Asymmetric Total Synthesis of Janthinoid A

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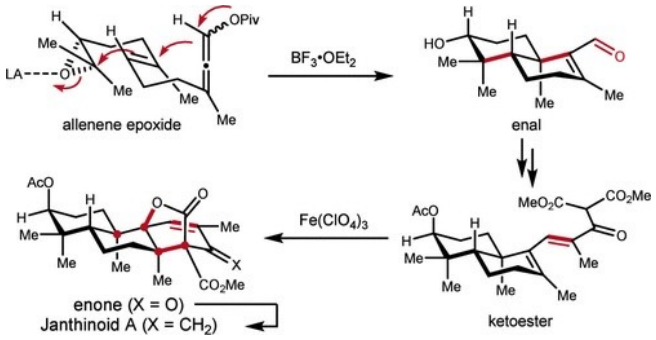
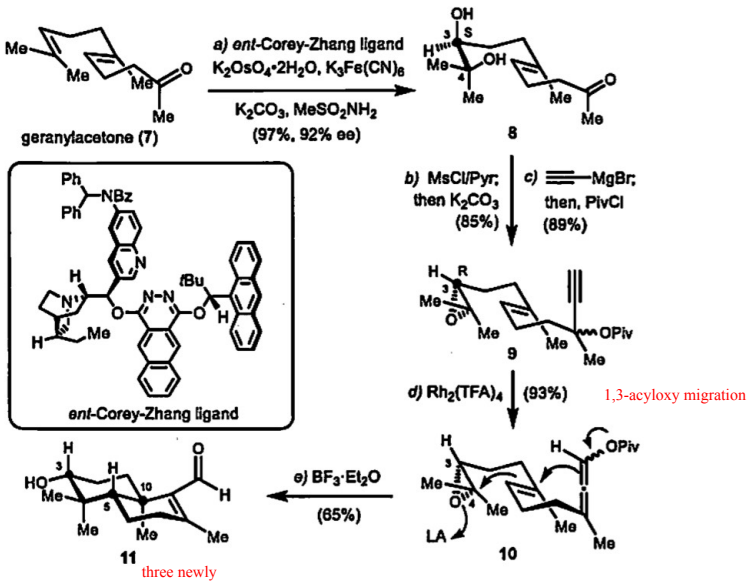
3,5-Dimethylorsellinic acid (DMOA)-derived meroterpenoid

without using a protecting group
an epoxide-initiated cationic -cyclization reaction

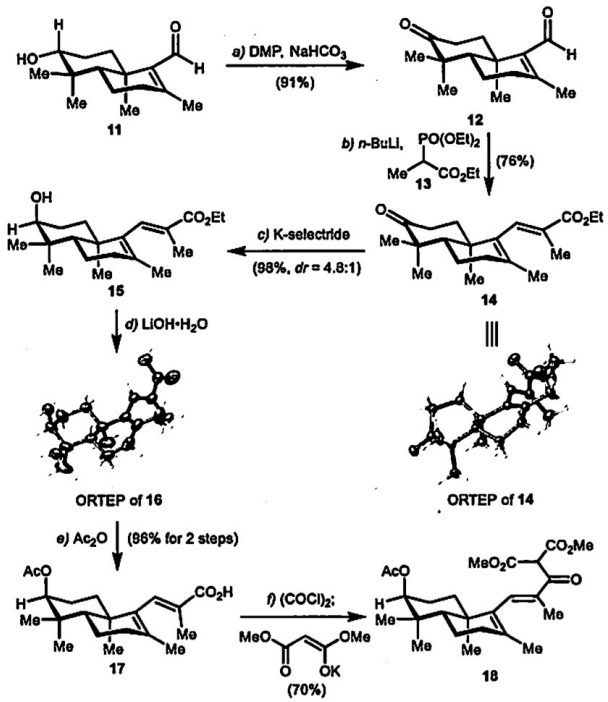


Scheme 1. Synthesis of Aldehyde 11[a]



[a]*Reagents and conditions*: (a) enantiomer of Corey–Zhang ligand (1.0 mol %), $K_2OsO_4{\cdot}2H_2O$ (0.5 mol %), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH/H_2O = 1:1, rt, 24 h, 97%, 92% ee, *rr* > 20:1; (b) MsCl (1.2 equiv), pyridine (15 equiv), DCM, rt, 7 h; then K_2CO_3 (10.0 equiv), MeOH, rt, 6 h, 85%; (c) ethynyl magnesium bromide (0.5 M in THF, 1.5 equiv), THF, 0 °C to rt, 1 h; then PivCl (4.0 equiv), rt, 10 h, 89%; (d) $Rh_2(TFA)_4$ (1.0 mol %), PhMe, 60 °C, 19 h, 93%; (e) $BF_3{\cdot}Et_2O$ (4.0 equiv), DCM, 0 °C to rt, 12 h, 65%.

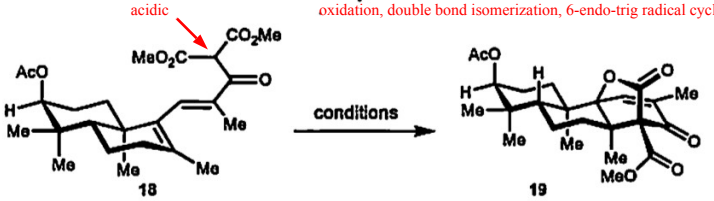
Scheme 2. Synthesis of Enol 18[a]



[a]*Reagents and conditions:* (a) Dess–Martin periodinane (1.5 equiv), $NaHCO_3$ (1.5 equiv), DCM, rt, 1 h, 91%; (b) triethyl 2-phosphonopropionate (10.0 equiv), *n*-BuLi (10.0 equiv), THF, rt, 36 h, 76%; (c) K-selectride (2.0 equiv), THF, rt, 1 h, 98%, *dr* = 4.8:1; (d) LiOH·H_2O (10.0 equiv), THF/MeOH/H_2O = 4:1:1, rt, 12 h. (e) Ac_2O (2.0 equiv), Et_3N (2.0 equiv), DMAP (0.2 equiv), DCM, rt, 1 h, 96% over 2 steps; (f) $(COCl)_2$ (2.0 equiv), DMF (10.0 mol %), DCM, rt, 3 h, then dimethyl malonate (1.5 equiv), KHMDS (1.0 M in THF, 1.5 equiv), THF, rt, 0.5 h, 70%.

Table 1. Oxidative Cascade Cyclization of Ketoester 18[a]

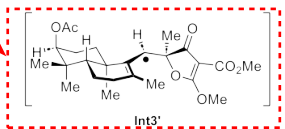
acidic — oxidation, double bond isomerization, 6-endo-trig radical cyclization, and



entry	conditions	outcome/yield
1	$Mn(OAc)_3{\cdot}2H_2O$ (2.2 equiv), $Cu(OAc)_2$ (1.0 equiv), AcOH, 25 °C, 1 h	decomposed
2	$Mn(OAc)_3{\cdot}2H_2O$ (2.2 equiv), $Cu(OAc)_2$ (1.0 equiv), MeCN, 25 °C to reflux, 18 h	no reaction
3	$Mn(OAc)_3{\cdot}2H_2O$ (2.2 equiv), DCM, 25 °C to reflux, 18 h	no reaction
4	$Mn(OAc)_3{\cdot}2H_2O$ (2.2 equiv), TFA (1.0 equiv), DCM, 25 °C, 18 h	20%
5	$Fe(ClO_4)_3{\cdot}9H_2O$ (2.2 equiv), MeCN, 25 °C, 18 h	55%
6	$Fe(ClO_4)_3{\cdot}9H_2O$ (2.2 equiv), MeCN, 0 °C, 18 h	46%
7	$Fe(ClO_4)_3{\cdot}9H_2O$ (2.2 equiv), MeCN, 50 °C, 18 h	40%
8	$Fe(ClO_4)_3{\cdot}9H_2O$ (2.2 equiv), DCM, 25 °C, 18 h	no reaction
9	$FeCl_3{\cdot}6H_2O$ (2.2 equiv), MeCN, 25 °C, 18 h	trace
10	$Fe(acac)_3$ (2.2 equiv), MeCN, 25 °C, 18 h	no reaction

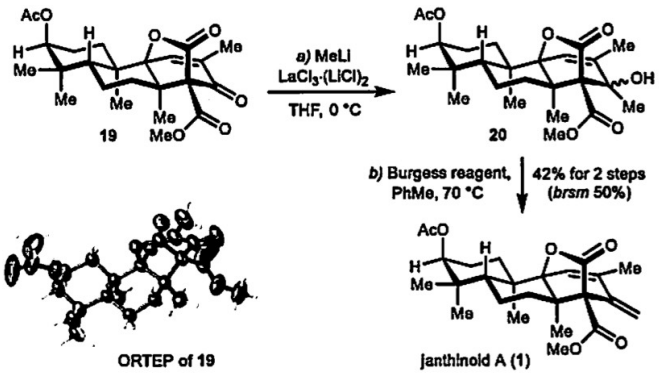
[a]Reactions were carried out at 100 mg scale of 18 at a concentration of 0.01 M.

E/Z isomerization: the optimal pathway among the proposed ones is the



Attempts to improve the yield by systematic profiling of the reaction conditions

Scheme 3. Total Synthesis of Janthinoid A (1)[a]



protecting-group-free synthesis in 14 steps

[a]*Reagents and conditions:* (a) MeLi (1.3 M in Et_2O, 1.1 equiv), Et_2O, 0 °C, 30 min; (b) Burgess reagent, toluene, 70 °C, 30 min. 42% in 2 steps.