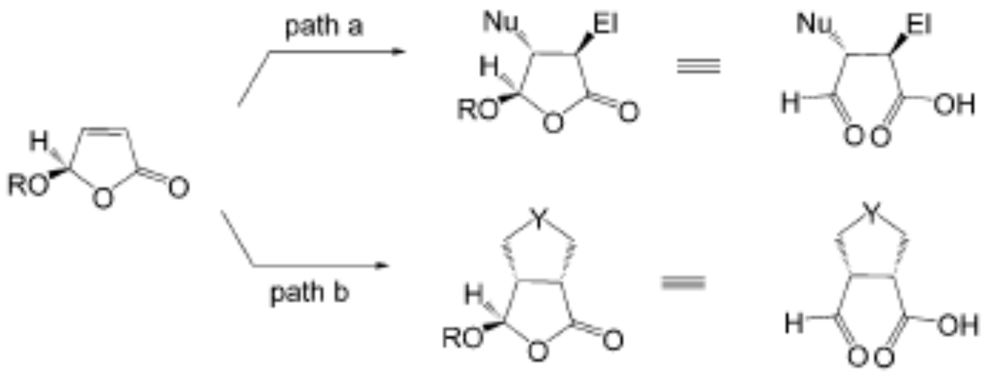
A “Chiral Aldehyde” Equivalent as a Building Block Towards Biologically Active Targets

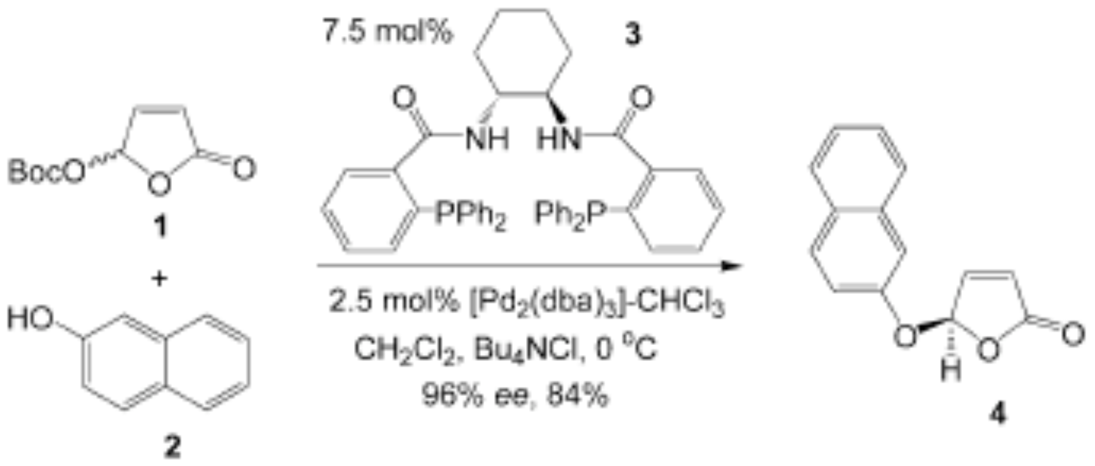
Barry M. Trost* and Matthew L. Crawley[a]

Chem. Eur. J. **2004**, *10*, 2237–2252

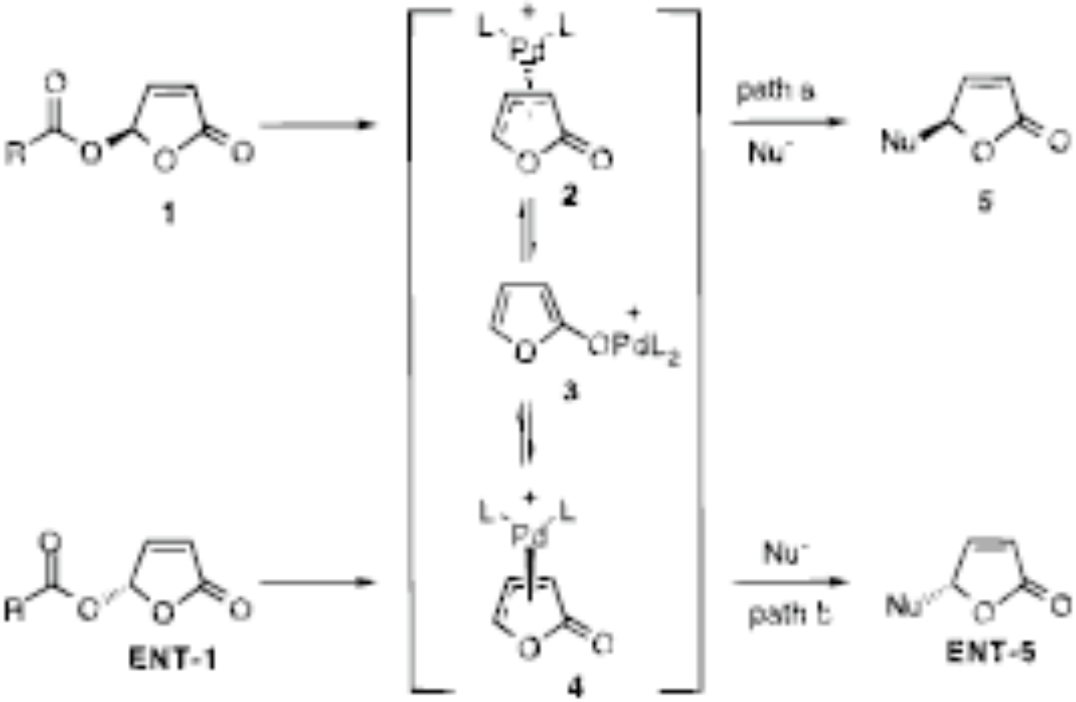


(1)

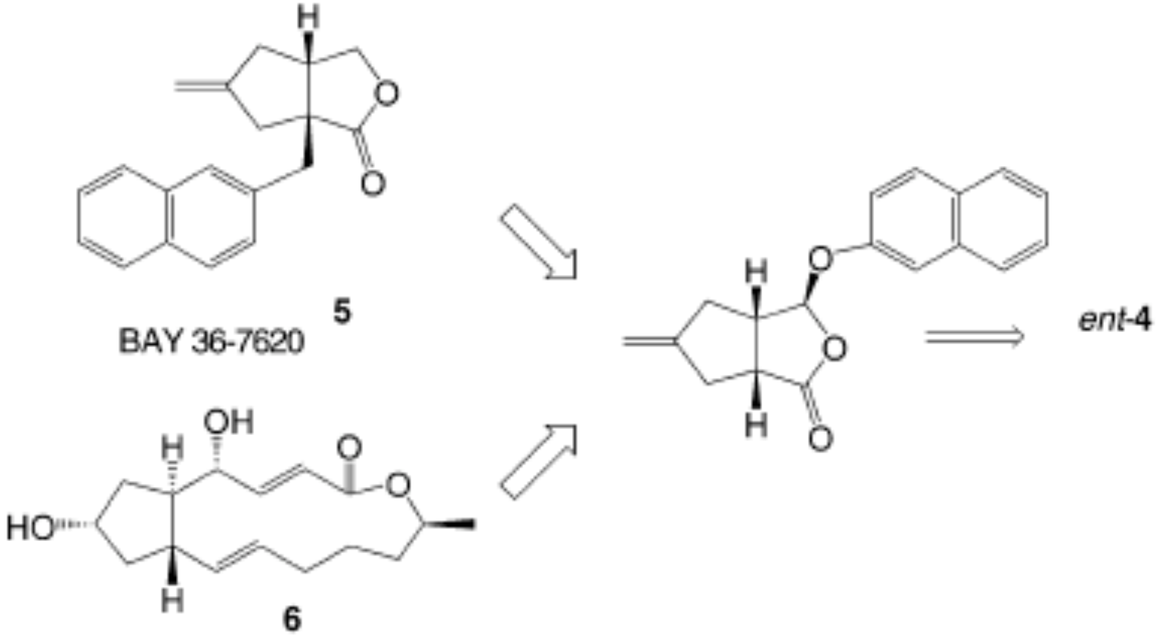
Dynamic **A**symmetric **K**inetic **T**ransformation



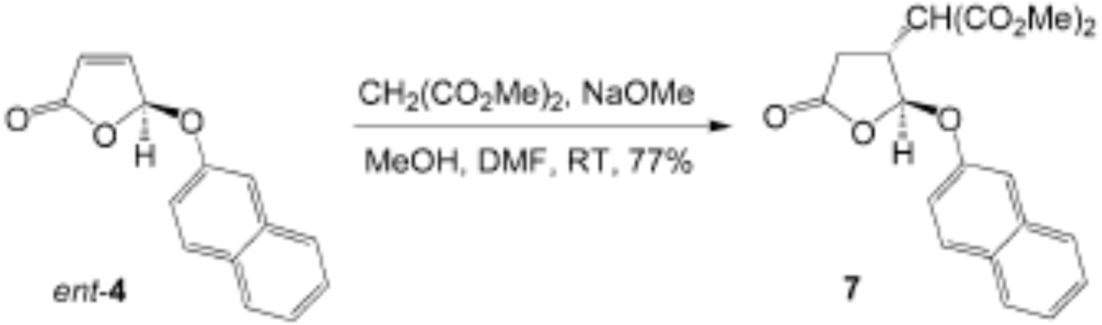
(2)



J. Am. Chem. Soc. **1999,** *121,* 3543−3544

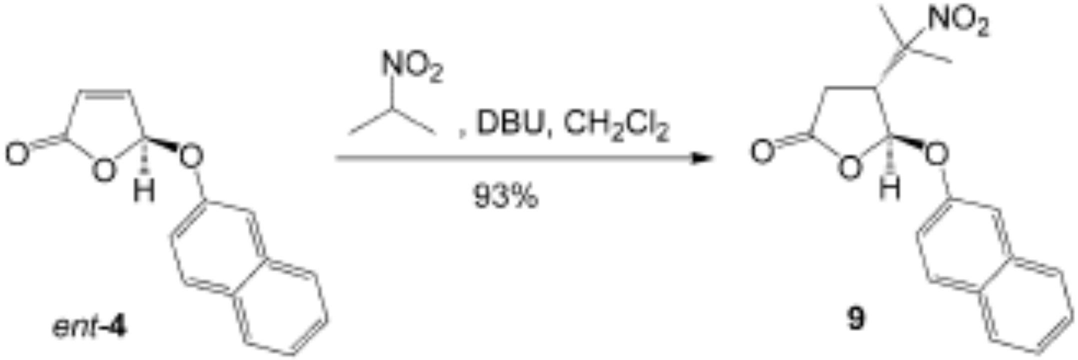


Scheme 1. Retrosynthetic analysis of BAY 36–7620 and (+)-brefeldin A.



ent-**4** → **7**

(3)

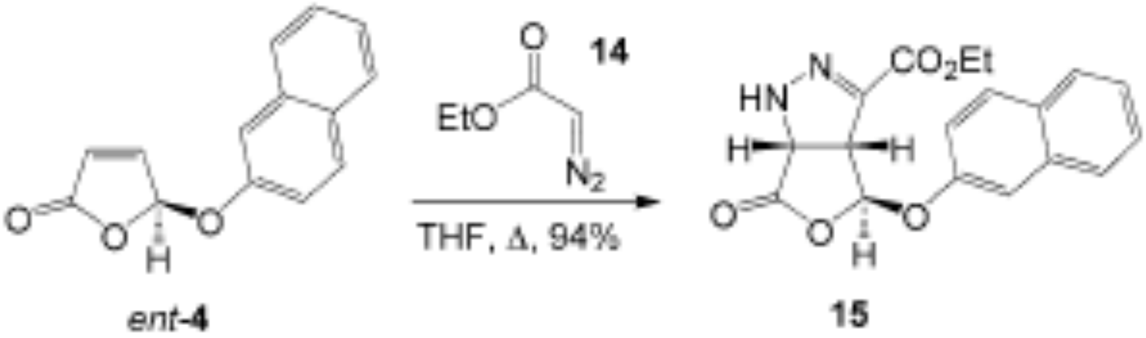


ent-**4** → **9**

(4)

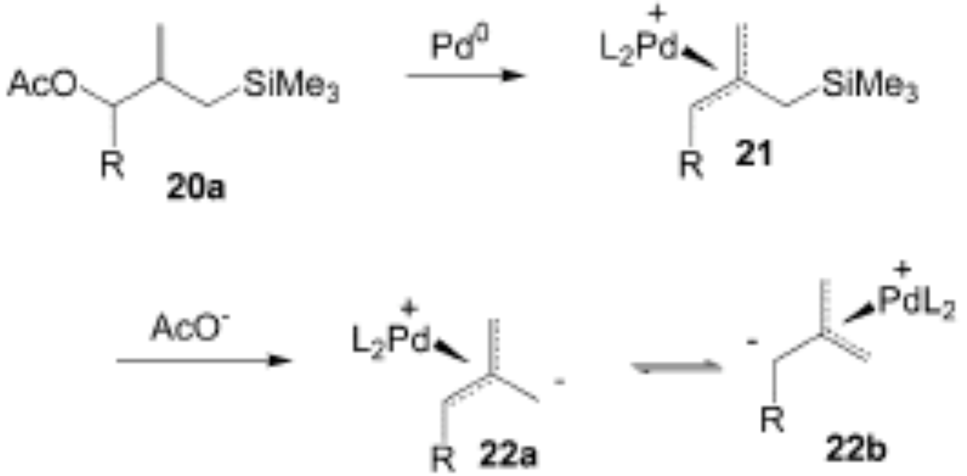

microwave, Δ
(150 °C), 1 h
, 88%
H
H
O
O
H
O
O
O
H
O
ent-4
12
13

(6)

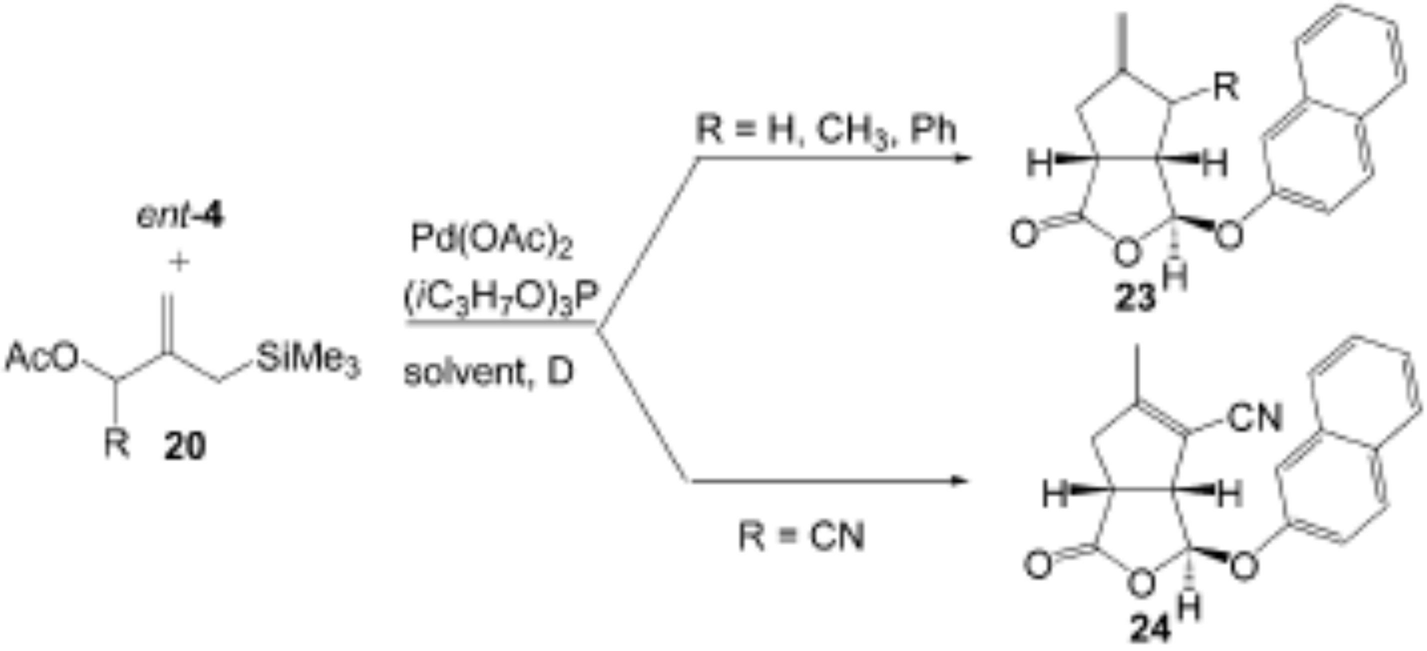

O
14
EtO
N2
THF, Δ, 94%
HN
N
CO2Et
H
H
O
O
H
O
O
O
H
O
ent-4
15

(7)

Pd mediated TMM reaction



(10)



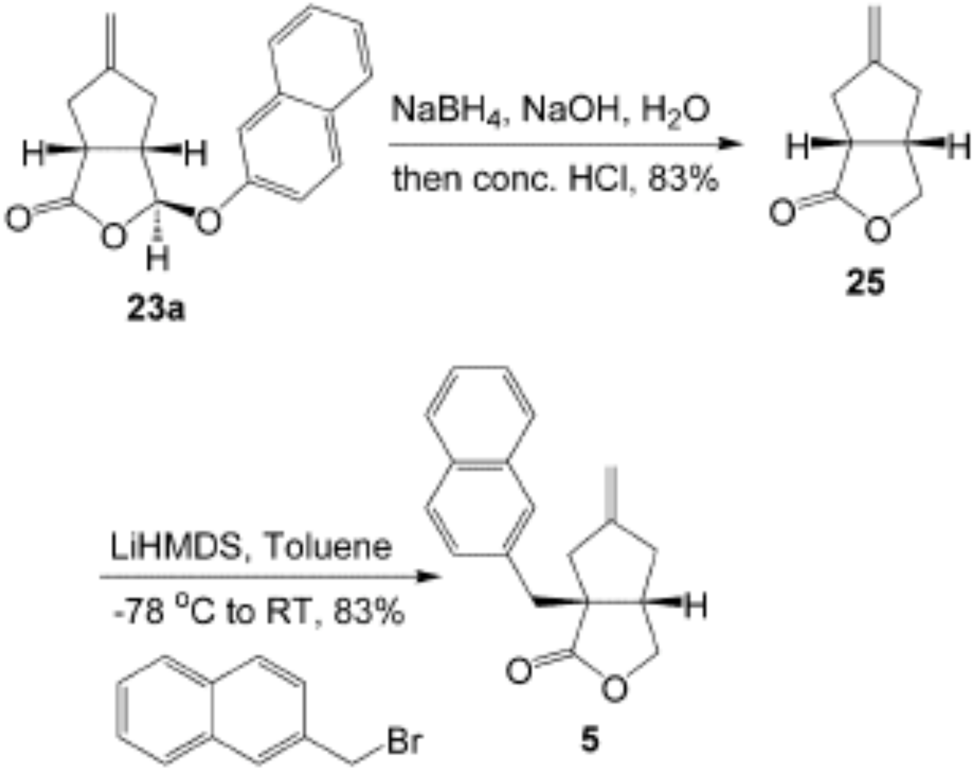
(11)

a) R = H; b) R = CN; c) R = OAc; d) R = Me; e) R = Ph

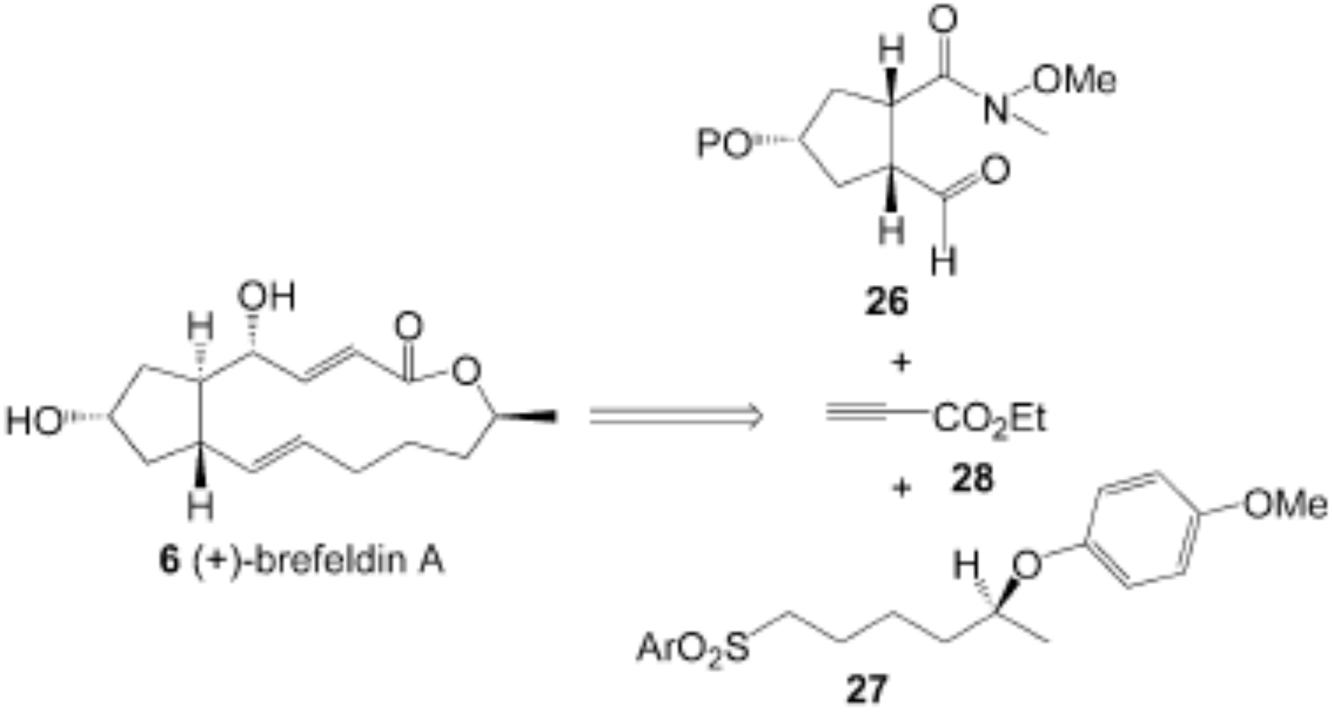
Table 1. TMM cycloadditions to butenolide *ent*-**4**.[a]

Entry	Substrate	Conditions	Product	Yield [%]	*dr* (epimers)[b]
1	**20 a**	toluene, 100°C, 12 h	**23a**	93	> 98:2
2	**20 a**	THF, 65°C, 24 h	**23a**	93	> 98:2
3	**20 b**	THF, 65°C, 12 h	**24**	94	5.5:1
4	**20 b**	toluene, 100°C, 12 h	**24**	91	94:6
5	**20 c**	toluene, 100°C, 12 h	–	–	–
6	**20 d**	toluene, 100°C, 48 h	**23d**	60	> 98:2 (1:1)
7	**20 e**	toluene, 100°C, 24 h	**23e**	79	> 98:2 (4:1)

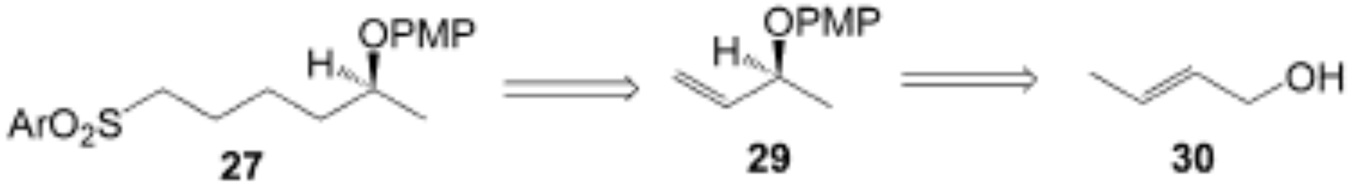
[a] All reactions were run as summarized in Equation (11). [b] Diastereomeric ratios are of the crude reaction mixture.



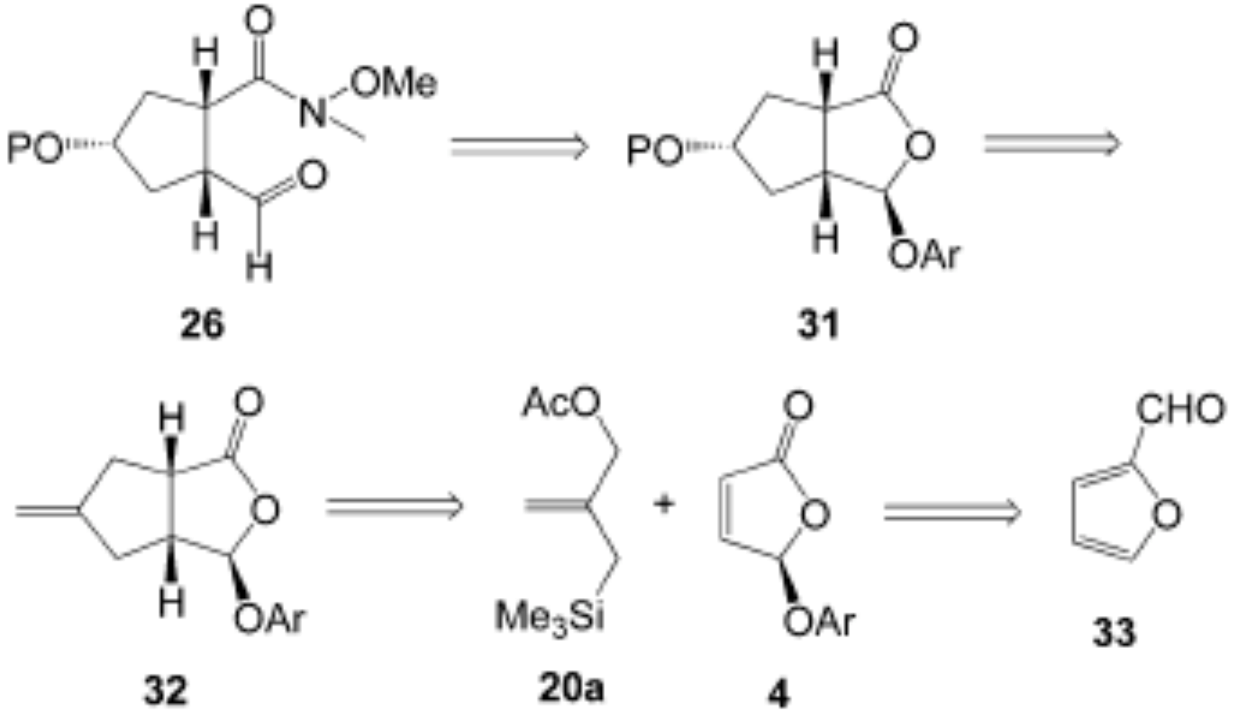
Scheme 2. Synthesis of Bayer drug 36–7620 (5).



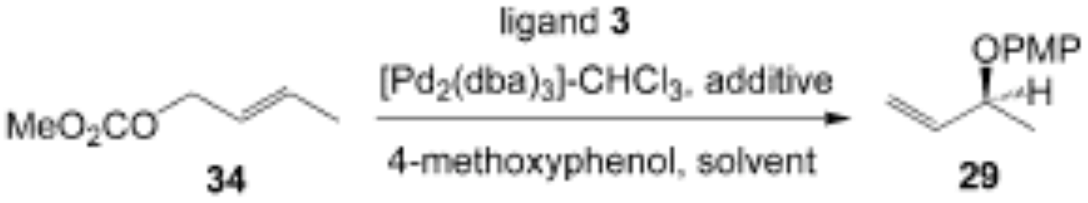
Scheme 3. Retrosynthetic analysis of (+)-brefeldin A (6).



Scheme 4. Retrosynthetic analysis of the lower side chain **27**.



Scheme 5. Retrosynthetic analysis of the cyclopentane core **26**.

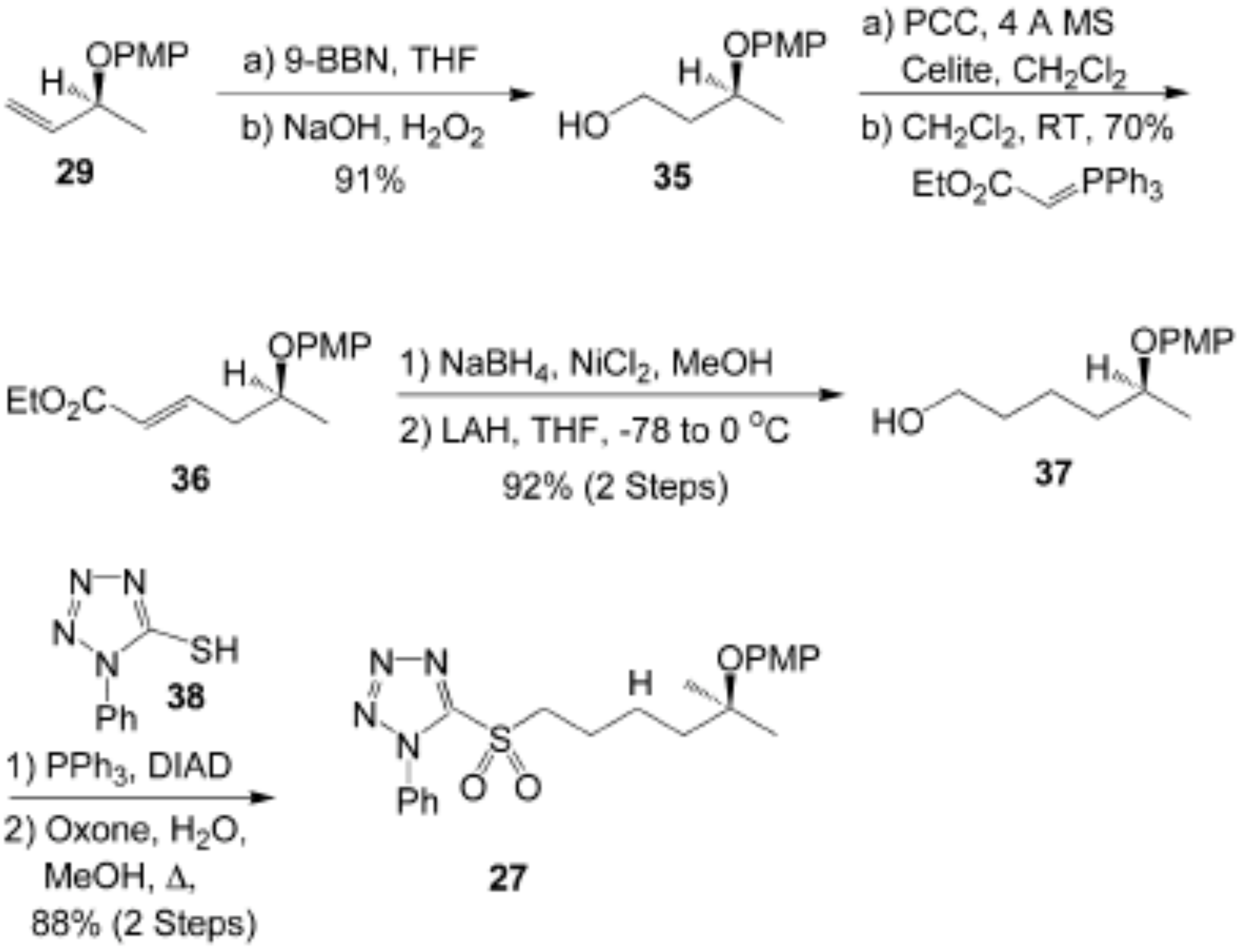


(12)

Table 2. Asymmetric allylic alkylation of 4-methoxyphenol with crotyl carbonate.[a]

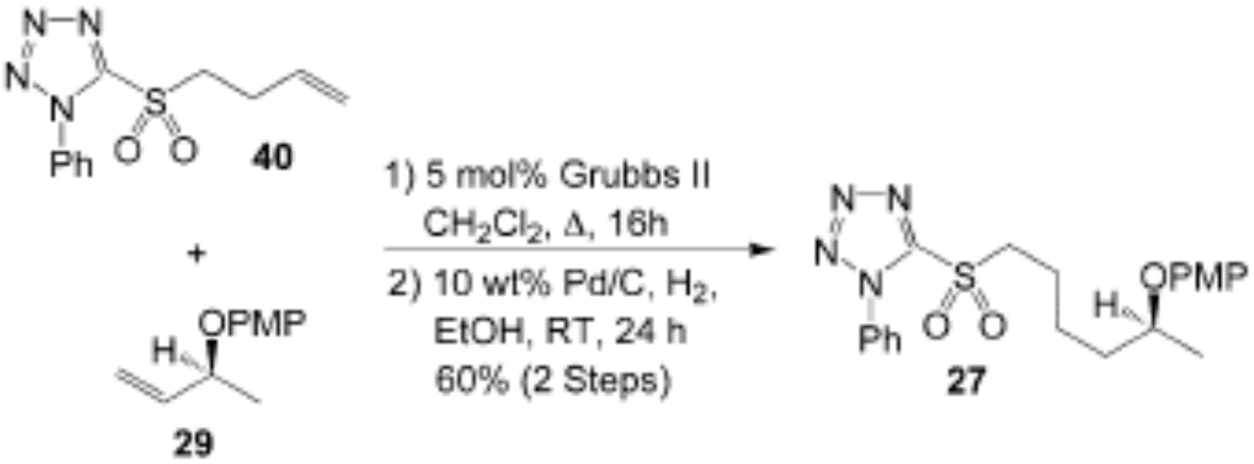
Entry	Pd_2dba_3 [mol %]	Ligand [mol %]	Conditions	Yield [%]	branched/ linear	% *ee*
1	1.0	3.0	THF, RT, 0.5 M	85	87:13	60
2	1.0	3.0	CH_2Cl_2, 0 °C, 0.5 M	78	92:8	71
3	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, 30 % Bu_4NCl	86	97:3	31
4	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M	75	95:5	81
5	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, K_2CO_3	75	93:7	81
6	**0.25**	**0.75**	**toluene, 0 °C, 0.1 M**	**95**	**96:4**	**90**
7	0.25	0.75	branched SM, as entry 4	92	96:4	32

[a] All reactions run as summarized in Equation (12).



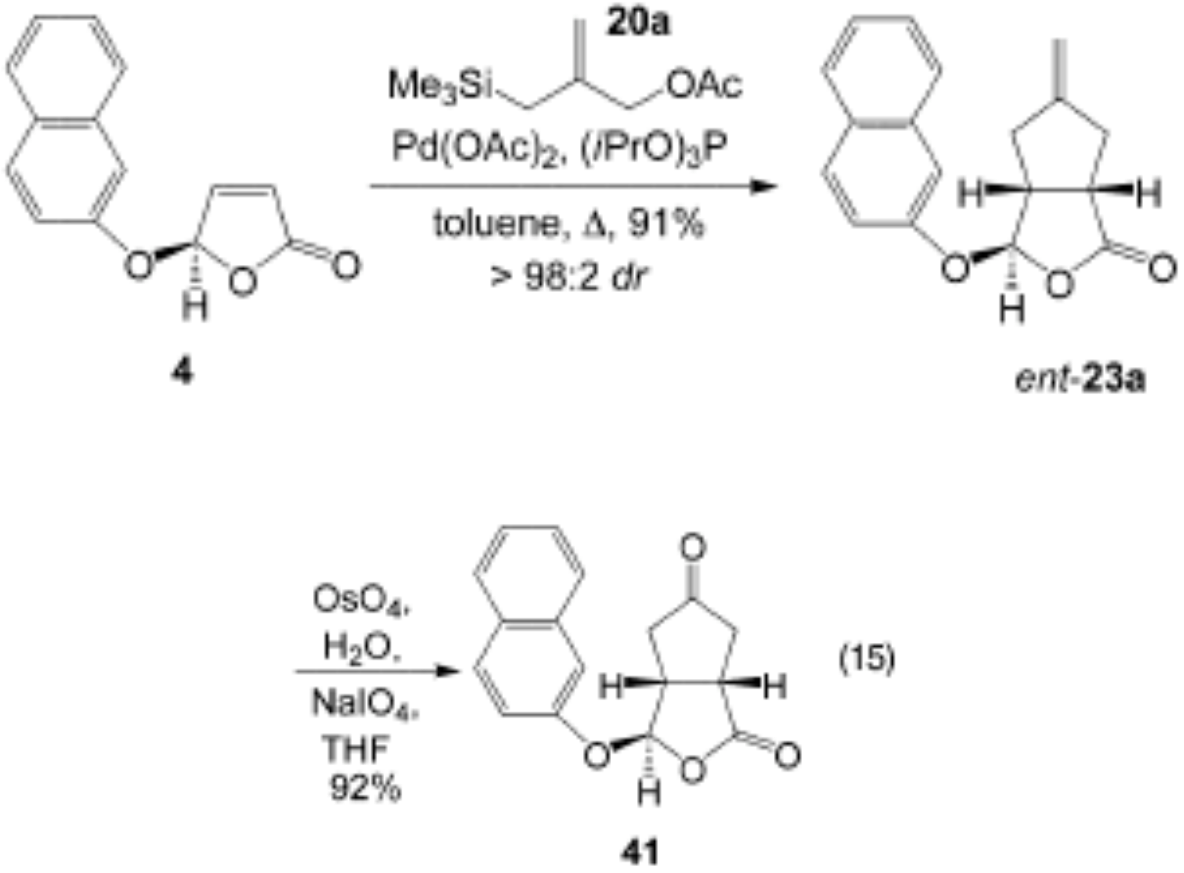
Scheme 6. Completion of the C(11)–C(16) lower side chain fragment **27**.

An alternative approach to the lower side chain

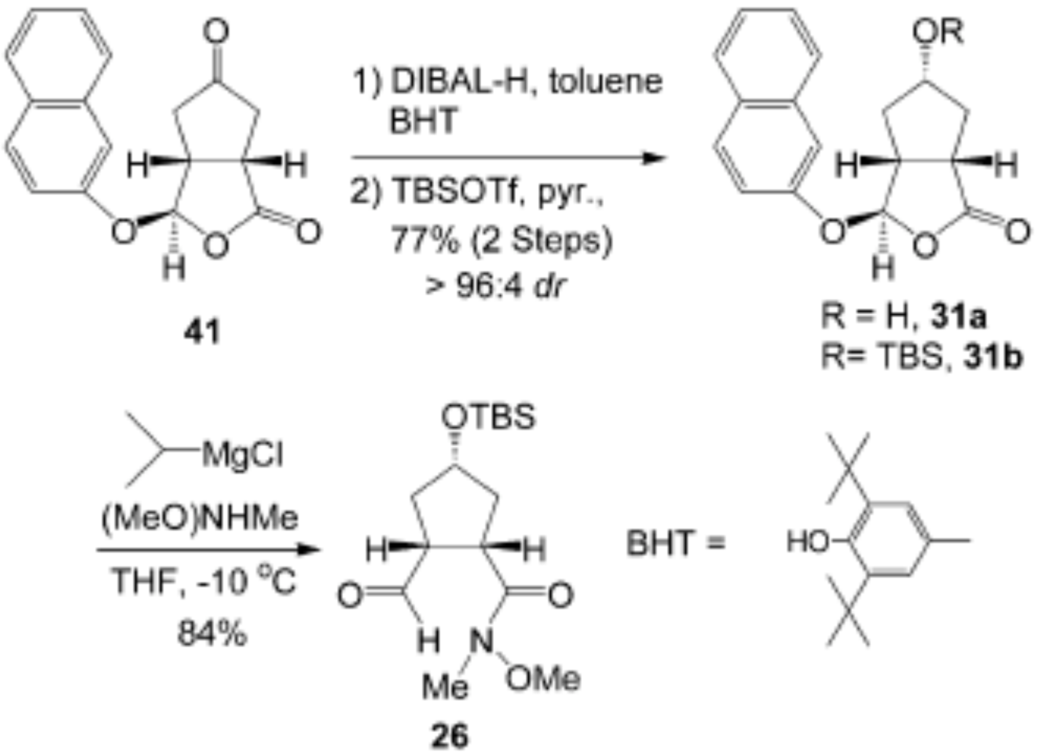


(14)

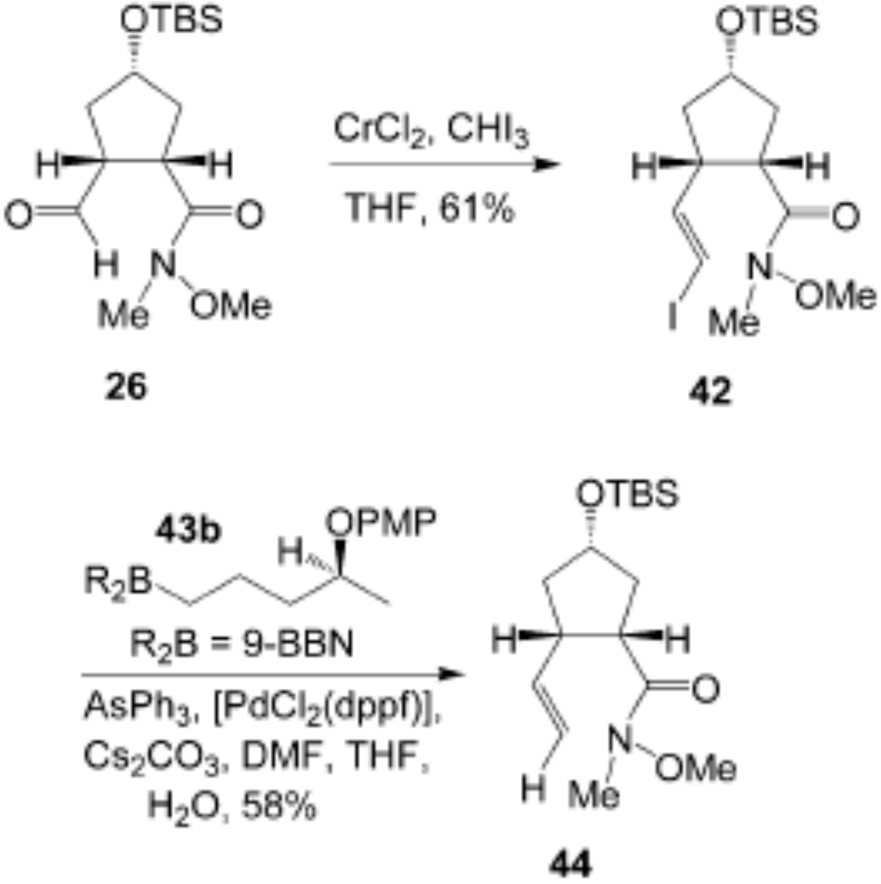
Synthesis of the core—a first-generation approach



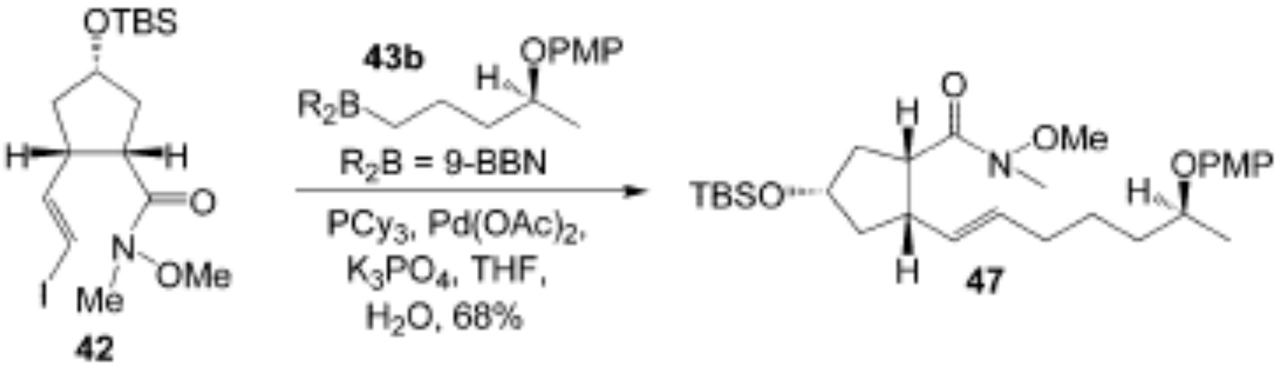
(15)



Scheme 7. First-generation synthesis of the core **26**.

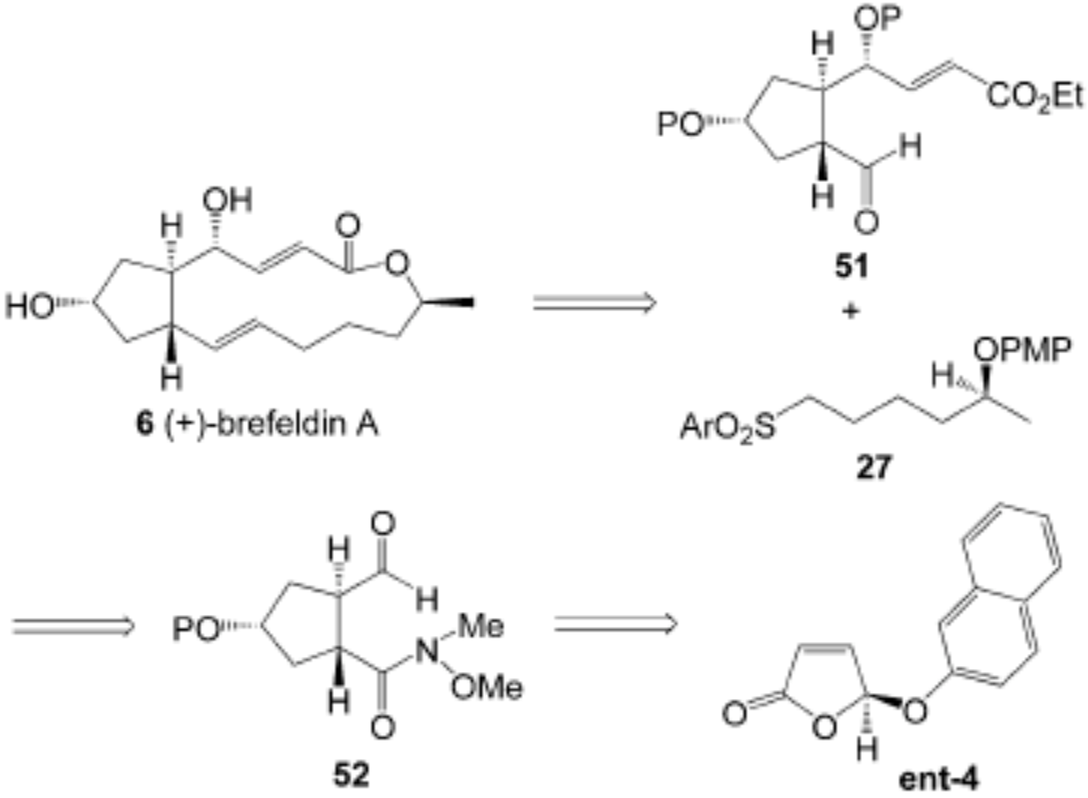


Scheme 8. Further efforts towards the cyclopentane core.

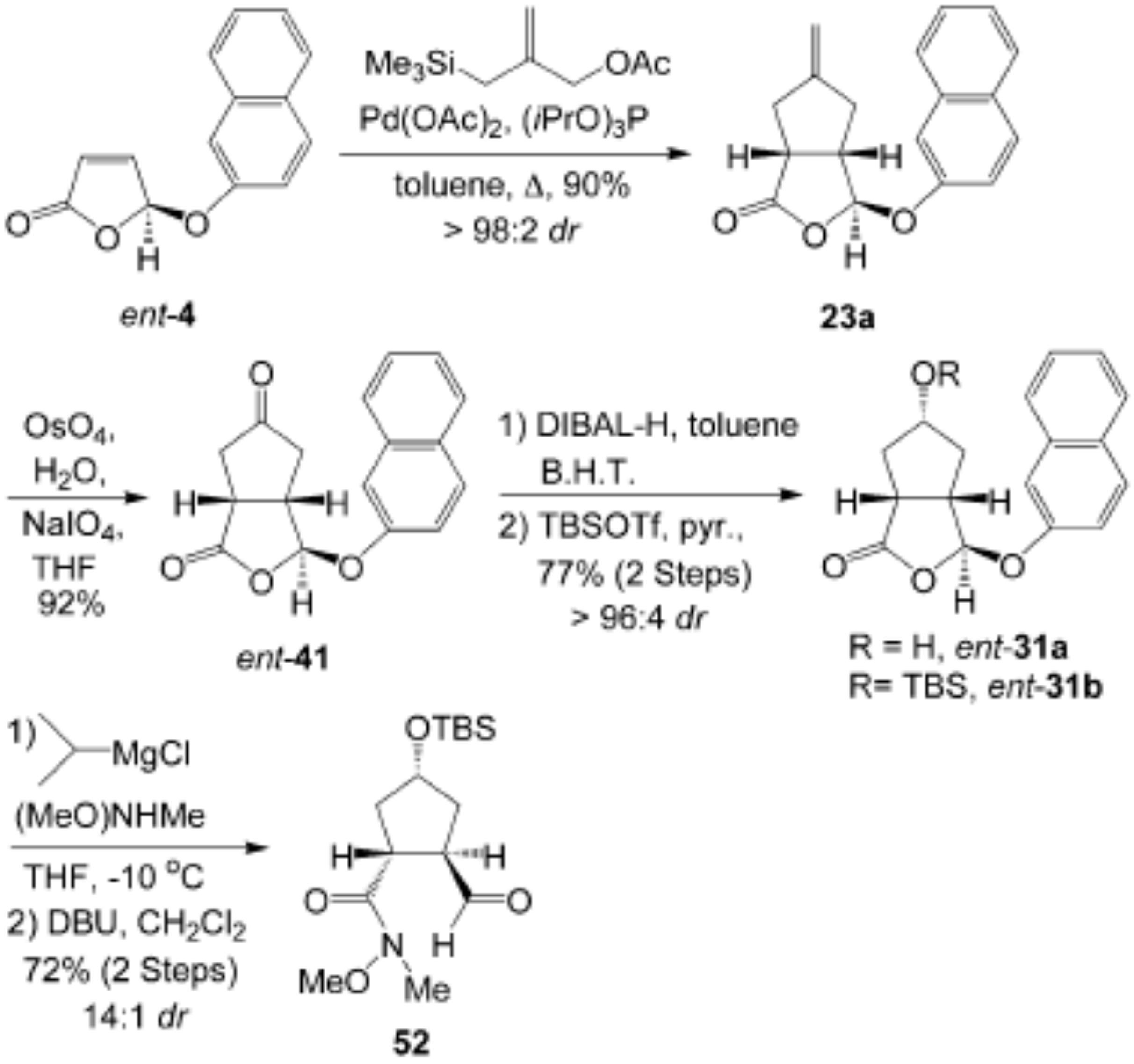

OTBS
H
H
O
N
OMe
Me
I
42
43b
OPMP
H
R$_2$B
R$_2$B = 9-BBN
PCy$_3$, Pd(OAc)$_2$,
K$_3$PO$_4$, THF,
H$_2$O, 68%
TBSO
H
O
N
OMe
OPMP
H
H
47

(17)

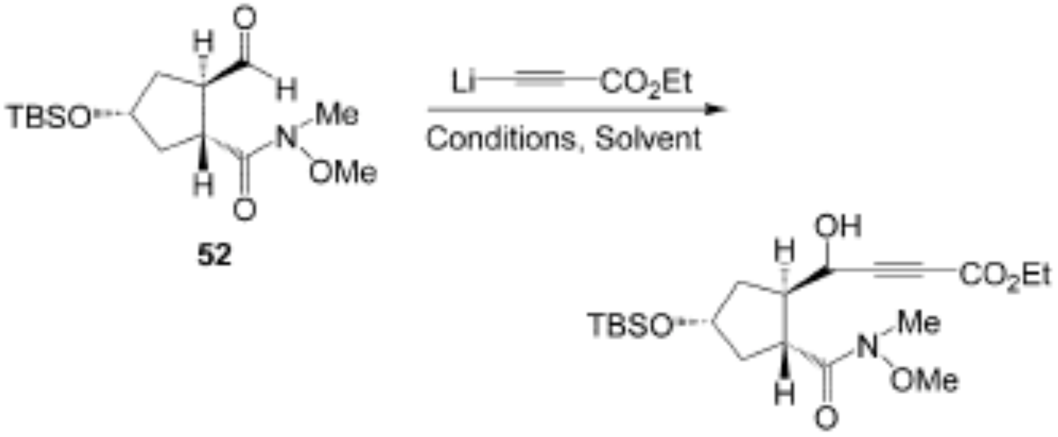
Synthesis of the core—a second-generation approach:



Scheme 10. Revised retrosynthetic analysis.



Scheme 11. Second-generation route to the core **52**.



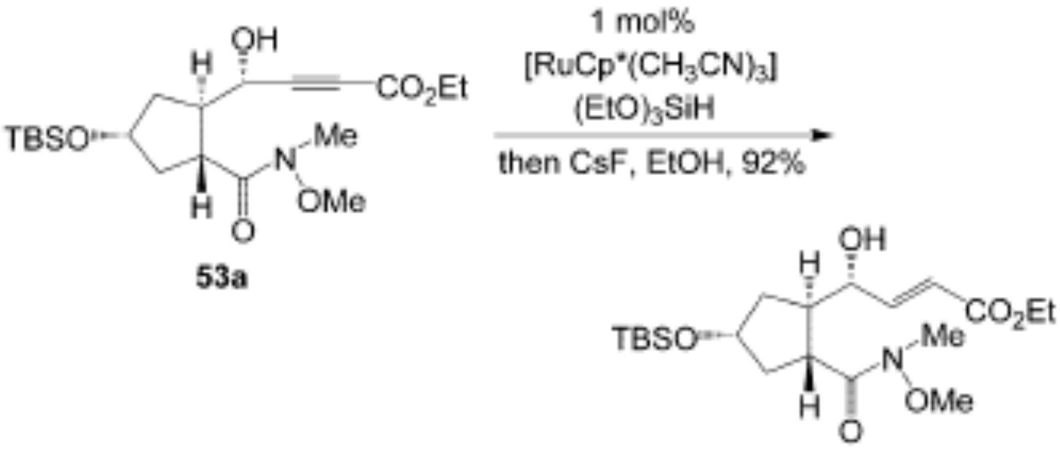
53

(19)

Table 4. Diastereoselective alkylation of the C(4)-aldehyde.[a]

Entry	Solvent(s)	Conditions	4-(*S*)/4-(*R*)	Yield [%]
1	THF/HMPA 5:1	–78 °C, 4 h	6.0:1.0	88
2	THF/HMPA 9:1	–78 °C, 4 h	4.5:1.0	84
3	THF	–78 °C, 4 h	1.0:3.0	86
4	THF	–78 °C, 4 h, $MgBr_2$	1.0:3.5	80
5	DME	–78 °C, 2 h	1.0:5.0	92
6	DME	–78 °C, 2 h, $MgBr_2$	1.0:6.0	91

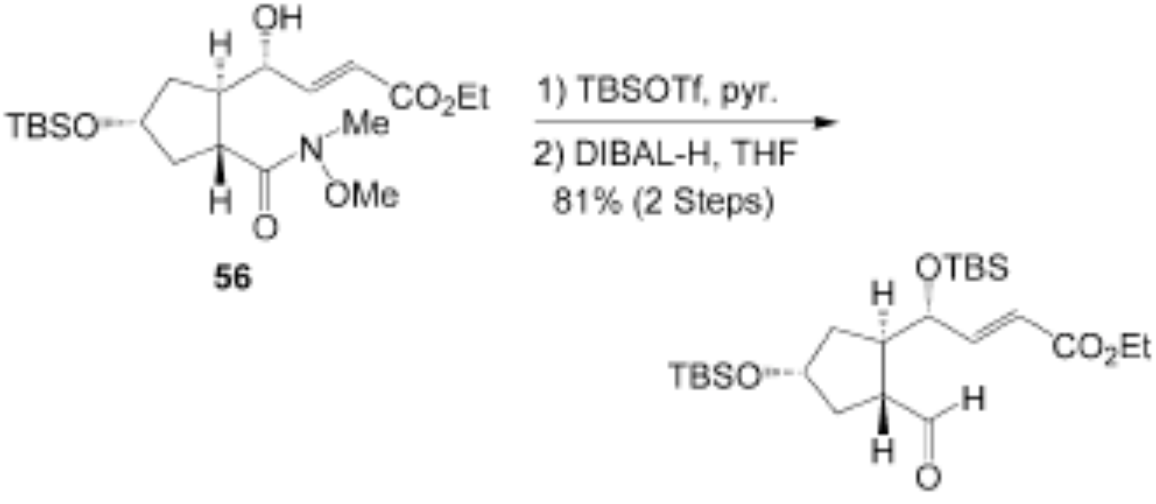
[a] Reaction as depicted in Equation (19).



53a

56a

(20)



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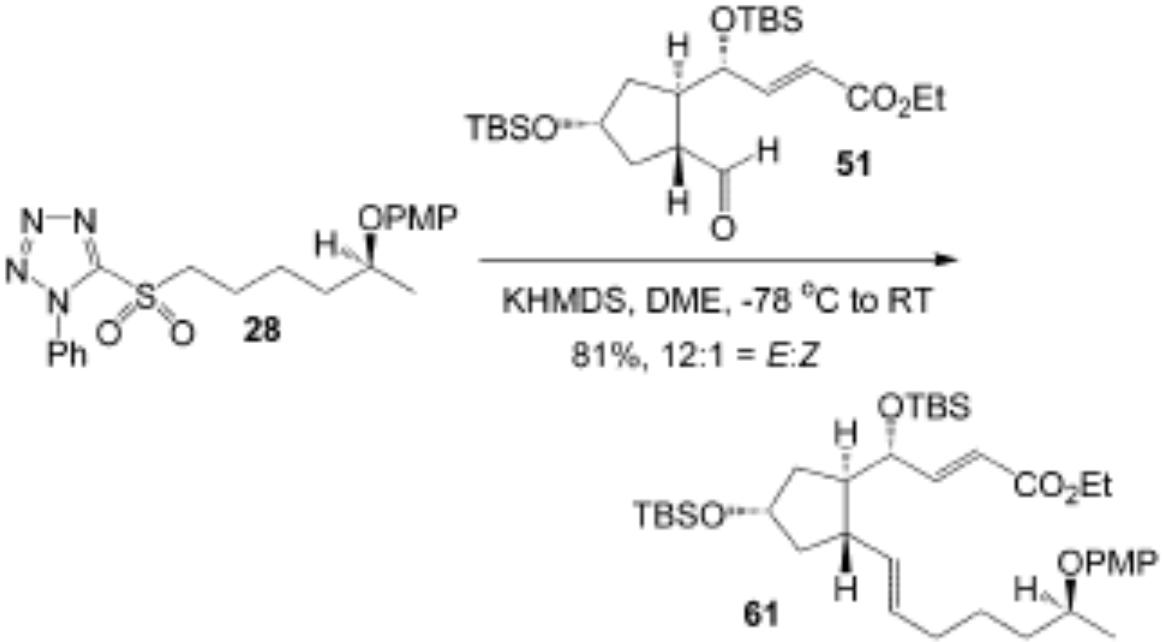
51

(21)



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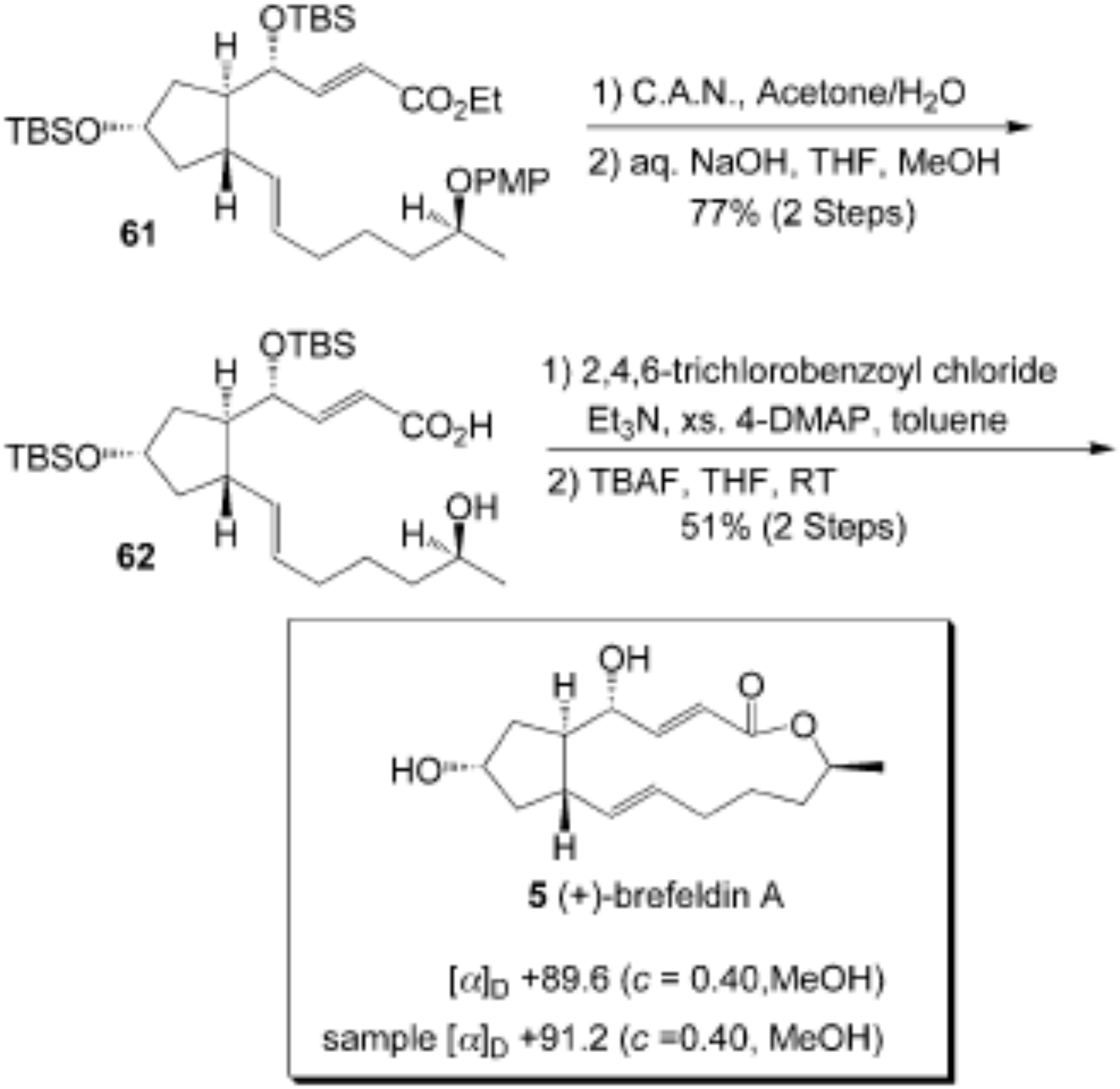

Scheme 14. Completion of the total synthesis of (+)-brefeldin A (6).

Conclusion

- The highly convergent total synthesis of (+)brefeldin A was achieved in 18 linear steps with 6% yield
- A concise, 6-step synthesis of Bayer 36-7620 was completed in 44% yield, compared to the 8-step and 16% yield process
- The enantiopure furanone has shown its utility as a versatile “chiral aldehyde” building block.
- TMM cycloaddition to the chiral butenolide gave excellent regio- and diastereoselectivity
- The first total synthesis to employ trans hydrosilylation of alkynes.