Enantioselective total synthesis of (-)-lucidumone enabled by tandem prins cyclization/cycloetherification sequence

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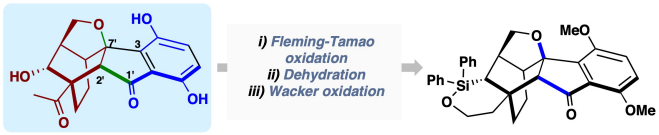
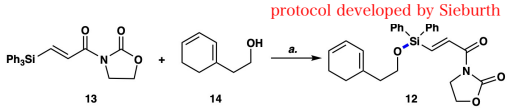


(–)-1: lucidumone

7

Isolated as a racemate

protocol developed by Sieburth



[Cu]	Ligand	Yield	ee
$Cu(SbF_6)_2$	L1	88	92
$Cu(OTf)_2$	L1	96	92
$Cu(OTf)_2$	L2	90	85
$Cu(OTf)_2$	L3	86	63

a Cu-catalyzed enantioselective silicontethered intramolecular Diels-Alder cycloaddition

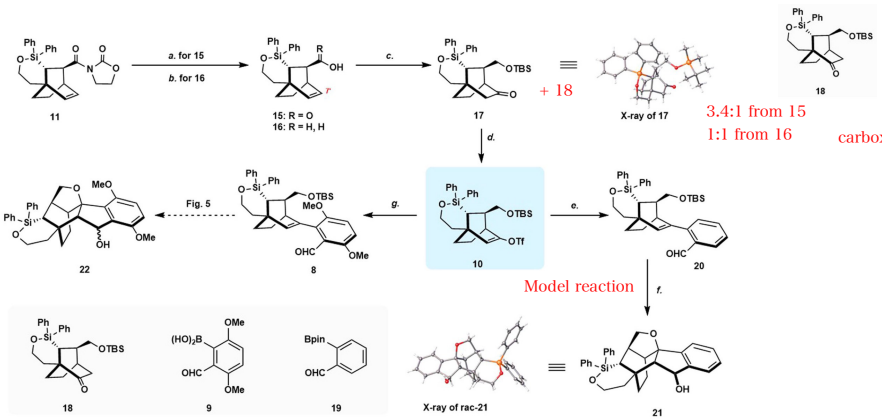
a single endo diastereoisomer

gram scale

99% *ee* after recrystallization

Following Evans's pioneering work

Fig. 3 | Synthesis of chiral bicyclo[2.2.2]octane 11. Reagents and conditions: **a** TfOH (2.2 equiv), 2,6-lutidine (2.4 equiv), DCM, –78 to 0 °C, then **14**, 91%; **b** $Cu(OTf)_2$ (0.1 equiv), **L1** (0.11 equiv), DCM, 50 °C, 96% yield, 92% *ee*. TfOH triflic acid, 2,6-lutidine 2,6-dimethylpyridine, DCM dichloromethane.



3.4:1 from 15

1:1 from 16

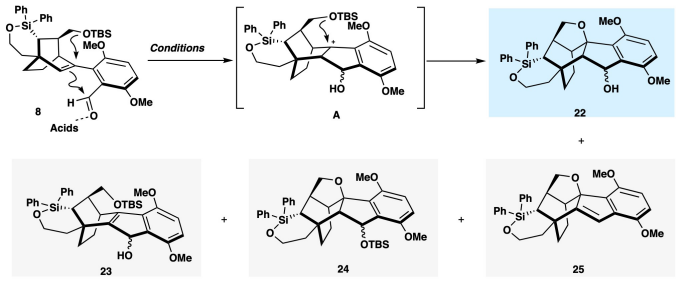
carboxylic acid is a better-directing group

Model reaction

Fig. 4 | Synthesis of hexacyclic intermediate 22. Reagents and conditions: **a** LiOH (3.0 equiv), H_2O_2 (8.8 equiv), THF-H_2O (v:v = 2:1), 0 °C to RT, 94%; **b** $LiBH_4$ (4.0 equiv), THF, 0 °C, 85%; **c** i. BH_3·THF (5.0 equiv), THF, –30 °C to RT, $NaBO_3$ ·$4H_2O$ (10.0 equiv). ii. TBSCl (3.0 equiv), imid (5.0 equiv), DCM, RT. iii. DMP (2.0 equiv), $NaHCO_3$ (10 equiv), RT, 69% for **17**, 20% for **18**; **d** KHMDS (1.4 equiv), $PhNTf_2$ (1.4 equiv), THF, –78 °C, 94%; **e 19** (2.0 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), K_3CO_3 (3.0 equiv), DMSO, 80 °C, 96%; **f** HCl (2 M in ethyl acetate) (10.0 equiv), DCM, –10 °C, 89%; **g 9** (2.0 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), S-Phos (0.2 equiv), K_3PO_4 (3.0 equiv), DMF, 80 °C, 69%. THF tetrahydrofuran, TBSCl *tert*-Butyldimethylsilyl chloride, imid Imidazole, DMP Dess–Martin periodinane, KHMDS potassium bis(trimethylsilyl) amide, $PhNTf_2$ N-phenyl-bis(trifluoromethanesulfonimide), S-Phos 2-dicyclohex-ylphosphino-2′,6′-dimethoxybiphenyl, DMF N, N-dimethylformamide.

a domino deprotection/Prins reaction/cycloetherification/oxidation sequence

the reaction temperature and time have to be carefully controlled in order to avoid the formation of by-products.



Entry[a]	Acid (equiv)	Temp. (°C)	Yield of 22 (%)	Yield of 23 (%)	Yield of 24 (%)	Yield of 25 (%)
1	HCl (10 eq)	–10 °C	-	-	-	-
2	BF_3·Et_2O(1.0 eq)	–78 °C	19	42	-	-
3	TBSOTf (1.0 eq)	–78 °C	-	18	trace	-
4	TMSOTf (1.0 eq)	–78 °C	trace	-	-	53
5	$AlCl_3$ (1.0 eq)	–78 °C	23	35	-	-
6	$Sc(OTf)_3$ (1.0 eq)	–78 °C	15	54	-	-
7	(-)-CSA (1.0 eq)	–78 °C	-	85	-	-
8	*p*-TSA·H_2O (1.0 eq)	–78 °C	trace	65	-	-
9	TFA (1.0 eq)	–78 °C	trace	53	-	-
10	HCl (1.0 eq)	–78 °C	12	75	-	-
11	HCl (10.0 eq)	–78 °C	86	-	-	-
12	Silica gel	rt	-	47	-	-

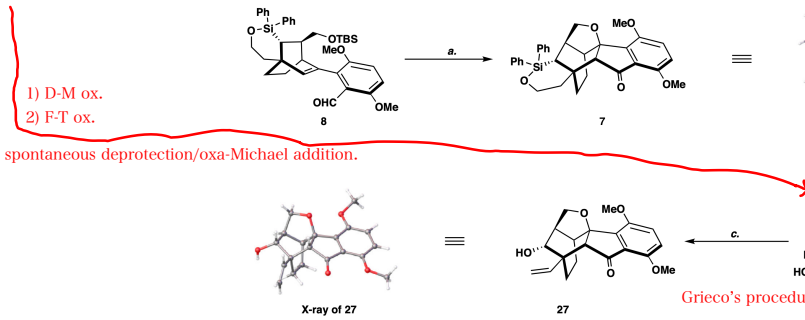
Fig. 5 | Optimization of tandem O-deprotection/Prins cyclization/Cycloetherification conditions. [a]Conditions: **8** (0.03 mmol), DCM (1.5 mL, *c* 0.02 M), N_2 atmosphere.

Prins cyclization product

1) D-M ox.

2) F-T ox.

spontaneous deprotection/oxa-Michael addition.



Fleming–Tamao oxidation

Grieco's procedure

aldehyde resulting from the anti-Markovnikov addition

Condition	Yield of 28
$PdCl_2$/CuCl, DMF/H_2O, O_2	N.D.
$Fe(acac)_2$/PHMS/*t*-BuOH/Air	N.R.
$Fe(acac)_2$/EtOH/$PhSiH_3$/Air	50
$Fe(dbm)_2$/EtOH/$PhSiH_3$/Air	65

Han's and Knölker's conditions

Fig. 6 | Total synthesis of (–)-lucidumone [(–)–1]. Reagents and conditions: **a** HCl (2 M in ethyl acetate) (10.0 equiv), DCM, –78 °C, then DMP (2.0 equiv), $NaHCO_3$ (10.0 equiv), RT, 80%; **b** KF (5.0 equiv), H_2O_2 (20 equiv), $KHCO_3$ (1.6 equiv), MeOH-THF (v:v = 1:1), 50 °C, 91%; **c** 2-nitrophenylselenocyanate (1.2 equiv), Py (1.2 equiv), PBu_3 (1.2 equiv), H_2O_2 (24 equiv), THF, 50%; **d** $Fe(dbm)_3$ (0.1 equiv), $PhSiH_3$ (10 equiv), EtOH, RT, 65%; **e** $AlCl_3$ (10 equiv), 1-dodecanethiol (20 equiv), DCM, RT, 70%.