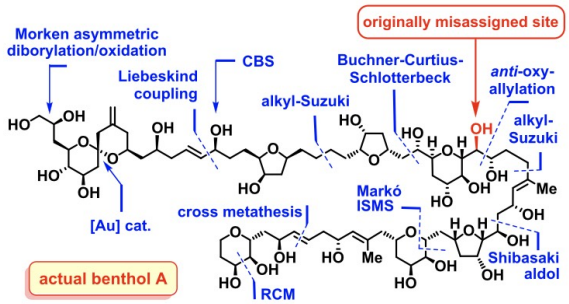
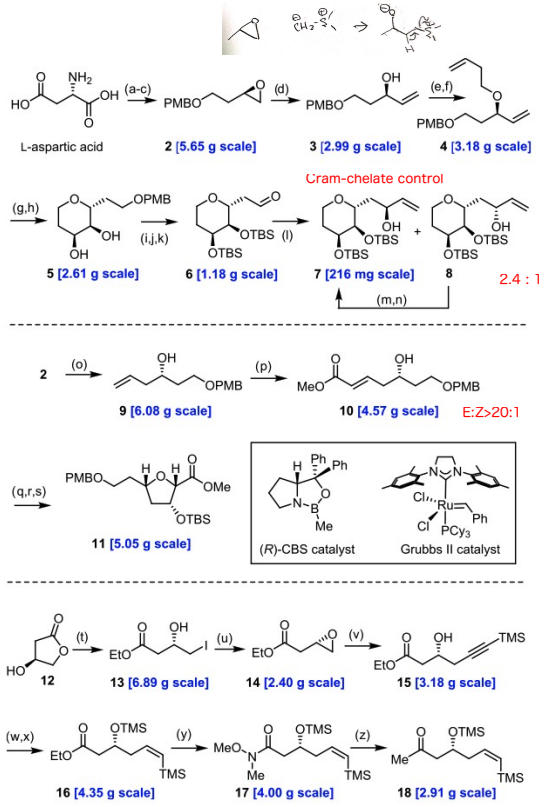
Total Synthesis of Benthol A: The Nominal and the Actual Natural Product

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Journal American Chemical Society 2026, 148 (29): 30731–30743.

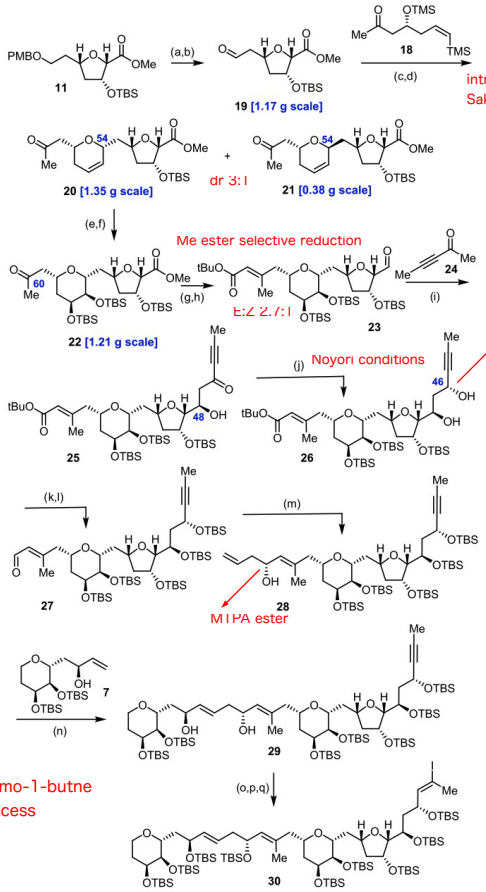




[a]Reagents and Conditions: (a) $NaNO_2$, KBr, H_2SO_4 cat., H_2O, −5°C, 88% [13 g scale]; (b) BH_3·THF, THF, −5°C to RT, 96% [5.39 g scale]; (c) NaH, THF/DMF, −5°C, then PMBBr, 92%; (d) $[Me_2S]I$, *n*BuLi, THF, 0 °C, 93%; (e) 1,4-dibromobutane, KOH, *n*Bu_4NBr (10 mol %), toluene, RT, 92% [4.45 g scale]; (f) *t*BuOK, 18-crown-6 (15 mol %), toluene, 0 °C to RT, 92%; (g) Grubbs II catalyst (1 mol %), CH_2Cl_2, reflux, 95% [2.73 g scale]; (h) OsO_4 (10 mol %), NMO, THF/H_2O (3:1), RT, 84%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant. [4.70 g scale]; (j) DDQ, CH_2Cl_2/H_2O (95:5), RT, quant. [3.35 g scale]; (k) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, quant.; (l) vinylmagnesium bromide, THF, 0 °C, 61% (**7**) + 25% (**8**); (m) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT; (n) (*R*)-CBS catalyst (20 mol %), BH_3·SMe_2, THF, −20 °C to 0 °C, 52% (over two steps [125 mg scale], dr = 18:1); (o) vinylmagnesium bromide, CuI (25 mol %), THF, −78 °C, 95%; (p) methyl acrylate, Grubbs II catalyst (2 × 1 mol %), CH_2Cl_2, reflux, 93%; (q) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C; (r) $(DHQD)_2PHAL$ (4 mol %), $K_2OsO_2(OH)_4$ (2 mol %), $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, *t*BuOH, H_2O, CH_2Cl_2, 0 °C to RT; (s) (i) 2,6-lutidine, 120°C; (ii) TBSCl, imidazole, DMAP cat., DMF, 0 °C to RT, 77% (over four steps, dr >20:1); (t) Me_2SiI, EtOH, CH_2Cl_2, 0°C to RT, 89%; (u) Ag_2O, MeCN, reflux, 92%; (v) trimethylsilylacetylene, *n*BuLi, Et_2AlCl, toluene, −35°C to 0 °C, 91%; (w) $Ni(OAc)_2$·$4H_2O$, $NaBH_4$, H_2 (1 atm), ethylenediamine, EtOH, RT, 86% [2.26 g scale]; (x) TMSCl, Et_3N, CH_2Cl_2, 0 °C to RT, 96%; (y) MeNH(OMe)·HCl, *i*PrMgCl, THF, −20°C, 88%; (z) MeMgBr, Et_2O, 0 °C, 85%.

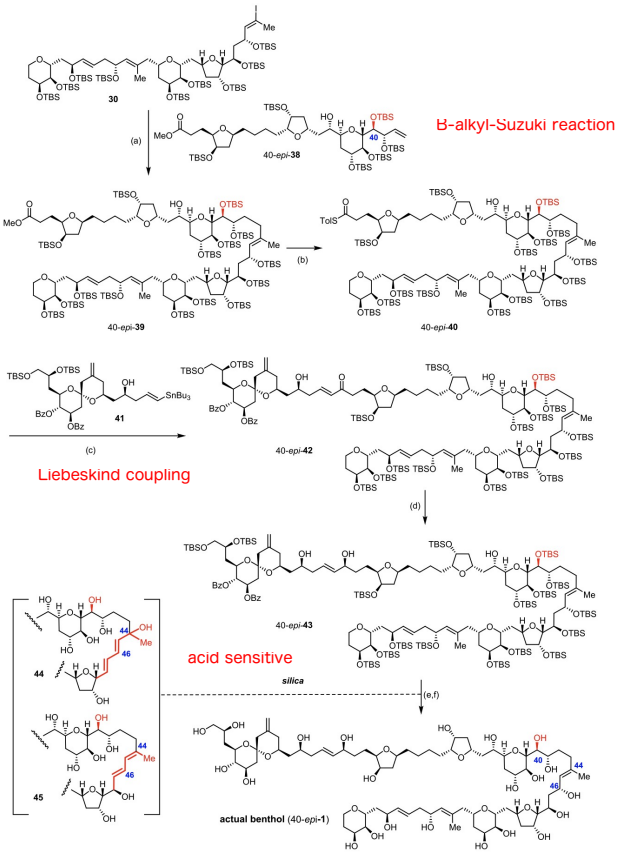
P2-nickel

4-bromo-1-butne unsuccess



[a]Reagents and Conditions: (a) DDQ, CH_2Cl_2/H_2O, RT, quant. [1.57 g scale] (b) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to RT, 77%; (c) **18**, TMSOTf, CH_2Cl_2, −78 °C, (d) TBSCl, imidazole, DMAP cat., DMF, 0 °C to RT, **20** (70%, over two steps) + **21** (20%); (e) OsO_4 (5 mol %), NMO, THF/H_2O, RT, 80% (dr = 9:1 [1.07 g scale]); (f) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to 0 °C; (ii) aq. HCl, RT, 98%; (g) *t*BuOOCCH$_2$P(O)(OEt)$_2$, NaH, LiBr, THF, 0 °C to RT, 68% (*E*-isomer [681 mg scale]) + 25% (*Z*-isomer); (h) Dibal-H, CH_2Cl_2, −95 °C; (i) **24**, $CuBF_4$·$(MeCN)_4$ (5 mol %), (*S*)-(+)-DTBM-SEGPHOS (5 mol %), F_3CCH_2OLi (5 mol %), CF_3CH_2OH (40 mol %), THF, −40°C, **25** (60% (83% brsm) over two steps, [474 mg scale]) + 48-*epi*-**25** (not shown; 12%); (j) RuCl[(*R*,*R*)-Ts-DPEN](mesitylene) (5 mol %), HCOOH, Et_3N, CH_2Cl_2, RT, **26** (68% [352 mg scale]) + 46-*epi*-**26** (16%); (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 98% [440 mg scale]; (l) (i) Dibal-H, toluene, −78 °C; (ii) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to RT, 79% (over two steps) [322 mg scale]; (m) allylmagnesium bromide, (+)-Ipc$_2$BOMe, Et_2O, −95 °C, 82% [188 mg scale]; (n) **7**, **31** (5 mol %), CH_2Cl_2, RT, 73% [174 mg scale]; (o) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 95% [193 mg scale]; (p) *n*Bu$_3$SnH, $[(P(o\text{-tolyl})_3)_2PdCl_2]$ (10 mol %), THF, RT; (q) I_2, CH_2Cl_2, 0 °C, 82% (over two steps [89 mg scale]).

hydrolize the Si enol ether of methyl ketone

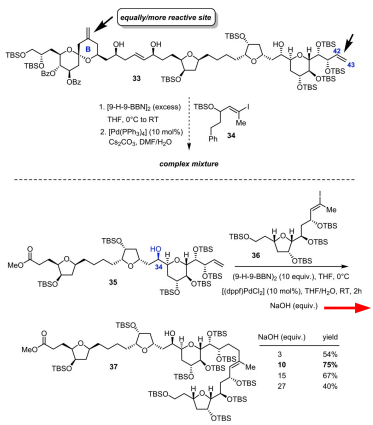


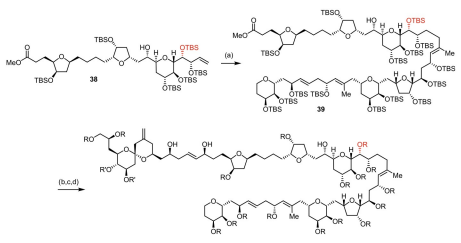
[a]Reagents and Conditions: (a) (i) 40-*epi*-**38**, $[9\text{-H-9-BBN}]_2$, THF, 0 °C to RT; (ii) **30**, $[(dppf)PdCl_2]$ (10 mol %), NaOH (10 equiv), THF/H_2O (5:1), RT, 55% (66% brsm); (b) (*p*-tolyl*S*)$_3$Al, toluene, RT, 77%; (c) $[Pd_2(dba)_3]$·$CHCl_3$ (10 mol %), P(2-furyl)$_3$ (80 mol %), $Ph_3P(O)OCu$, THF/hexanes (1:1), 50°C, 86%; (d) (*R*)-CBS catalyst, catecholborane, THF, −78 °C to −20 °C, 93%; (e) K_2CO_3, THF/MeOH, RT; (f) TBAF, THF, 0 °C to RT, 92% (over two steps).

freshly prepared

unsucceeded model plan

FragmentA + B → A+B+C





[a]Reagents and Conditions: (a) (i) **38**, $[9\text{-H-9-BBN}]_2$, THF, 0 °C to RT; (ii) **30**, $[(dppf)PdCl_2]$ (10 mol %), NaOH (10 equiv), THF/H_2O (5:1), RT, 55% (75% brsm); (b) (*p*-tolyl*S*)$_3$Al, toluene, RT, 89%; (c) **41**, $[Pd_2(dba)_3]$·$CHCl_3$ (10 mol %), P(2-furyl)$_3$ (80 mol %), $Ph_3P(O)OCu$, THF/hexanes (1:1), 50 °C, 84%; (d) (*R*)-CBS catalyst, catecholborane, THF, −78 °C to −20 °C, 70%; (e) K_2CO_3, THF/MeOH, RT; (f) TBAF, THF, 0°C to RT, 74% (over two steps).