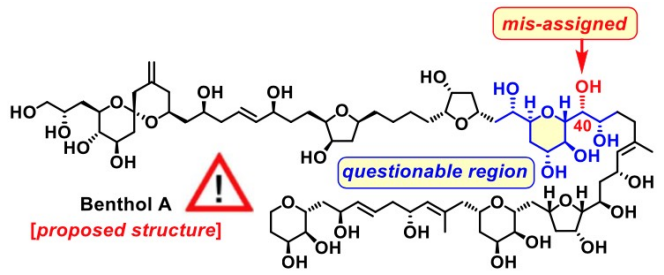
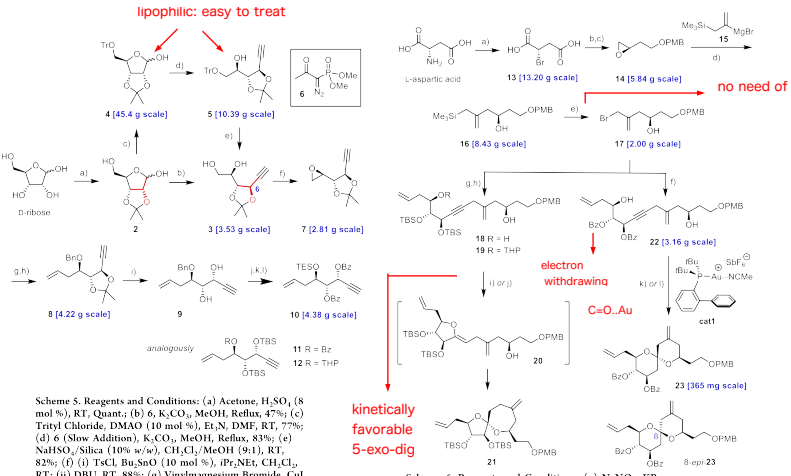
Total Synthesis of Benthol A: Evidence for a Structure Revision

Guanghao Huang, Andrea Tomio, Thomas Varlet, Conny Wirtz, Alois Fürstner

Journal American Chemical Society 2026, 148 (29): 30717–30730.



"super-carbon-chain compound" (SCCC)



Scheme 5. Reagents and Conditions: (a) Acetone, H_2SO_4 (8 mol %), RT, Quant.; (b) 6, K_2CO_3, MeOH, Reflux, 47%; (c) Trityl Chloride, DMAO (10 mol %), Et_3N, DMF, RT, 77%; (d) 6 (Slow Addition), K_2CO_3, MeOH, Reflux, 83%; (e) $NaHSO_4$/Silica (10% w/w), CH_2Cl_2/MeOH (9:1), RT, 82%; (f) (i) TsCl, Bu_2SnO (10 mol %), iPr_2NEt, CH_2Cl_2, RT; (ii) DBU, RT, 88%; (g) Vinylmagnesium Bromide, CuI (20 mol %), THF, −78 °C, 98% [3.24 g Scale]; (h) BnBr, NaH, DMF, 0 °C to RT, 89%; (i) HOAc/H_2O (4:1), 65 °C; (j) Benzoyl Chloride, Pyridine, 0 °C to RT, 93% [6.20 g Scale] (Over Two Steps); (k) DDQ, *hν* (Blue LED), CH_2Cl_2/H_2O (99:1), RT, 76% [3.79 g Scale]; (l) TESOTf, 2,6-Lutidine, CH_2Cl_2, 0 °C, 88%; the Scales Indicated in This and the Following Schemes Refer to the Amount of Product in the Single Largest Batch

chemo-orthogonal to the π-bonds

Scheme 6. Reagents and Conditions: (a) $NaNO_2$, KBr, H_2SO_4 Cat., H_2O, 0–10 °C, 88%; (b) BH_3·THF, THF, 0 °C, 94% [5.28 g Scale]; (c) NaH, THF, −5 °C, Then PMBBr, 89%; (d) 15, CuI (15 mol %), THF, −50 °C, 93%; (e) NBS, THF, −78 °C, 85%; (f) (i) 10, CuI (25 mol %), DBU (10 mol %), Na_2SO_3, K_2CO_3, DMF, RT; (ii) CSA (10 mol %), CH_2Cl_2/MeOH (4:1), RT, 82%; (g) 11, CuI (10 mol %), K_2CO_3, Na_2SO_3, DBU (30 mol %), DMF, RT, 94%; (h) Dibal-H, CH_2Cl_2, −78 °C, THF, 97% (18); (i) cat1 (10 mol %), CSA (20 mol %), CH_2Cl_2, −78 °C, Then RT, 80% (from 18 (R = H)); (j) cat1 (20 mol %), PPTS (20 mol %), CH_2Cl_2, −50 °C to RT, 70% (from 19 (R = THP)); (k) cat1 (20 mol %), CSA (10 mol %), CH_2Cl_2, −10 °C, 50% (23 + 8-*epi*-23, dr ≈ 1.5:1); (l) cat1 (2 mol %), CSA (10 mol %), CH_2Cl_2, −78 °C, Then RT, 76% (23) + 9% (8-*epi*-23)

mild

matched with natural source

Scheme 7. Reagents and Conditions: (a) Pt(dba)$_3$ (5 mol %), (*R*,*R*)-30 (7.5 mol %), B_2(pin)$_2$, THF, Reflux, Then $NaBO_3$·H_2O, H_2O, 81% (dr ≥ 10:1); (b) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0 °C; (c) DDQ, CH_2Cl_2/H_2O (20:1), RT, 84% (over Two Steps); (d) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, RT, 90%; (e) 26, (−)-Ipc$_2$BH, Et_2O, Then 25, −78 °C, 71%; (f) (i) K_2CO_3, MeOH, RT; (ii) TBAF, THF, 0 °C to RT, Then DOWEX, 68% (over Two Steps); (iii) O_3, CH_2Cl_2/MeOH (1:1), −78 °C, Then $NaBH_4$

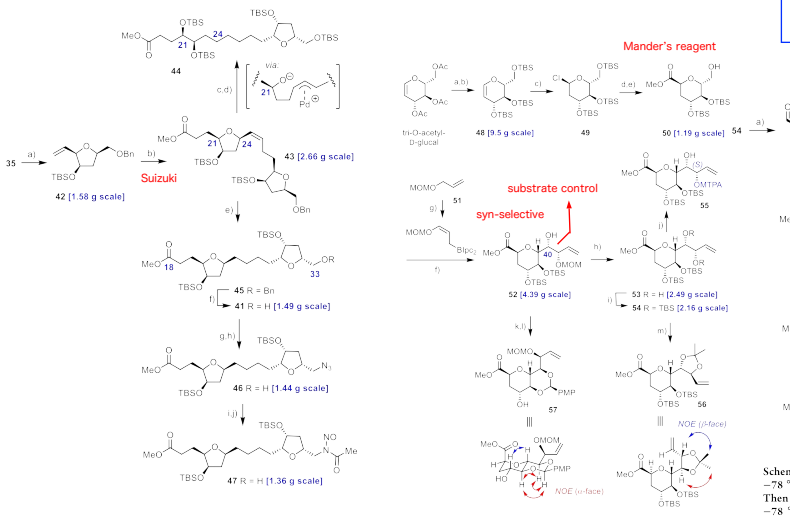
Buchner–Curtius–Schlotterbeck reactions

antiperiplanar

"eclipsed" orientation of the zwitterionic/polar groups

Buchner–CurtiusSchlotterbeck reaction)

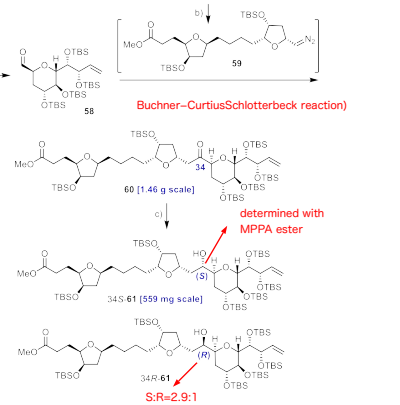
Scheme 8. Reagents and Conditions: (a) Vinylmagnesium Bromide, CuI (20 mol %), THF, −78–0 °C; (b) Methyl Acrylate, Grubbs II Catalyst (2 × 1 mol %), CH_2Cl_2, Reflux, 98% (over Two steps; *E*/*Z* = 28:1 [10.90 g Scale]); (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; (d) $K_2OsO_2(OH)_4$ (2 mol %), $(DHQD)_2PHAL$ (4 mol %), $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH, H_2O, CH_2Cl_2, 0 °C to RT; (e) 2,6-Lutidine, 120 °C, 80% [8.48 g Scale] (over Two Steps; +10% of Isomers); (f) TBSCl, DMAP Cat., Imidazole, DMF, RT, Quant.; (g) Dibal-H, CH_2Cl_2, −78 °C; (h) 6, K_2CO_3, MeOH, 0 °C to RT, 90% (over Two Steps); (i) Ph_3P = CHCOOMe, CH_2Cl_2, 0 °C to RT, 94% (over Two Steps); (j) H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, RT, 94%; (k) DMSO, $(CO)_2Cl_2$, CH_2Cl_2, Then Et_3N, −78–0 °C; (l) $[Ph_3PCH_3]I$, KHMDS, HMPA, THF, −78–0 °C, 85% (over Two Steps); (m) $[(Ph_3P)_2PdCl_2]$ (10 mol %), CuI (20 mol %), Et_3N, RT, 93%



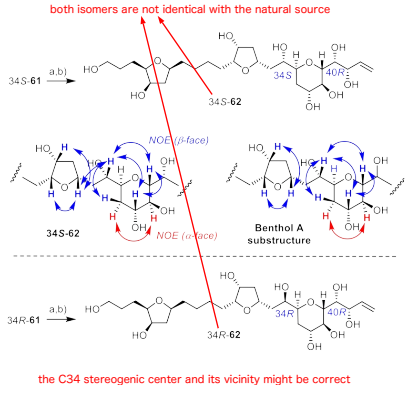
Scheme 9. Reagents and Conditions: (a) (i) Dibal-H, CH_2Cl_2, −78 °C; (ii) Ph_3P = CH_2, THF, 0 °C, 91% (over Two Steps); (b) (9-H-9-BBN)$_2$, THF, Then 39, $[(dppf)PdCl_2]$ (10 mol %), Ph_3As (40 mol %), Cs_2CO_3, DMF/THF/H_2O, RT, 96%; (c) H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, RT, ; (d) TBSCl, DMAP Cat., Imidazole, DMF, RT, up to 40% (See Text); (e) H_2 (1 atm), Raney-Ni, EtOAc, RT; (f) H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, RT, 84–94% (over Two Steps); (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaN_3, DMF, 100 °C, 79% (over Two Steps); (i) H_2 (1 atm), Pd/C, Ac_2O, MeOH, 0 °C to RT, 90% [1.27 g Scale]; (j) $NaNO_2$, Ac_2O, HOAc, 0 °C, 84%

Scheme 10. Reagents and Conditions: (a) K_2CO_3, MeOH, RT; (b) TBSCl, Imidazole, DMF, 0 °C to RT, 97% (over Two Steps); (c) HCl in 1,4-Dioxane, THF, 0 °C to RT; (d) Lithium Naphthalenide, THF, −95 °C, Then MeOC(O)CN, −95 °C to RT; (e) PTSA·H_2O Cat., MeOH, 0 °C, 55% (over Three Steps); (f) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to RT; (g) 51, *sec*-BuLi, (−)-Ipc$_2$BOMe (See Text), BF_3·OEt_2, THF, −95 °C to RT, Then aq. H_2O_2, $NaHCO_3$, 0 °C to RT, 82% (over Two Steps); (h) Me_3SiBr, CH_2Cl_2, −78 °C to −10 °C, 62%; (i) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0 °C to RT, Quant.; (j) (*S*)-(+)- or (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl Chloride, Pyridine, DMAP Cat., CH_2Cl_2, RT, 69–72%; (k) TBAF, THF, RT, 84%; (l) $MeOC_6H_4CH(OMe)_2$, PTSA·H_2O Cat., THF, RT, Quant.; (m) 2,2-Dimethoxypropane, PPTS Cat., RT, 80%

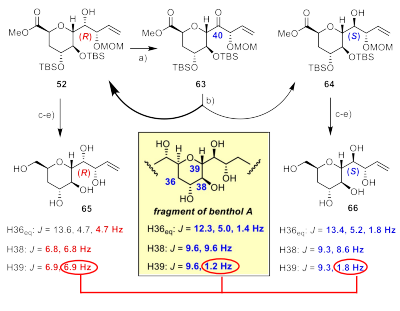
2.9 : 1



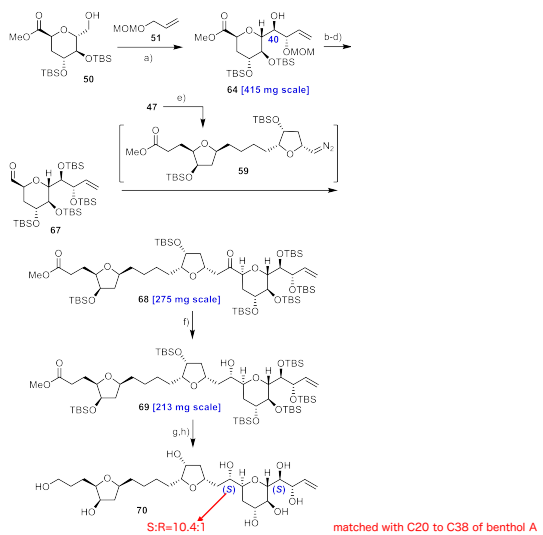
Scheme 11. Reagents and Conditions: (a) Dibal-H, CH_2Cl_2, −78 °C; (b) aq. KOH, Toluene/MeOH, 0 °C, Then $MgSO_4$; Then 58, Toluene, 0 °C to RT, 65%; (c) L-Selectride, THF, −78 °C, 65% (34*S*-61), 23% (34*R*-61)



Scheme 12. Reagents and Conditions: (a) Dibal-H, CH_2Cl_2, −78 °C to RT; (b) TBAF, THF; RT, 77% (34*S*-62), 93% (34*R*-62); Comparison of the NOEs Observed for 34*S*-62 and the Corresponding Subsection of Authentic Benthol A



Scheme 13. Reagents and Conditions: (a) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to RT, 86%; (b) $NaBH_4$, EtOH, 0 °C, 48% (52) + 19% (64); (c) Me_3SiBr, CH_2Cl_2, −78 °C to −10 °C, 94% (40*S* Series), 62% (40*R* Series); (d) Dibal-H, CH_2Cl_2, −78 °C to RT; (e) TBAF, THF, RT; 81% (66), 66% (65)



Scheme 14. Reagents and Conditions: (a) (i) Dess-Martin Periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to RT; (ii) 51, *sec*-BuLi, $ZnCl_2$, −78–0 °C, 78% (over Two Steps; dr = 28:1); (b) Me_3SiBr, CH_2Cl_2, −78 °C to −10 °C, 81%; (c) TBSOTf, 2,6-Lutidine, CH_2Cl_2, 0 °C to RT, 97%; (d) Dibal-H, CH_2Cl_2, −78 °C; (e) aq. KOH, Toluene/MeOH, 0 °C, Then $MgSO_4$; Then 67, Toluene, 0 °C to RT, 74%; (f) L-Selectride, THF, −78 °C, 77% (dr = 10.4:1); (g) Dibal-H, CH_2Cl_2, −78 °C to RT; (h) TBAF, THF, RT, Quant. (over Two Steps)