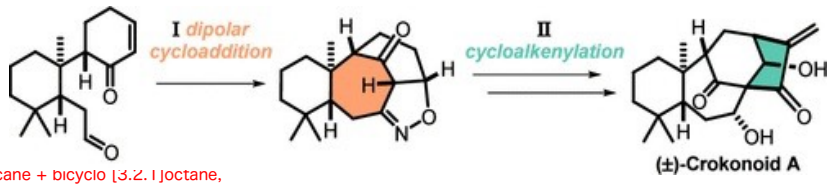
Total Synthesis of (±)-Crokonoid A

Tristano MartiniNobel SaabJonathan MuschiettiErick M. Carreira*

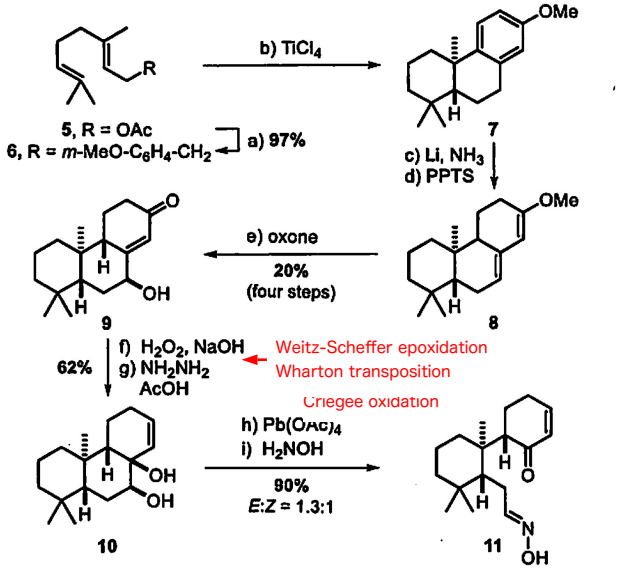
J. Am. Chem. Soc. 2025, 147, 34, 30606–30612.

tricyclo[4.4.1.1^{1,4}]dodecane scaffold

= bicyclo[4.3.1]decane + bicyclo [3.2.1]octane,

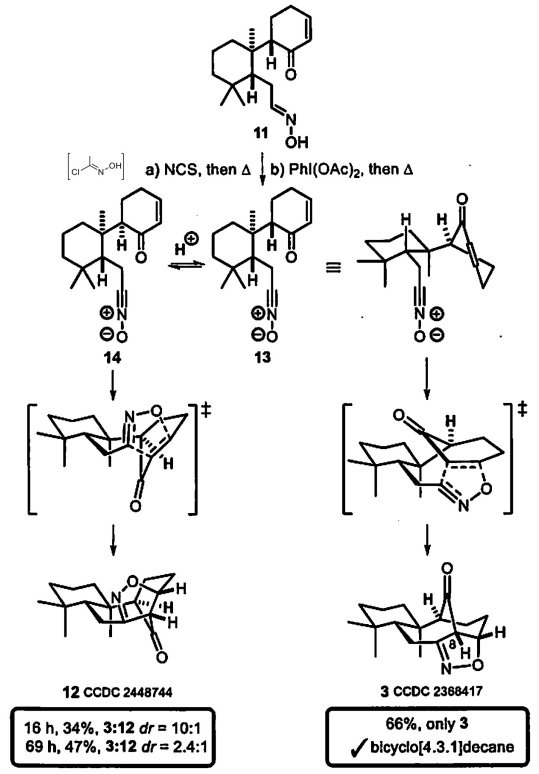


Scheme 3. Synthesis of Aldoxime 11[a]



[a]Reagents and conditions: (a) Li_2CuCl_4 (10 mol %), *m*-MeO-C_6H_4–CH_2MgCl, THF, 0 °C to rt, 97%; (b) $TiCl_4$, CH_2Cl_2, rt, 51% (NMR); (c) Li, NH_3, THF–EtOH, −40 °C; (d) PPTS (3 mol %), CH_2Cl_2, rt; (e) THF–1,4-dioxane, aq $NaHCO_3$, aq oxone, 0 °C to rt, 20% (four steps); (f) H_2O_2, NaOH, MeOH, 0 °C, quant.; (g) $NH_2NH_2{\cdot}H_2O$, then AcOH, MeOH, 0 °C, 62%; (h) $Pb(OAc)_4$, MeCN, rt, 90%; (i) $H_2NOH{\cdot}HCl$, EtOH–py, rt, quant., *E*:*Z* = 1.3:1.

Scheme 4. Dipolar Cycloaddition[a]



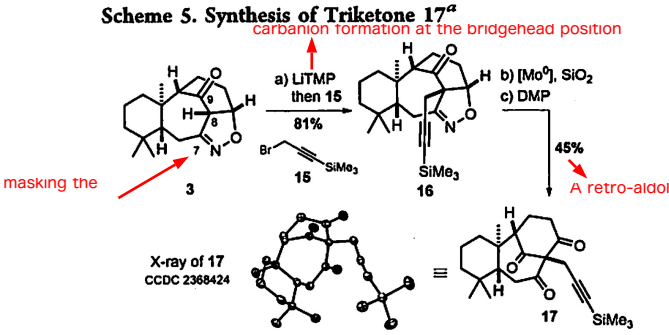
[a]Reagents and conditions: (a) NCS, PhMe, 1 h, rt then 105 °C, 16 h, 34%, 3:12 *dr* = 10:1 *or* 105 °C, 69 h, 47%, 3:12 *dr* = 2.4:1; (b) $PhI(OAc)_2$, MeOH, 0 °C then PhMe, 105 °C, 2 h, 66%, single diastereomer.

Scheme 5. Synthesis of Triketone 17[a]

carbanion formation at the bridgehead position

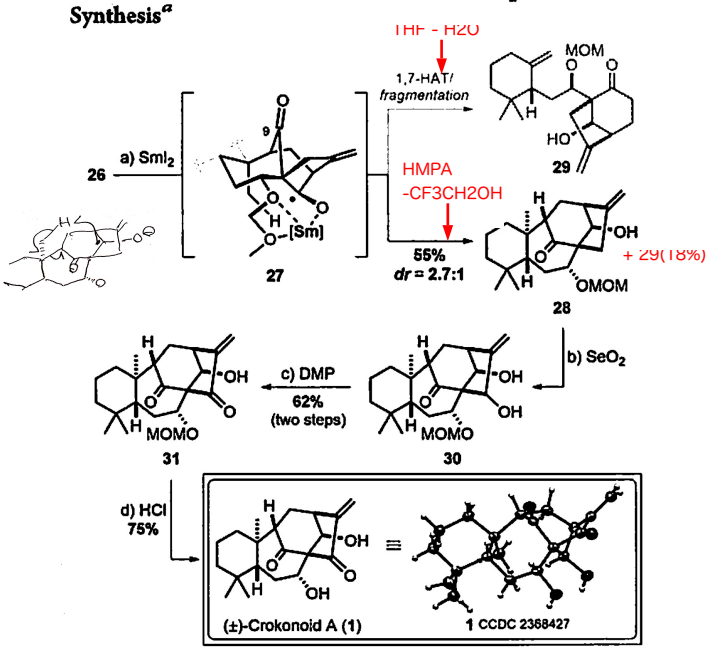
masking the

A retro-aldol side-reaction: responsible for the moderate yield



[a]Reagents and conditions: (a) LiTMP, THF, −78 °C, then **15**, 81%; (b) $Mo(CO)_3(NCMe)_3$, MeCN–H_2O, then SiO_2; (c) DMP, CH_2Cl_2, 0 °C, 45% (two steps).

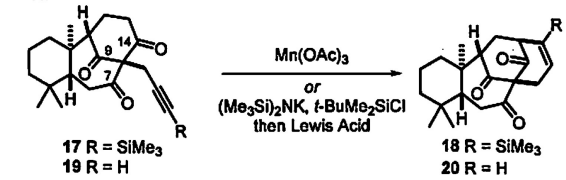
Scheme 7. C14 Ketone Reduction and Completion of the Synthesis[a]



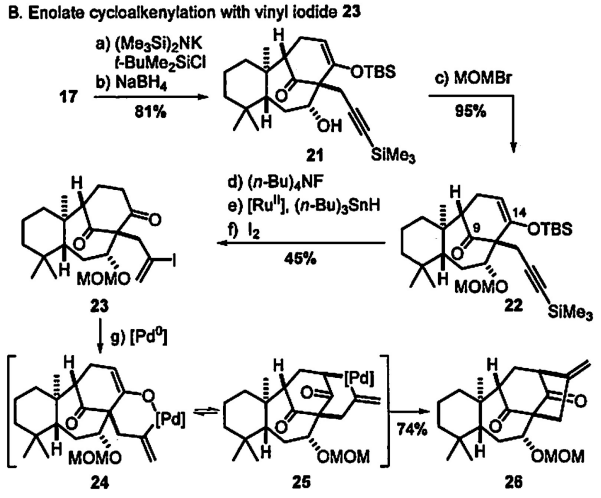
[a]Reagents and conditions: (a) SmI_2, HMPA, THF–F_3CCH_2OH, −78 °C, 55%, *dr* = 2.7:1; (b) SeO_2, *t*-BuOOH, DCE, 50 °C; (c) DMP, wet CH_2Cl_2, 62% (two steps); (d) aq HCl, MeOH, 30 °C, 75%.

oxidative radical or metal-mediated Conia-ene-type

A. Studies with triketone 17



B. Enolate cycloalkenylation with vinyl iodide 23



[a]Reagents and conditions: (a) $(Me_3Si)_2NK$, THF, −78 °C, then *t*-$BuMe_2SiCl$; (b) $NaBH_4$, MeOH, −78 to 0 °C, 81% (two steps); (c) MOMBr, $(i\text{-}Pr)_2NEt$, $(n\text{-}Bu)_4NI$, PhMe, 95 °C, 95%; (d) $(n\text{-}Bu)_4NF$, THF, 0 °C; (e) RuCp*$(MeCN)_3{\cdot}PF_6$ (20 mol %), $(n\text{-}Bu)_3SnH$, CH_2Cl_2, rt; (f) I_2, 2,6-lutidine, CH_2Cl_2, −20 °C, 45% (three steps); (g) $Pd_2(dba)_3$ (10 mol %), Xantphos (22 mol %), Cs_2CO_3, THF, rt to 85 °C, 74%.

crucial: the wide bite-angle of Xantphos favors challenging