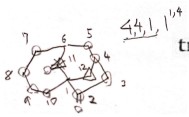
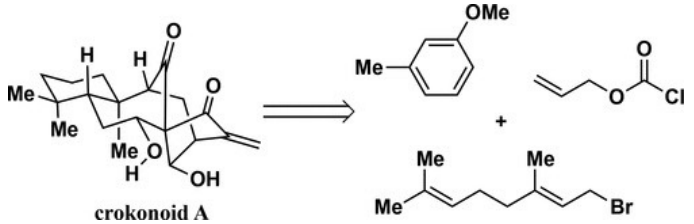
Total Synthesis of (±)-Crokonoid A

Dan Forster, Qian Wang, and Jieping Zhu*

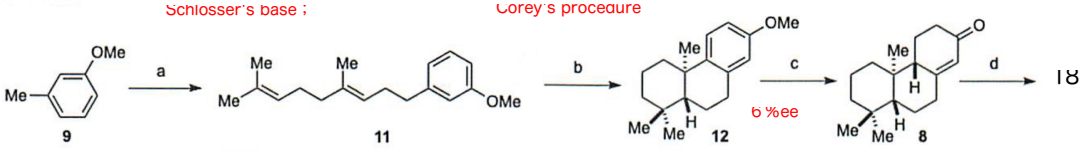
Journal of the American Chemical Society 2025, 147, 40, 36090-36096.



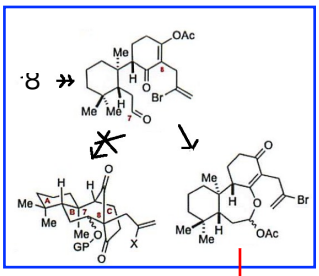
tricyclo[4.4.1.1^{1,4}]dodecane-2,11-dione



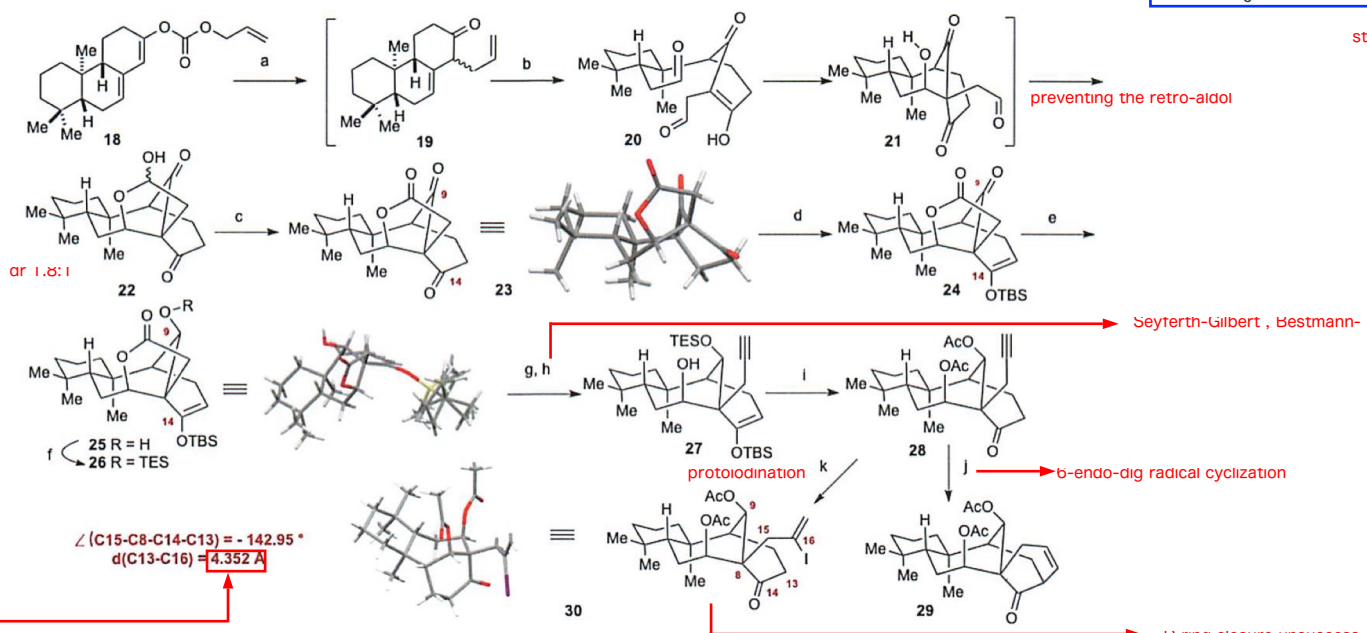
Schlosser's base ; Corey's procedure ; modified Birch conditions



"Reagents and conditions: (a) *n*BuLi (2.0 equiv), KO*t*Bu (2.0 equiv), HTMP (6.0 mol %), THF, −78 °C, then **10**, 1 h; (b) $SbCl_5$ (0.5 equiv), (*S*)-BINOL (0.5 equiv), DCM, −78 to 0 °C, 30 min; (c) Li (7.5 equiv), ethylenediamine (20 equiv), *t*BuOH (6.0 equiv), THF, 0 °C, 45 min, then HCl (3 N), MeOH, 90 °C, 1 h, 21% from geraniol; (d) KHMDS (1.1 equiv), TMEDA (2.0 equiv), ~~bromo~~allyl chloroformate (1.1 equiv), THF, rt, 45 min, ~~77% yield~~; (e)

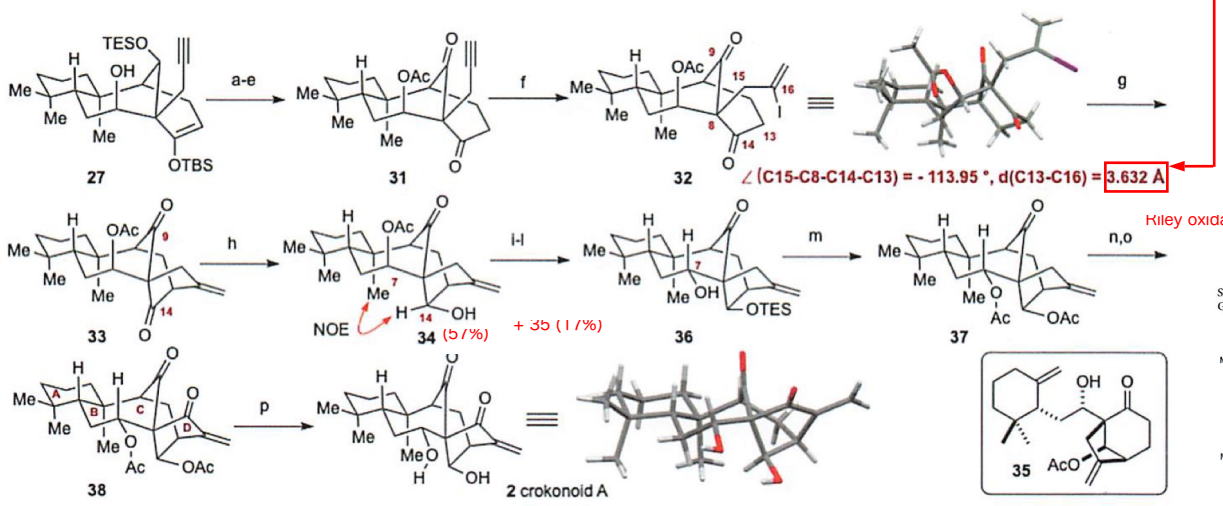


Scheme 4. Domino Ozonolysis/Aldol/Acetalization for Constructing the Tetracyclic Lactone and Its Subsequent Transformations[a]



"Reagents and conditions: (a) $Pd_2(dba)_3$ (5.0 mol %), PPh_3 (20.0 mol %), DCM, 0 °C, 30 min; (b) O_3, DCM, −78 °C, then PPh_3, rt, 5 days; (c) PCC (2.0 equiv), DCM, 40 °C, 2 h, 31% yield from **18**; (d) TBSOTf (5.0 equiv), NEt_3 (10.0 equiv), DCM, rt, 4 h, 95%; (e) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 15 min, 84%; (f) TESCl (4.7 equiv), NEt_3 (4.7 equiv), KHMDS (4.4 equiv), THF, −78 °C, 30 min, 93%; (g) DIBAL-H (1.3 equiv), DCM, −78 °C, 5 min; (h) LDA (21 equiv), $TMSCHN_2$ (19 equiv), THF/toluene, −78 °C to rt, 5 h, 91% yield over two steps; (i) TFA (6.0 equiv), DCM, rt, 18 h, then Ac_2O (30 equiv), pyridine (50 equiv), 4-PPY (0.1 equiv), toluene, rt, 24 h, 69% yield; (j) $Mn(OAc)_3$, AcOH, 80 °C, 3 days, 63% yield; (k) dicyclohexyl iodoborane (5.2 equiv), 2,6-di-*tert*-butylpyridine (5.4 equiv), toluene, rt, 3 h, then AcOH (27 equiv), rt, 30 min, 64%. PCC = pyridinium chlorochromate; LDA = lithium diisopropylamide; 4-PPY = 4-pyrrolidinylpyridine; TFA = trifluoroacetic acid.

Scheme 5. Total Synthesis of Crokonoid A[a]



"Reagents and conditions: (a) TFA (6.0 equiv), DCM, rt, 18 h; (b) TESOTf (1.5 equiv), NEt_3 (3.0 equiv), DCM, −78 °C, 30 min; (c) Ac_2O (5.6 equiv), DMAP (7.0 equiv), toluene, rt, 18 h; (d) TfOH (1.1 equiv), DCM, −78 °C, 15 min; (e) DMP (2.0 equiv), $NaHCO_3$ (4.0 equiv), DCM, rt, 15 min, 66% (five steps); (f) *B*-Iodo-9-BBN (5.0 equiv), 2,6-di-*tert*-butylpyridine (7.5 equiv), toluene, rt, 4 h, then AcOH (27.0 equiv), rt, 30 min, 83%; (g) Pd_2dba_3 (12.0 mol %), Xantphos (26.0 mol %), K_3PO_4 (5.0 equiv), toluene, 75 °C, 8 h, 65%; (h) SmI_2/HMPA (1:5), THF/H_2O (10:1 v/v), −78 °C, 15 min, 57%; (i) TESOTf (1.8 equiv), NEt_3 (3.5 equiv), DCM, 0 °C, 15 min; (j) K_2CO_3 (12.5 equiv), MeOH, rt, 18 h; (k) DMP (3.0 equiv), $NaHCO_3$ (6.0 equiv), DCM, 0 °C, 15 min; (l) DIBAL-H (1.1 equiv), DCM, −78 °C, 5 min, 77% (four steps); (m) Ac_2O (10 equiv), $Sc(OTf)_3$ (0.1 equiv), CH_3CN/DCM (3:1), 0 °C, 5 min; (n) SeO_2 (20.0 equiv), 1,4-dioxane, 75 °C, 6 h; (o) DMP (2.0 equiv), DCM, 0 °C, 15 min, 44% (three steps); (p) $Ti(OiPr)_4$ (43.5 equiv), THF, 70 °C, 24 h, 79%. HMPA = hexamethylphosphoramide; *B*-iodo-9-BBN = 9-iodo-9-borabicyclo[3.3.1]nonane.

Scheme 6. SmI_2-Mediated Reduction of the C14 Carbonyl Group: Stereodivergence and Byproduct Formation