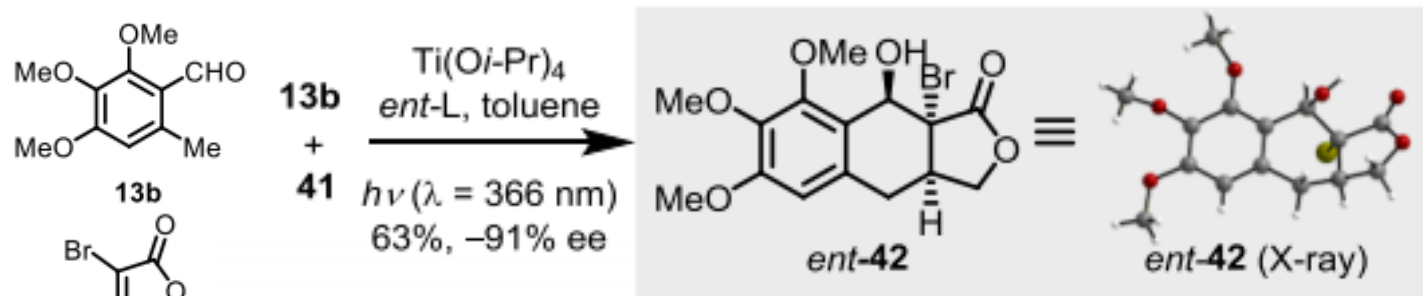
synthetic aglacin B

$[\alpha]_D^{20} = -41.2$
(c 0.46, CHCl₃)

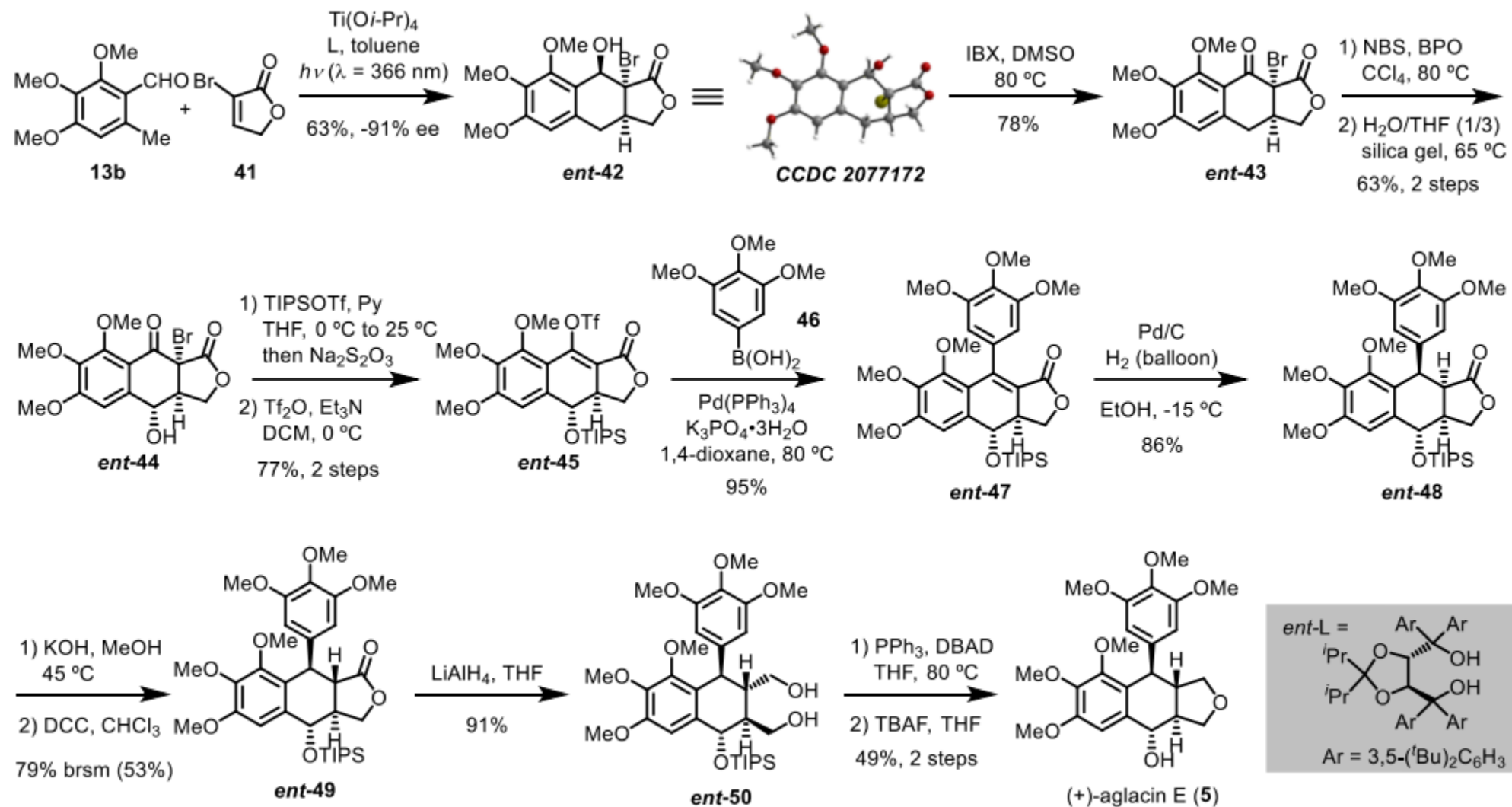
natural aglacin B

$[\alpha]_D^{20} = +45.0$
(c 0.38, CHCl₃)

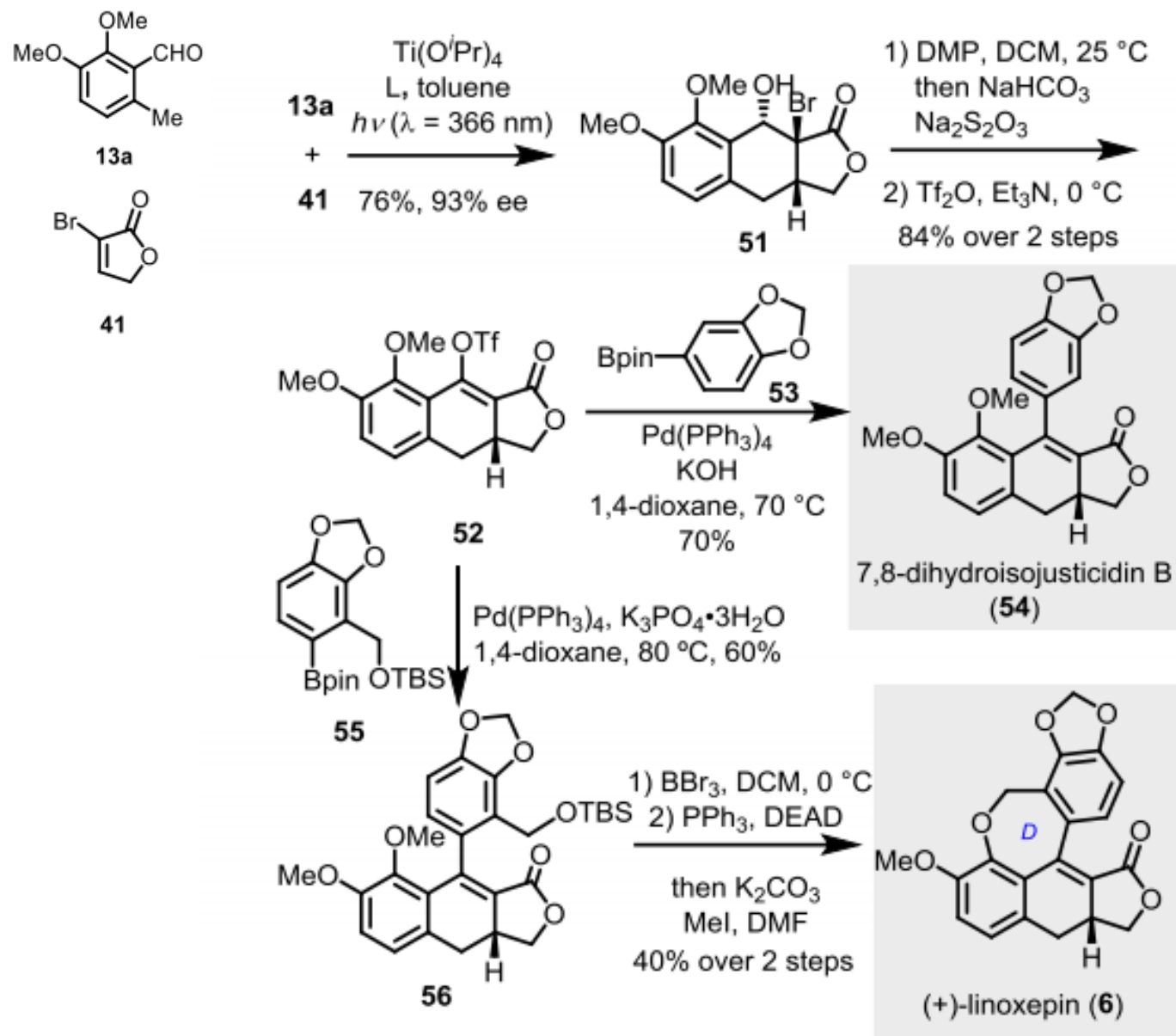




Scheme 4. Total synthesis of (+)-aglacins A, B and E.



Scheme S1. Total synthesis of (+)-Aglacin E



Scheme 5. Total synthesis of (+)-linoxepin and 7,8-dihydroisojusticidin B. DMP = Dess-Martin periodinane, DEAD = diethyl azodicarboxylate.