Supporting Information

Enantioselective Alcohol C-H Functionalization for Polyketide Construction: Unlocking Redox-Economy and Site-Selectivity for Ideal Chemical Synthesis

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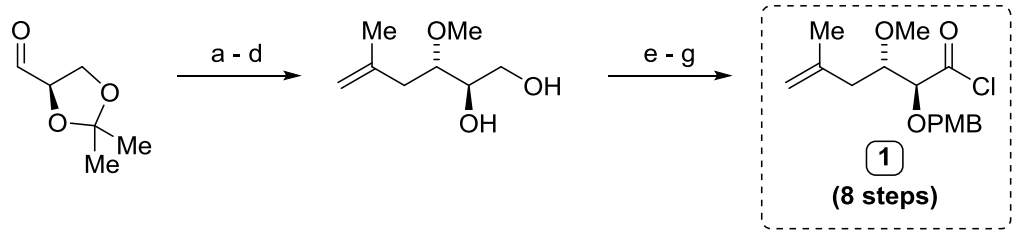
Rules for Calculating Step Counts

"*Given the fact that every reaction may be optimized… the total number of chemical transformations is the only variable in the determination of strategic efficiency.*" Qiu, F. *Can J. Chem.* 2008, 86, 903. In our analysis, a step is defined as an operation that does not involve any intervening purification/separation, including removal of solvent, commencing with compounds that are over $50/gram. The longest linear sequence (LLS) refers to the longest route from a starting material to the natural product. Total steps (TS) account for steps outside the longest linear sequence. Stoichiometric reagents, such as chiral auxiliaries, that are not commercially available for less than $50 USD/g that require synthesis contribute to step count. Substoichiometric reagents, such as catalysts and ligands that require synthesis do not contribute to step count. In formal syntheses, step counts are calculated up to the fragment that intercepts the total synthesis and therefrom to the natural product.

Graphical Summary of Previous Syntheses of Psyberin (Irciniastatin A)

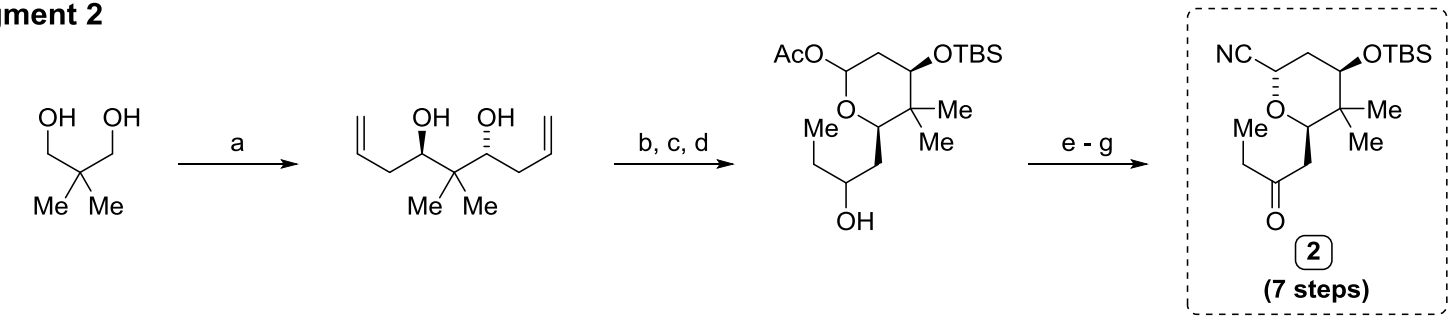
A. De Brabander *et al. J. Am. Chem. Soc.* **2005**, *127*, 11254; *J. Am. Chem. Soc.* **2012**, *134*, 17083.

Fragment 1



Key: a) (–)-$(Ipc)_2BOMe$, $CH_2=C(Me)CH_2Li$; b) NaH, MeI; c) PPTS; d) TBSCl, Imidazole; e) PMBCl ; f) DMP; g) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene h) $COCl_2$.

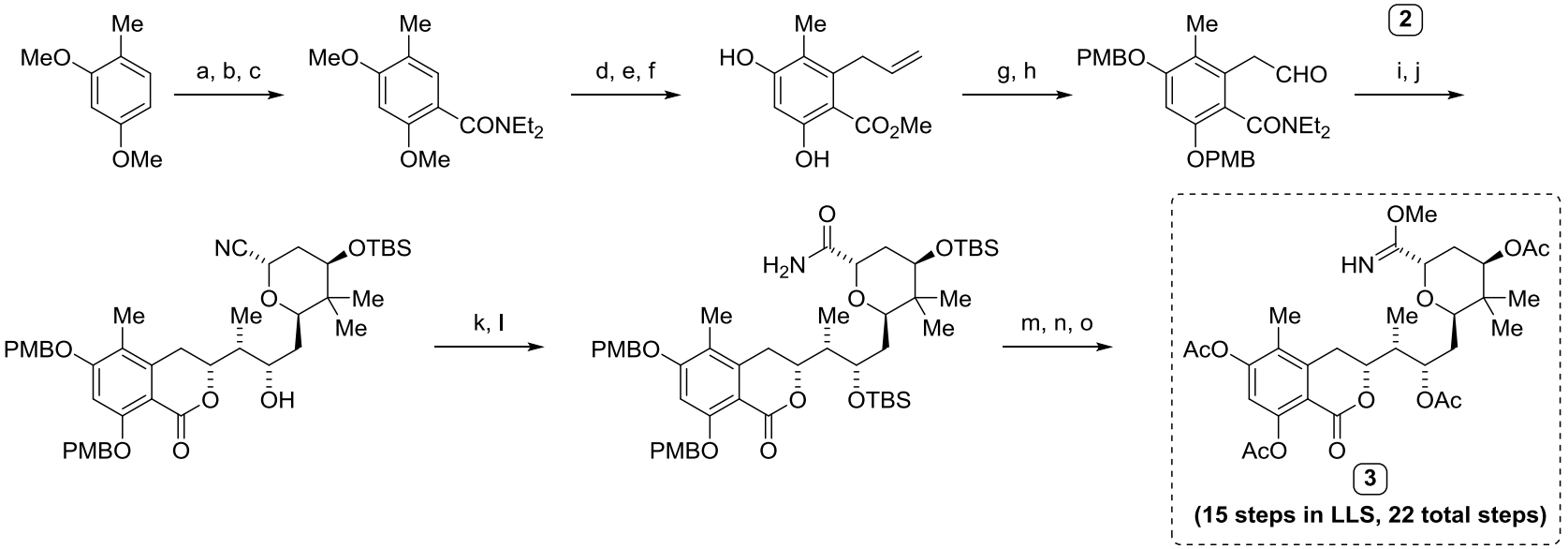
Fragment 2



Key: a) $[Ir(cod)Cl]_2$, (*R*)-Cl,MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-BzOH, allyl acetate; b) TBSOTf, 2,6-lutidine; c) O_3, then PPh_3; d) Ac_2O, NEt_3, DMAP; e) Et_2Zn, $Ti(Oi\text{-}Pr)_4$, *N,N'*-(1*R*,2*R*-cyclohexane-1,2-diyl)bis(trifluoromethanesulfonamide), Et_2Zn; f) TMSCN, then ZnI_2, then HCl; g) DMP.

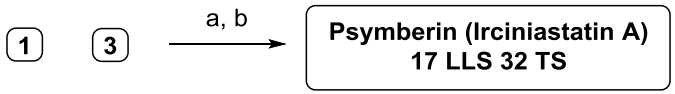
A. De Brabander *et al. J. Am. Chem. Soc.* **2005**, *127*, 11254; *J. Am. Chem. Soc.* **2012**, *134*, 17083. (Cont'd)

Fragment 3



Key: a) DMF $POCl_3$; b) NaH_2PO_4, $NaClO_2$, 2-Me-2-butene; c) $SOCl_2$, Et_2NH; d) *s*-BuLi, CuBr-SMe_2, $H_2C{=}CHCH_2Br$; e) BBr_3; f) Me_3O-BF_4, Na_2CO_3; g) PMBCl, TBAI, K_2CO_3; h) OsO_4 (cat.), NMO, $NaIO_4$; i) **2**, $PhBCl_2$, *i*-Pr_2NEt; j) HB(cat), NaOH; k) TBAF; l) EtOH/ H_2O, $[PtH(PMe_2OH)(PMe_2O)H]$; m) H_2, Pd/C; n) Ac_2O, pyridine; o) Me_3O-BF_4, PVP.

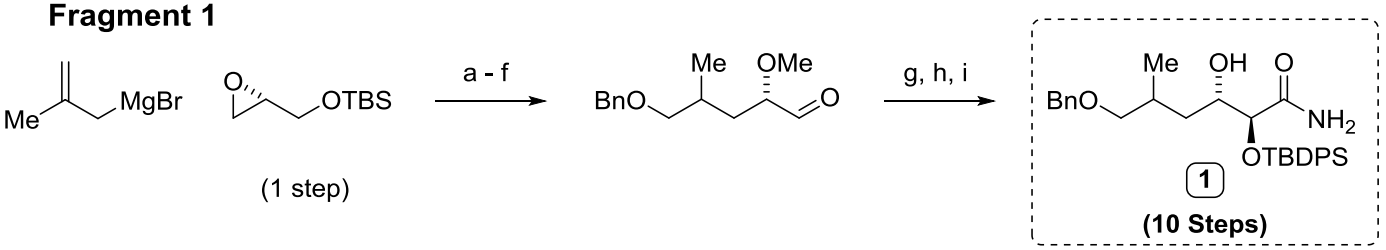
Fragment Union and End Game



Key: a) *i*-Pr_2NEt, **1**, then $NaBH_4$; b) LiOH.

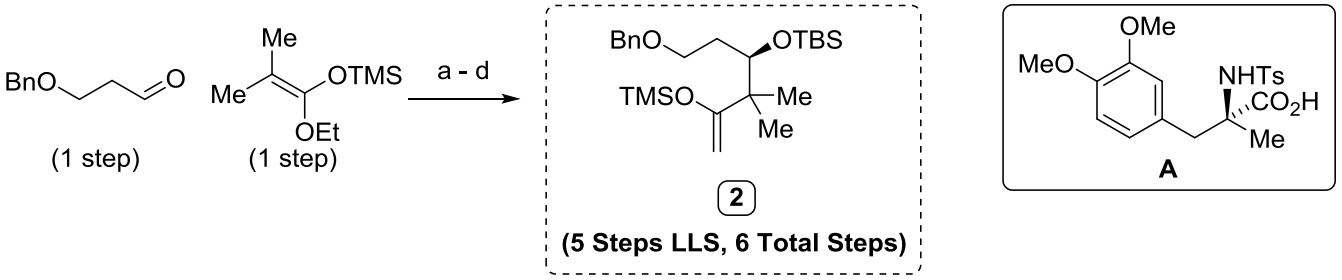
B. Huang *et al. Org. Lett.* **2007**, *9*, 2597.

Fragment 1



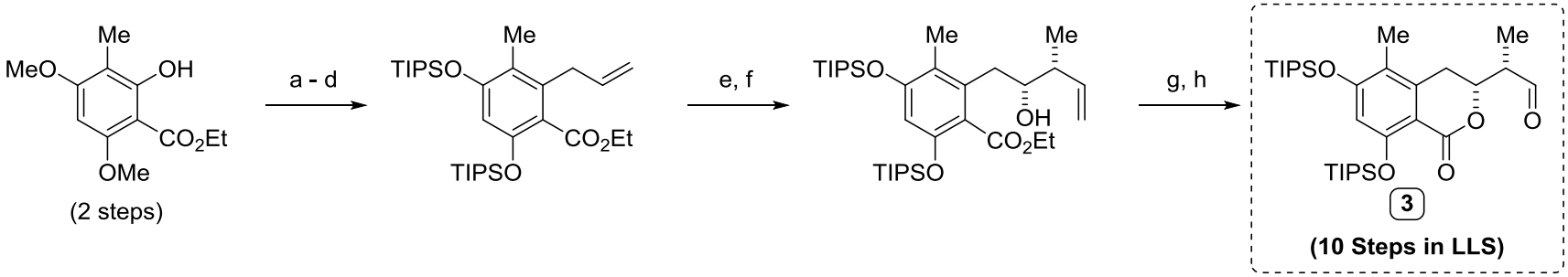
Key: a) CuI; b) Me_3O-BF_4, proton sponge; c) BH_3, then H_2O_2, NaOH; d) BnBr, NaH; e) TBAF; f) $(COCl)_2$, DMSO, NEt_3; g) TMSCN, $AlCl_3$; h) TBDPSCl, NEt_3, DMAP; i) $MeCONH_2$, $PdCl_2$, H_2O.

Fragment 2



Key: a) BH_3-THF, **A**; b) TBSOTf, 2,6-lutidine; c) $TMSCH_2Li$; d) TMSOTf, NEt_3.

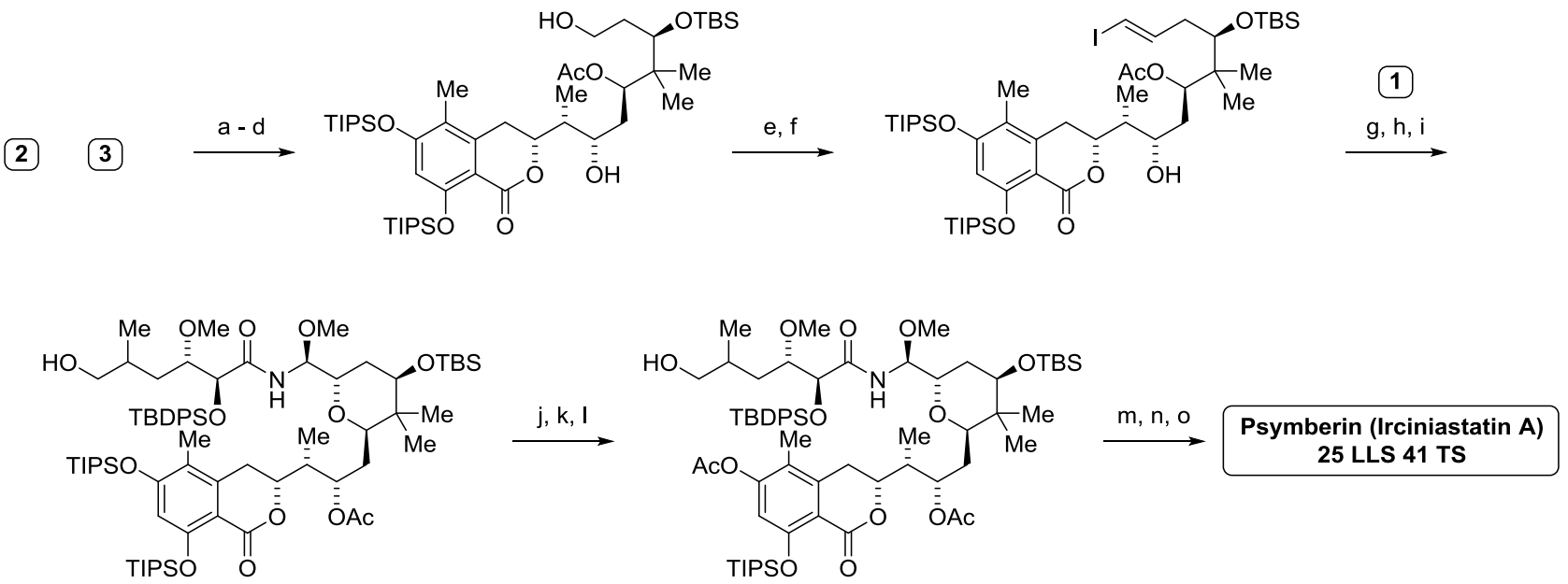
Fragment 3



Key: a) Tf_2O, pyridine; b) $Pd(PPh_3)_4$, allylSnBu$_3$, LiCl; c) BBr_3; d) TIPSOTf, 2,6-lutidine; e) OsO_4, NMO, then $NaIO_4$; f) (*Z*)-2-butene, *n*-BuLi, KO*t*-Bu, (–)-$(Ipc)_2$BOMe, BF_3•OEt_2; g) Amberlyst 15; OsO_4, NMO, then $NaIO_4$.

B. Huang *et al. Org. Lett.* **2007**, *9*, 2597. (Cont'd)

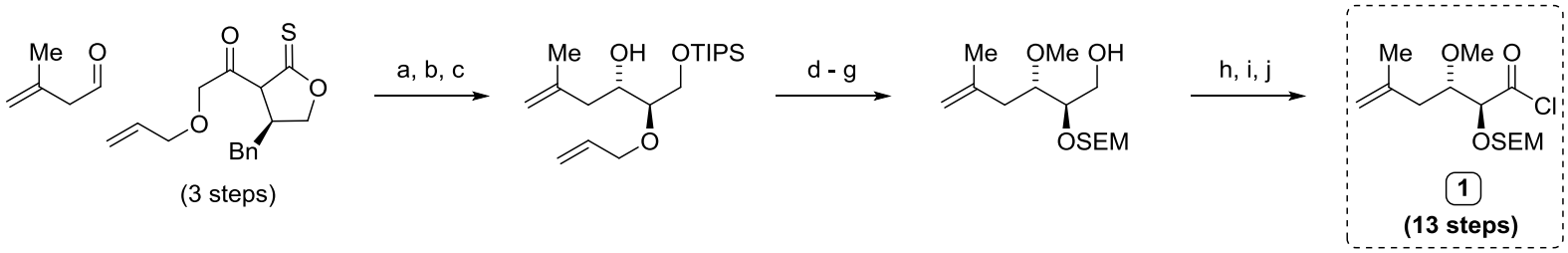
Fragment Union and End Game



Key: a) BF_3-OEt_2; b) HB(cat); c) Ac_2O; d) H_2, Pd/C; e) DMP; f) $CrCl_2$, HCl_3; g) **1**, CuI, $MeNH(CH_2)_2NHMe$, Cs_2CO_3; h) NaOMe; i) Ac_2O, pyridine, DMAP; j) $PhI(OAc)_2$, MeOH, HFIP; k) Ac_2O, pyridine, DMAP; l) H_2, Pd/C; m) 4-NO_2-PhSeCN, PBu_3; n) H_2O_2; o) TBAF.

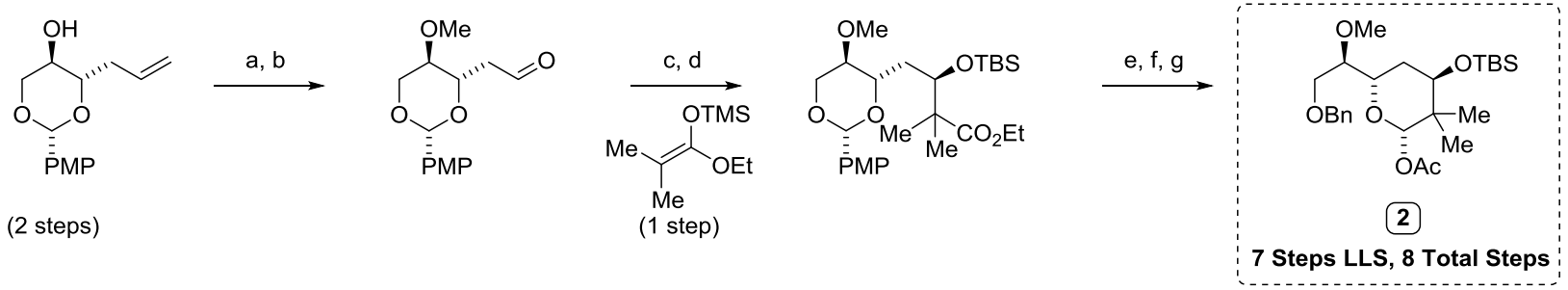
C. Crimmins *et al. Org. Lett.* **2009**, *11*, 3990.

Fragment 1



Key: a) $TiCl_4$, (–)-sparteine; b) $LiBH_4$; c) TIPSCl, imidazole; d) NaH, MeI; e) Ti(O*i*-Pr)$_4$, *n*-BuMgCl; f) SEMCl, *i*-PrNEt$_2$; g) TBAF; h) SO_3-pyr, DMSO, *i*-Pr$_2$NEt; i) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene; j) $SOCl_2$, pyridine.

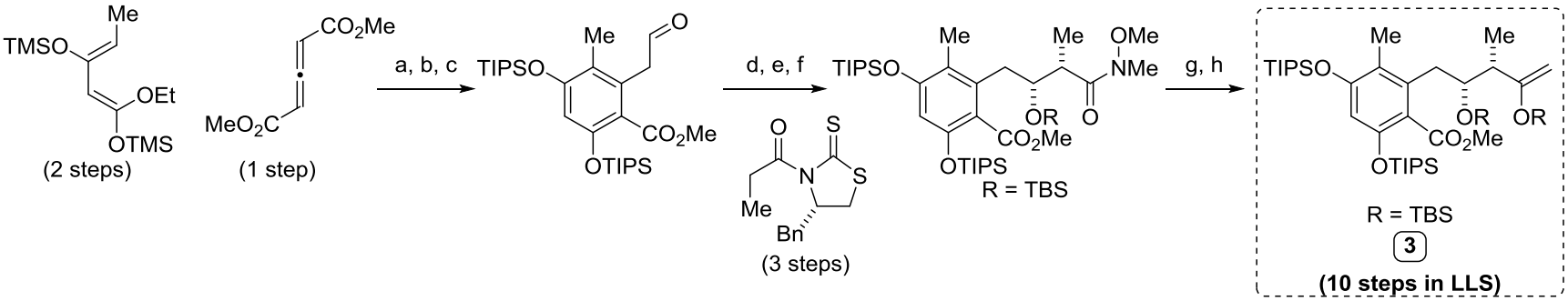
Fragment 2



Key: a) NaH, MeI; b) OsO_4, NMO, then $NaIO_4$; c) enolate, BH_3, Ts-*N*-valine; d) TBSOTf, 2,6-lutidine; e) HCl, then TFA; f) NaH, BnBr, TBAI; g) DIBAL-H, then Ac_2O, pyridine, DMAP.

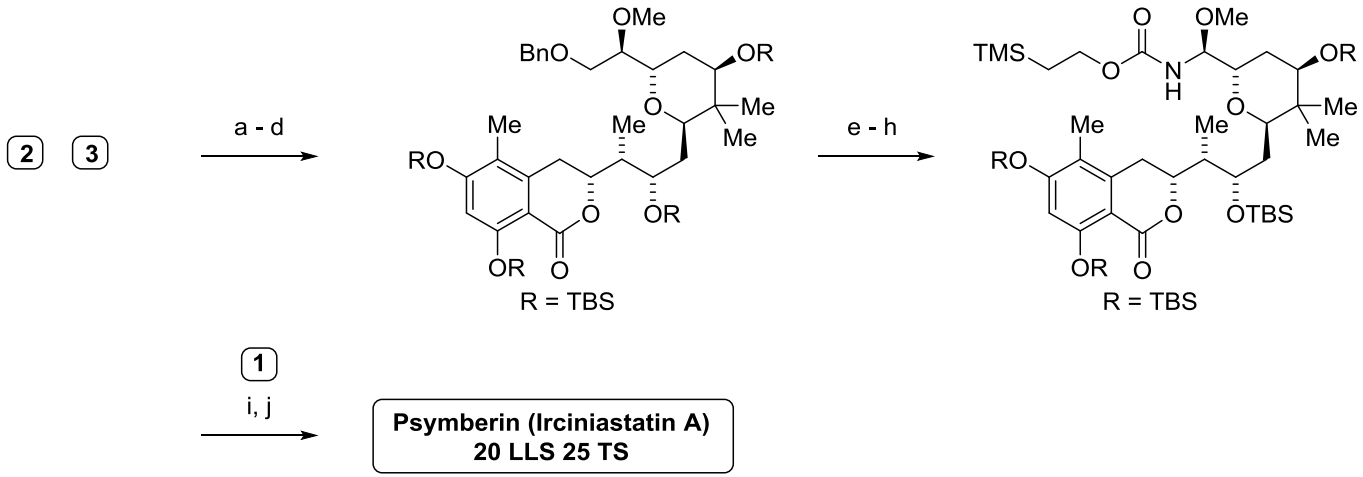
C. Crimmins *et al. Org. Lett.* **2009**, *11*, 3990. (Cont'd)

Fragment 3



Key: a) neat, then Et_3N-HF; b) TIPSOTf, 2,6-lutidine; c) DIBAL-H; d) auxiliary, $TiCl_4$, (–)-sparteine, *N*-Me-pyrolidine; e) (MeO)NHMe-HCl, imidazole; f) TBSOTf, 2,6-lutidine; g) MeMgBr; h) TBSOTf, *i*-Pr_2NEt.

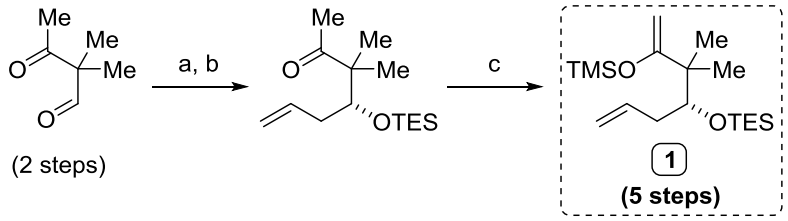
Fragment Union and End Game



Key: a) BF_3•Et_2O; b) BH_3•THF, (*R*)4-Me-CBS; c) TBAF; d) TBSOTf, 2,6-lutidine; e) H_2, $Pd(OH)_2$/C; f) $(COCl)_2$, DMSO, Et_3N; g) $NaClO_2$, 2-Me-2-butene; h) NaN_3, Et_3N, EtO_2CCl, then PhMe, reflux; then CuCl, $TMS(CH_2)_2OH$; i) **1**, *i*-PrMgCl; j) TASF.

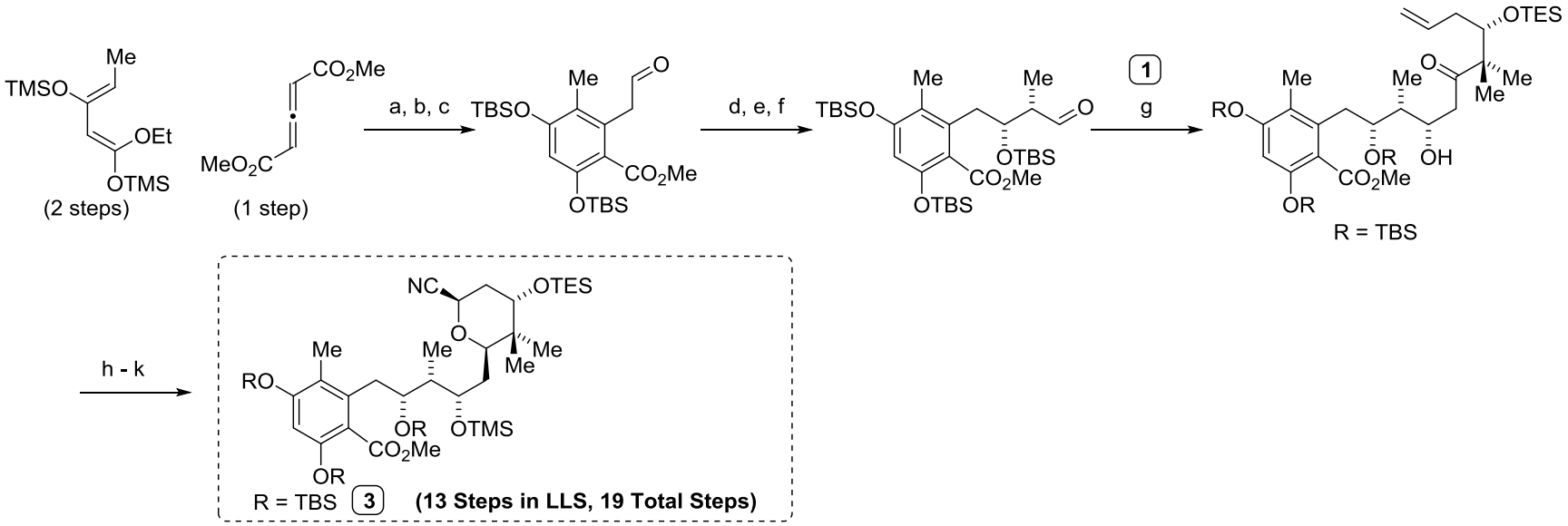
D. Floreancig *et. al. J. Am. Chem. Soc.* **2011**, *133*, 16668.

Fragment 1



Key: a) $[Ir(cod)Cl]_2$, *i*-PrOH, Cs_2CO_3, (*R*)-Cl,MeO-BIPHEP, *m*-NO_2BzOH; b) TESCl, Imidazole; c) LDA, TMSCl.

Fragment 2

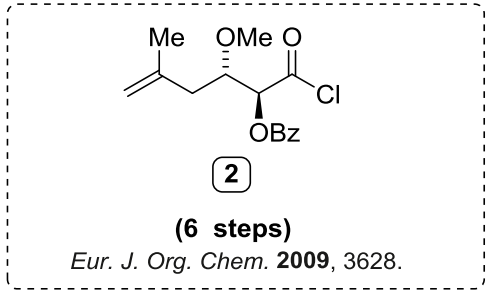


Key: a) neat, then Et_3N-HF; b) TBSOTf, 2,6-lutidine; c) DIBAL-H; d) (*Z*)-$Ipc_2NCH_2CH{=}CHMe$; e) TBSOTf, 2,6-lutidine; f) O_3, then PPh_3; g) **1**, BF_3-OEt_2; h) $NaBH_4$, Et_2BOMe; i) O_3, then PPh_3, j) Ac_2O, Et_3N, DMAP, then TMSCl; k) TMSCN, TMSOTf.

D. Floreancig *et. al. J. Am. Chem. Soc.* **2011**, *133*, 16668. (Cont'd)

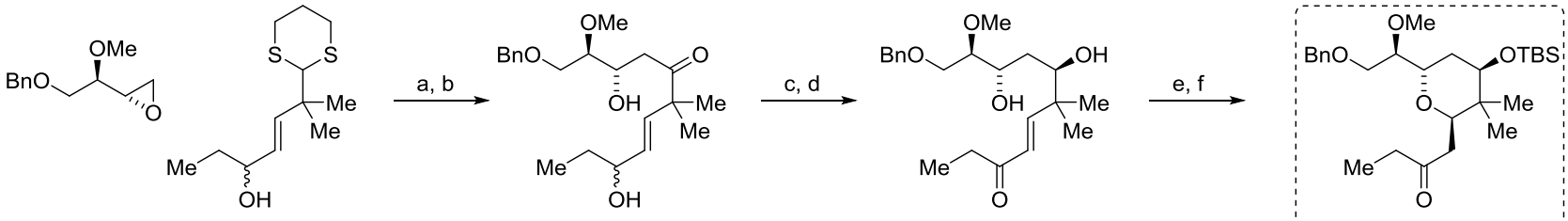
Fragment Union and End Game

Key: a) $Cp_2Zr(H)Cl$, then **2**, then $Zn(OTf)_2$, $(MeO)_3CH$; b) TBAF.



E. Hong *et al. Org. Lett.* **2011**, *13*, 5816.

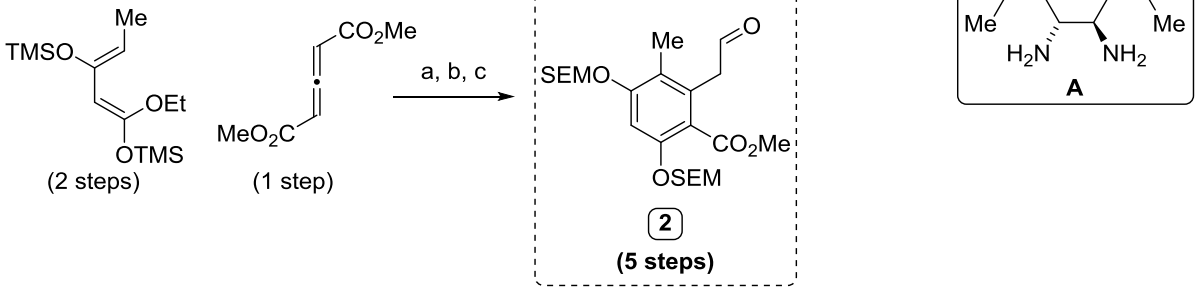
Fragment 1



(3 steps) (6 steps)

Key: a) *t*-BuLi, HMPA; b) I_2, $NaHCO_3$; c) Et_2BOMe, $NaBH_4$, d) MnO_2; e) **A** (cat.), 9-anthracenecarboxylic acid; f)TBSOTf, 2,6-lutidine.

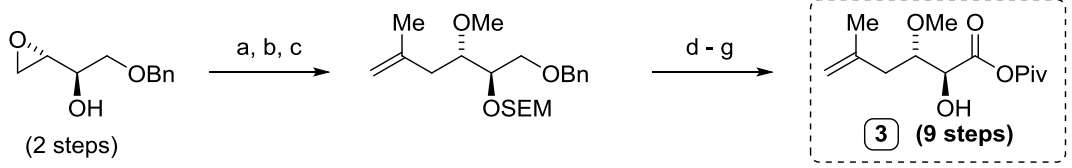
Fragment 2



(2 steps) (1 step)

Key: a) neat, then Et_3N-HF; b) SEMCl, NaH; c) DIBAL-H.

Fragment 3

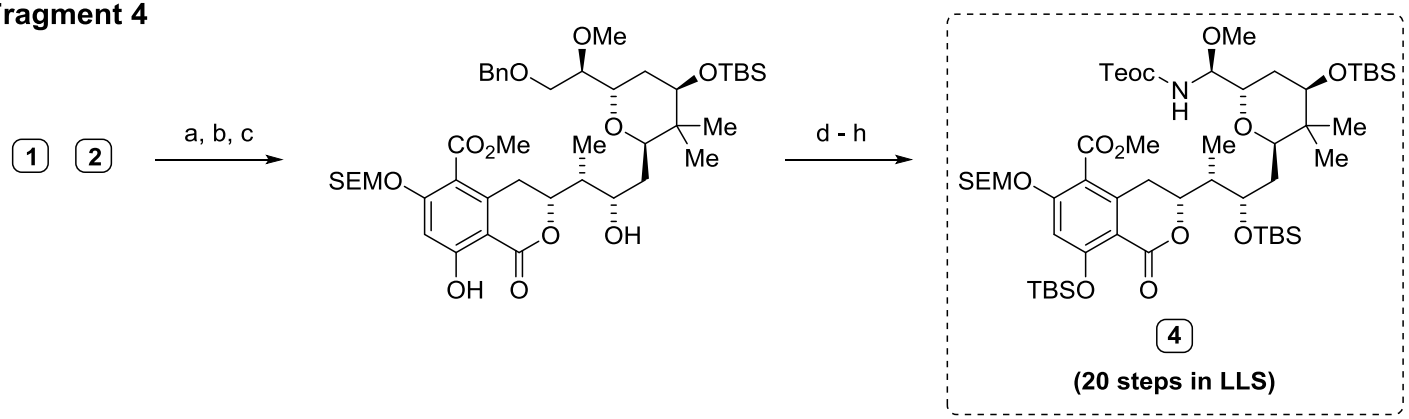


(2 steps)

Key: a) NaH, SEMCl; b) CH_2=C(Me)MgBr, CuI; c) NaH, MeI; d) DDQ; e) SO_3-pyridine, DMSO, *i*-Pr_2NEt; f) 2-Me-2-butene, *t*-BuOH, $NaClO_2$, NaH_2PO_4; g) PivCl, base.

E. Hong *et al. Org. Lett.* **2011**, *13*, 5816. (Cont'd)

Fragment 4



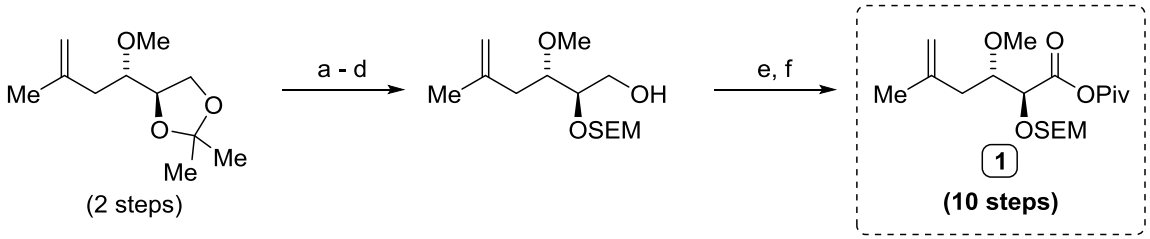
Key: a) $PhBCl_2$, *i*-Pr_2NEt, then **2**; b) Et_2BOMe, $NaBH_4$; c) CSA; d) TBSOTf, 2,6-lutidine; e) H_2, Pd/C; f) DMP; g) 2-Me-2-butene, *t*-BuOH, $NaClO_2$; h) Et_3N, EtO_2CCl, then NaN_3, then PhMe, 110 ^oC; then $TMSCH_2CH_2OH$.

Fragment Union and End Game

Key: a) LiHMDS, the **3**; b) TASF.

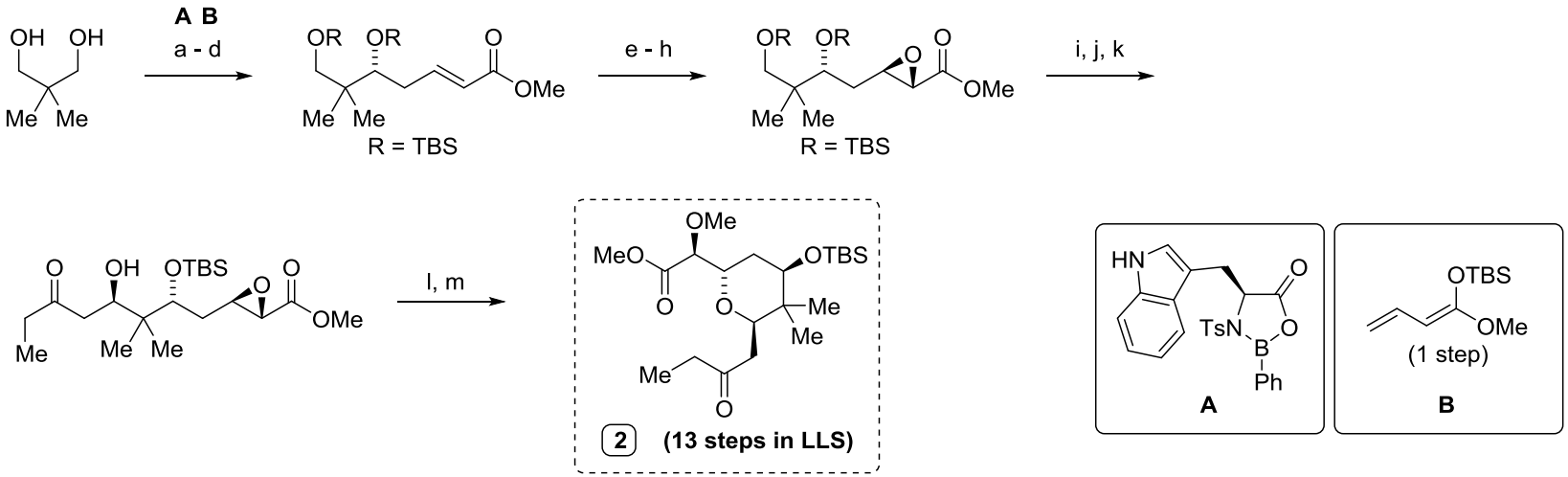
F. Smith *et al. Org. Lett.* **2008**, *10*, 5625; *J. Org. Chem.* **2013**, *78*, 4278.

Fragment 1



Key: a) HCl; b) PivCl, pyridine; c) SEMCl, *i*-Pr_2NEt; d) DIBAL-H; e) SO_3-pyridine, DMSO, *i*-Pr_2NEt; f) $NaClO_2$, NaH_2PO_4, 2-Me-2-butene, *t*-BuOH; g) PivCl, base.

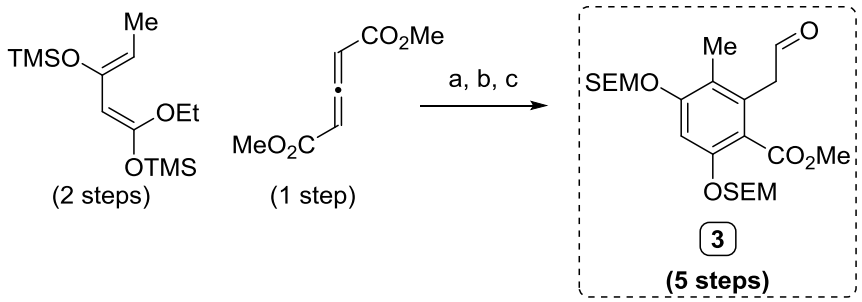
Fragment 2



Key: a) NaH, TBSCl; b) SO_3-pyridine, DMSO, *i*-Pr_2NEt, DMSO; c) **A**, **B**, *n*-butyonitrile, *i*-PrOH; d) TBSOTf, 2,6-lutidine; e) DIBAL-H; f) (–)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, 4Å MS; g) TEMPO, $NaClO_2$, NaOCl, pH 7 buffer; h) $TMSCHN_2$; i) HF-pyr; j) SO_3-pyridine, DMSO, NEt_3, DMSO; k) 2-butanone, (–)-DIPCl, NEt_3; l) CSA; m) Me_3O-BF_4, proton sponge.

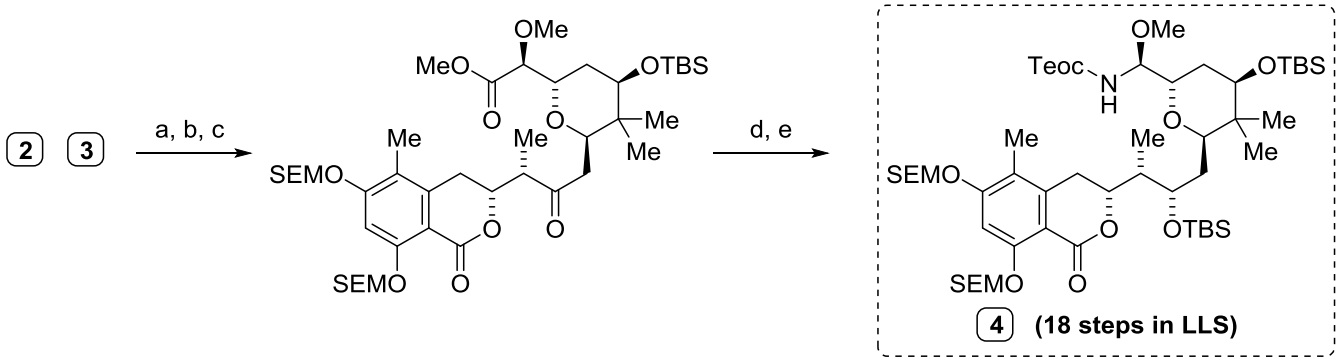
F. Smith *et al. Org. Lett.* **2008**, *10*, 5625; *J. Org. Chem.* **2013**, *78*, 4278. (Cont'd)

Fragment 3



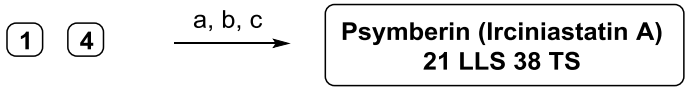
Key: a) neat, then Et_3N-HF; b) SEMCl, NaH; c) DIBAL-H.

Fragment 4



Key: a) Cl_2BPh, *i*-Pr_2NEt; b) Et_2BOMe, $NaBH_4$; c) LiOH, H_2O; d) *i*-Pr_2NEt, *i*-BuO_2CCl, then NaN_3, then PhMe, 80 ^oC; then $TMSCH_2CH_2OH$; e) TBSOTf, 2,6-lutidine.

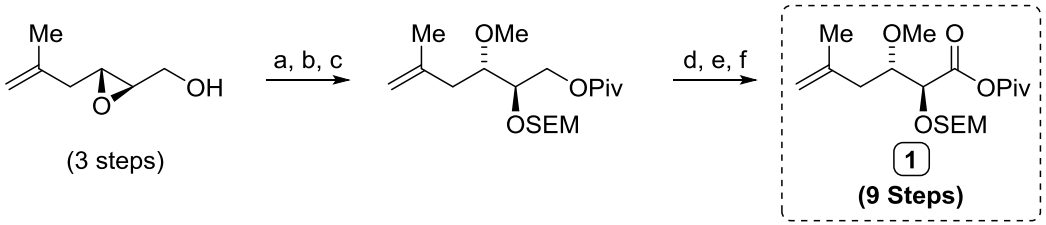
Fragment Union and End Game



Key: a) LiHMDS, then **1**; b) TASF; c) $MgBr_2$, $MeNO_2$.

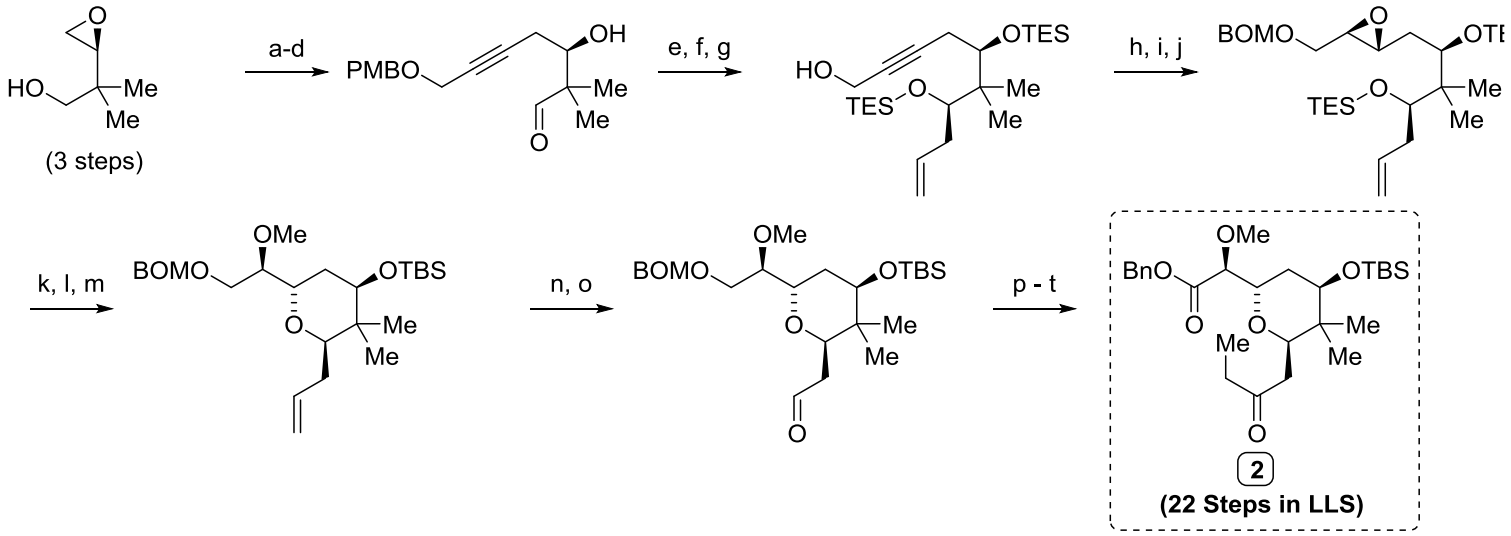
G. Iwabuchi *et al. Org. Lett.* **2010**, *12*, 1040; *J. Org. Chem.* **2015**, *80*, 12333.

Fragment 1



Key: a) $Eu(OTf)_3$ (cat.), 2,6-(*t*-Bu)$_2$-4-Me-pyridine (cat.); b) PivCl, pyridine; c) SEMCl, *i*-Pr_2NEt; d) DIBAL-H; e) 1-Me-AZADO, $PhI(OAc)_2$; f) PivCl, base.

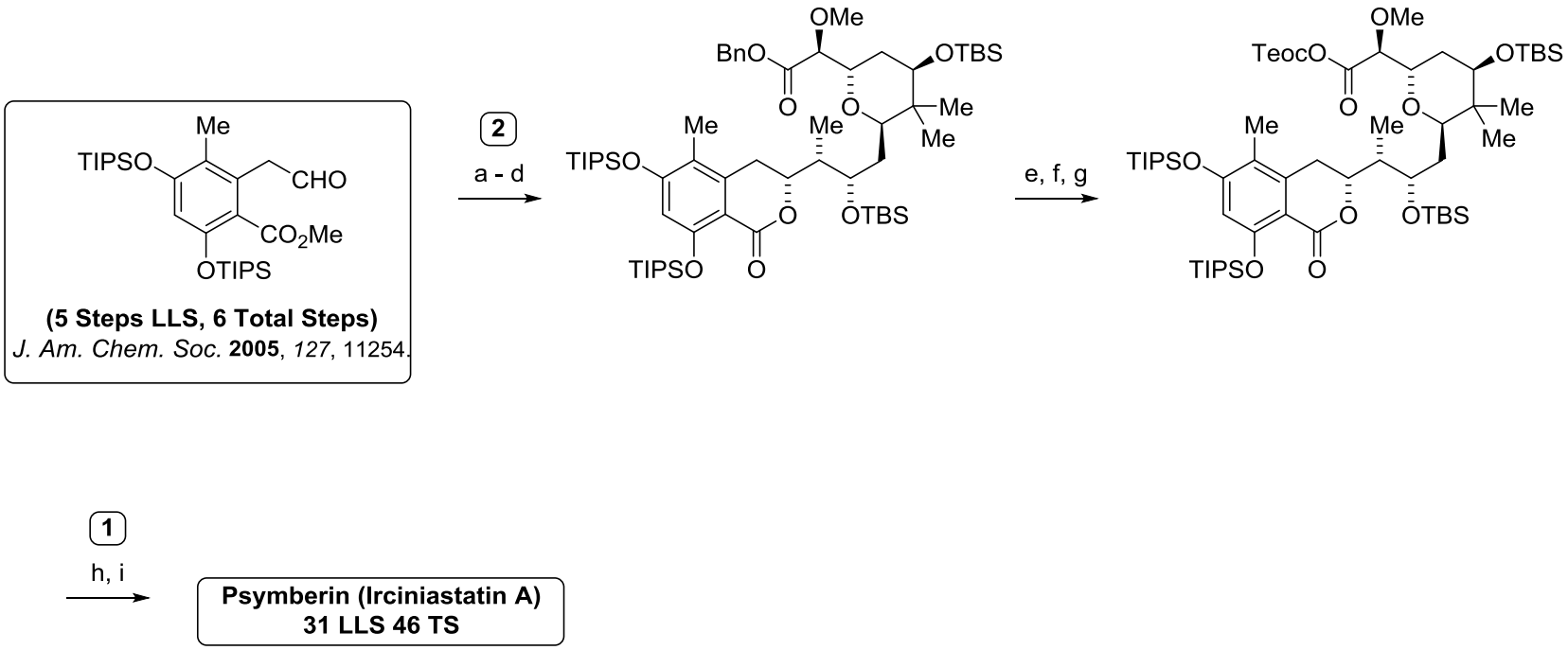
Fragment 2



Key: a) DHP, PPTS; b) $HCCCH_2OPMB$, *n*-BuLi, BF_3-OEt_2; c) PPTS; d) TEMPO, $PhI(OAc)_2$; e) allylSn(Bu)$_2$, $MgBr_2$-OEt_2; f) TESCl, imidazole; DDQ; h) Red-Al; i) (–)-DET, Ti(O*i*-Pr)$_4$, TBHP, 4 Å MS; j) BOMCl, *i*-Pr_2NEt; k) CSA; l) NaH, Me_2SO_4; m) TBSOTf, 2,6-lutidine; n) OsO_4, NMO,

G. Iwabuchi *et al. Org. Lett.* **2010**, *12*, 1040; *J. Org. Chem.* **2015**, *80*, 12333. (Cont'd)

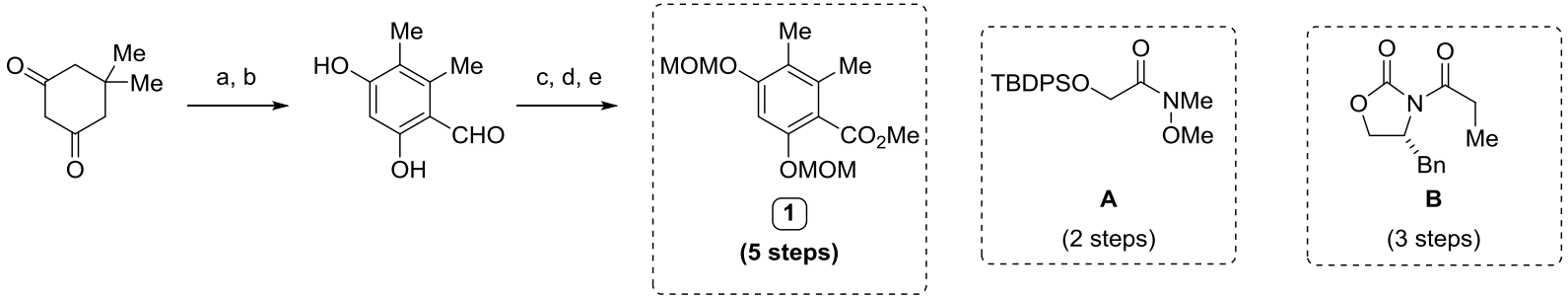
Fragment Union and End Game



Key: a) $PhBCl_2$, *i*-Pr_2NEt; b) $NaBH_4$, Et_3B; c) CSA; d) TBSOTf, 2,6-lutidine; e) H_2, Pd/C; f) EtO_2CCl, NMM, then NaN_3; g) $TMS(CH_2)_2OH$; h) **1**, LiMHDS, 4Å MS; i) TASF.

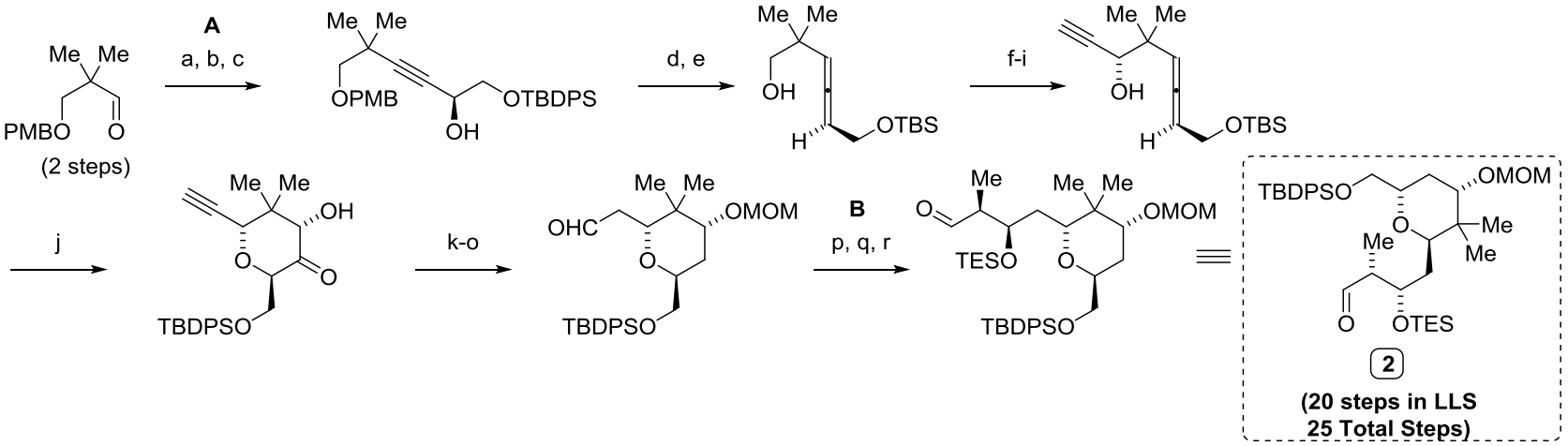
H. Williams *et al. Org. Lett.* **2007**, *9*, 1093.

Fragment 1 and Reagents



Key: a) $(CF_3CO)_2O$, H_2SO_4; b) $Zn(CN)_2$, HCl; c) MOMCl, *i*-Pr_2NEt; d) NaH_2PO_4, $NaClO_2$, 2-Me-2-butene; e) DIAD, PPh_3.

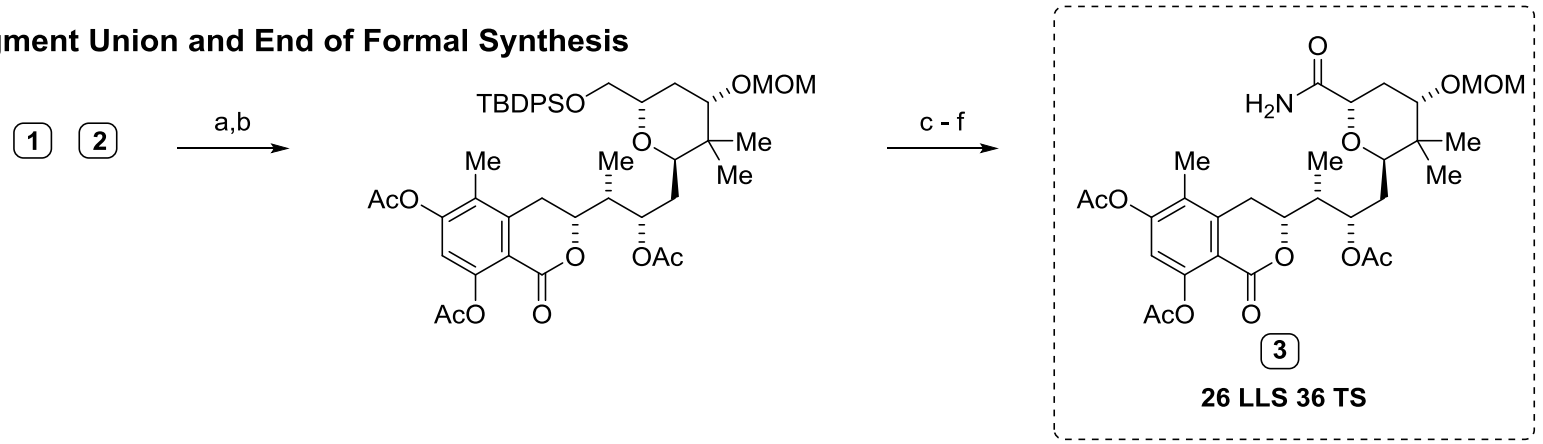
Fragment 2



Key: a) $MeCOCH_2PO(OMe)_2$, TsN_3, K_2CO_3; b) *n*-BuLi, **2**; c) Noyori Catalyst, *i*-PrOH; d) PPh_3, DIAD, 2-NO_2-$PhSO_2NhNH_2$; e) DDQ; f) DMP; g) HCCMgBr; h) DMP; i) (*S*)-CBS, BH_3-SMe_2; j) DMDO, then MeOH; k) $Me_4NBH(OAc)_3$; l) NaH, TsCl; m) DIBAL-H; n) MOMCl, *i*-Pr_2NEt; o) BH_3-THF, 2-Me-2-butene; p) *n*-Bu_2BOTf, Et_3N, **3**; q) Me_3Al, MeONHMe; r) TESCl, Imidazole, then DIBAL-H.

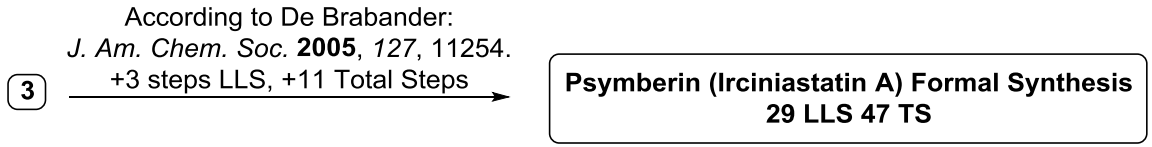
H. Williams *et al. Org. Lett.* **2007**, *9*, 1093. (Cont'd)

Fragment Union and End of Formal Synthesis



Key: a) BrB(cat); b) Ac_2O, pyridine; c) HF-pyridine; d) DMP; e) NaH_2PO_4, $NaClO_2$, 2-Me-2-butene; f) $(COCl)_2$, then NH_3.

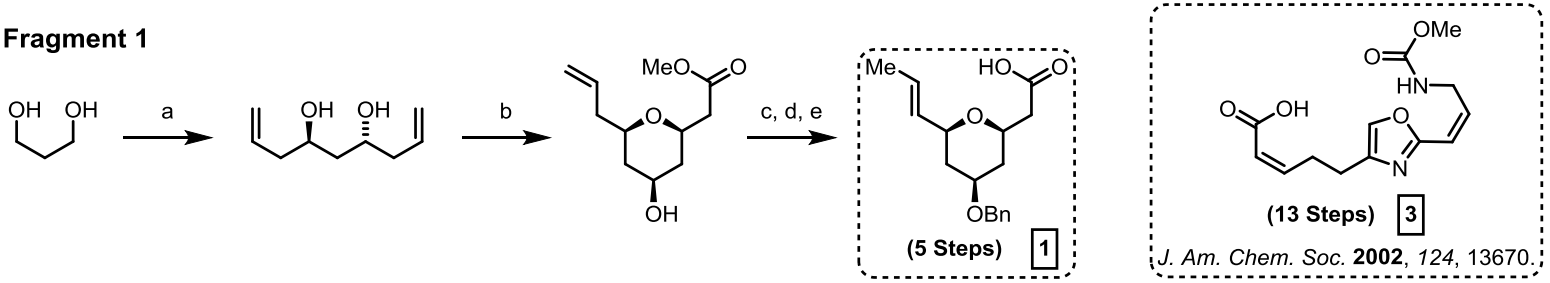
Formal Synthesis to Natural Product



Graphical Summary of Previous Syntheses of Neopeltolide

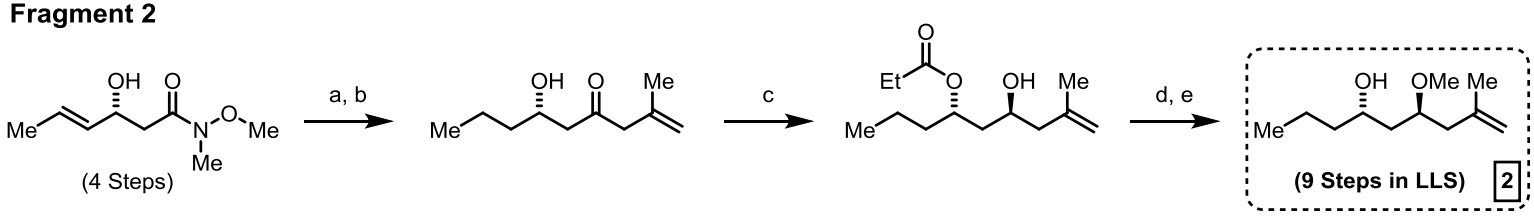
A. She *et al. Org. Lett.* **2011**, *13*, 5916.

Fragment 1



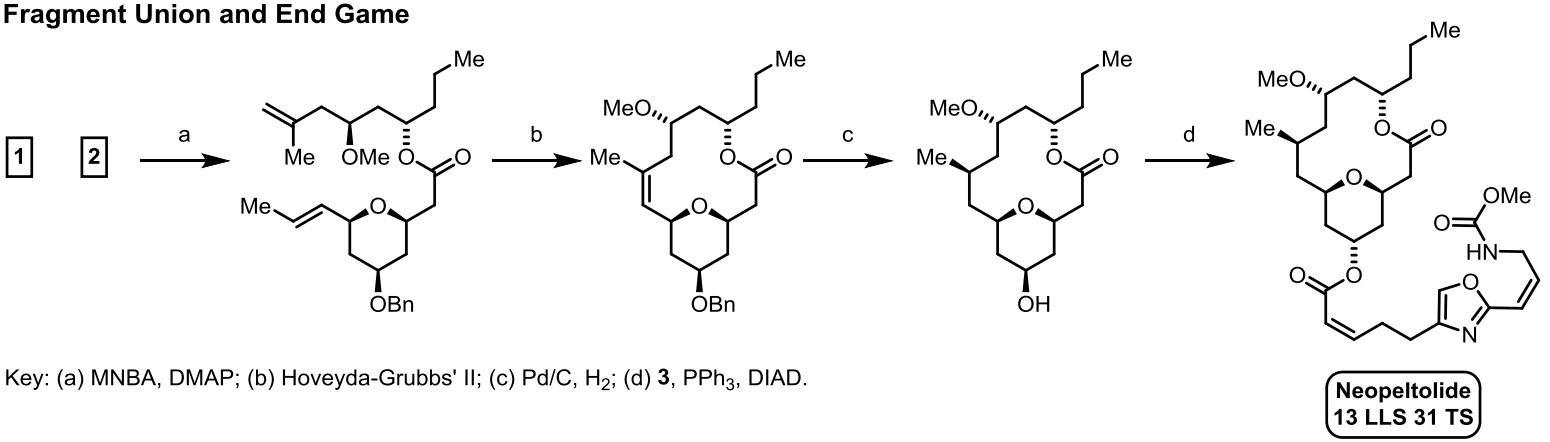
Key: (a) Allyl acetate, $[Ir(cod)Cl]_2$, (*R*)-Cl,MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-BzOH; (b) $PdCl_2$, $CuCl_2$, CO; (c) $BnO(NH{=}C)CCl_3$, MsOH; (d) Grubbs' II; (e) LiOH.

Fragment 2



Key: (a) Raney-Ni, H_2; (b) MethallylMgBr; (c) SmI_2, EtCHO; (d) Me_3OBF_4, proton sponge; (e) K_2CO_3, MeOH.

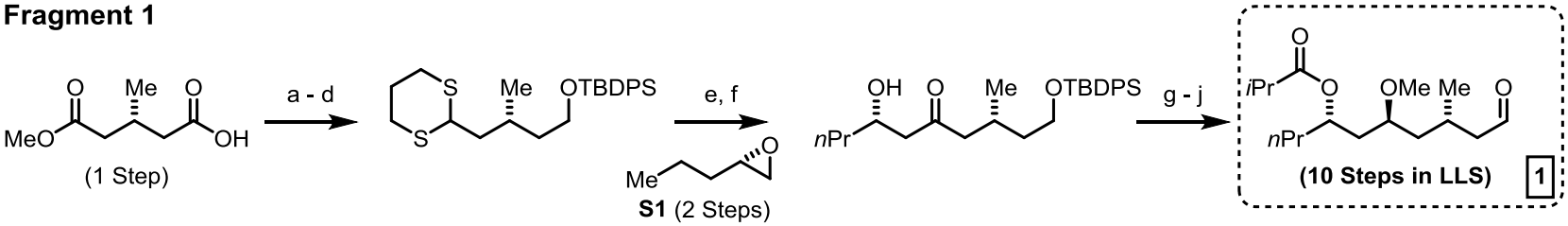
Fragment Union and End Game



Key: (a) MNBA, DMAP; (b) Hoveyda-Grubbs' II; (c) Pd/C, H_2; (d) **3**, PPh_3, DIAD.

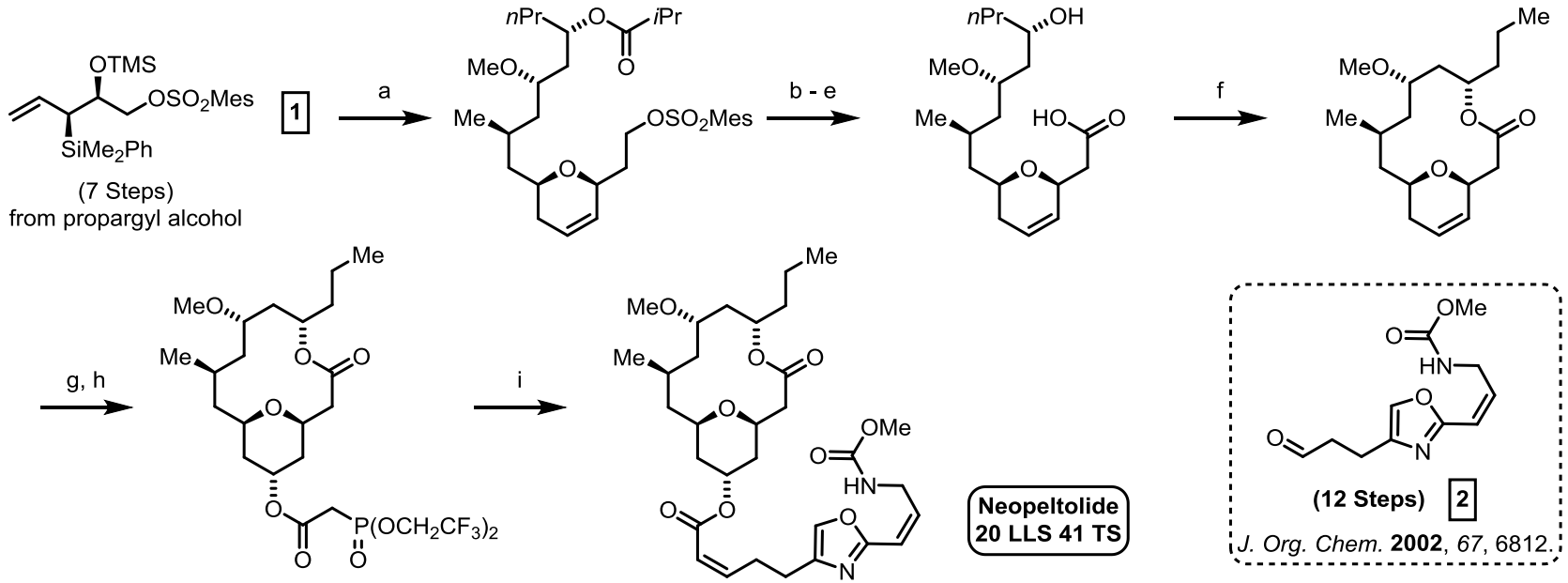
B. Panek *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 9211.

Fragment 1



Key: (a) BH_3•SMe_2; (b) TBDPSCl, imidazole; (c) DIBAL-H; (d) $HS(CH_2)_4SH$, I_2; (e) *t*BuLi, **S1**, HMPA; (f) $CaCO_3$, MeI; (g) $Zr(OtBu)_4$, *i*PrCHO; (h) Me_3OBF_4, proton sponge, 4A MS; (i) 49% HF(aq.); (j) $(COCl)_2$, DMSO, Et_3N.

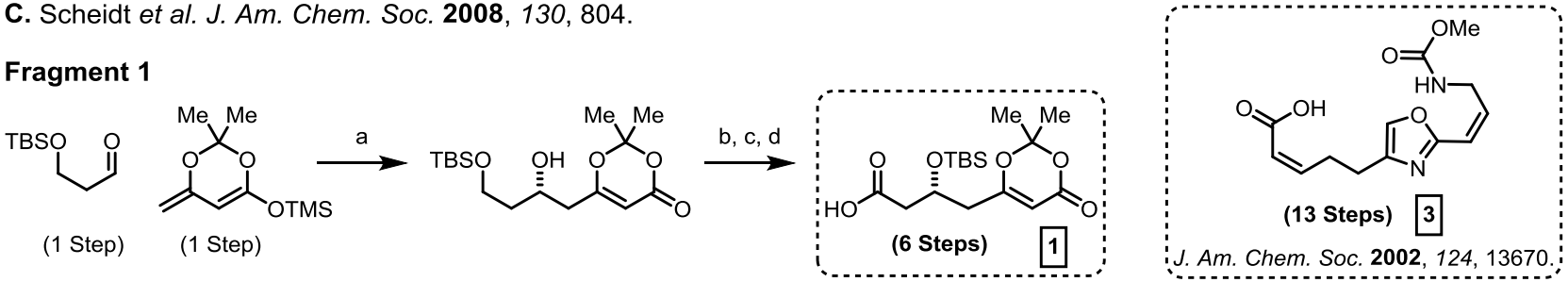
Fragment Union and End Game



Key: (a) TfOH; (b) NaCN; (c) DIBAL-H, Et_2O; (d) DIBAL-H, DCM; (e) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4•H_2O; (f) TCBC, DMAP, Et_3N; (g) $Hg(O_2CCF_3)_2$, then $NaBH_4$; (h) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI•HCl, HOBT•$H_2O$; (i) 18-Crown-6, KHMDS, then **2**.

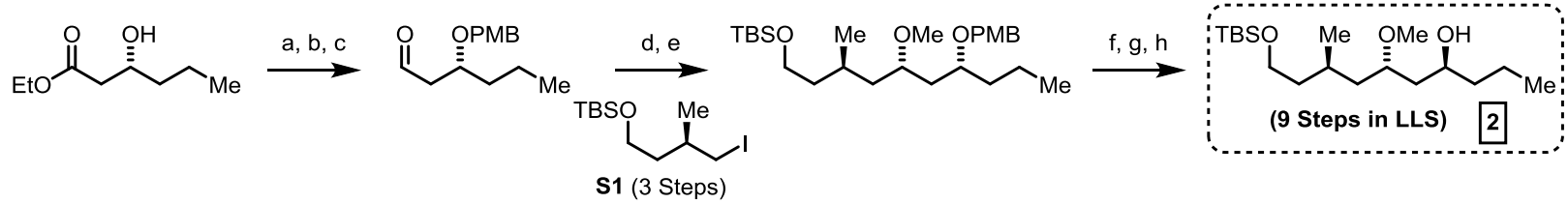
C. Scheidt *et al. J. Am. Chem. Soc.* **2008**, *130*, 804.

Fragment 1



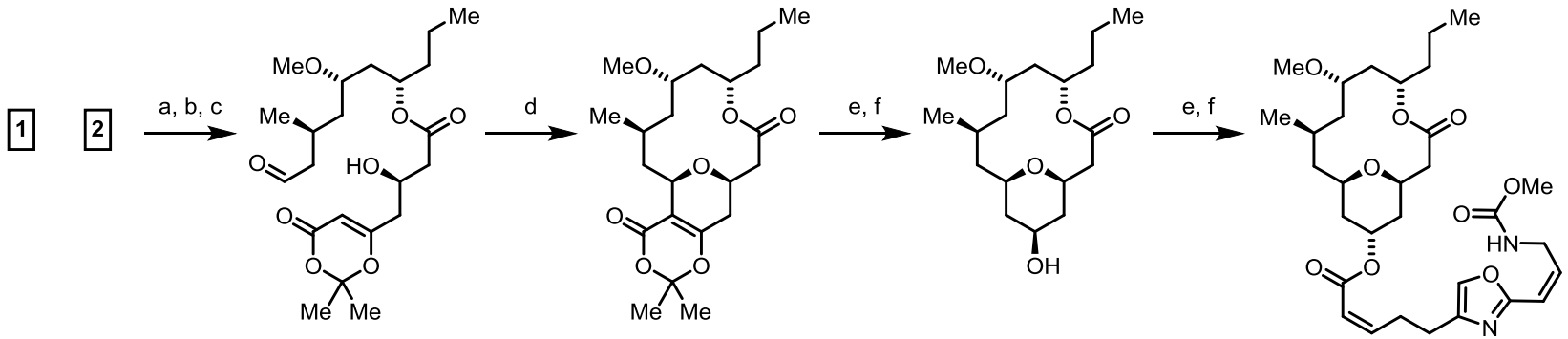
Key: (a) Ti(O*i*Pr)$_4$, (*R*)-BINOL, 4A MS; (b) TBSOTf, 2,6-lutidine; (c) PPTS; (d) PDC.

Fragment 2



Key: (a) MeNH(OMe)•HCl, *i*PrMgBr; (b) PMBO(NH=C)CCl$_3$, PPTS; (c) DIBAL-H; (d) *t*BuLi, **S1**; (e) MeOTf, DTBMP; (f) DDQ, pH 7 buffer; (g) 4-NO$_2$-BzOH, PPh$_3$, DEAD; (g) K$_2$CO$_3$, MeOH.

Fragment Union and End Game

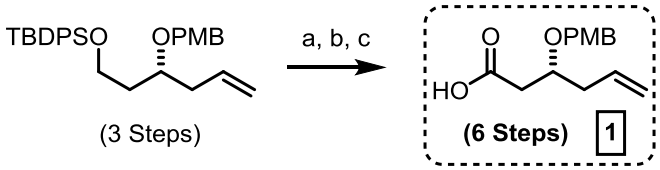


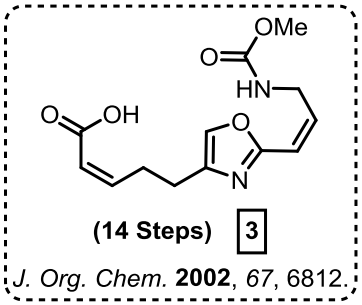
Key: (a) TCBC, DMAP; (b) HF•py; (c) TEMPO, PhI(OAc)$_2$; (d) Sc(OTf)$_3$, CaSO$_4$; (e) DMSO, H$_2$O; (f) NaBH$_4$; (g) **3**, PPh$_3$, DIAD.

Neopeltolide
16 LLS 38 TS

D. Lee *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 3242.

Fragment 1

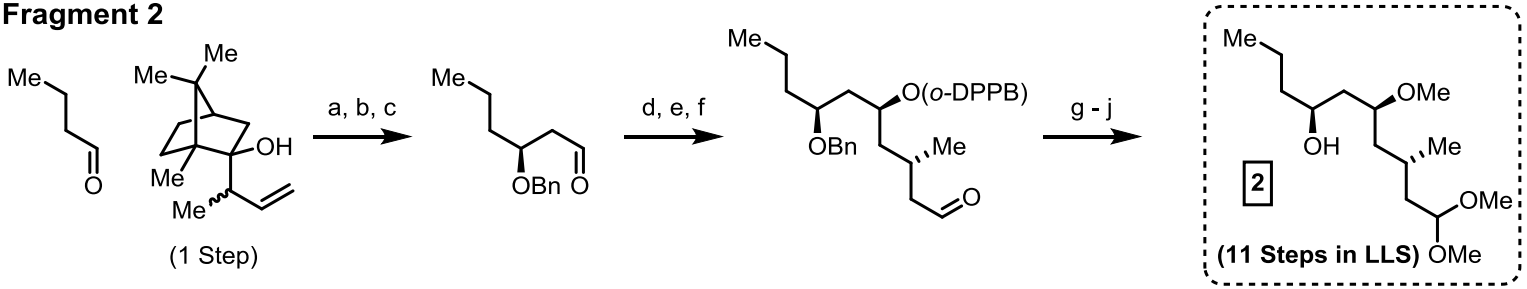




J. Org. Chem. **2002**, *67*, 6812.

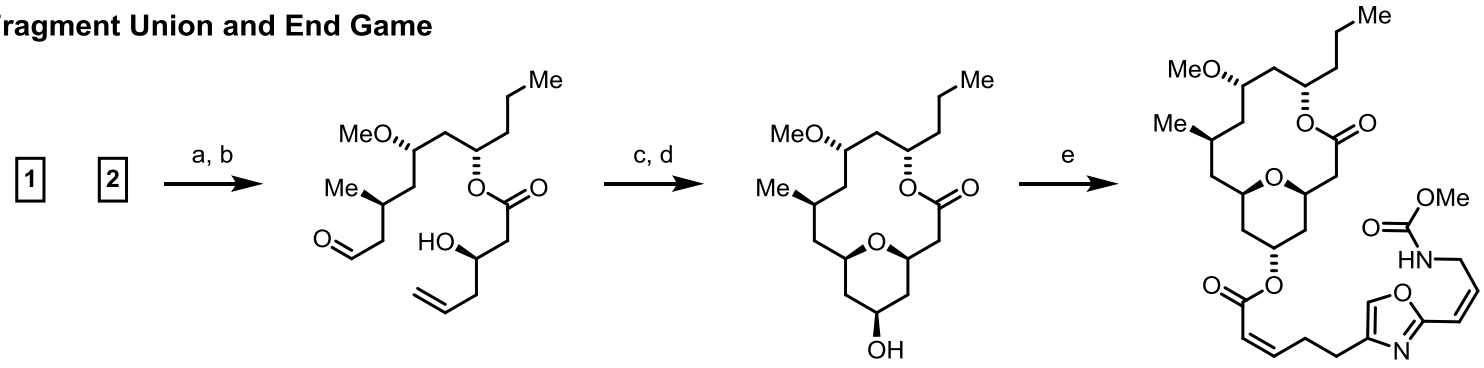
Key: (a) TBAF; (b) DMP; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene.

Fragment 2



Key: (a) CSA; (b) NaH, BnBr, TBAI; (c) O_3, then PPh_3; (d) CH_2=C(Me)CH_2TMS, $TiCl_4$; (e) 2-Ph_2P-BzOH, DCC, DMAP; (f) $Rh(CO)_2(acac)$, $P(OPh)_3$, H_2/CO; (g) $HC(OMe)_3$, H_2SO_4; (i) NaH, MeI; (j) H_2, Pd/C.

Fragment Union and End Game

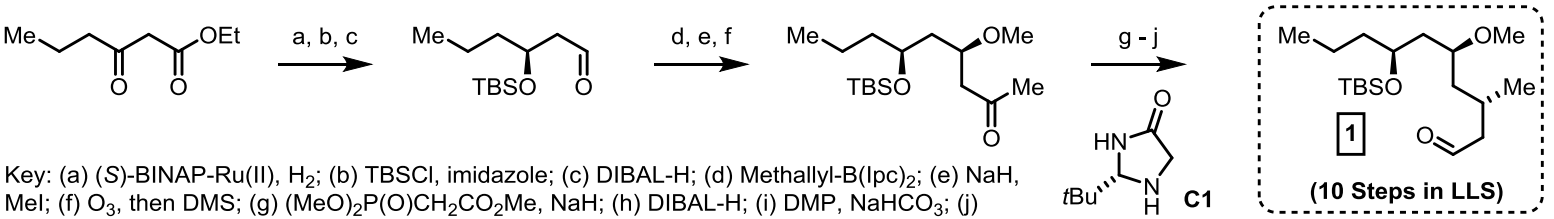


Key: (a) DCC, DMAP; (b) DDQ, pH 7 buffer; (c) TESOTf, TMSOAc; (d) K_2CO_3, MeOH; (e) **3**, PPh_3, DIAD.

Neopeltolide
16 LLS 36 TS

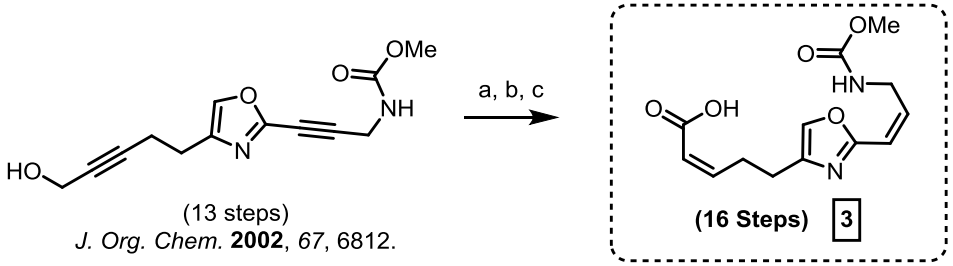
E. Paterson *et al. Chem. Commun.* **2008**, 4708.

Fragment 1



Key: (a) (*S*)-BINAP-Ru(II), H_2; (b) TBSCl, imidazole; (c) DIBAL-H; (d) Methallyl-B(Ipc)$_2$; (e) NaH, MeI; (f) O_3, then DMS; (g) $(MeO)_2P(O)CH_2CO_2Me$, NaH; (h) DIBAL-H; (i) DMP, $NaHCO_3$; (j) **C1**•TFA, Hantzch ester.

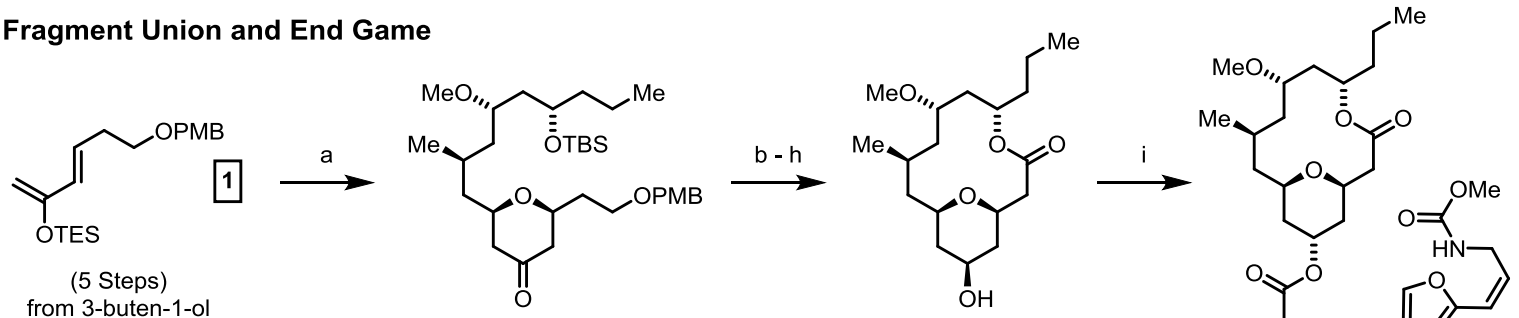
Fragment 2



(13 steps)
J. Org. Chem. **2002**, *67*, 6812.

Key: (a) H_2, Lindlar cat.; (b) DMP, $NaHCO_3$; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene.

Fragment Union and End Game



(5 Steps)
from 3-buten-1-ol

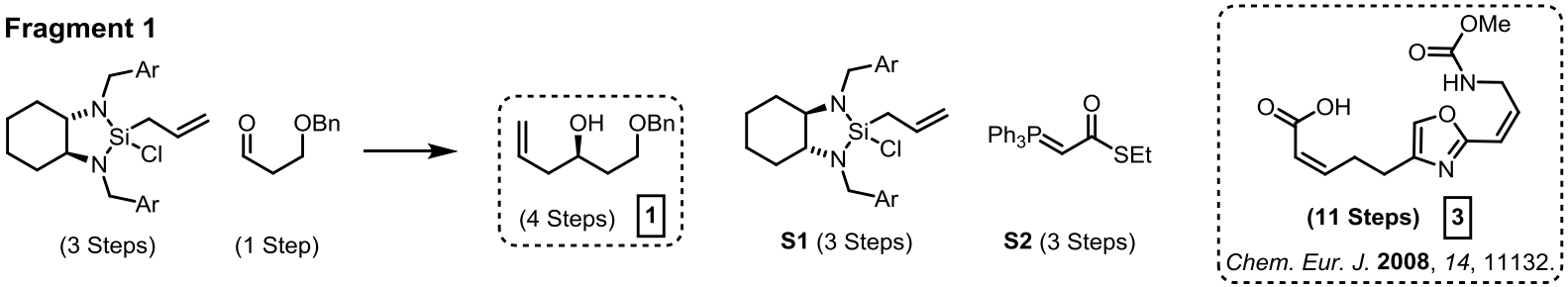
Neopeltolide
19 LLS 40 TS

Key: (a) Cr(III) cat., 4A MS, then H^+; (b) DDQ, pH 7 buffer; (c) DMP, $NaHCO_3$; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (e) TBAF; (f)* TCBC, Et_3N, THF; (g)* DMAP, toluene; (h) $NaBH_4$; (i) **3**, PPh_3, DIAD.

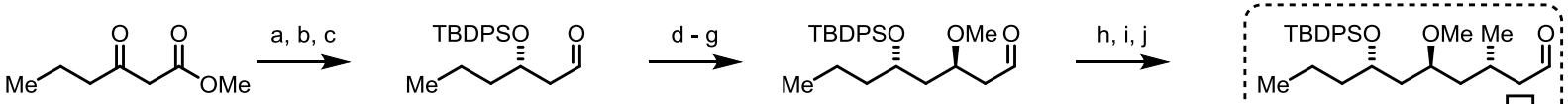
* The Yamaguchi lactonization is considered as a two-step sequence because experimental protocol involves evaporation/exchage of solvent and more than one functional group transformation. See "Rules for Calculating Step Counts" section for more details.

F. Maier *et al. Org. Lett.* **2008**, *10*, 1239.

Fragment 1

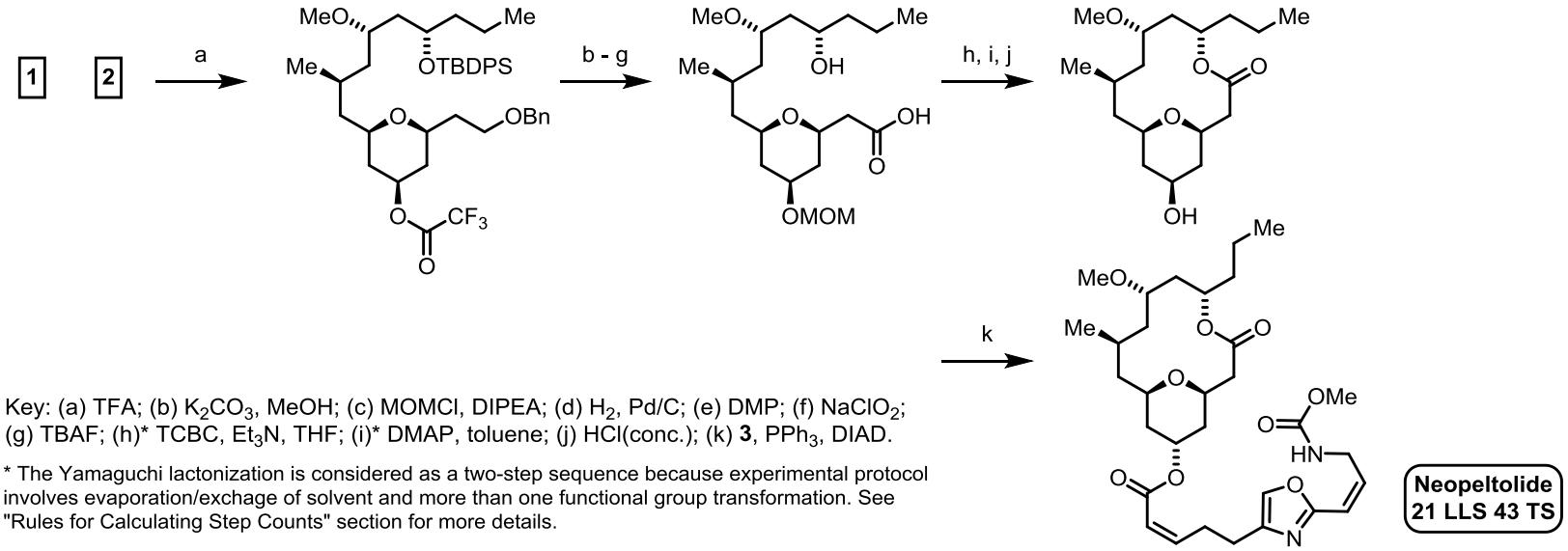


Fragment 2



Key: (a) (*S*)-BINAP-Ru(II), H_2; (b) TBDPSCl, imidazole; (c) DIBAL-H; (d) **S1**; (e) Me_3OBF_4, proton sponge; (f) OsO_4, NMO; (g) $NaIO_4$; (h) **S2**; (i) MeMgBr, CuBr•SMe_2, (*S,R*)-Josiphos; (j) Et_3SiH, Pd/C.

Fragment Union and End Game

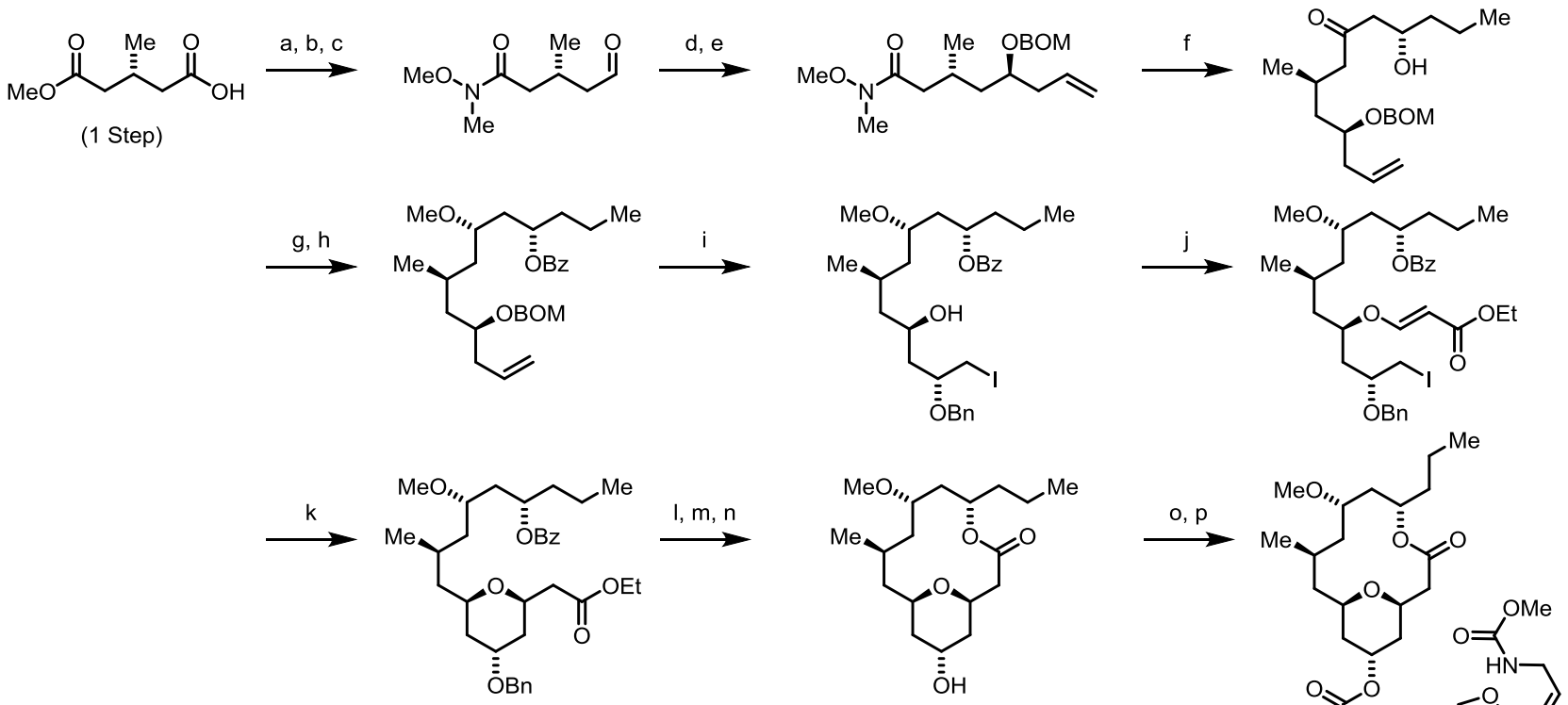


Key: (a) TFA; (b) K_2CO_3, MeOH; (c) MOMCl, DIPEA; (d) H_2, Pd/C; (e) DMP; (f) $NaClO_2$; (g) TBAF; (h)* TCBC, Et_3N, THF; (i)* DMAP, toluene; (j) HCl(conc.); (k) **3**, PPh_3, DIAD.

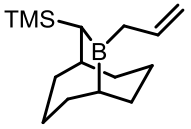
* The Yamaguchi lactonization is considered as a two-step sequence because experimental protocol involves evaporation/exchage of solvent and more than one functional group transformation. See "Rules for Calculating Step Counts" section for more details.

G. Taylor *et al. Org. Lett.* **2008**, *10*, 5047.

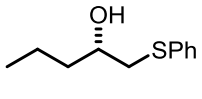
Completion of Synthesis



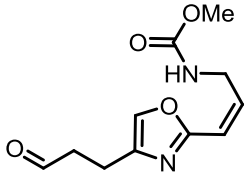
Key: (a) BH_3•SMe_2; (b) MeNH(OMe)•HCl, *i*PrMgBr; (c) DMP; (d) **S1**, BF_3•OEt_2; (e) BOMCl, DIPEA; (f) **S2**, *n*BuLi, LiDBB; (g) SmI_2, PhCHO; (i) Me_3OBF_4, proton sponge; (j) ICl, $Na_2S_2O_3$(aq.); (k) Ethyl propiolate, PBu_3; (l) AIBN, nBu_3SnH; (m) KOH; (n) TCBC, Et_3N, DMAP; (n) H_2, Pd/C; (o) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI•HCl, HOBT•$H_2O$; (p) 18-Crown-6, KHMDS, then **1**.



S1 (3 Steps)



S2 (2 Steps)

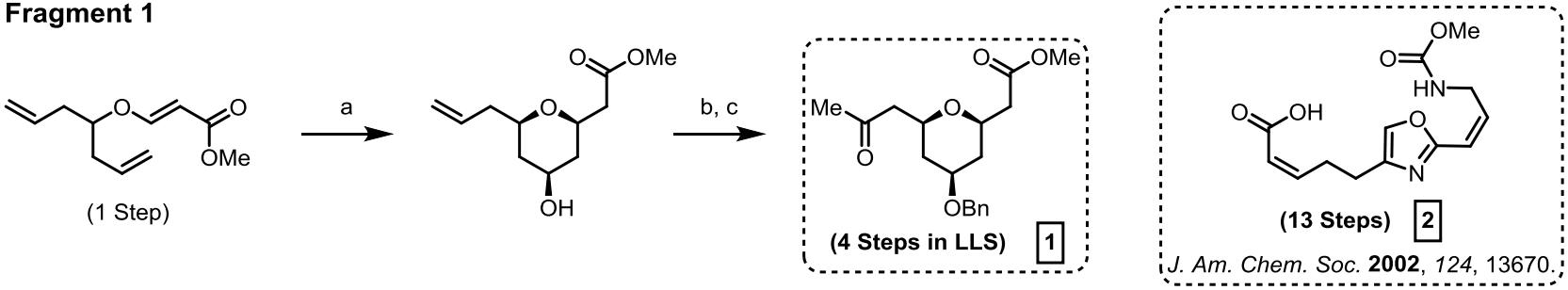


(12 Steps) **1**

J. Org. Chem. **2002**, *67*, 6812.

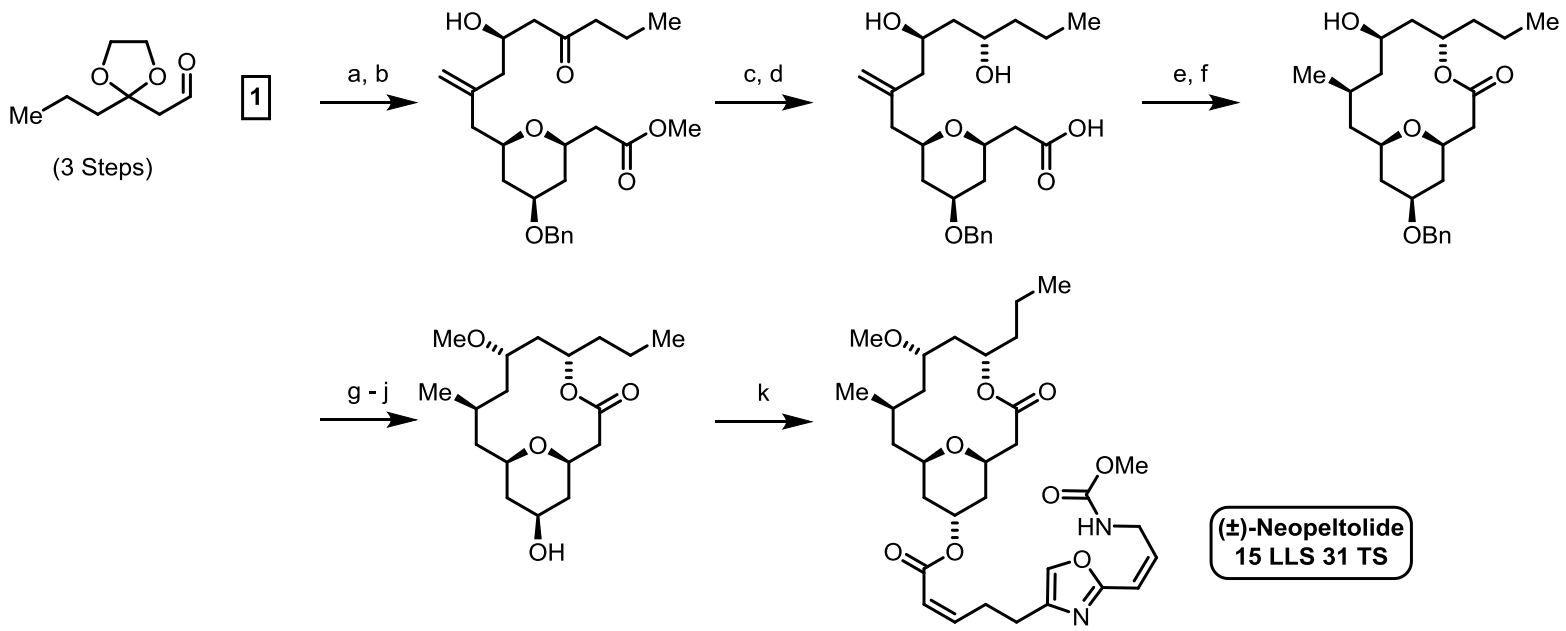
H. Kozmin *et al. Nat. Chem. Biol.* **2008**, *4*, 418. (racemic)

Fragment 1



Key: (a) TFA, then $NH_3•H_2O$; (b) $BnO(C=NH)CCl_3$, TfOH; (c) $PdCl_2$, CuCl, O_2.

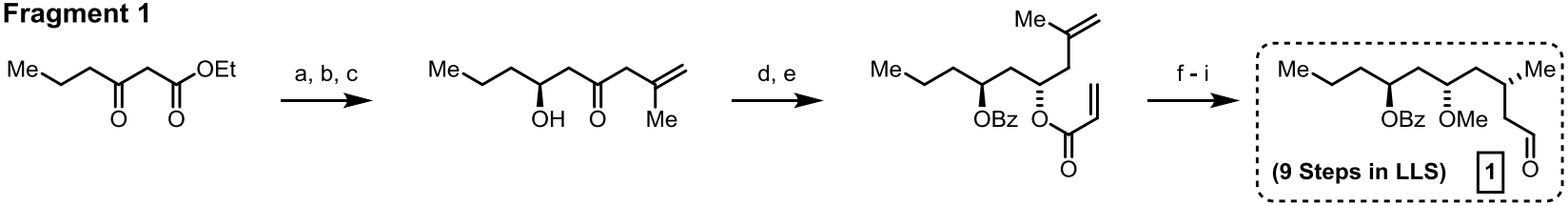
Fragment Union and End Game



Key: (a) Cy_2BCl, Et_3N; (b) Ph_3PMeBr, KHMDS, then HCl; (c) Et_2BOMe, $NaBH_4$; (d) TMSOK; (e) TCBC, Et_3N, DMAP; (f) H_2, Pd/C; (g) 4-NO_2-BzOH, PPh_3, DEAD; (h) K_2CO_3, MeOH; (i) Me_3OBF_4, proton sponge; (j) H_2, $Pd(OH)_2$; (k) **2**, PPh_3, DIAD.

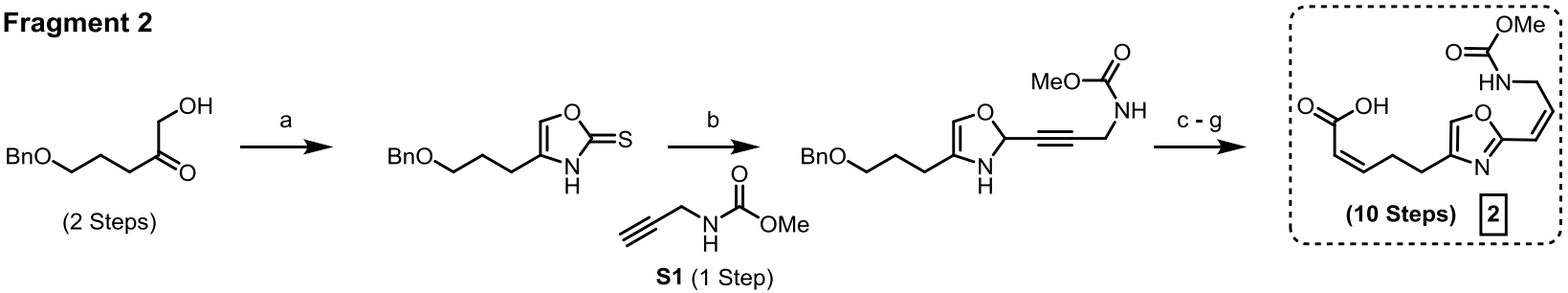
I. Roulland *et al. Org. Lett.* **2009**, *11*, 4700.

Fragment 1



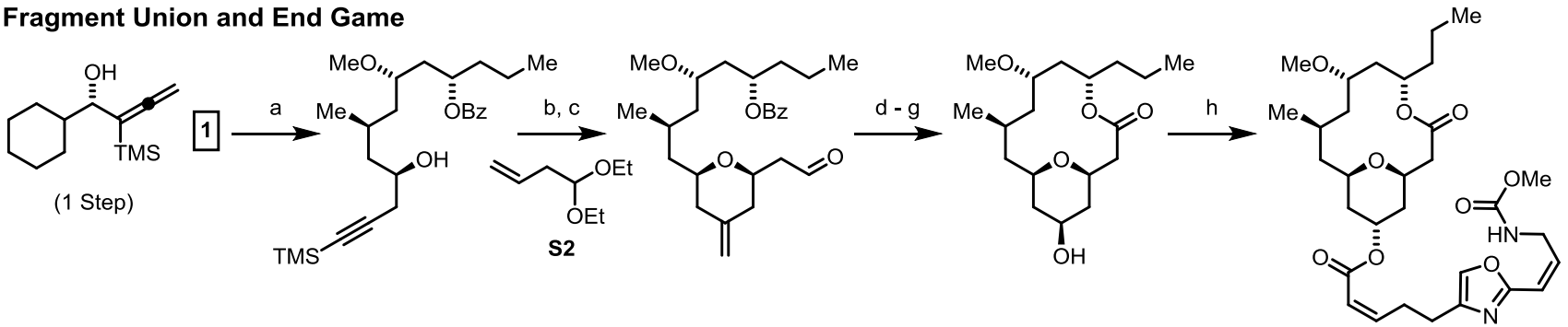
Key: (a) Ru(II) cat., (*R*)-SYNPHOS, H_2; (b) MeNH(OMe)•HCl, $AlMe_3$; (c) MethallylMgBr; (d) PhCHO, SmI_2; (e) Acryloyl chloride, DIPEA; (f) Grubbs' II; (g) H_2, Pd/C, then PPTS; (h) Me_3OBF_4, proton sponge; (i) DIBAL-H.

Fragment 2



Key: (a) KSCN, HCl; (b) **S1**, $Pd(PPh_3)_4$, CuTC, CuI, Et_3N, MW; (c) H_2, Lindlar cat.; (d) BCl_3; (e) DMP, py; (f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6; (g) LiOH.

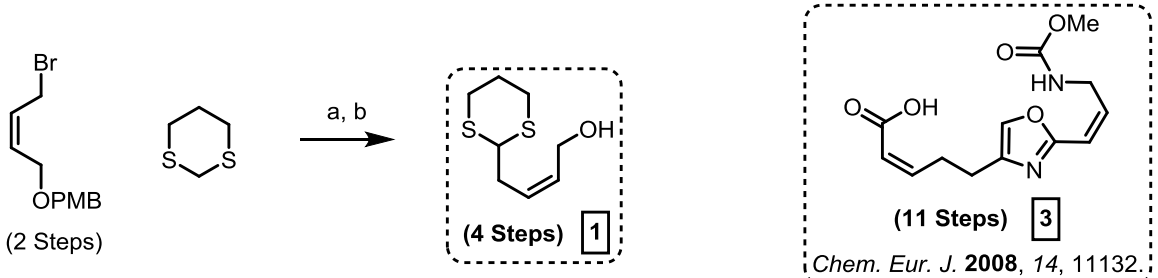
Fragment Union and End Game



Key: (a) $InBr_3$; (b) K_2CO_3, MeOH; (c) **S2**, $[CpRu(MeCN)_3]PF_6$, AcOH, then $LiBF_4$, H_2O; (d) OsO_4, $NaIO_4$; (e) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene; (f) TCBC, Et_3N, DMAP; (g) $NaBH_4$; (h) **2**, PPh_3, DIAD.

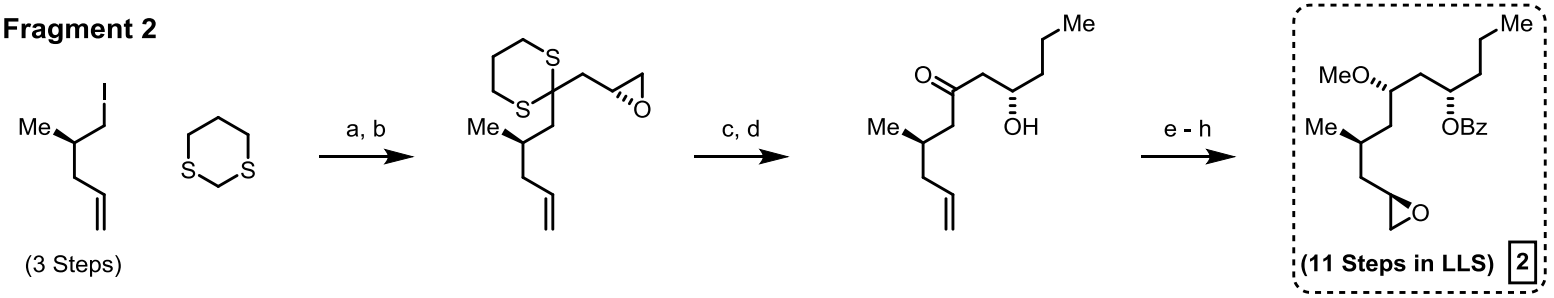
J. Hong *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 7577.

Fragment 1



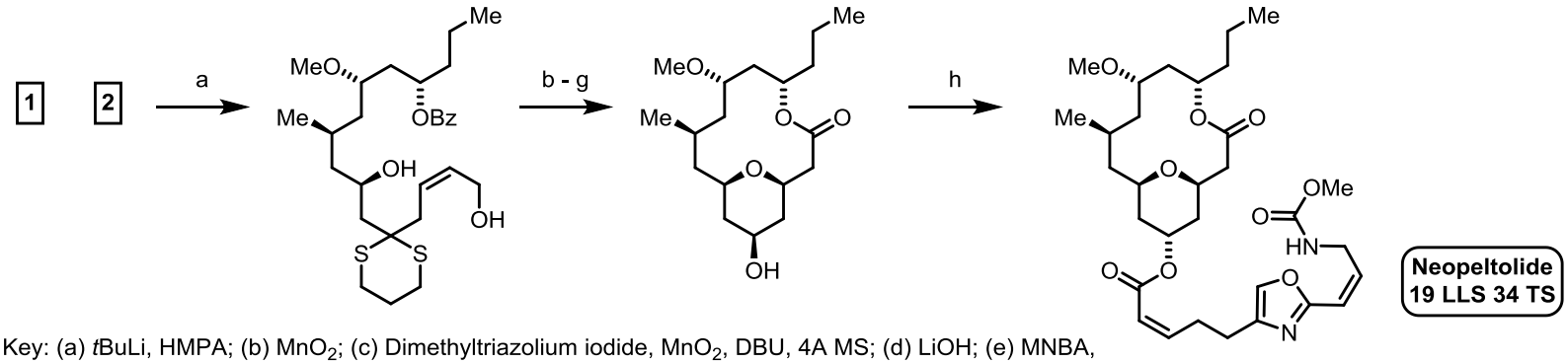
Key: (a) *n*BuLi; (b) TsOH.

Fragment 2



Key: (a) *n*BuLi; (b) *n*BuLi, then (*R*)-epichlorohydrin; (c) EtMgBr, CuI; (d) MeI, $CaCO_3$; (e) PhCHO, SmI_2; (f) Me_3OBF_4, proton sponge; (g) AD mix-β; (h) NaH, *N*-4-toluenesulfonylimidazole.

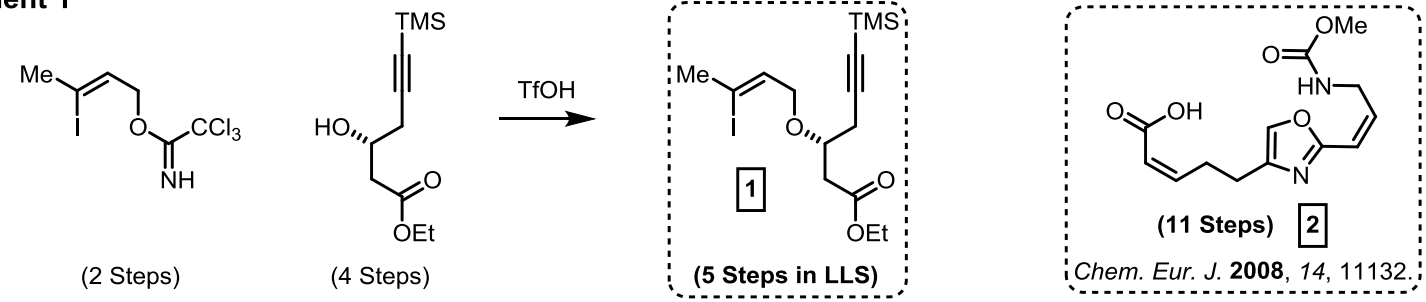
Fragment Union and End Game



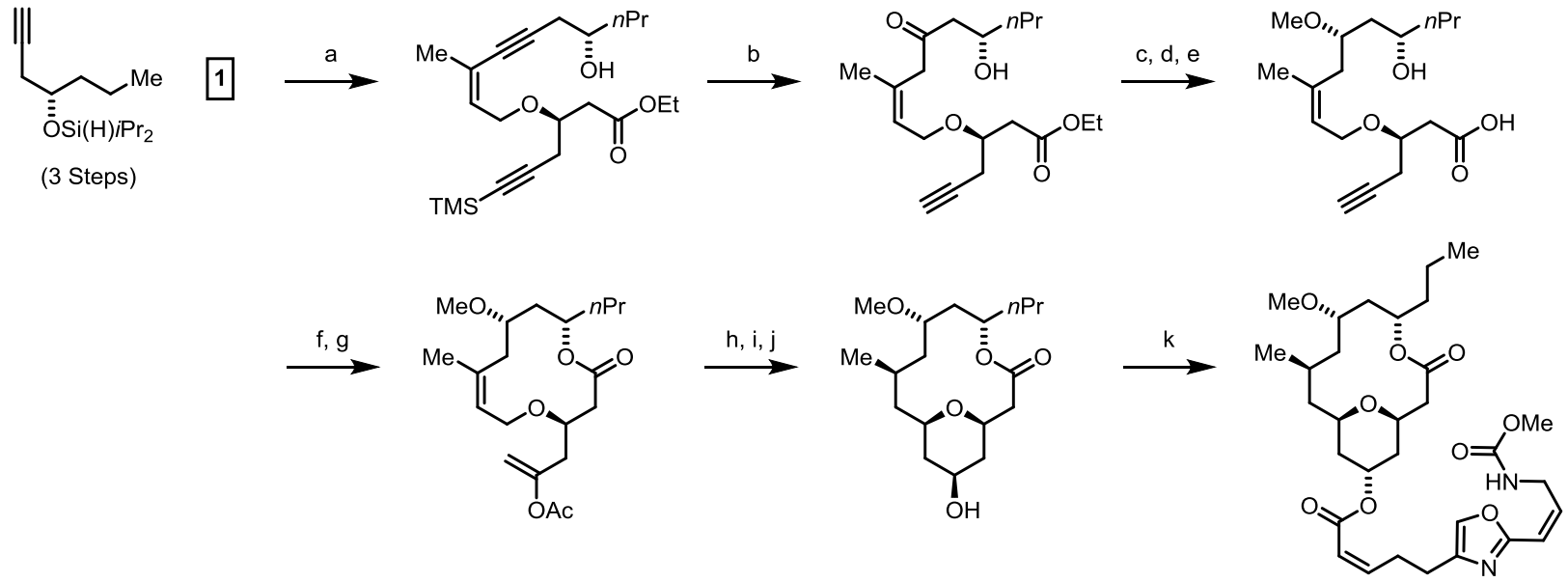
Key: (a) *t*BuLi, HMPA; (b) MnO_2; (c) Dimethyltriazolium iodide, MnO_2, DBU, 4A MS; (d) LiOH; (e) MNBA, DMAP; (f) MeI, $CaCO_3$; (g) $NaBH_4$; (h) **3**, PPh_3, DIAD.

K. Floreancig *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 4567.

Fragment 1



Fragment Union and End Game

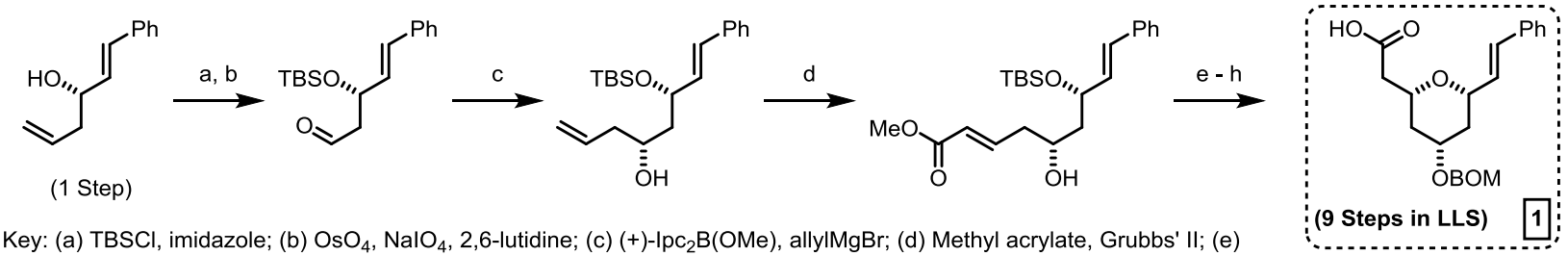


Key: (a) $(PPh_3)PdCl_2$, CuI, iPr_2NH; (b) Pt(DVDS), then H_2O_2, KF, TBAF, $KHCO_3$; (c) EtCHO, SmI_2; (d) Me_3OBF_4, proton sponge; (e) LiOH; (f) TCBC, Et_3N, DMAP; (g) $[Ru(p\text{-cymene})Cl_2]_2$, $(2\text{-furyl})_3P$, 1-decyne, HOAc, Na_2CO_3; (h) DDQ, 2,6-Cl_2py, $LiClO_4$; (i) H_2, Pd/C; (j) $NaBH_4$; (k) **2**, PPh_3, DIAD.

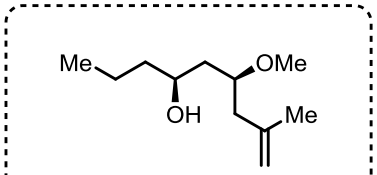
Neopeltolide
18 LLS 34 TS

L. Fuwa & Sasaki *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 3041.

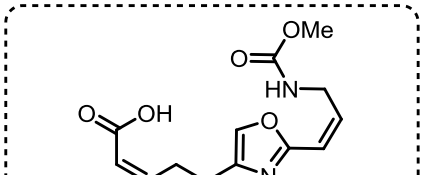
Fragment 1



Key: (a) TBSCl, imidazole; (b) OsO_4, $NaIO_4$, 2,6-lutidine; (c) (+)-$Ipc_2B(OMe)$, allylMgBr; (d) Methyl acrylate, Grubbs' II; (e) BOMCl, DIPEA, TBAI; (f) TBAF, AcOH; (g) DBU; (h) TMSOK.

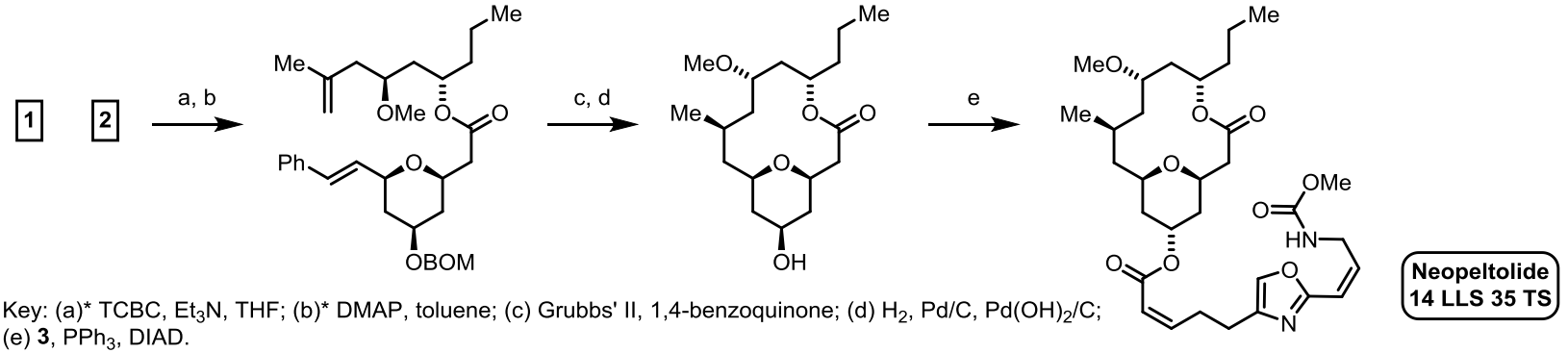


Chem. Eur. J. **2009**, *15*, 12807.



J. Am. Chem. Soc. **2002**, *124*, 13670.

Fragment Union and End Game

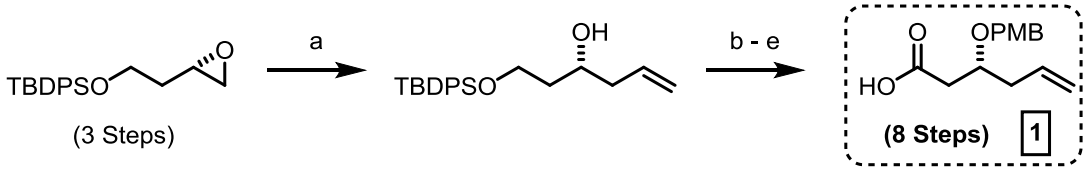


Key: (a)* TCBC, Et_3N, THF; (b)* DMAP, toluene; (c) Grubbs' II, 1,4-benzoquinone; (d) H_2, Pd/C, $Pd(OH)_2$/C; (e) **3**, PPh_3, DIAD.

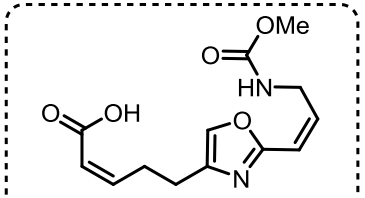
* The Yamaguchi lactonization is considered as a two-step sequence because experimental protocol involves evaporation/exchage of solvent and more than one functional group transformation. See "Rules for Calculating Step Counts" section for more details.

M. Yadav *et al. Tetrahedron* **2010**, *66*, 480.

Fragment 1

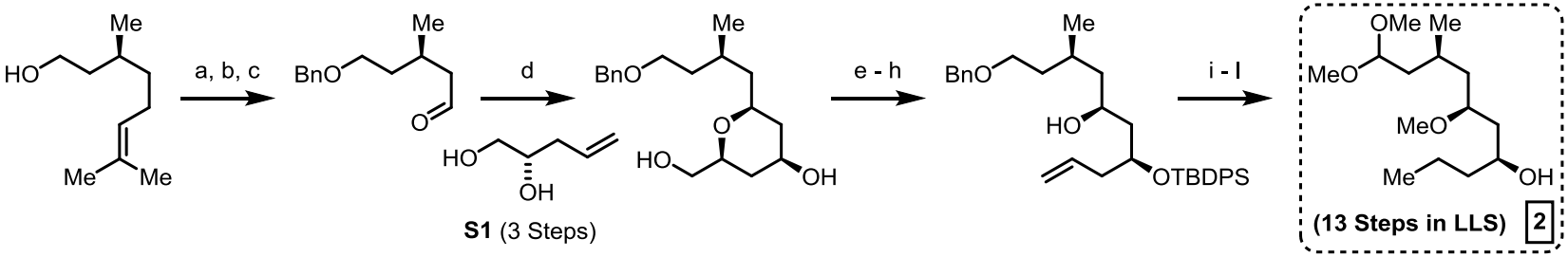


Key: (a) VinylMgBr, CuI; (b) $PMBO(C{=}NH)CCl_3$, CSA; (c) TBAF; (d) DMP; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene.



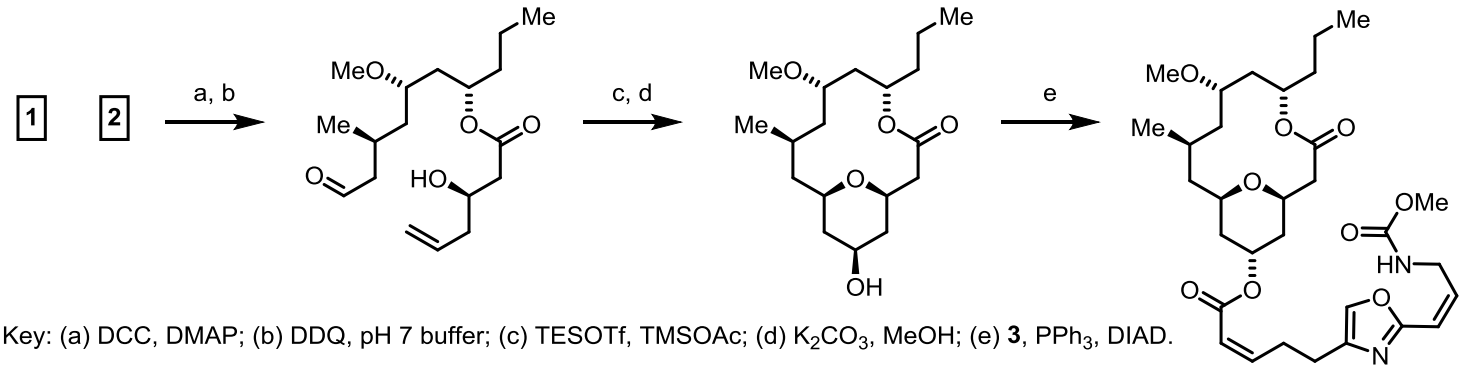
J. Org. Chem. **2002**, *67*, 6812.

Fragment 2



Key: (a) BnBr, NaH, TBAI; (b) H_2O_2, $(PhSe)_2$, *t*BuOOH, $MgSO_4$; (c) O_3, then DMS; (d) **S1**, TFA, then K_2CO_3; (e) TsCl, Et_3N; (f) TBDPSCl, DMAP, imidazole; (g) NaI; (h) Zn; (i) Me_3OBF_4, proton sponge; (j) H_2, Raney Ni; (k) DMP, $NaHCO_3$; (l) PTSA, $CH(OMe)_3$.

Fragment Union and End Game

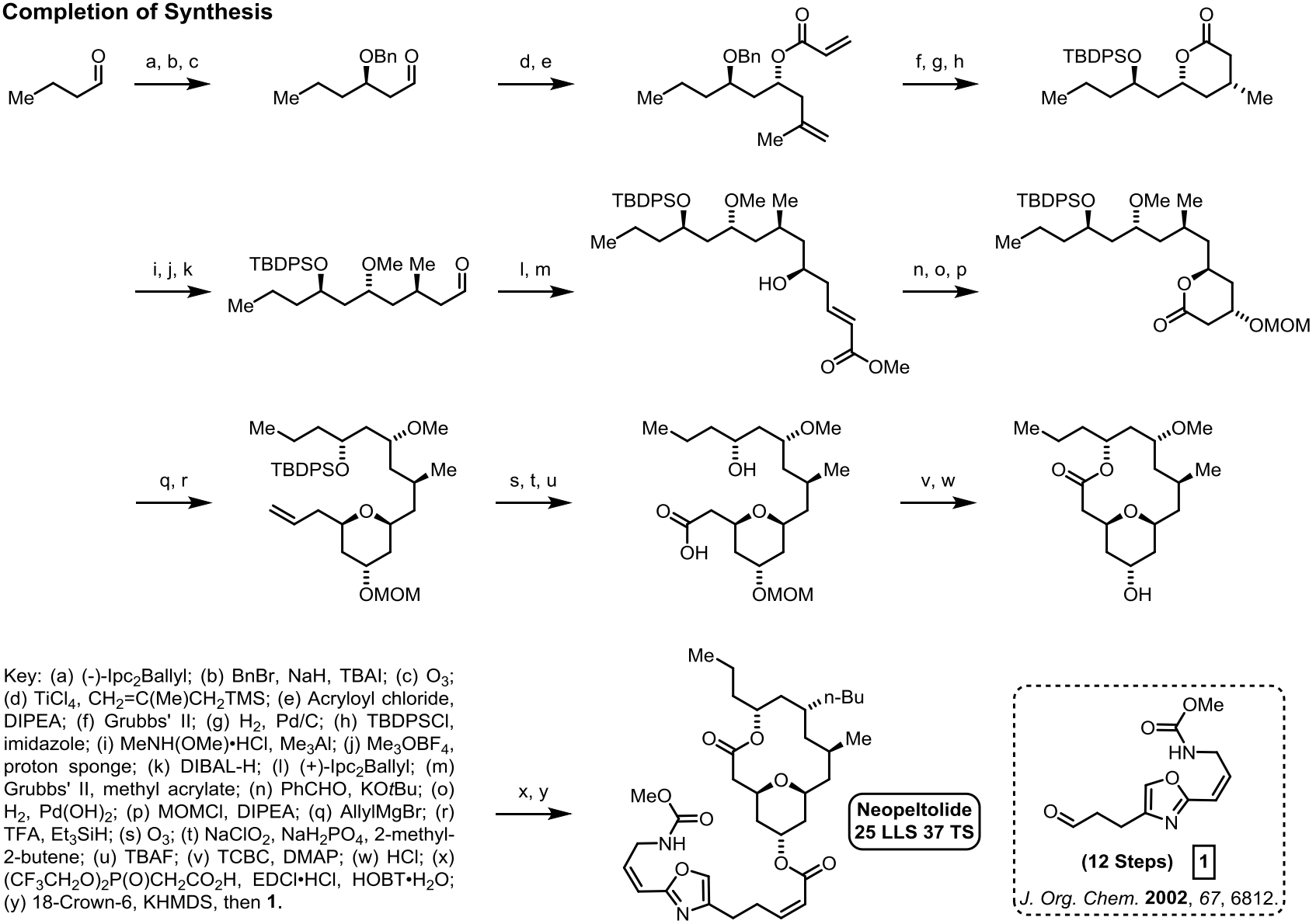


Key: (a) DCC, DMAP; (b) DDQ, pH 7 buffer; (c) TESOTf, TMSOAc; (d) K_2CO_3, MeOH; (e) **3**, PPh_3, DIAD.

Neopeltolide
18 LLS 42 TS

N. Jennings *et al. J. Org. Chem.* **2010**, *75*, 4095.

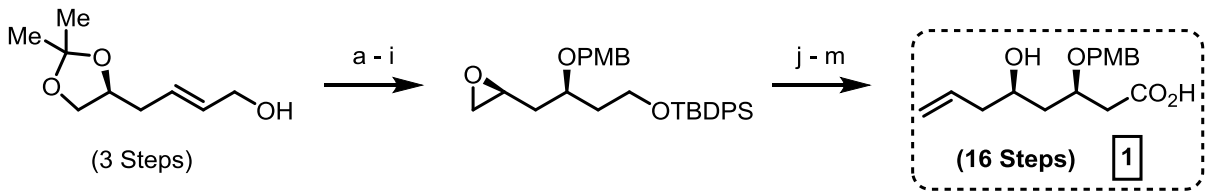
Completion of Synthesis

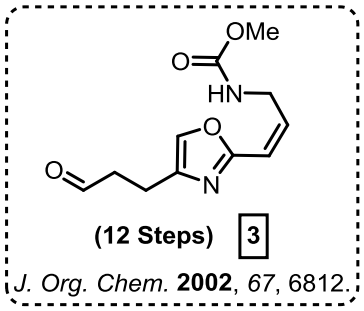


Key: (a) (-)-Ipc$_2$Ballyl; (b) BnBr, NaH, TBAI; (c) O_3; (d) $TiCl_4$, CH_2=C(Me)CH_2TMS; (e) Acryloyl chloride, DIPEA; (f) Grubbs' II; (g) H_2, Pd/C; (h) TBDPSCl, imidazole; (i) MeNH(OMe)•HCl, Me_3Al; (j) Me_3OBF_4, proton sponge; (k) DIBAL-H; (l) (+)-Ipc$_2$Ballyl; (m) Grubbs' II, methyl acrylate; (n) PhCHO, KO*t*Bu; (o) H_2, $Pd(OH)_2$; (p) MOMCl, DIPEA; (q) AllylMgBr; (r) TFA, Et_3SiH; (s) O_3; (t) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (u) TBAF; (v) TCBC, DMAP; (w) HCl; (x) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI•HCl, HOBT•$H_2O$; (y) 18-Crown-6, KHMDS, then **1**.

O. Sharma *et al. Org. Biomol. Chem.* **2012**, *10*, 3689.

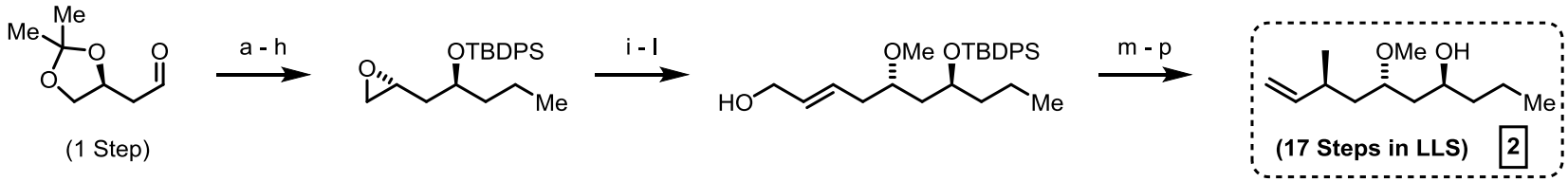
Fragment 1





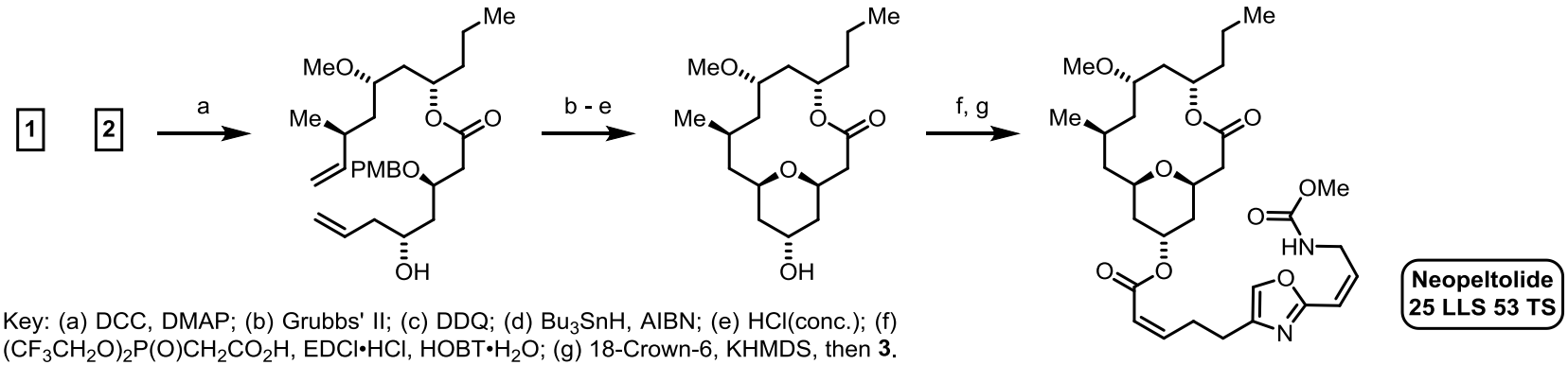
Key: (a) (-)-DIPT, $Ti(OiPr)_4$, cumene hydroperoxide, 4A MS; (b) Red-Al; (c) $NaIO_4$, $NaHCO_3$; (d) $PMPCH(OMe)_2$, PPTS; (e) DIBAL-H; (f) TBDPSCl, imidazole; (g) $CuCl_2•2H_2O$; (h) TsCl, Bu_2SnO, Et_3N; (i) K_2CO_3, MeOH; (j) VinylMgBr, CuI; (k) MOMCl, DIPEA, DMAP; (l) TBAF; (m) TEMPO, BAIB.

Fragment 2



Key: (a) *n*-PrBr, Mg; (b) $(COCl)_2$, DMSO, Et_3N; (c) LAH, LiI; (d) TBDPSCl, imidazole; (e) $CuCl_2•2H_2O$; (f) BzCl, Bu_2SnO, Et_3N; (g) TsCl, DMAP, Et_3N; (h) K_2CO_3, MeOH; (i) *n*BuLi, $BF_3•OEt_2$; (j) MeI, NaH; (k) PPTS; (l) Red-Al; (m) (-)-DIPT, $Ti(OiPr)_4$, cumene hydroperoxide, 4A MS; (n) Me_3Al; (o) PPh_3, I_2, imidazole; (p) TBAF.

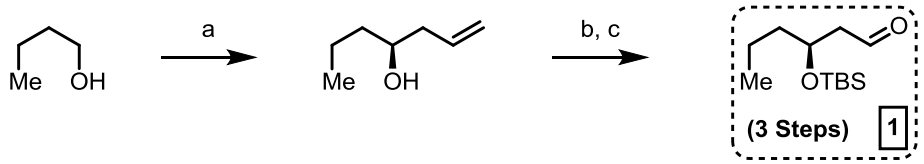
Fragment Union and End Game

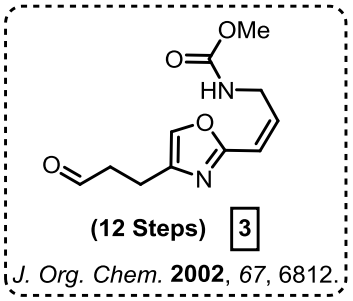


Key: (a) DCC, DMAP; (b) Grubbs' II; (c) DDQ; (d) Bu_3SnH, AIBN; (e) HCl(conc.); (f) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI•HCl, HOBT•$H_2O$; (g) 18-Crown-6, KHMDS, then **3**.

P. Raghavan *et al. Org. Lett.* **2012**, *14*, 2346.

Fragment 1

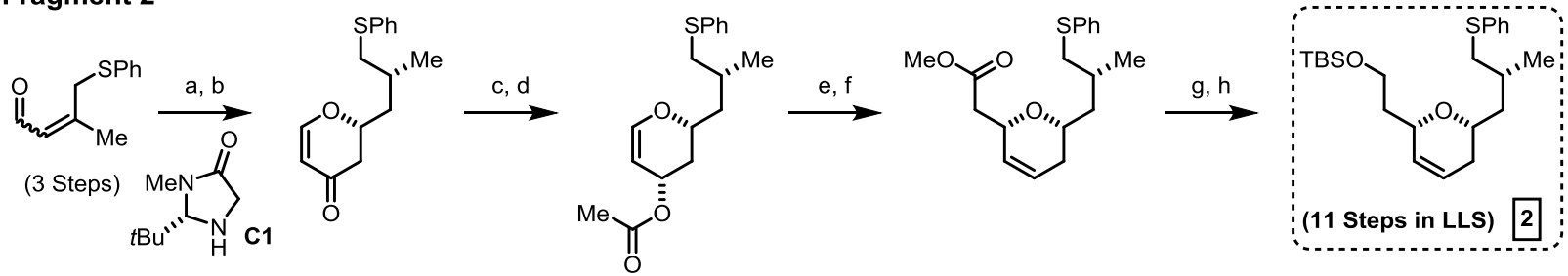




J. Org. Chem. **2002**, *67*, 6812.

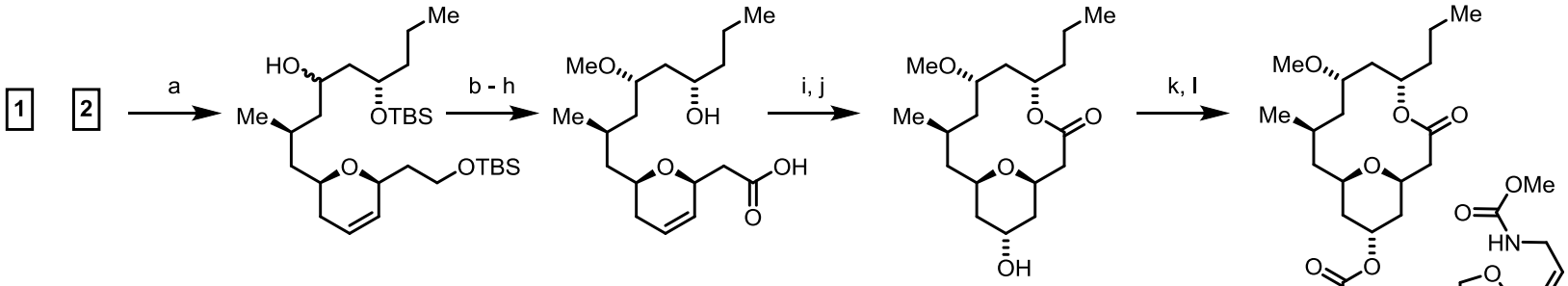
Key: (a) Allyl acetate, Krische's Ir cat.; (b) TBSCl, imidazole; (c) O_3, then DMS.

Fragment 2



Key: (a) Hantzch ester, **C1**•CCl_3CO_2H; (b) Danishefsky's diene, Jacobsen's Cr(III) cat., then TFA; (c) $NaBH_4$, $CeCl_3$•$7H_2O$; (d) Ac_2O, Et_3N, DMAP; (e) LDA, TMSCl, then HCl; (f) CH_2N_2; (g) LAH; (h) TBSCl, imidazole.

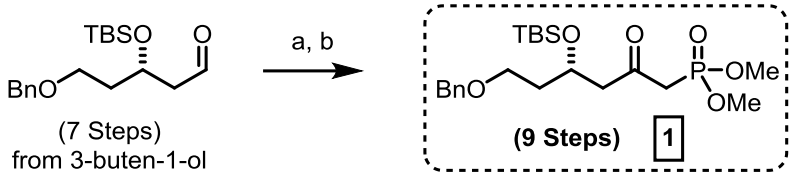
Fragment Union and End Game



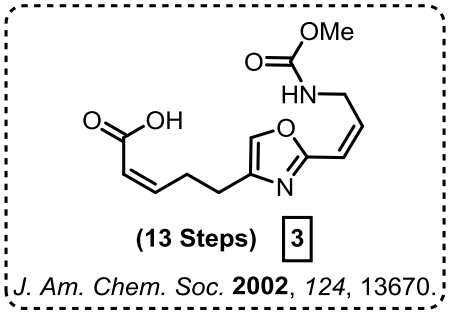
Key: (a) LDBB; (b) IBX; (c) TBAF, AcOH; (d) Isobutanal, $Zr(OtBu)_4$; (e) NaH, MeI; (f) K_2CO_3, MeOH; (g) $PhI(OAc)_2$, TEMPO; (h) $NaClO_2$, cyclohexene; (i) TCBC, DMAP; (j) $Hg(OTFA)_2$, then NaOH(aq.), $NaBH_4$; (k) $(CF_3CH_2O)_2P(O)CH_2CO_2H$, EDCI•HCl, HOBT•$H_2O$; (l) 18-Crown-6, KHMDS, then **3.**

Q. Ghosh *et al. J. Org. Chem.* **2012**, *77*, 9840.

Fragment 1

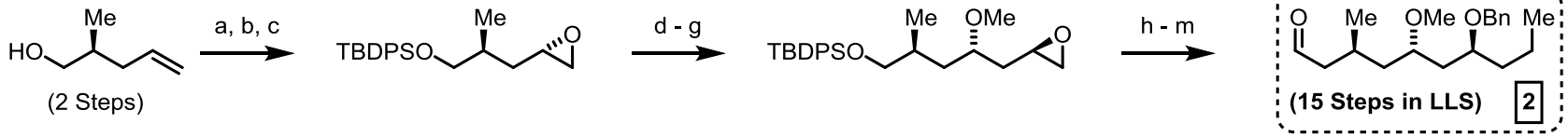


Key: (a) *n*BuLi, $MePO(OMe)_2$; (b) DMP.



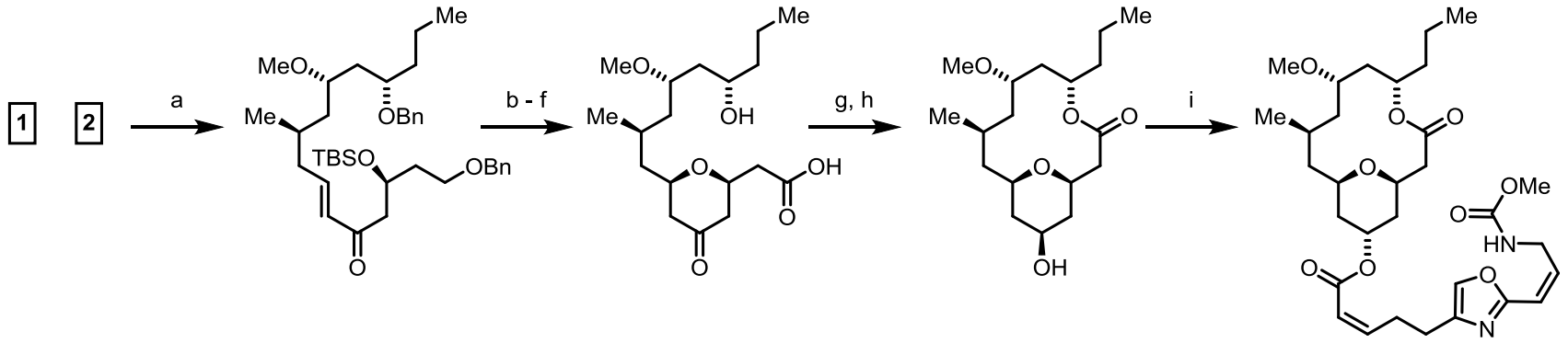
J. Am. Chem. Soc. **2002**, *124*, 13670.

Fragment 2



Key: (a) TBDPSCl, Et_3N, DMAP; (b) *m*CPBA; (c) Jacobsen's (*S*,*S*)-Co(III) cat., H_2O; (d) VinylMgBr, CuI; (e) KH, MeI; (f) *m*CPBA; (g) Jacobsen's (*R*,*R*)-Co(III) cat., H_2O; (h) EtMgBr, CuI; (i) $BnO(C{=}NH)CCl_3$, TfOH; (j) TBAF; (k) TsCl, Et_3N, DMAP; (l) NaCN, NaI; (m) DIBAL-H, then NaOH(aq.).

Fragment Union and End Game

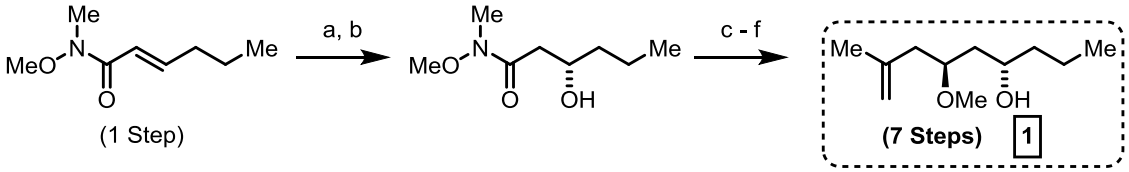


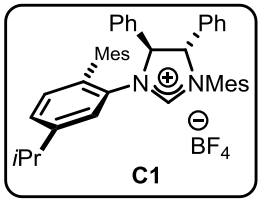
Key: (a) LiCl, DIPEA; (b) HF•py; (c) $Pd(CH_3CN)_4BF_4$; (d) H_2, Pd/C; (e) TEMPO, BAIB; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (g) TCBC, Et_3N, DMAP; (h) $NaBH_4$; (i) **3**, PPh_3, DIAD.

Neopeltolide
24 LLS 46 TS

R. Hoveyda *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 215.

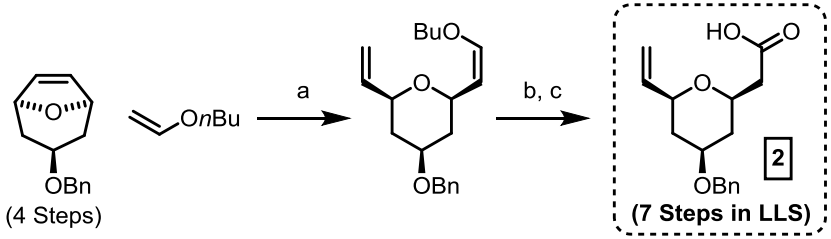
Fragment 1

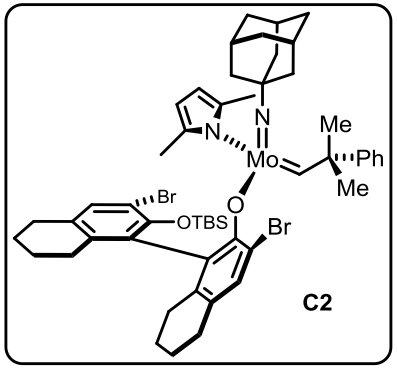


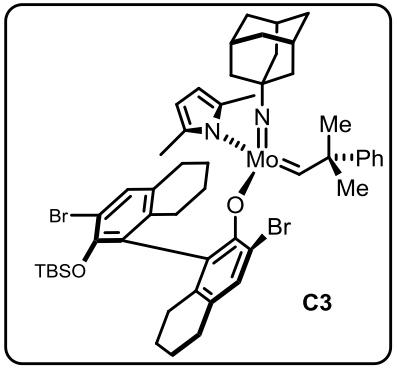


Key: (a) **C1**, $B_2(pin)_2$, DBU; (b) $NaBO_3$; (c) methallylMgCl; (d) SmI_2, PhCHO; (e) Me_3OBF_4, proton sponge; (f) KOH, MeOH.

Fragment 2

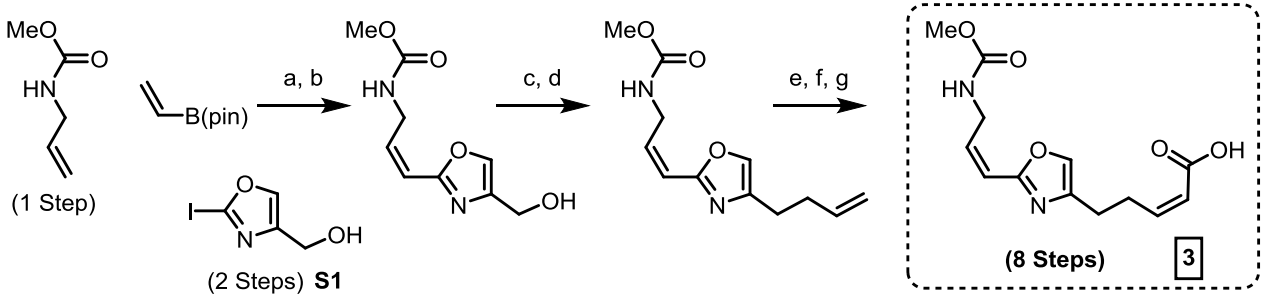


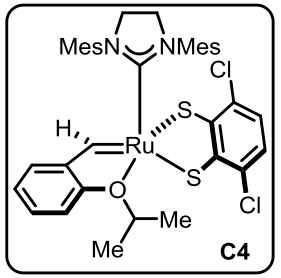




Key: (a) **C2**; (b) HCl (aq); (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene.

Fragment 3

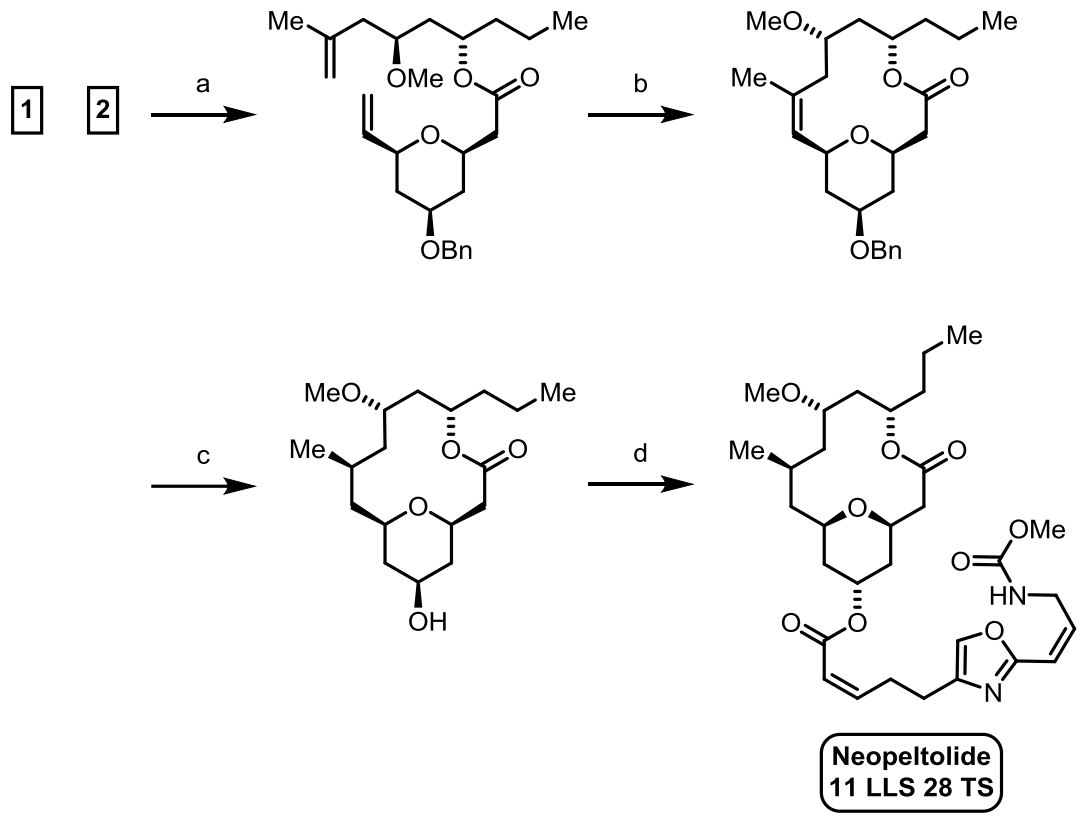


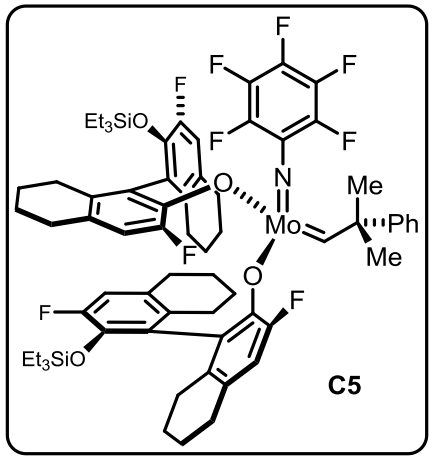


Key: (a) **C3**; (b) **S1**, $Pd(dppf)Cl_2$, K_3PO_4; (c) PPh_3, CBr_4, 2,6-lutidine; (d) CuCN, allylMgBr; (e) **C4**, 2-buten-1,4-diol; (f) DMP, $NaHCO_3$; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene.

R. Hoveyda *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 215. (Cont'd)

Fragment Union and End Game



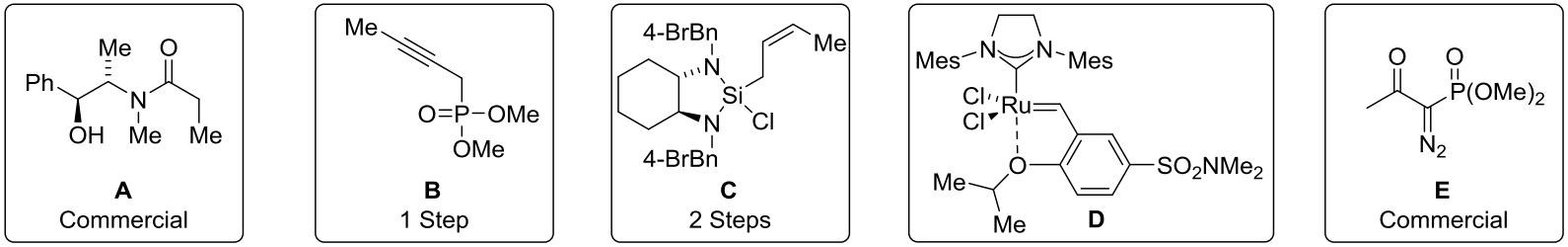


Key: (a) EDC, DMAP, Et_3N; (b) **C5**, 7 torr; (c) 10% Pd/C, H_2; (d) **3**,PPh_3, DIAD.

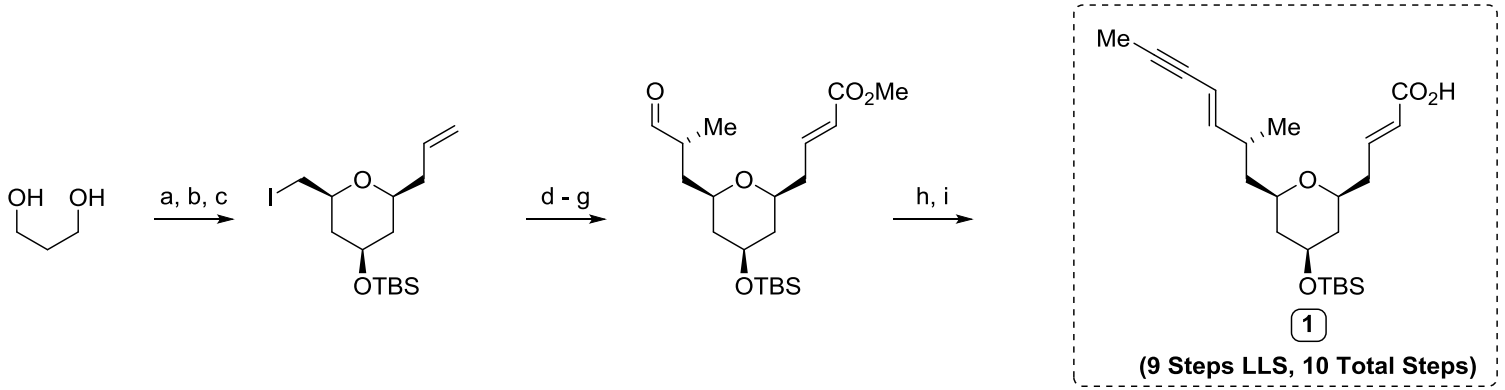
Graphical Summary of Previous Syntheses of Mandelalide

A. Fürstner *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 4217; *Chem. Eur. J.* **2015**, *21*, 10416.

Reagents:



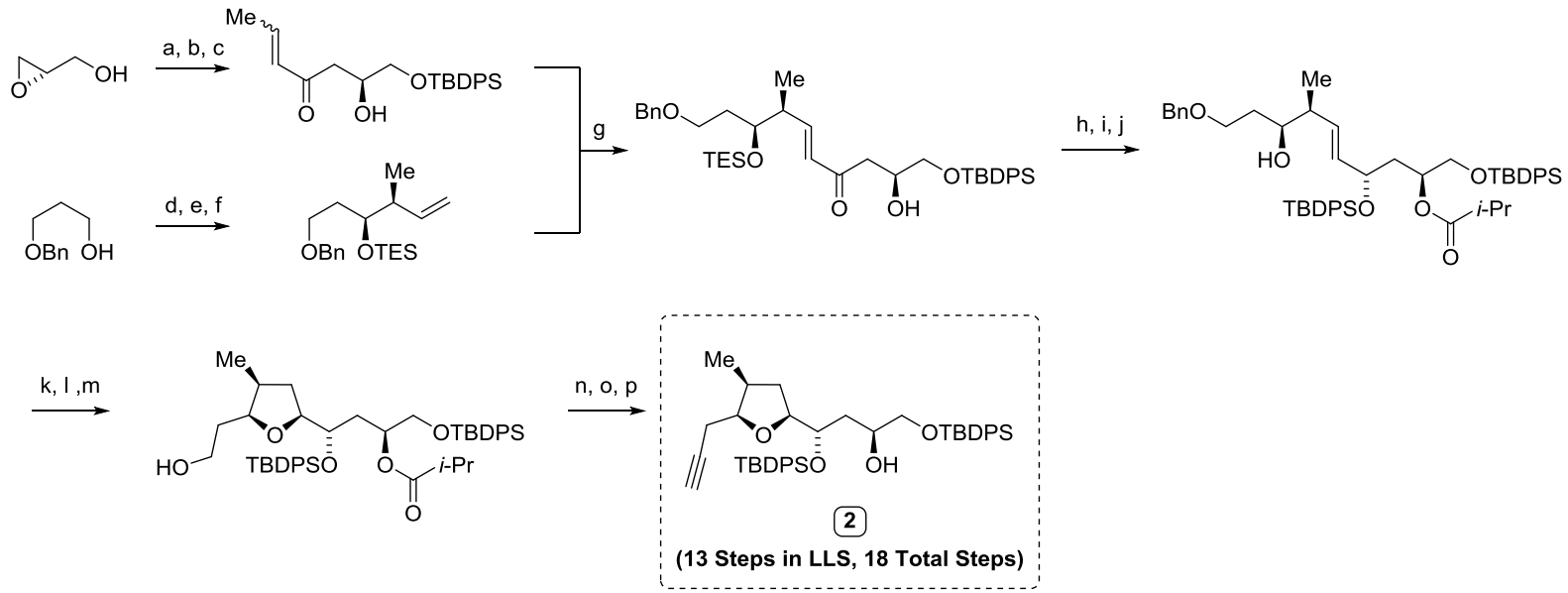
Fragment 1



Key: a) $[Ir(cod)Cl]_2$, (*S*)-Cl,MeO-BIPHEP, 3-NO_2-4-Cl-$PhCO_2H$, allyl acetate, Cs_2CO_3; b) I_2, $NaHCO_3$; c) TBSOTf, 2,6-lutidine; d) LDA, LiCl, **A**; e) LDA, BH_3-NH_3; f) methyl acrylate, HG-II; g) DMP; h) LiHMDS, **B**; i) Me_3SiOK.

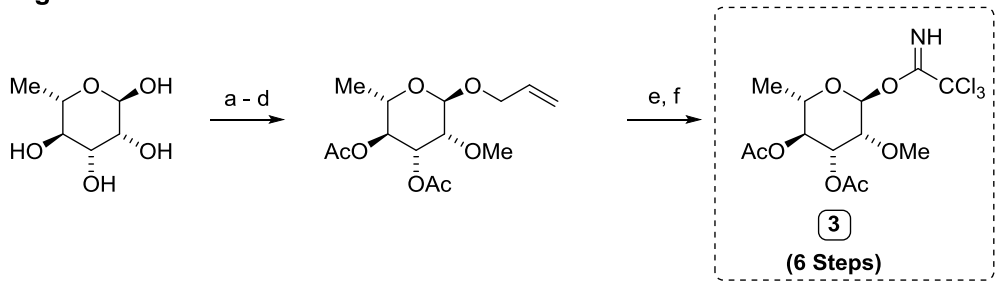
A. Fürstner *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 4217; *Chem. Eur. J.* **2015**, *21*, 10416. (Cont'd)

Fragment 2



Key: a) TBDPSCl, imidazole; b) $Co_2(CO)_8$ (cat.), CO, *N*-(TMS)-morpholine; c) Me(H)C=CHMgBr; d) $[Cu(MeCN)_4]BF_4$ (cat.), bpy (cat.); TEMPO, *N*-Me-imidazole, air; e) **C**, $Sc(OTf)_3$ (cat.); f) TESCl, NEt_3; DMAP; g) **D**; h) *i*-PrCHO, SmI_2; i) TBDPSCl, imidazole; j) CSA; k) *N*-(PhSe)-phthalimide, TFA, $Ph_3P{=}S$; l) Bu_3SnH, AIBN; m) $Pd(OH)_2/C$, H_2; n) DMP; o) **E**, NaOMe; p) DIBAL-H.

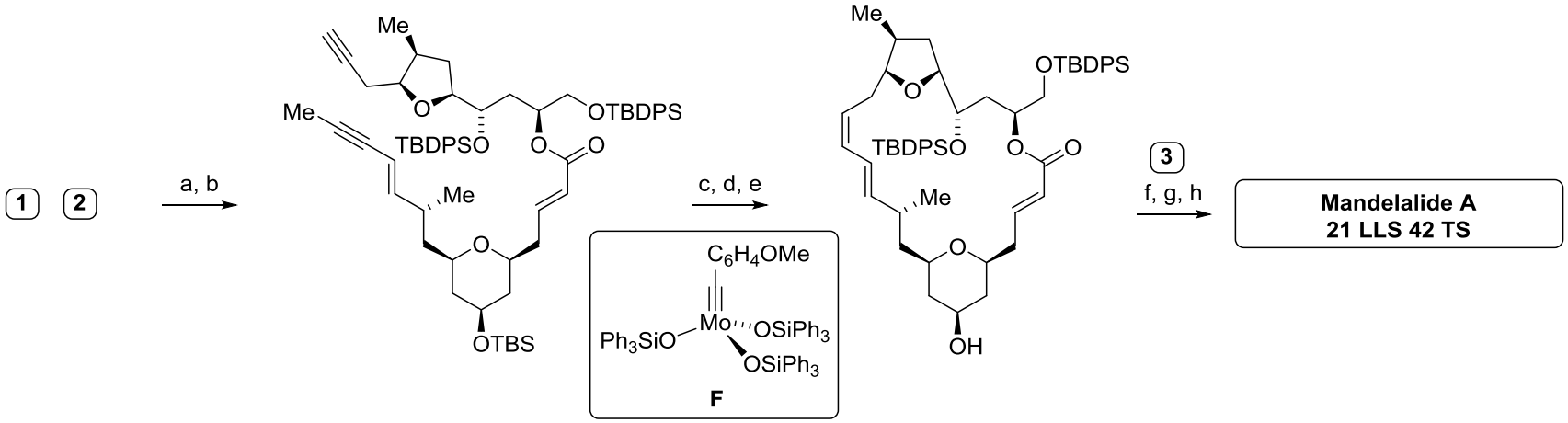
Fragment 3



Key: a) Allyl alcohol, H_2SO_4; b) butane-2,3-dione, $MeC(OMe)_3$, $TsOH{\cdot}H_2O$; c) NaH, MeI; d) TFA, then Ac_2O, DMAP, NEt_3; e) SeO_2, HOAc; f) Cl_3CCN, Cs_2CO_3.

A. Fürstner *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 4217; *Chem. Eur. J.* **2015**, *21*, 10416. (Cont'd)

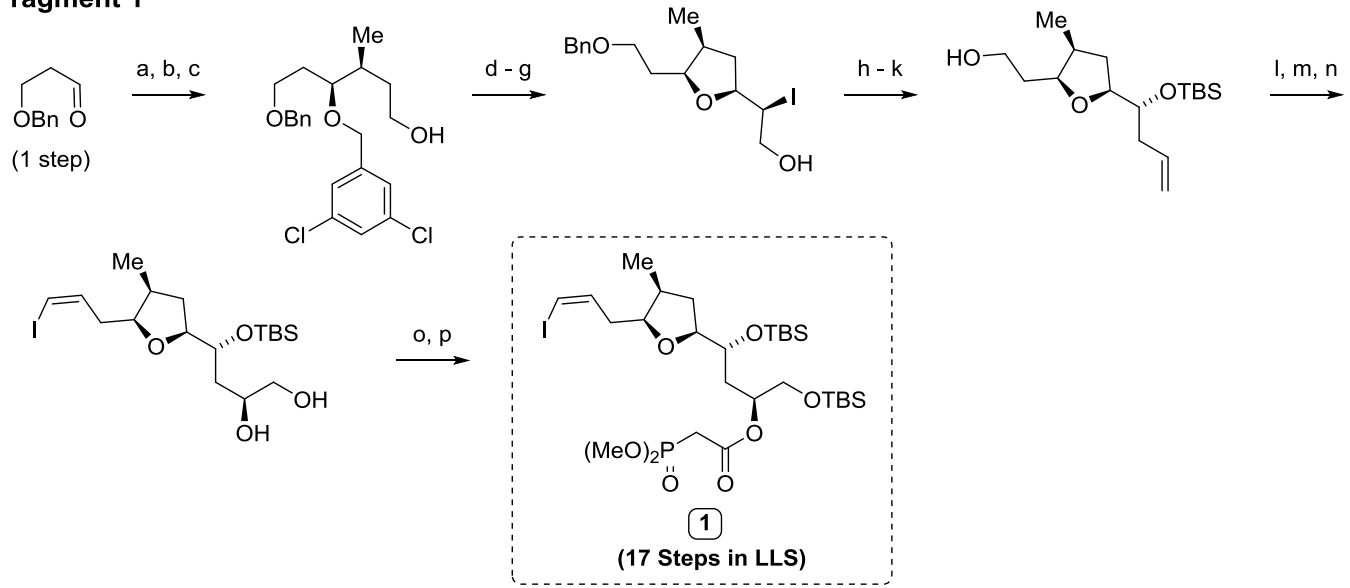
Fragment Union and End Game



Key: a) DCC, DMAP; b) DBU; c) **F**, 4 and 5Å MS; d) Zn(Cu/Ag); e) TsOH-H_2O; f) **3**, TESOTf, 4Å MS; g) K_2CO_3; h) HF-pyridine.

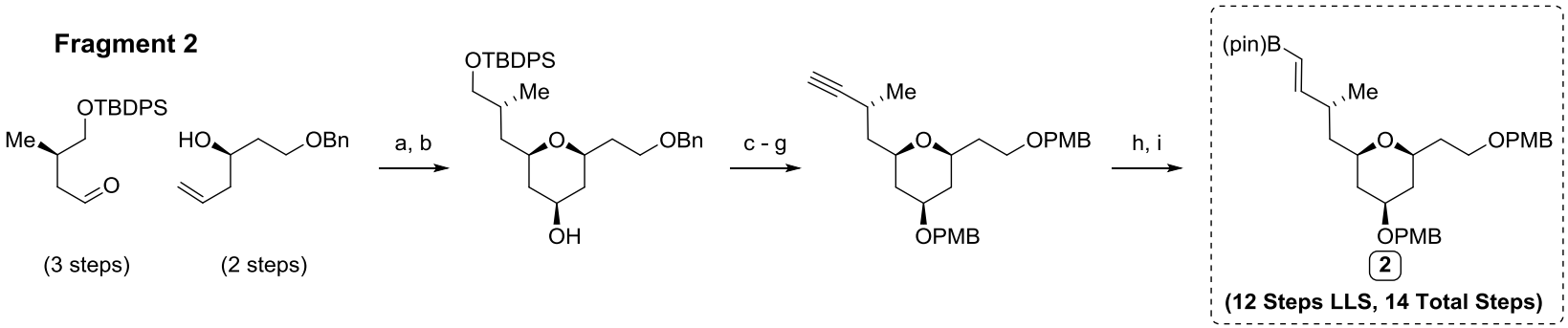
B. Xu & Ye *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 6533.

Fragment 1



Key: a) (*Z*)-2-butene, *n*-BuLi, *t*-BuOK, (+)-(Ipc)$_2$BOMe, BF_3-OEt_2, then H_2O_2, NaOH; b) NaH, 2,6-Cl_2BnBr, TBAI; c) 9-BBN, then H_2O_2, NaOH; d) DMP, $NaHCO_3$; e) LiCl, $(MeO)_2P(O)CH_2CO_2Me$, *i*-Pr_2NEt; f) DIBAL-H; g) I_2; h) K_2CO_3; i) CuI, vinylMgBr; j) TBSOTf, 2,6-lutidine; k) DDQ; l) DMP, $NaHCO_3$; m)$(ICH_2PPh_3)I$, NaHMDS; n) AD-MIX-β; o) TBSCl, imidazole, DMAP; p) $(MeO)_2P(O)CH_2CO_2H$, 2,4,6-Cl_3BzCl, Et_3N, DMAP.

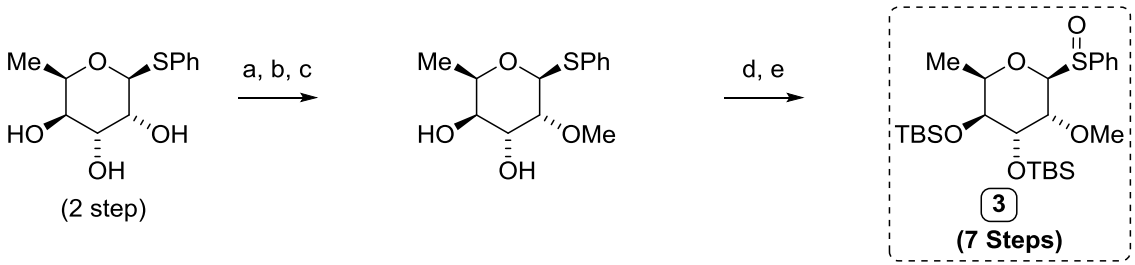
Fragment 2



Key: a) TFAI; b) K_2CO_3; c)Pd/C, H_2; d) NaH, PMBBr, TBAI; e) TBAF; f) DMP, $NaHCO_3$; g) $MeC(N_2)P(O)(OMe)_2$, K_2CO_3; h) HB(pin), Cy_2BH; i) DDQ.

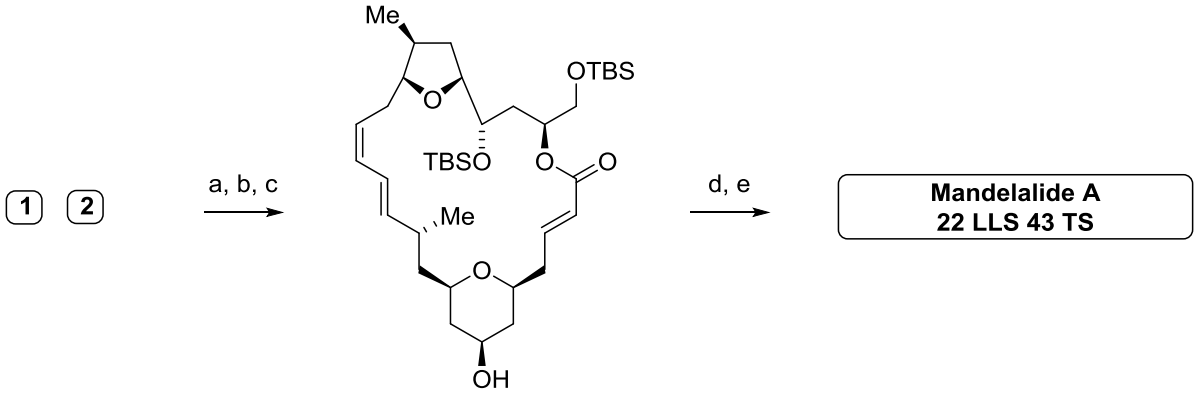
B. Xu & Ye *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 6533. (Cont'd)

Fragment 3



Key: a) $HC(OMe)_3$, 2,2,3,3-$(OMe)_4$-butane, CSA; b) NaH, MeI; c) TFA; d) TBSOTf, 2,6-lutidine; e) *m*-CPBA.

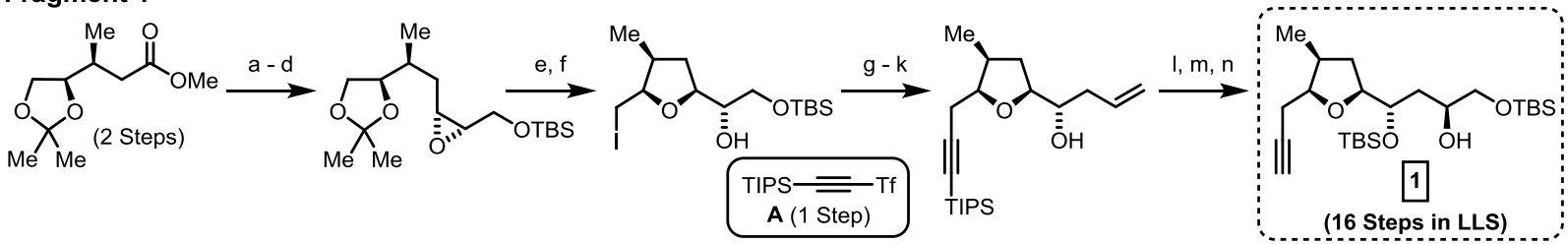
Fragment Union and End Game



Key: a) $Pd(PPh_3)_4$, Ag_2O; b) TEMPO, $PhI(OAc)_2$; c) LiCl, *i*-Pr_2NEt; d) **3**, 4Å MS, 2,6-(*t*-$Bu)_2$-4-Me-pyridine Tf_2O; e) TASF.

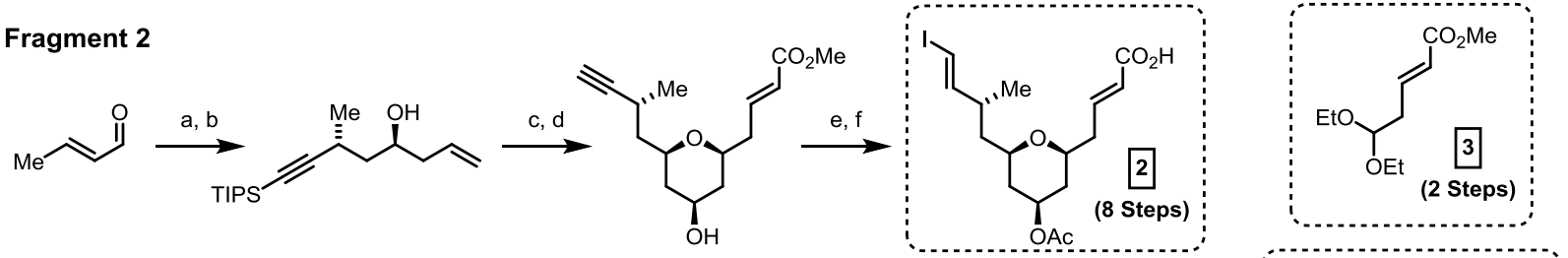
C. Altmann *et al. Chem. Eur. J.* **2016**, *22*, 1292.

Fragment 1

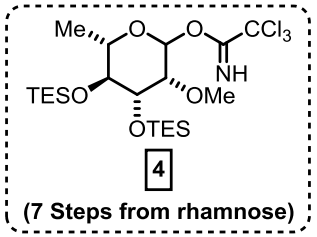


Key: a) DIBAL-H; b) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6; c) DIBAL-H; d) D-(-)-diethyl tartrate, $Ti(O\textit{i}\text{-}Pr)_4$, *t*-BuOOH then imidazole, DMAP, TBSCl; e) $FeCl_3{\bullet}6H_2O$; (f) PPh_3, I_2, imidazole; g) $(Bu_3Sn)_2$, UV, **A**; h) AcOH; i) PPh_3, I_2, imidazole; j) NaH; k) vinylMgBr, CuI; (l) TBAF, then TBSOTf, 2,6-lutidine; m) AD-mix-α; n) TBSCl, imidazole.

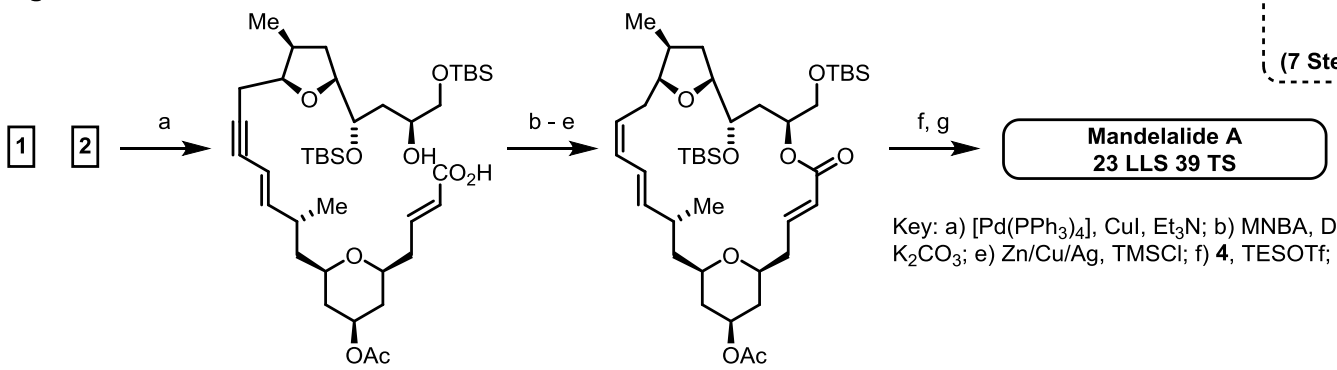
Fragment 2



Key: a) TIPS-acetylene, $[Rh(C_2H_4)_2OAc]_2$, (*S*)-DTBM-Segphos; b) (*S*)-BINOL, $Ti(O\textit{i}\text{-}Pr)_4$, $AllylSnBu_3$; c) **3**, TFA; d) TBAF; e) Bn_3SnH, $Pd(dppf)Cl_2$, I_2; f) TMSOK, then Ac_2O, DMAP, Et_3N.



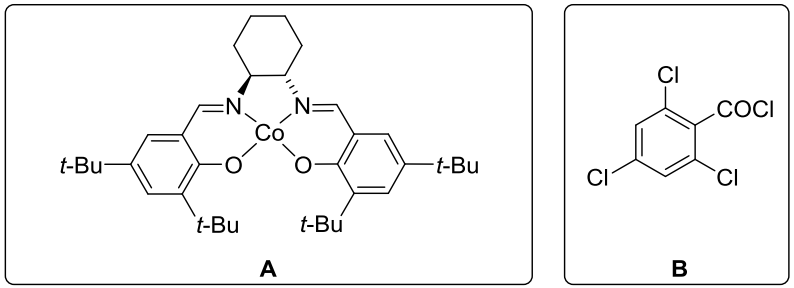
Fragment Union and End Game



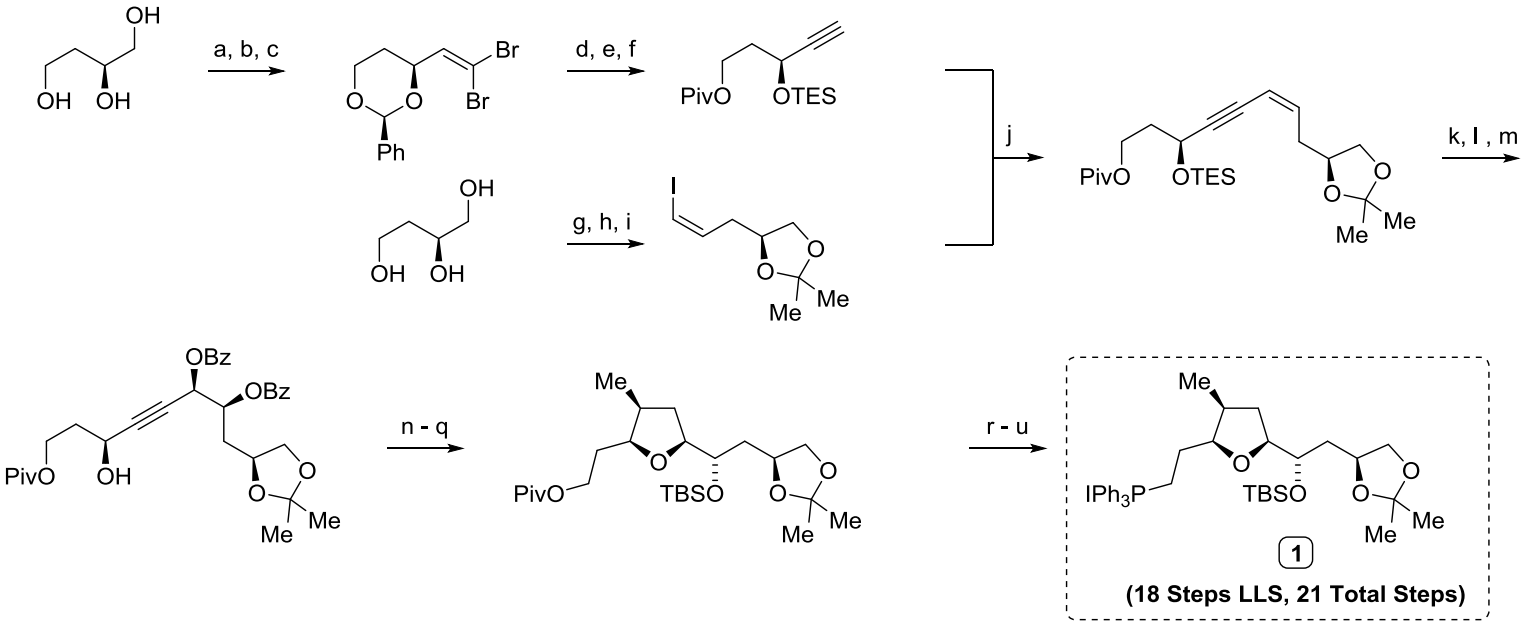
Key: a) $[Pd(PPh_3)_4]$, CuI, Et_3N; b) MNBA, DMAP; c) DBU; d) K_2CO_3; e) Zn/Cu/Ag, TMSCl; f) **4**, TESOTf; g) HF•Pyr, Pyr.

D. Carter *et al. J. Am. Chem. Soc.* **2016**, *138*, 770.

Reagents



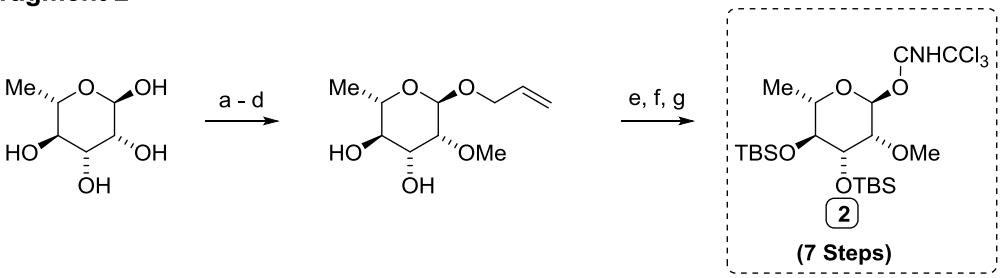
Fragment 1



Key: a) *p*-TsOH, $PhCH(OMe)_2$; b) $(COCl)_2$, DMSO, Et_3N; c)PPh_3, CBr_4; d) *n*-BuLi; e) *p*-TsOH; f) pyridine, PivCl, then DMAP, TESCl; g) *p*-TsOH, acetone; h) PCC, 3 Å MS; i) CH_2I-PPh_3I, NaHMDS, DMPU; j) $Pd(PPh_3)_4$, CuI, *i*-Pr_2NH; k) $(DHQD)_2PHAL$, K_2OsO_4, *t*-BuOH, H_2O; l) BzCl, Et_3N, m) HF-pyridine; n) $AgBF_4$ (cat.), then MeLi-LiBr; o) TBSOTf, 2,6-lutidine; p) Cp_2TiMe_2; q) Rh/Al_2O_3, H_2; r) DIBAL-Hl s) Ms_2O, Et_3N; t) NaI; u) PPh_3.

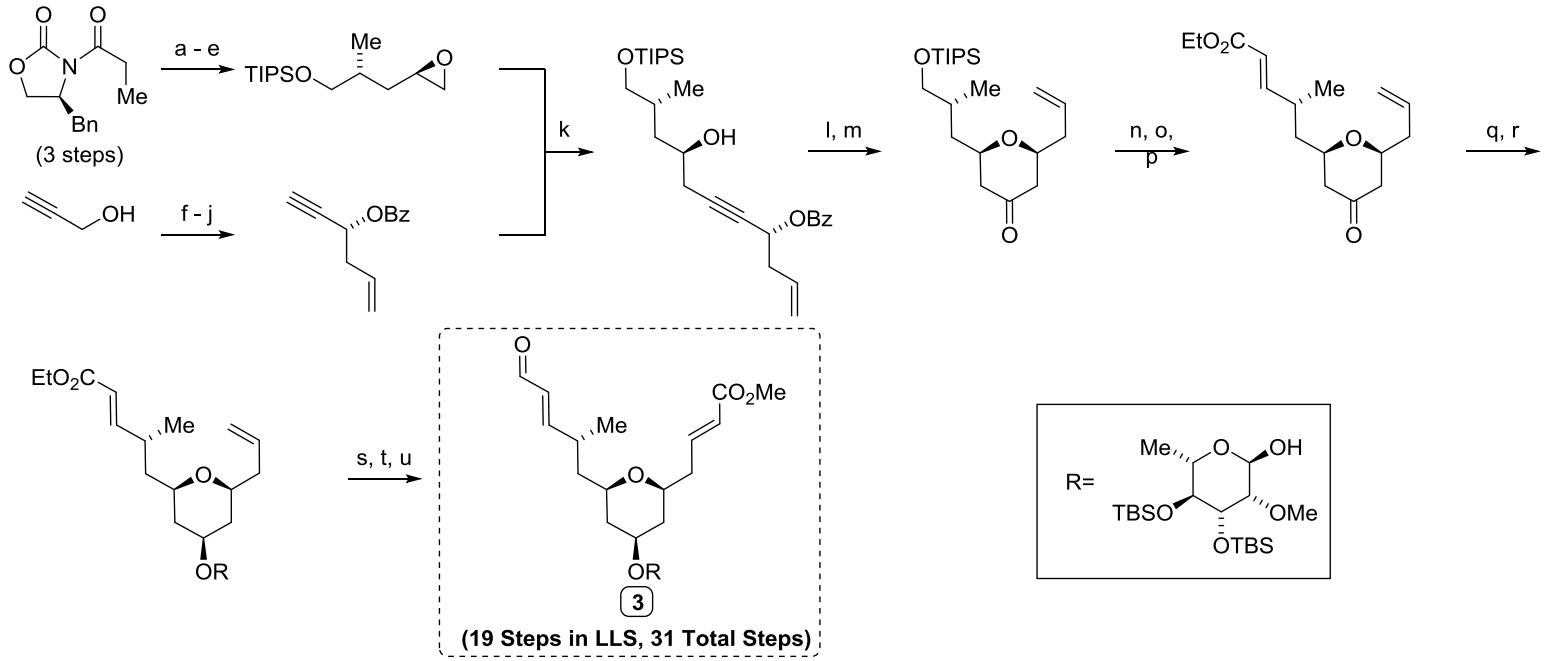
D. Carter *et al. J. Am. Chem. Soc.* **2016**, *138*, 770. (Cont'd)

Fragment 2



Key: a) Allyl alcohol, H_2SO_4; b) butane-2,3-dione, $MeC(OMe)_3$, TsOH-H_2O; c) NaH, MeI; d) TFA; e) TBSOTf, 2,6-lutidine; f) SeO_2, HOAc; g) Cl_3CCN, Cs_2CO_3.

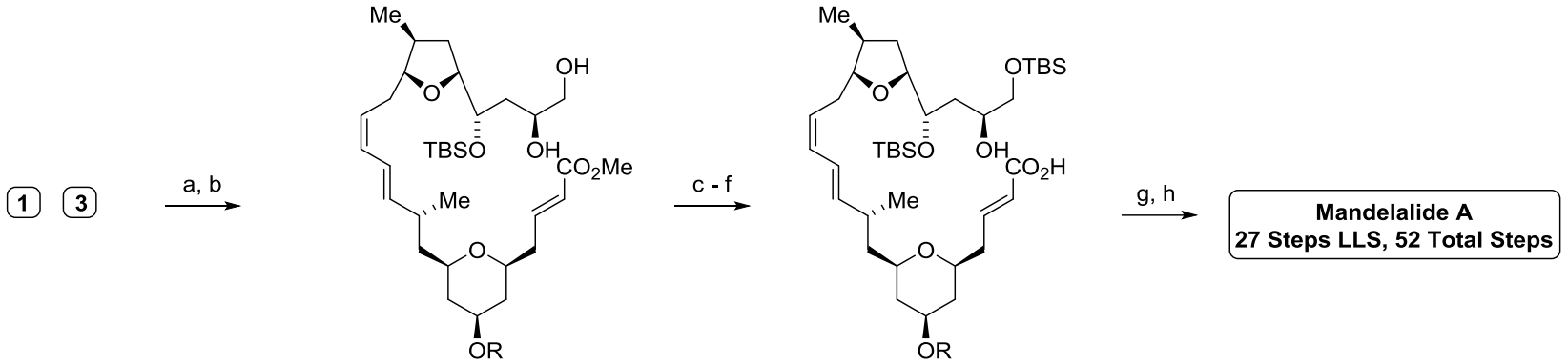
Fragment 3



Key: a) NaHMDS, allyl iodide; b) $LiBH_4$; c) TIPSOTf, Et_3N, DMAP; d) *m*-CPBA; e) **A** (cat.), HOAc, H_2O; f) *n*-BuLi, TMSCl, then HCl; g) PCC; h) Bu_3Sn-allyl, (*R*)-BINOL, Ti(O*i*-Pr)$_4$, 4 Å MS; i) BzCl, Et_3N, DMAP; j) TBAF; k) *n*-BuLi, BF_3-OEt_2; l) $AgBF_4$ (cat.); m) NaOMe; n) TBAF, o) DMP, $NaHCO_3$; p) $Ph_3P{=}CHCO_2Et$; q) $NaBH_4$; r) **2**, TIPSOTf, 4Å MS; s) DIBAL-H; t) DMP, $NaHCO_3$, u) Grubbs II, $H_2C{=}CHCO_2Me$.

D. Carter *et al. J. Am. Chem. Soc.* **2016**, *138*, 770. (Cont'd)

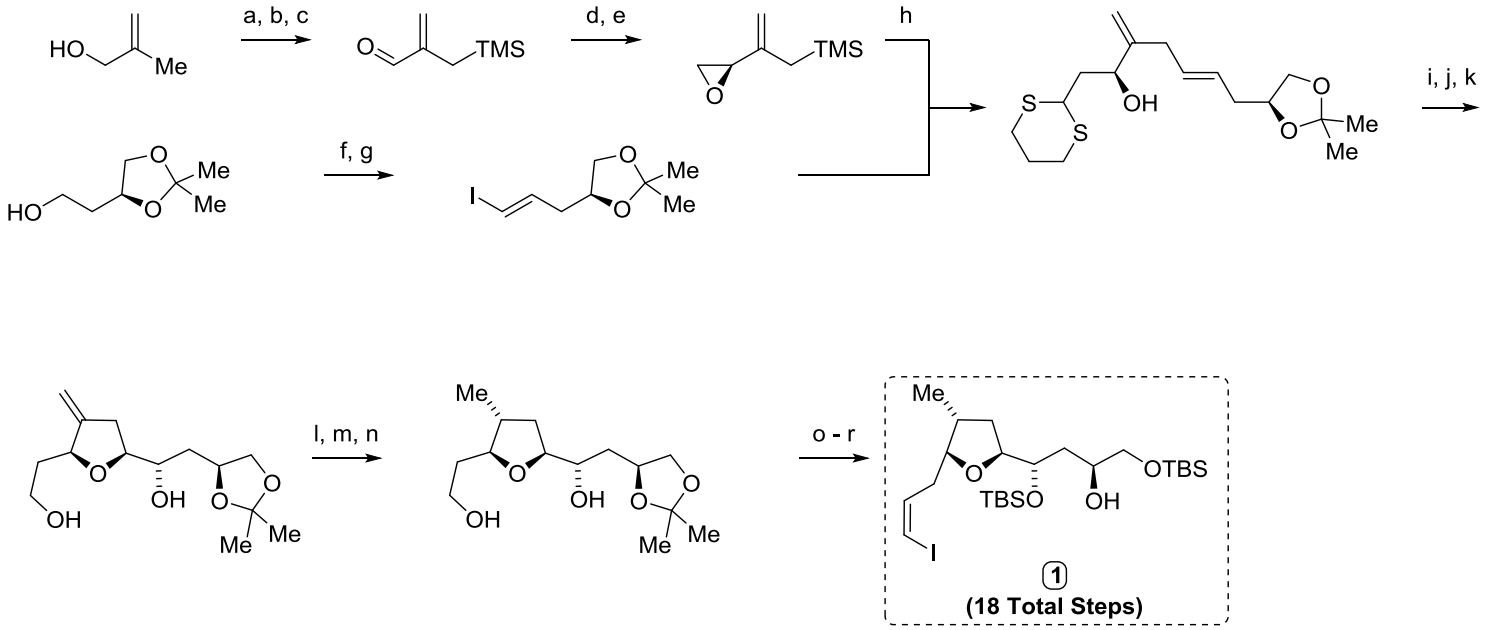
Fragment Union and End Game



Key: a) NaHMDS; b) TFA; c) TBSOTf, 2,6-lutidine; d) DIBAL-H; e) MnO_2; f) $NaClO_2$; g) **B**, Et_3N, DMAP; h) TASF.

E. Smith *et al. J. Am. Chem. Soc.* **2016**, *138*, 3675.

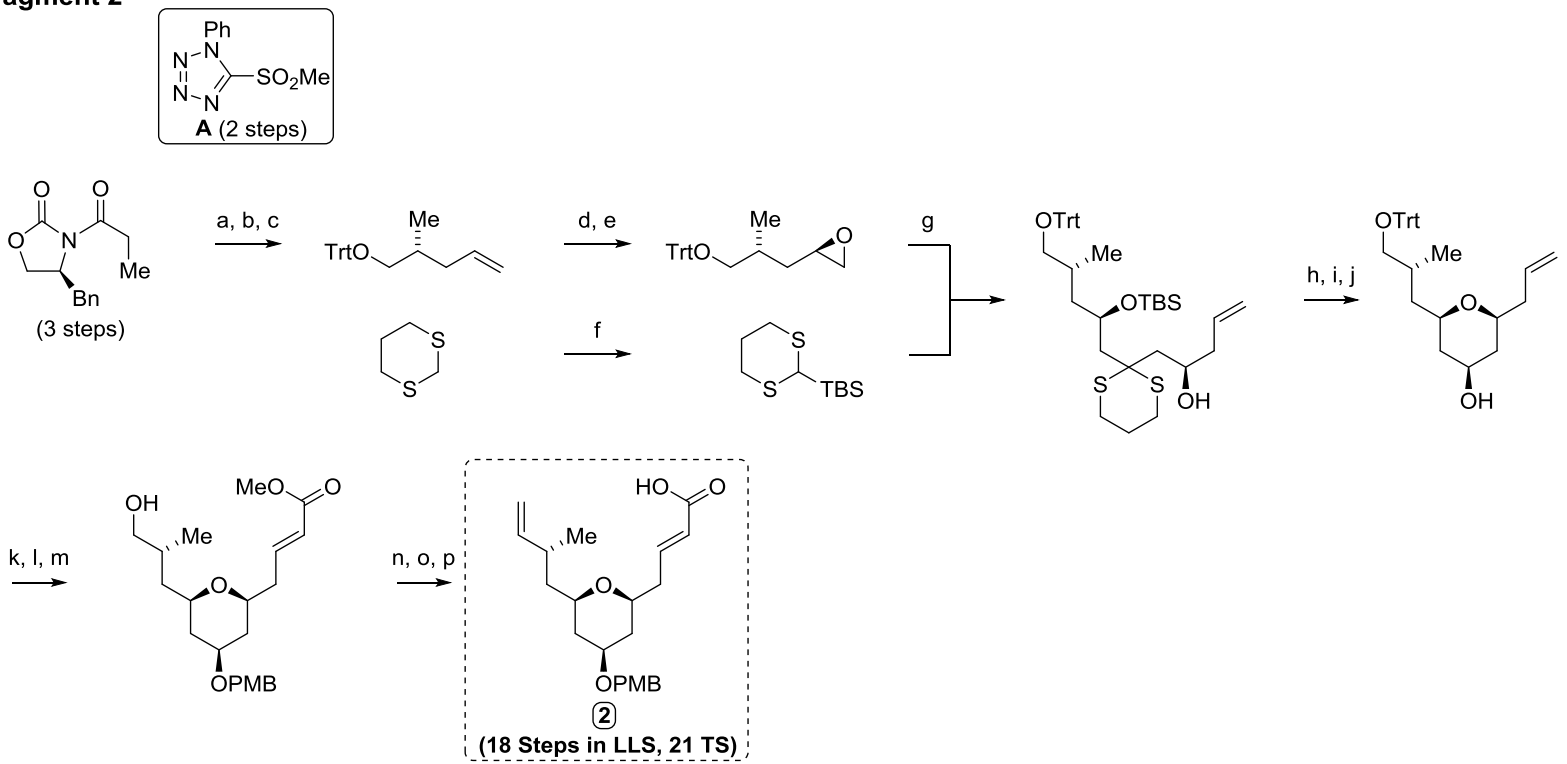
Fragment 1



Key: a) *n*-BuLi, TMEDA, then TMSCl; b) H_2SO_4; c) MnO_2; d) ICH_2Cl, *n*-BuLi, TBAI; e) (*R*,*R*)-Jacobsen Catalyst, H_2O (HKR); f) PCC, 4Å MS; g) CHI_3, $CrCl_2$; h) 1,3-dithiane, *n*-BuLi, then epoxide, HMPA then CuCN, vinyl iodide, then TBAF; i) MeI, $CaCO_3$; j) $NaBH_4$; k) K_2OsO_4, PNO, $Cu(OTf)_2$, citric acid; l) TBSOTf, 2,6-lutidine; m) $(Ph_3P)_3RhCl$, H_2; n) HF, pyridine; o) DMP; p) $Ph_3PCH_2I_2$, NaHMDS; q) $CeCl_3$-$7H_2O$, $(CO_2H)_2$; r) TBSCl, imidazole.

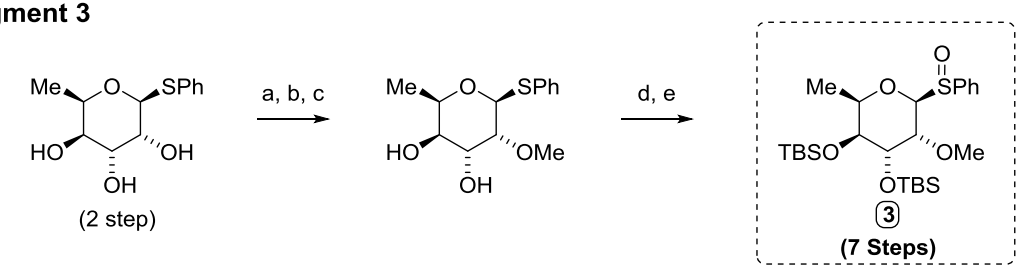
E. Smith *et al. J. Am. Chem. Soc.* **2016**, *138*, 3675. (Cont'd)

Fragment 2



Key: a) NaHMDS, then allyl iodide; b) $LiBH_4$; c) TrtCl, pyridine, DMAP; d) *m*-CPBA, Na_2HPO_4; e) (*R*,*R*)-Jacobsen Catalyst, H_2O (HKR); f) *n*-BuLi, TBSCl; g) *n*-BuLi, then epoxide, then HMPA, then (*S*)-epichlorohydrin, then vinyl-MgBr, CuI; h) MsCl, Et_3N, then TBAF; i) MeI, $CaCO_3$; j) $NaBH_4$; k) PMPBr; l) PPTS; m) methyl acrylate, Grubbs II; n) DMP, o) sulfone **A**; p) LiOH.

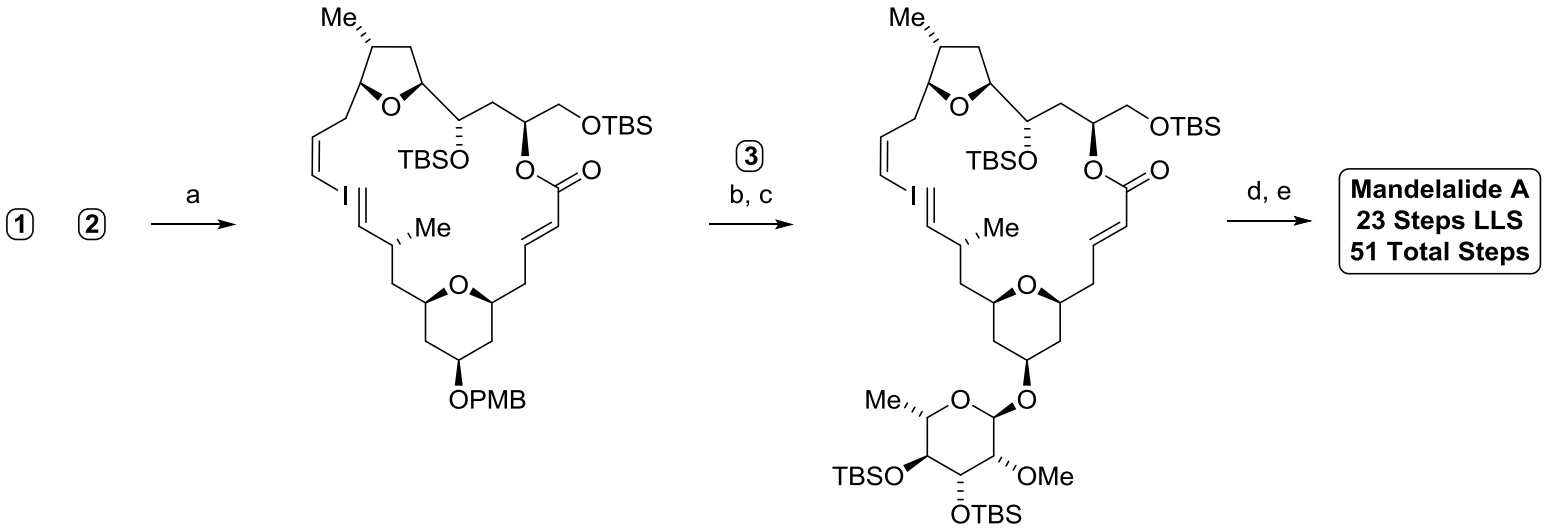
Fragment 3



Key: a) $HC(OMe)_3$, 2,2,3,3-$(OMe)_4$-butane, CSA; b) NaH, MeI; c) TFA; d) TBSOTf, 2,6-lutidine; e) *m*-CPBA.

E. Smith *et al. J. Am. Chem. Soc.* **2016**, *138*, 3675. (Cont'd)

Fragment Union and End Game

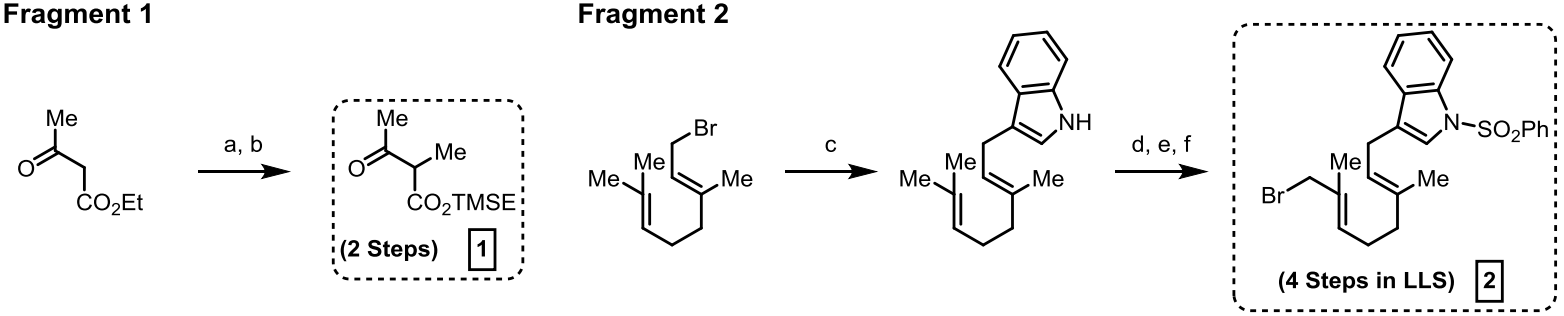


Key: a) 2,4,6-$(Cl)_3$BzCl, Et_3N, DMAP; b) DDQ; c) **3**, Tf_2O, 4Å MS, 2,6-(*t*-$Bu)_2$-pyridine; d) $Pd(OAc)_2$, Cs_2CO_3, Et_3N; e) HF-pyr.

Graphical Summary of Previous Syntheses of Oridamycins

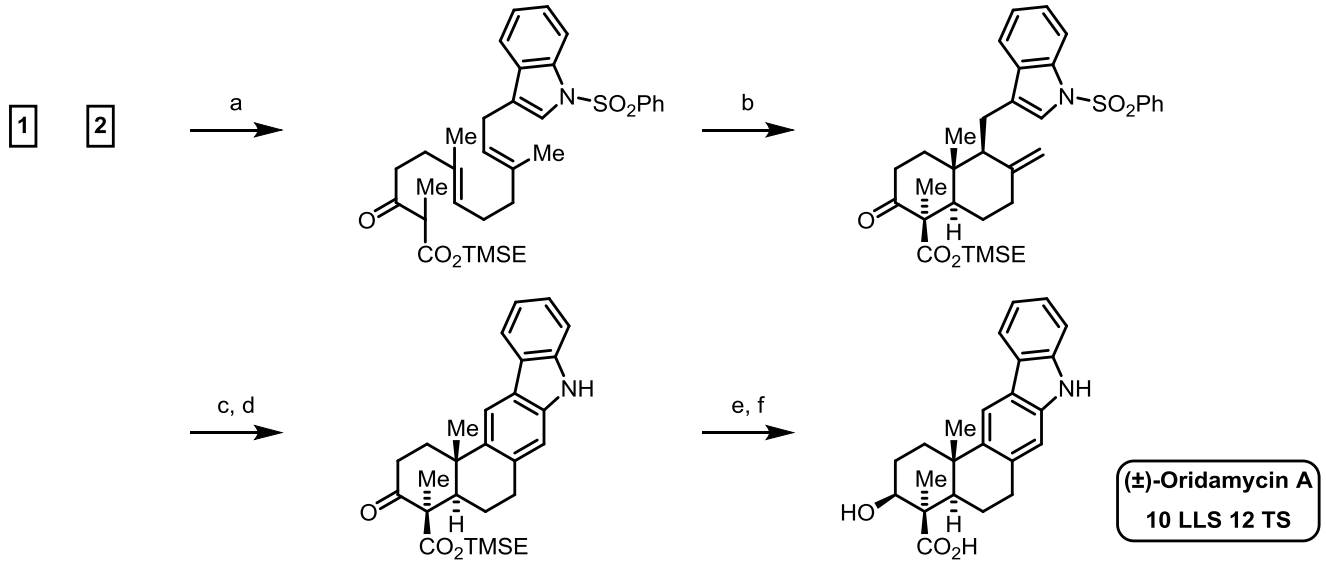
A. Li *et al. Nat. Commun.* **2015**, *6*, 6096. (racemic)

Fragment 1 **Fragment 2**



Key: (a) TMSEOH; (b) MeI, K_2CO_3; (c) Indole, NH_4HCO_3; (d) $PhSO_2Cl$, TBAB, NaOH; (e) SeO_2, TBHP; (f) MsCl, Et_3N, LiBr.

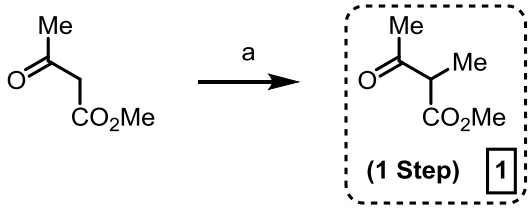
Fragment Union and End Game



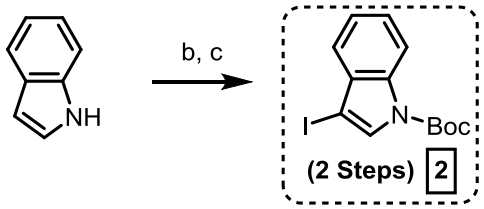
Key: (a) KH, then *n*BuLi, HMPA; (b) $Mn(OAc)_3 \cdot 3H_2O$, $Cu(OAc)_2 \cdot 2H_2O$; (c) Mg, NH_4Cl; (d) $Pd(OAc)_2$, 1,4-benzoquinone; (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$; (f) TASF.

B. Trotta *Org. Lett.* **2015**, *17*, 3358. (racemic)

Fragment 1

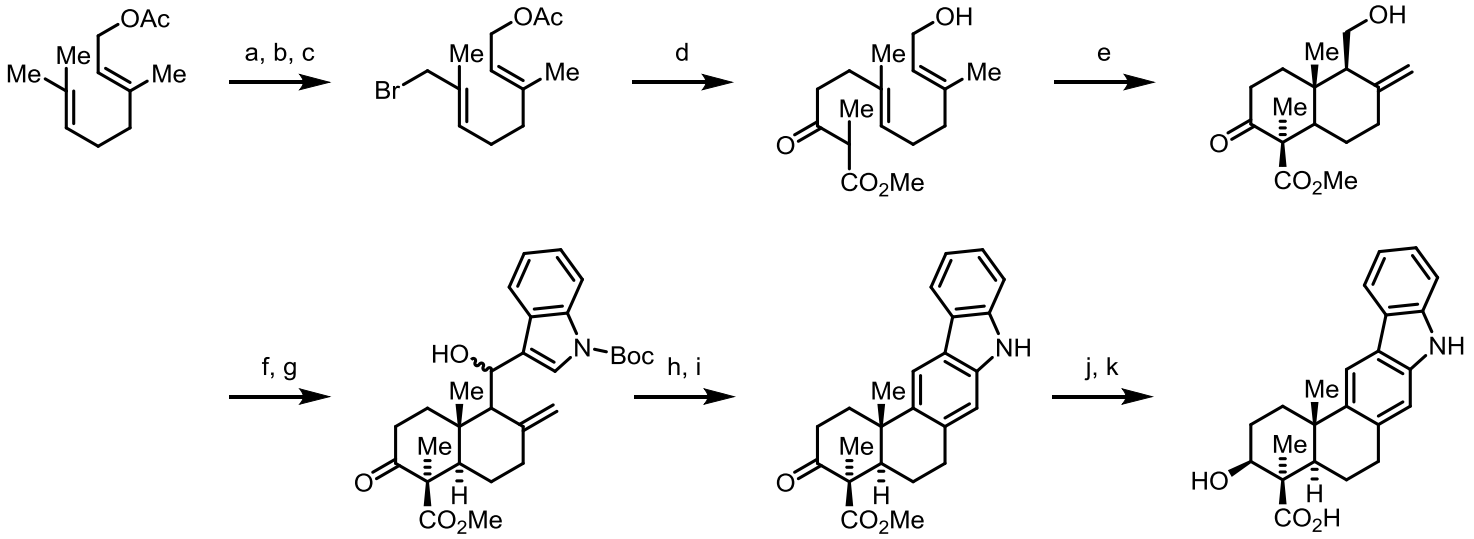


Fragment 2



Key: (a) MeI, K_2CO_3; (b) KOH, I_2; (c) Boc_2O, Et_3N, DMAP.

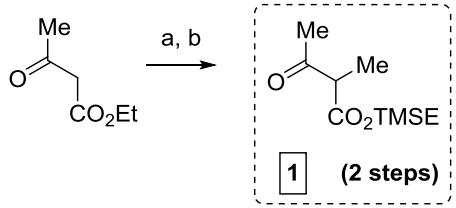
Fragment Union and End Game



Key: (a) SeO_2; (b) $NaBH_4$; (c) MsCl, Et_3N, LiBr; (d) **1**, NaH, then *n*BuLi, HMPA; (e) $Mn(OAc)_3 \cdot 3H_2O$, $Cu(OAc)_2 \cdot 2H_2O$; (f) DMP; (g) **2**, EtMgBr; (h) TFA; (i) Air, then TFA; (j) $NaBH_4$; (k) NaCN.

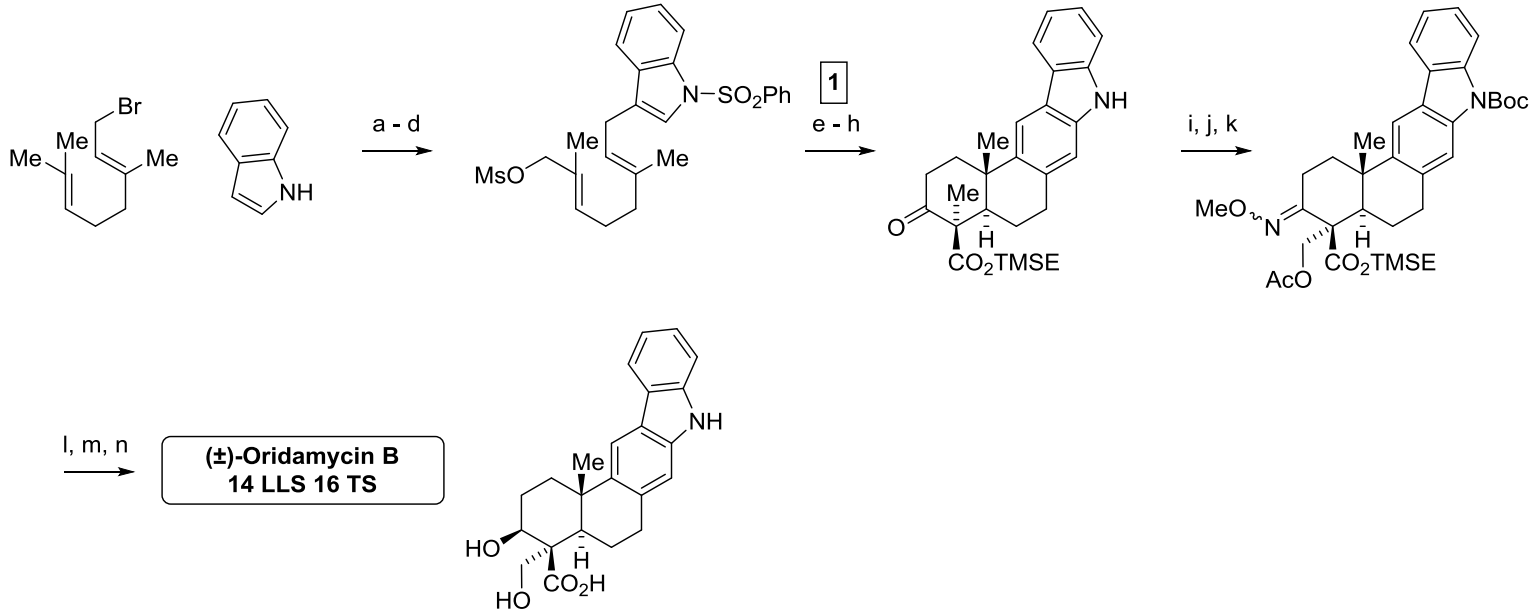
C. Li *et al. Nat. Commun.* **2015**, *6*, 6096. (racemic)

Fragment 1



Key: a) TMSEOH; b) MeI, K_2CO_3.

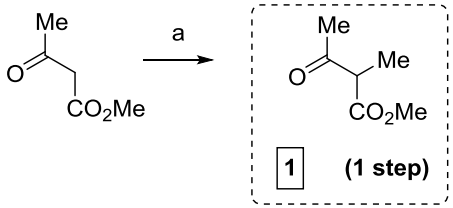
Completion of Synthesis



Key: a) NH_4HCO_3; b) $PhSO_2Cl$, TBAB, NaOH; c) SeO_2, TBHP; d) MsCl, NEt_3, LiBr; e) **1**, KH, then *n*-BuLi; f) $Mn(OAc)_3$-$2H_2O$, $Cu(OAc)_2$-H_2O; g) Mg, NH_4Cl; h) $Pd(OAc)_2$, benzoquinone; i) NH_2OMe; j) Boc_2O, DMAP; k) $Pd(OAc)_2$, $PhI(OAc)_2$; l) $HClO_4$; m) $NaBH_4$; n) TASF.

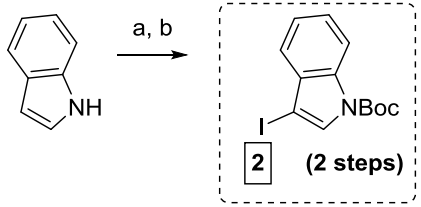
D. Trotta *Org. Lett*. **2015**, *17*, 3358. (racemic)

Fragments 1



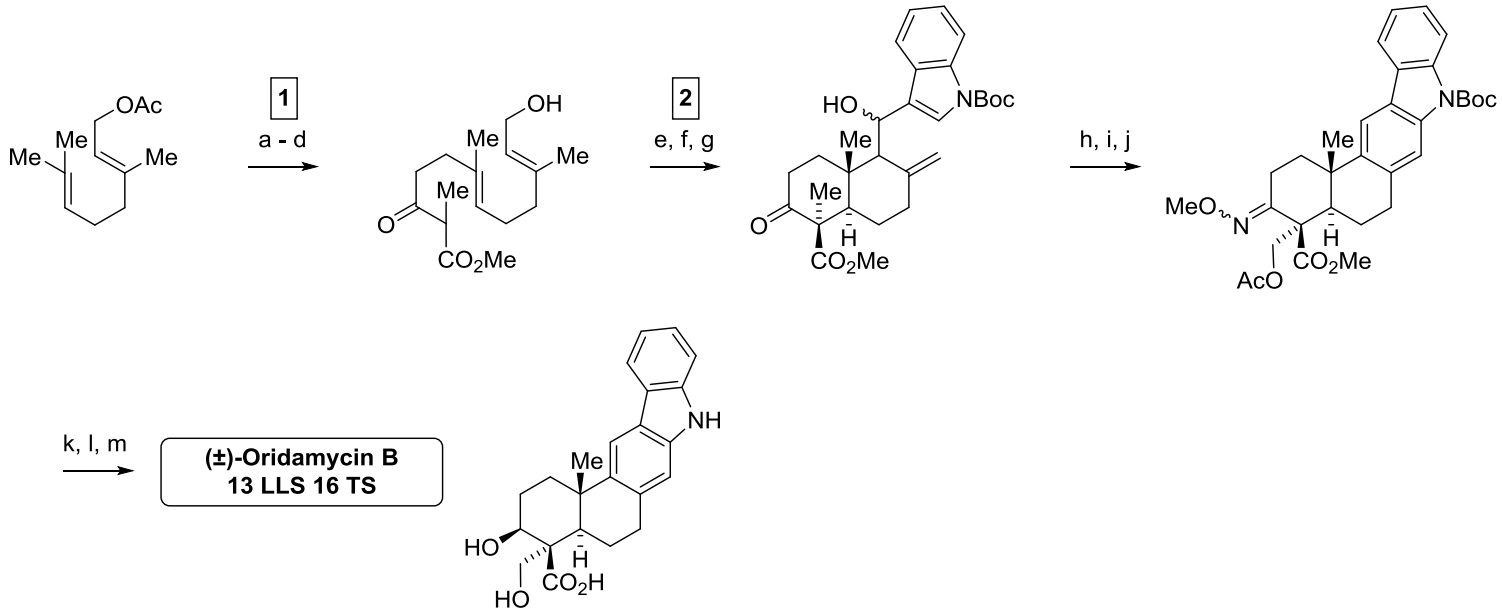
Key: a) MeI, K_2CO_3.

Fragments 2



Key: a) KOH, I_2; b) Boc_2O, Et_3N, DMAP.

Completion of Synthesis

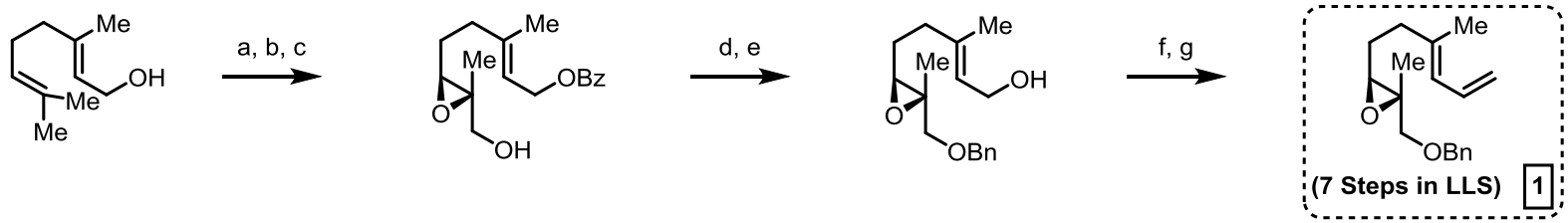


Key: a) SeO_2; b) $NaBH_4$; c) MsCl, NEt_3, then LiBr; d) **1**, NaH, then *n*-BuLi; e) $Mn(OAc)_2$, $Cu(OAc)_2$; f) DMP; g) **2**, EtMgBr; h) TFA; i) $MeONH_2$-HCl, pyridine; j) $Pd(OAc)_2$, $PhI(OAc)_2$; k) HCl; l) $NaBH_4$; m) NaCN.

Graphical Summary of Previous Syntheses of Xiamycin A

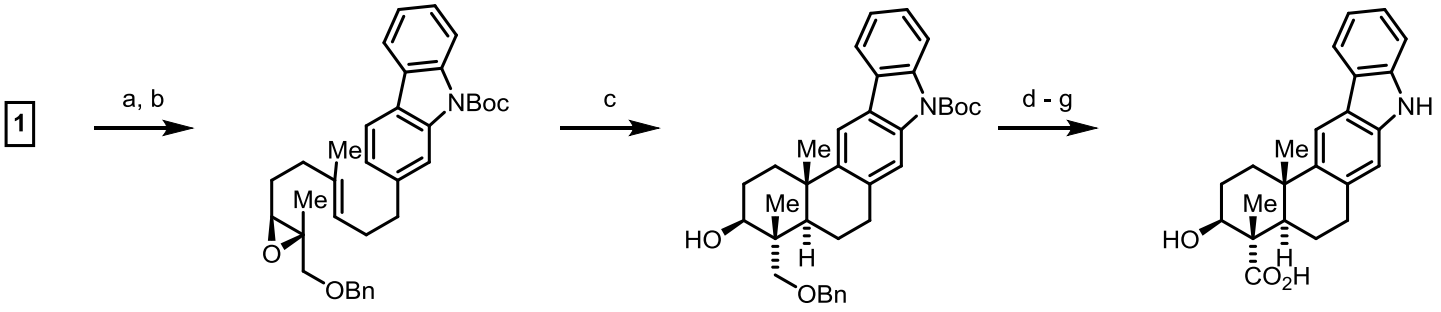
A. Baran *et al. J. Am. Chem. Soc.* **2014**, *136*, 5571.

Fragment 1



Key: (a) BzCl, py, DMAP; (b) SeO_2, TBHP; (c) (+)-DIPT, $Ti(OiPr)_4$, TBHP, 3A MS; (d) BnBr, NaH, TBAI; (e) NaOMe, TBAI; (f) SO_3•py, Et_3N; (g) Ph_3PMeI, *n*BuLi.

Fragment Union and End Game

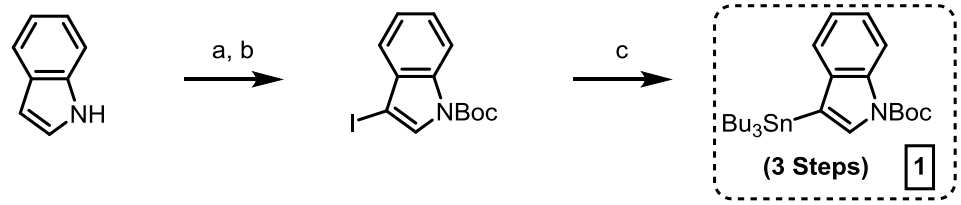


Key: (a) **1**, 9-BBN, then 2-bromo-9H-carbazole, $Pd(dppf)Cl_2$, NaOH; (b) Boc_2O, Et_3N, DMAP; (c) BF_3•OEt_2; (d) H_2, $Pd(OH)_2/C$; (e) TEMPO, NCS, TBAI, $NaHCO_3/KHCO_3$; (f) $NaClO_2$, NaH_2PO_4•H_2O, 2-methyl-2-butene; (g) EtOH, H_2O.

Xiamycin A
14 LLS 14 TS

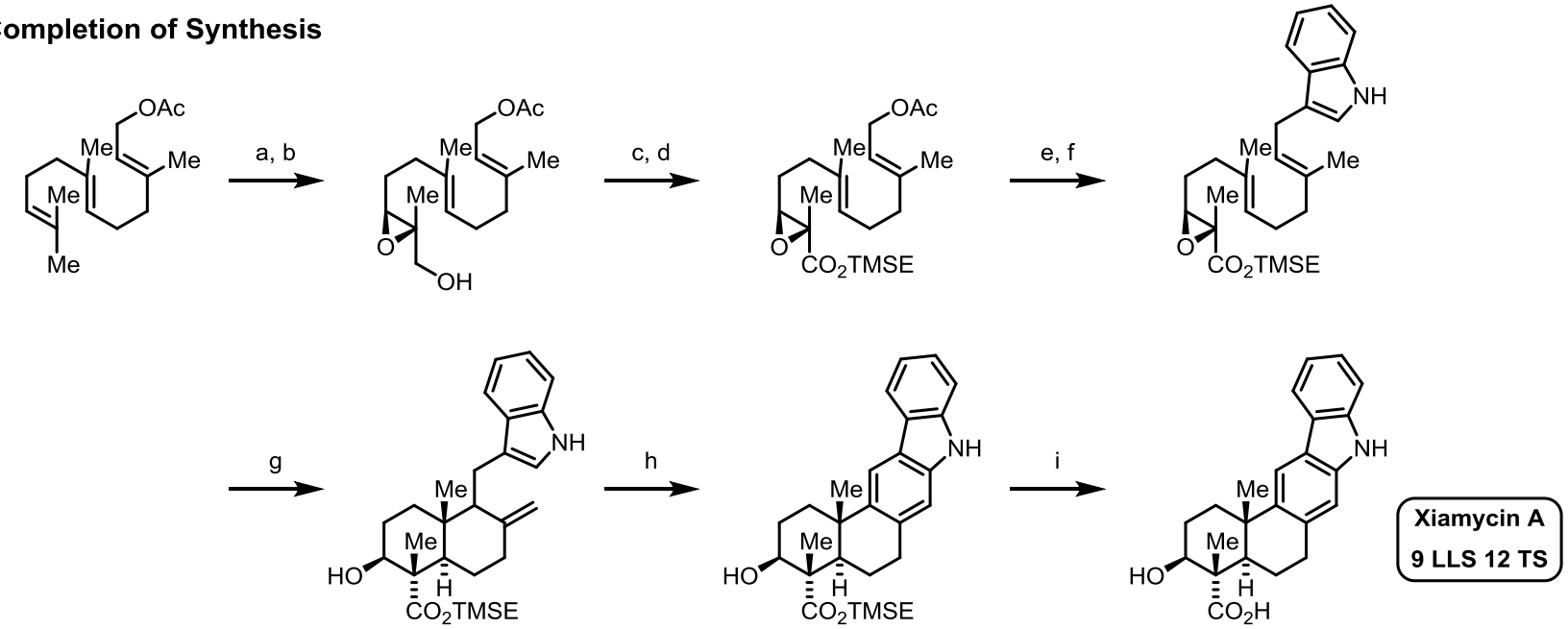
B. Li *et al. Nat. Commun.* **2015**, *6*, 6096.

Fragment 1



Key: (a) ICl, py; (b) Boc_2O, DMAP; (c) *n*BuLi, TMEDA, then Bu_3SnCl.

Completion of Synthesis

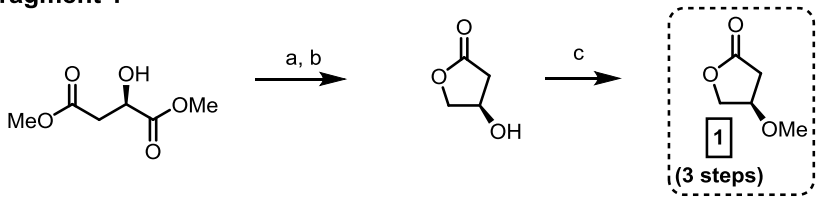


Key: (a) SeO_2, TBHP; (b) (+)-DET, $Ti(OiPr)_4$, TBHP; (c) AZADO, $PhI(OAc)_2$; (d) TMSEOH, EDC•HCl; (e) **1**, $Pd_2(dba)_3$, LiCl; (f) DMSO, 150 °C; (g) Cp_2TiCl_2, Mn, DIPEA, TMSCl; (h) $Pd(OAc)_2$, 1,4-benzoquinone, AcOH; (i) TASF.

Graphical Summary of Previous Syntheses of Triene-Containing C17-Benzene Ansamycins

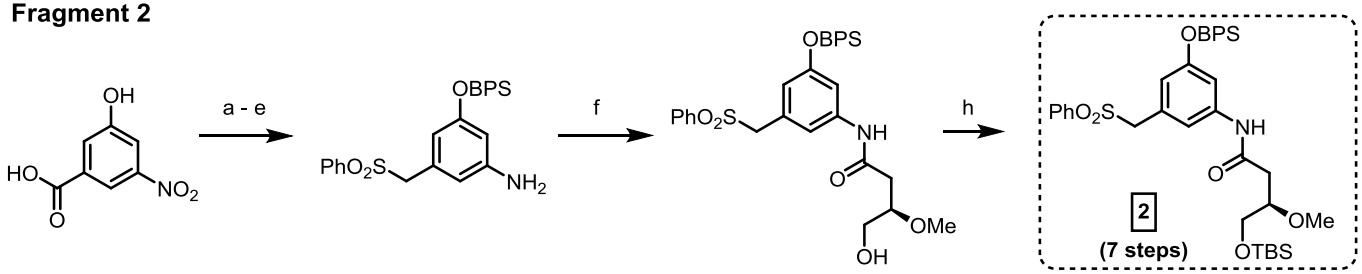
A. Smith *et al.* *J. Am. Chem. Soc.* **1995**, *117*, 10777; *J. Am. Chem. Soc.* **1996**, *118*, 8308; *Tetrahedron Lett.* **1991**, *32*, 1627.

Fragment 1



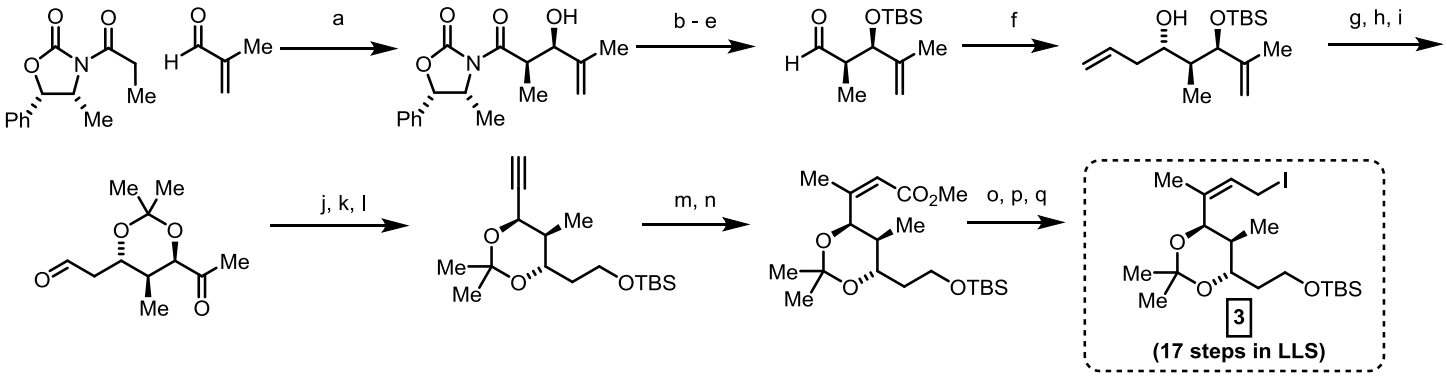
Key: (a) BH_3•Me_2S, $NaBH_4$; (b) CF_3CO_2H; (c) Ag_2O, MeI.

Fragment 2



Key: (a) BH_3; (b) CBr_4, PPh_3; (c) $PhSO_2Na$; (d) BPSCl; (e) H_2, Pd/C; (f) $AlMe_3$, **1**; (h) TBSCl.

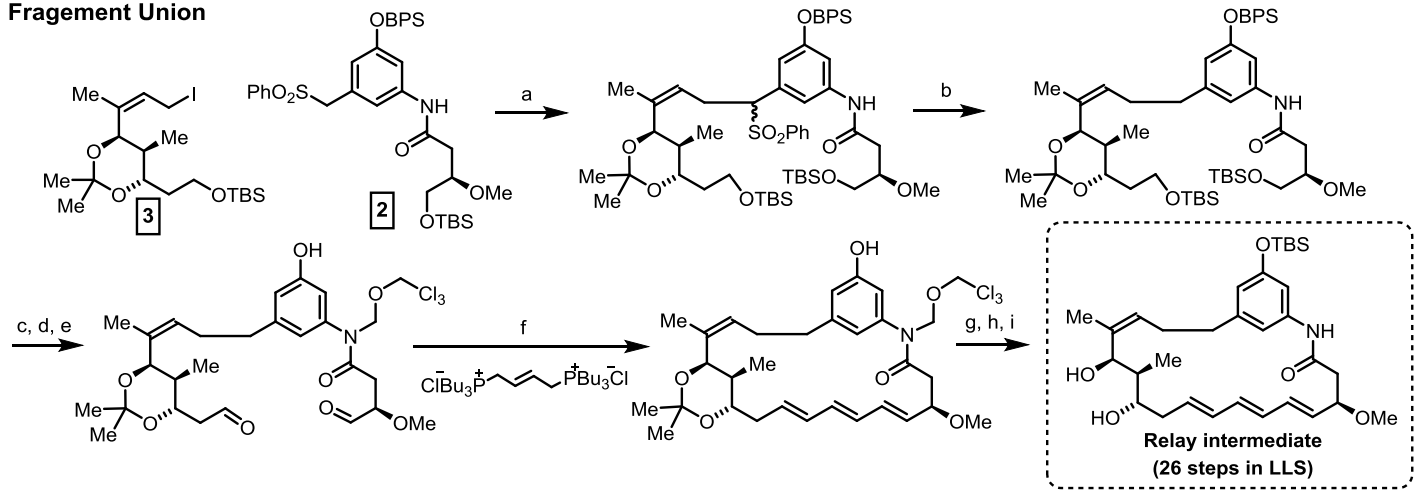
Fragment 3



Key: (a) *n*-Bu_2BOTf, NEt_3; (b) TBSOTf; (c) LiOOH; (d) CDI, MeO(Me)NH•HCl; (e) DIBAL-H; (f) (-)-B-allyl(diisopinocampheyl)-borane; (g) TBAF; (h) $Me_2C(OMe)_2$, PTSA; (i) O_3, PPh_3; (j) $LiAl[OC(Et_3)]_3H$; (k)TBSCl; (l) NaHMDS, $ClPO(Et)_2$, *t*-BuLi; (m) *t*-BuLi, $ClCO_2Me$; (n) Me_2CuLi; (o) DIBAL-H; (p) MsCl, LiCl; (q) NaI.

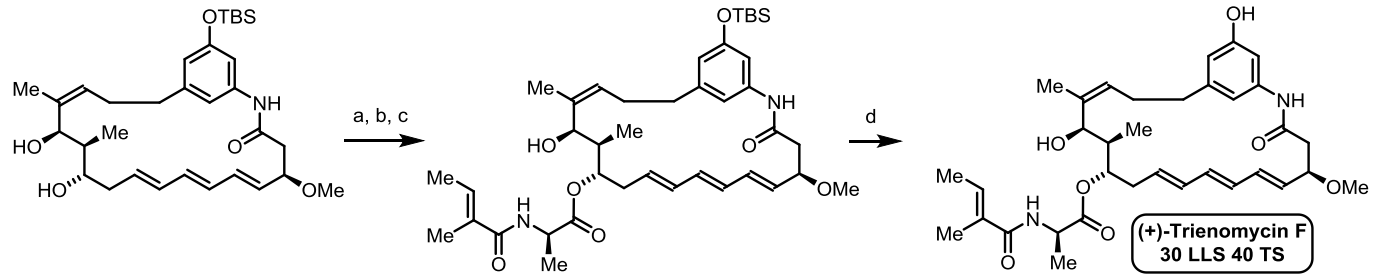
A. Smith *et al. J. Am. Chem. Soc.* **1995**, *117*, 10777; *J. Am. Chem. Soc.* **1996**, *118*, 8308; *Tetrahedron Lett.* **1991**, *32*, 1627. (Cont'd)

Fragement Union



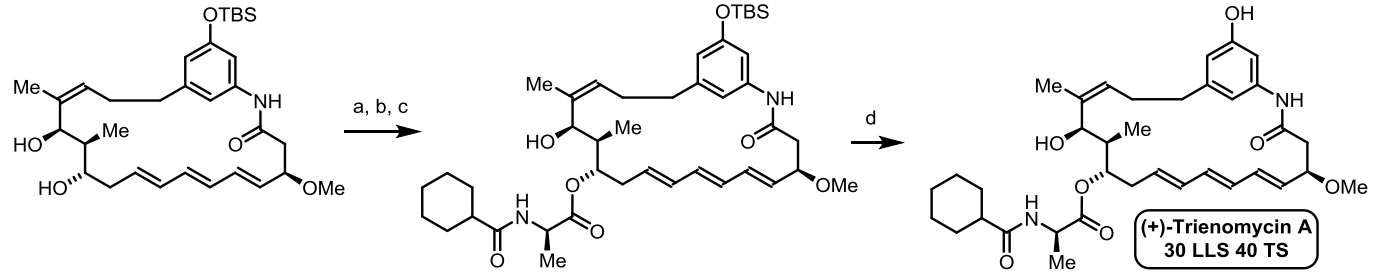
Key: (a) NaHMDS; (b) Na(Hg); (c) KH, $ClCH_2OCH_2CCl_3$; (d) TBAF; (e) $Pyr{\bullet}SO_3$; (f) NaHMDS; (g) TBSOTf; (h) Na(Hg); (i) CSA.

Trienomycin F End Game



Key: (a) $(FMOC\text{-}D\text{-}Ala)_2$, DMAP; (b) Et_2NH; (c) BOP, NEt_3, tiglic acid; (d) TBAF.

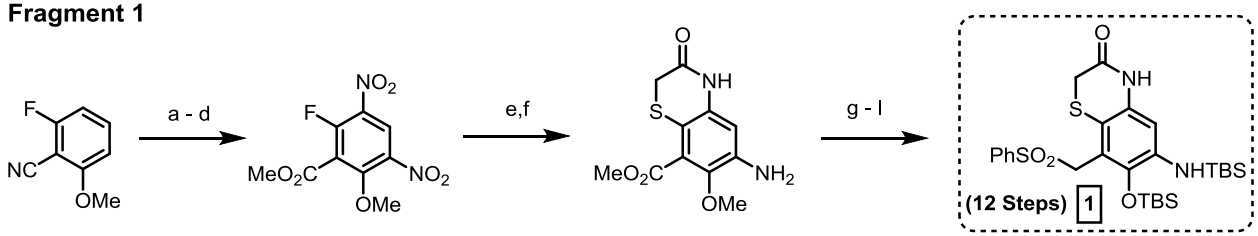
Trienomycin A End Game (Smith, *J. Am. Chem. Soc.* **1996**, *118*, 8308.)



Key: (a) $(FMOC\text{-}D\text{-}Ala)_2O$, DMAP; (b) Et_2NH; (c) BOP, NEt_3, cyclohexanecarboxylic acid; (d) TBAF.

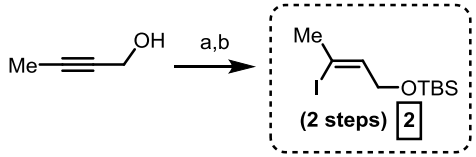
B. Smith *et al.* *Org. Lett.* **1999**, *1*, 1491.

Fragment 1



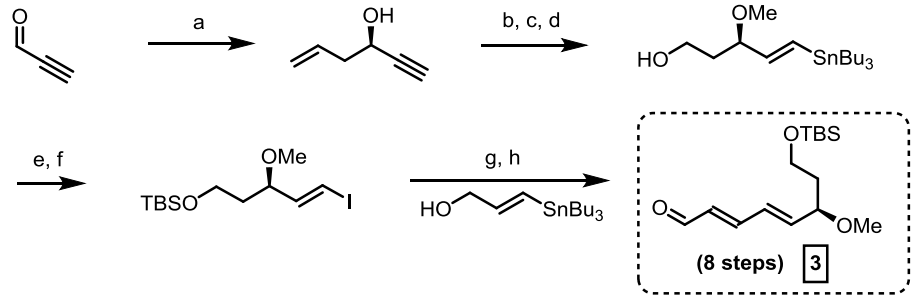
Key: (a) DIBAL-H; (b) $KMnO_4$; (c) CH_3OH; (d) NO_2BF_4; (e) $LiSCH_2CO_2Me$; (f) $SnCl_2$, 1N HCl; (g) CbzCl; (h) $LiHBEt_3$; (i) TsCl, DMAP; (j) $PhSO_2Na$, NaI; (k) BBr_3, (l) TBSOTf.

Fragment 2



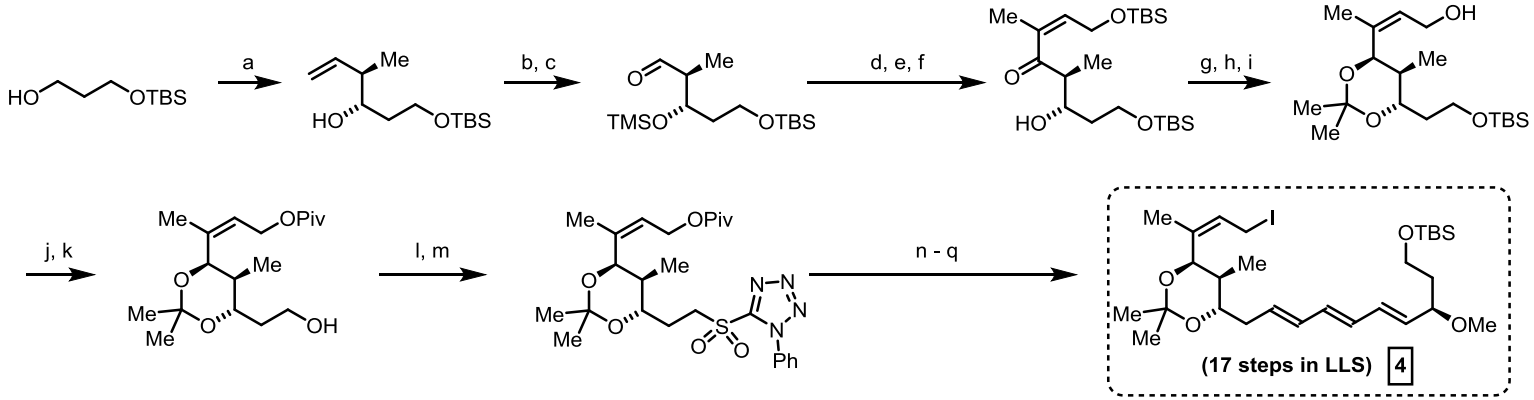
Key: (a) LAH, I_2; (b) TBSCl, NEt_3.

Fragment 3



Key: (a) (-)-B-allyl(diisopinocampheyl)-borane (b) MeI, *n*-BuLi; (c) O_3, PPh_3; (d) Bu_3SnH, AIBN; (e) TBSOTf; (f) I_2; (g) $Pd(CH_3CN)_2Cl_2$; (h) $COCl_2$, DMSO, NEt_3.

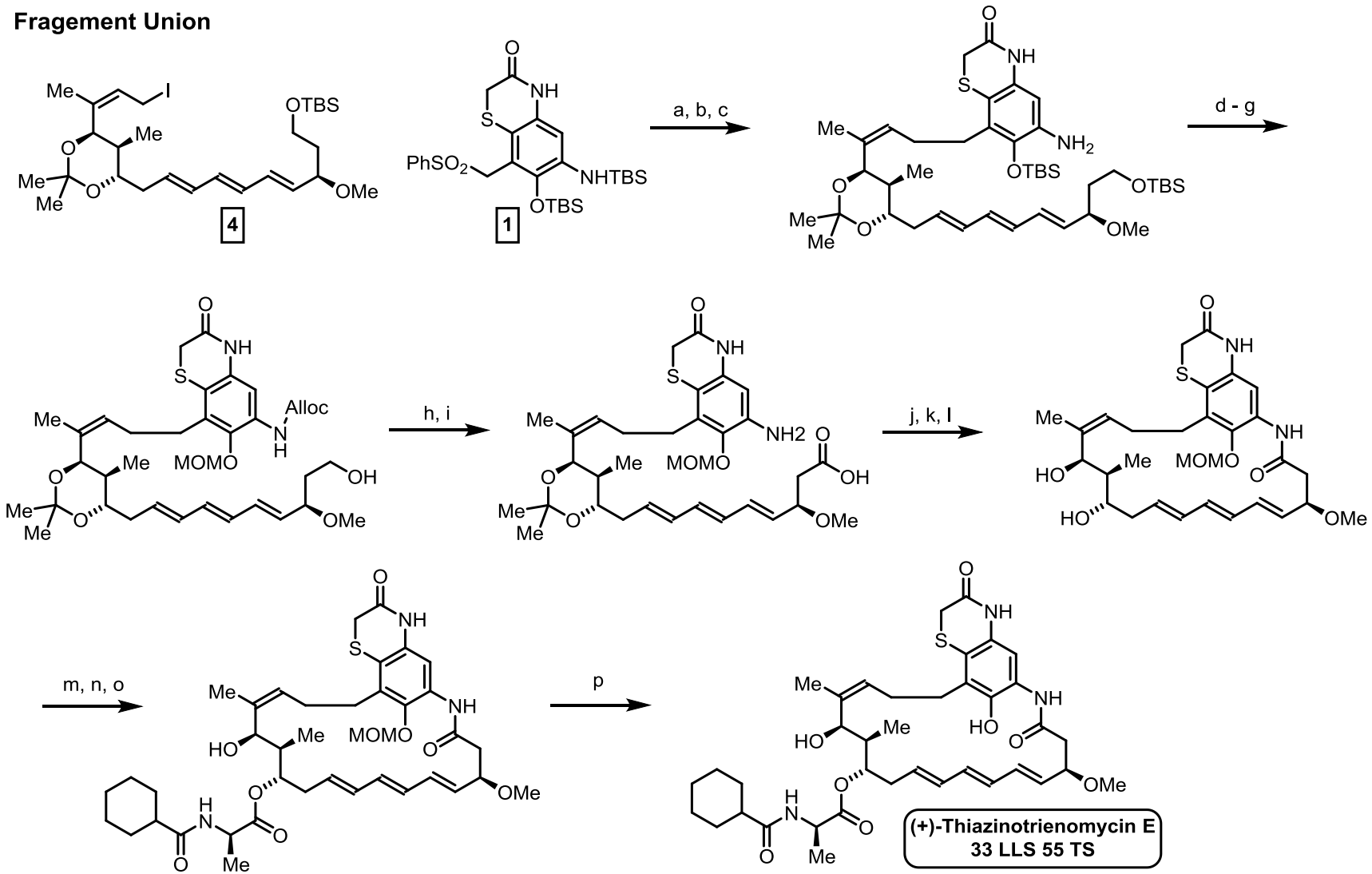
Fragement 4



Key: (a) Brown crotylation (b) TMSOTf; (b) O_3, PPh_3; (d) *t*-BuLi, **2**; (e) K_2CO_3, MeOH; (f) MnO_4; (g) $(CH_3)_4NBH(OAc)_3$; (h) $Me_2C(OMe)_2$; (i) NaOH; (j) PivCl; (k) TBAF; (l) 5-Mercapto-1-phenyltetrazole, PPh_3, DEAD; (m) H_2O_2; $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$; (n) KHMDS, **3**; (o) DIBAL-H; (p) MsCl, LiCl; (q) NaI.

B. Smith *et al. Org. Lett.* **1999**, *1*, 1491. (Cont'd)

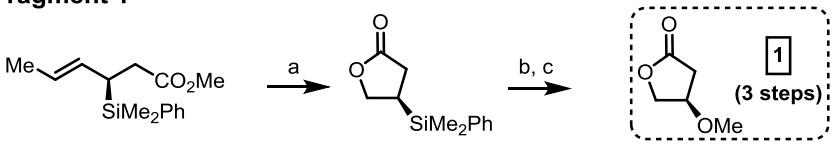
Fragement Union



Key: (a) NaHMDS; (b) Na(Hg); (c) SiO_2, $CHCl_3$; (d) AllocCl; (e) TBAF-HOAc; (f) MOMCl; (g) TBAF; (h) Py•SO_3; (i) $NaClO_2$; (j) $Pd(PPh_3)_4$, Dimedone; (k) Mukaiyama Salt, NEt_3; (l) CSA; (m) $(FMOC\text{-}D\text{-}Ala)_2O$, DMAP; (n) Et_2NH; (o) BOP, NEt_3, cyclohexanecarboxylic acid; (p) 3N HCl.

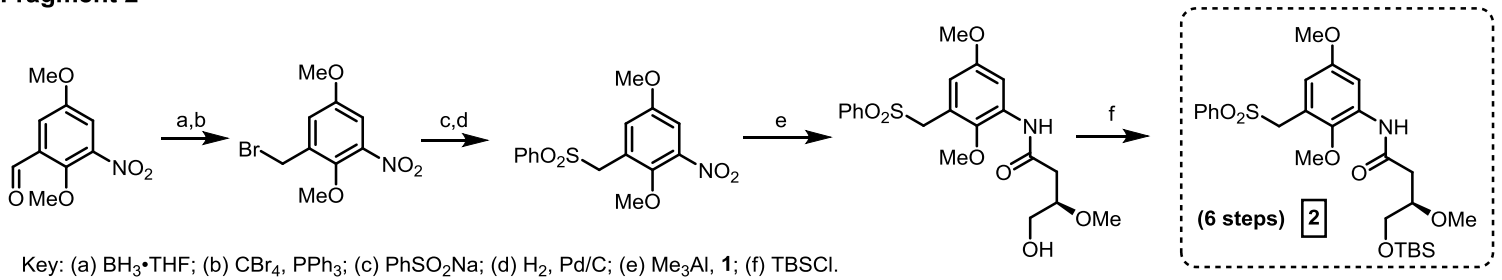
C. Panek *et al. J. Am. Chem. Soc.* **1998**, *120*, 4123.

Fragment 1



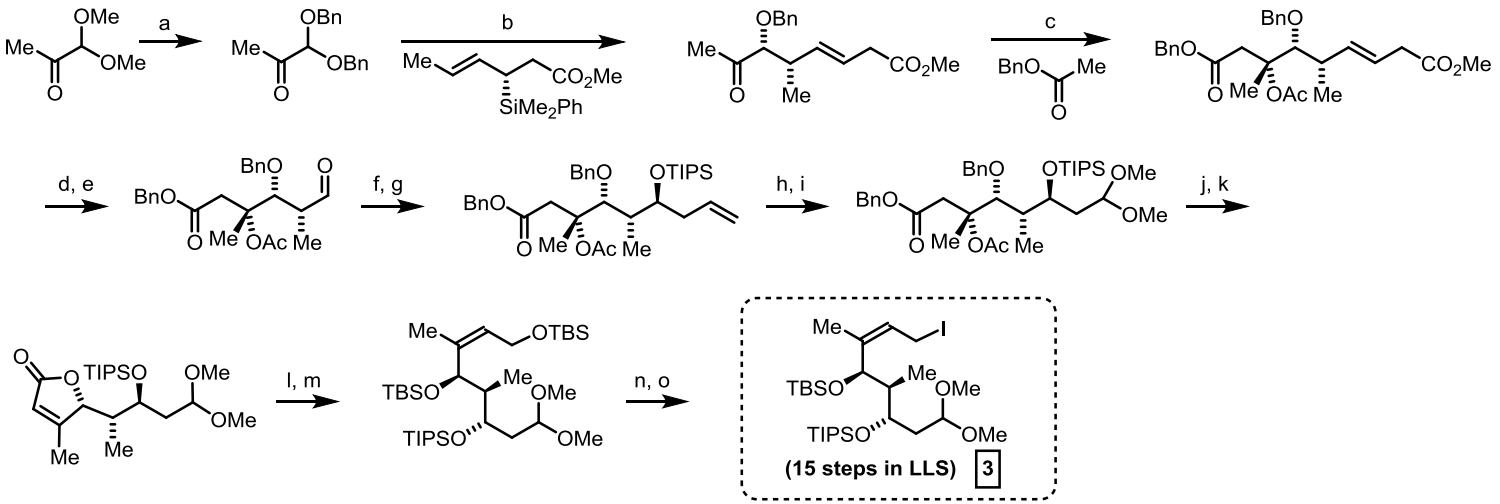
Key: (a) O_3, $NaBH_4$; (b) $Hg(OAc)_2$, CH_3CO_3H; (c) Ag_2O, MeI.

Fragment 2



Key: (a) BH_3•THF; (b) CBr_4, PPh_3; (c) $PhSO_2Na$; (d) H_2, Pd/C; (e) Me_3Al, **1**; (f) TBSCl.

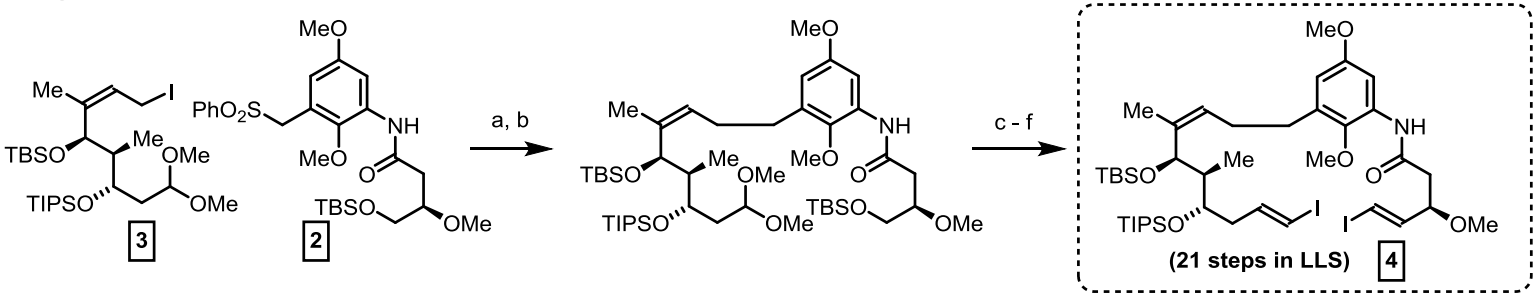
Fragment 3



Key: (a) benzyl alcohol, PTSA; (b) cat. TMSOTf; (c) LiHMDS; (d) Ac_2O, NEt_3, DMAP; (e) O_3, Me_2S; (f) $TiCl_4$, allyltrimethylsilane; (g) TIPSOTf; (h) O_3, Me_2S; (i) MeOH; (j) H_2, Pd/C; (k) DBU; (l) LiAH, TMEDA; (m) TBSOTf; (n) HF•Pyr; (o) $Me(PhO)_3PI$.

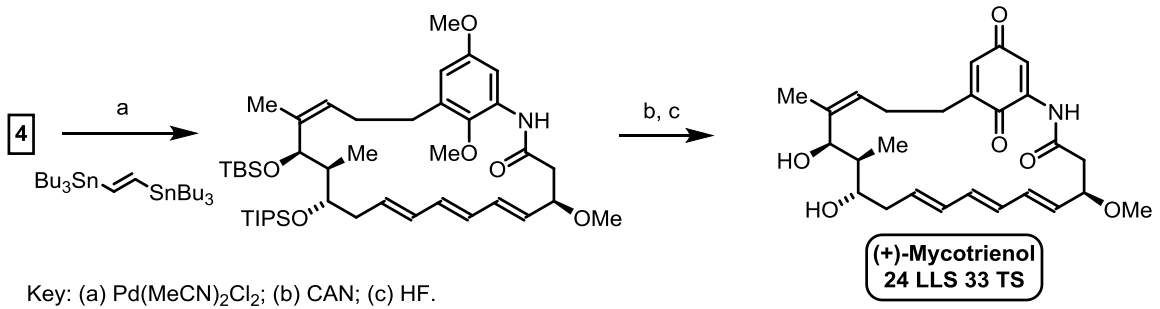
C. Panek *et al. J. Am. Chem. Soc.* **1998**, *120*, 4123. (Cont'd)

Fragement 4



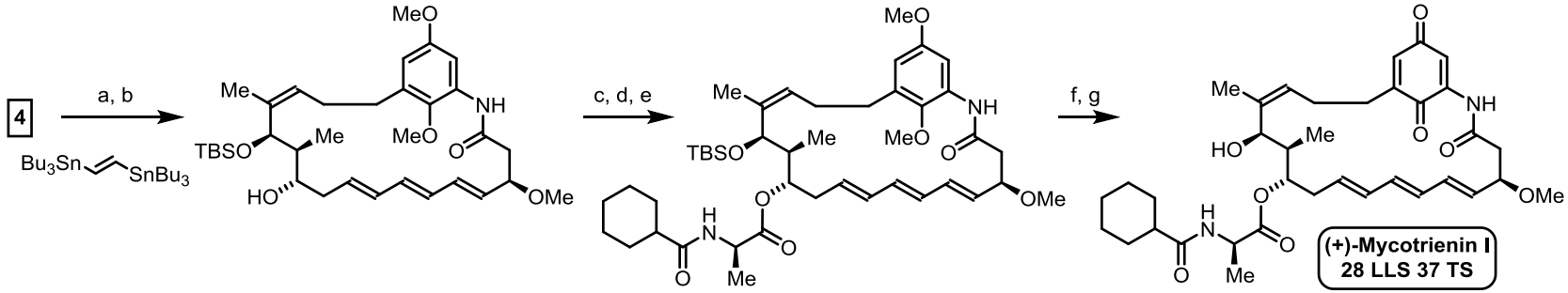
Key: (a) LiHMDS; (b) Na(Hg), Na_2HPO_4; (c) HF•Pyr; (d) Pyr•SO_3, DMSO; (e) PPTS, Acetone; (f) $CrCl_2$, CHI_3.

Mycotrienol End Game



Key: (a) $Pd(MeCN)_2Cl_2$; (b) CAN; (c) HF.

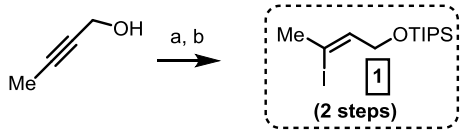
Mycotrienin I End Game



Key: (a) $Pd(MeCN)_2Cl_2$; (b) MeOH, PTSA; (c) $(FMOC\text{-}D\text{-}Ala)_2O$; (d) Et_2NH; (e) BOP, NEt_3, cyclohexanecarboxylic acid; (f) CAN; (g) HF.

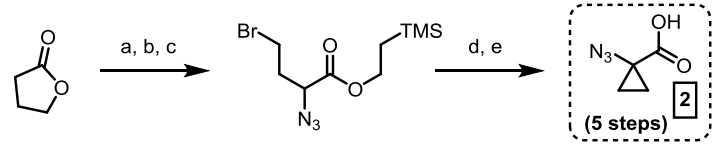
D. Hayashi *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 6657.

Fragment 1



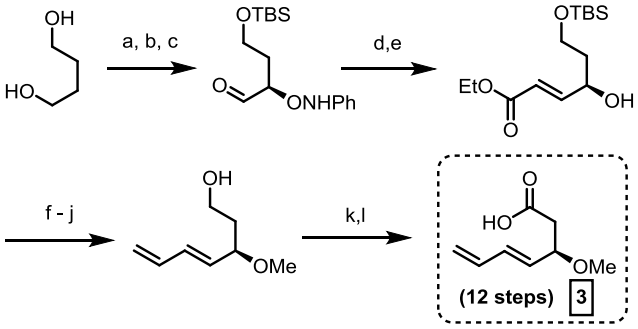
Key: (a) Red-Al, then I_2; (b) TIPSCl.

Fragment 2



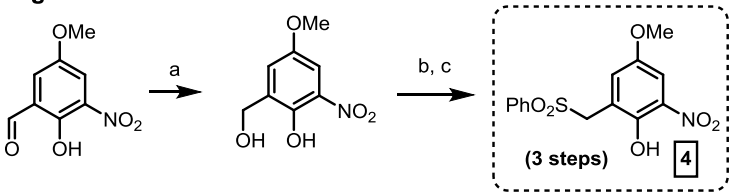
Key: (a) P, Br_2; (b) $TMSCH_2CH_2OH$; (c) NaN_3; (d) DBU; (e) TBAF.

Fragment 3

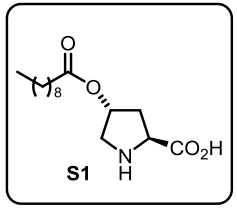


Key: (a) TBSCl; (b) $COCl_2$, DMSO, NEt_3; (c) nitrosobenzene, L-proline; d) triethyl phosphonoacetate, NaH; e) $CuSO_4$; (f) MeI, NaH; g) DIBAL-H; h) MnO_2; (i) $[Ph_3PCH_3]I$, tBuOK; (j) py(HF); (k) SO_3•pyr; (l) $NaClO_2$.

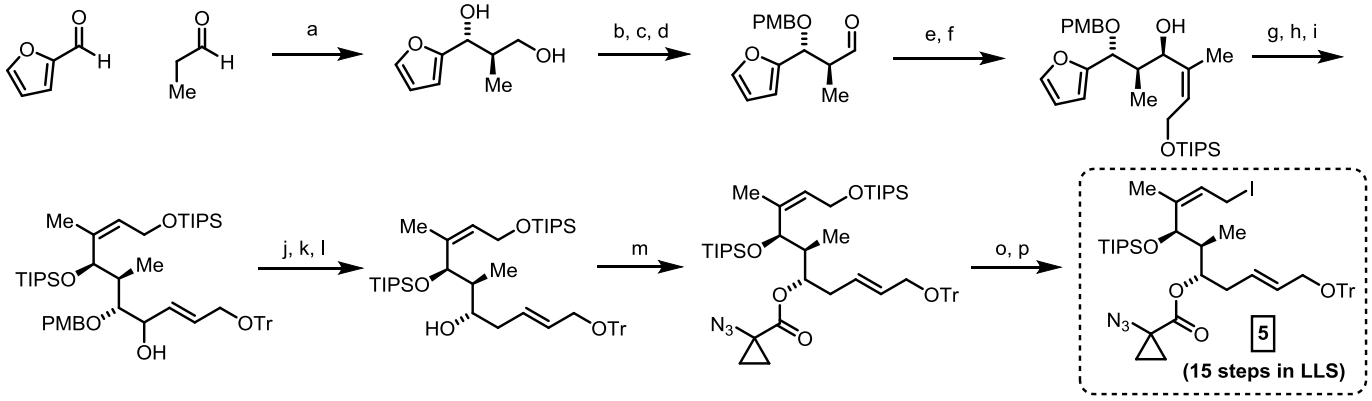
Fragment 4



Key: (a) $NaBH_4$; (b) HBr, AcOH; (c) $NaSO_2Ph$.



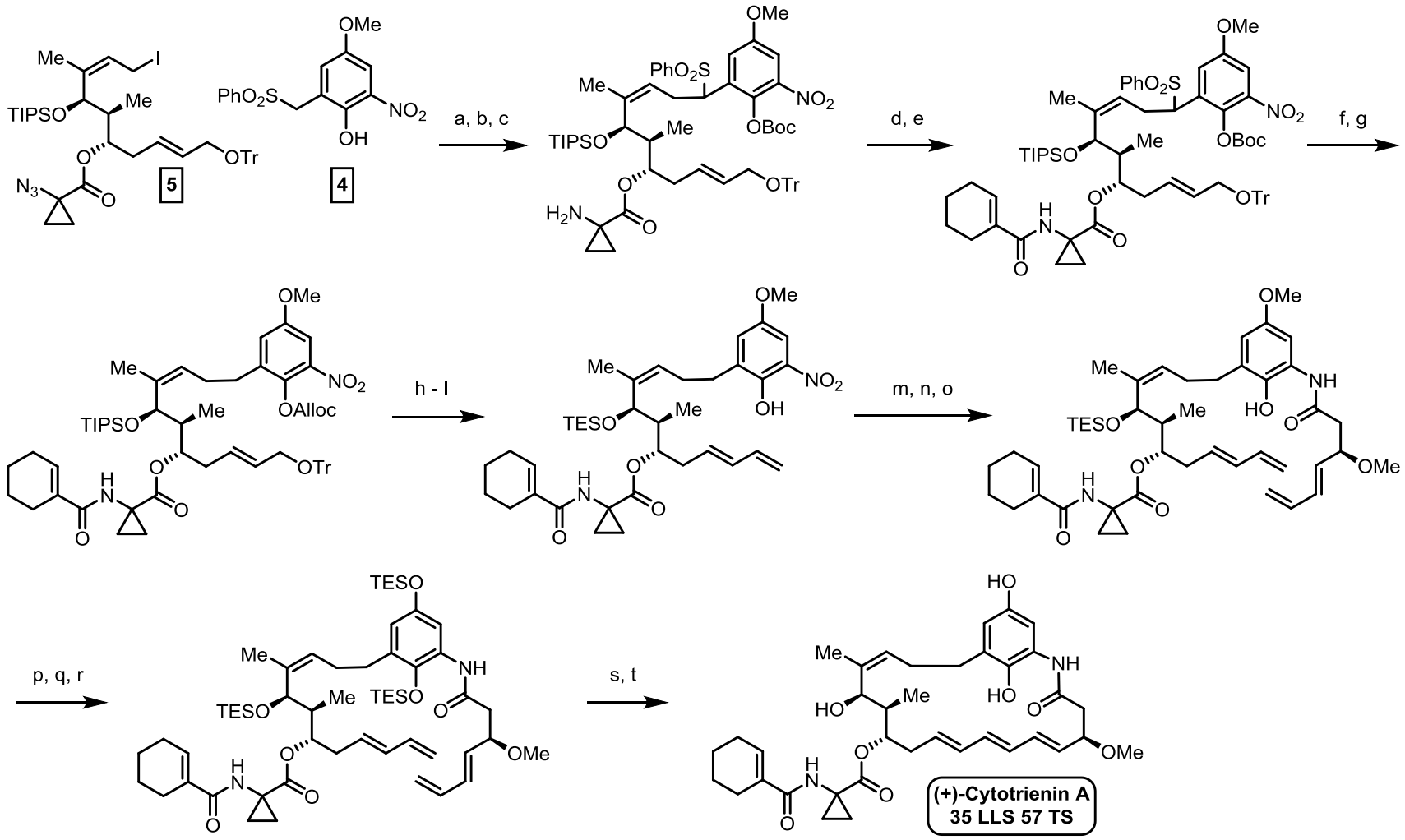
Fragment 5



Key: (a) neat **S1**, then $NaBH_4$; (b) p-MeOPhCH$(OMe)_2$, PPTS; (c) DIBAL-H; (d) SO_3•pyr; (e) **1**, tBuLi, Me_2Zn; (f) TIPSOTf; (g) O_2, Rose Bengal, Me_2S, DABCO; (h) $NaBH_4$, $CeCl_3$•$7H_2O$; (i) TrCl, Et_3N; (j) 1H-benzotriazole-1-carbaldehyde; (k) $[Pd_2(dba)_3]$•$CHCl_3$, $n$$Bu_3P$, HCO_2NH_4; (l) DDQ; (m) **2**, $COCl_2$, DMAP, Et_3N; (n) HF•Pyr; (o) I_2, Ph_3P, imidazole.

D. Hayashi *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 6657. (Cont'd)

Fragement Union

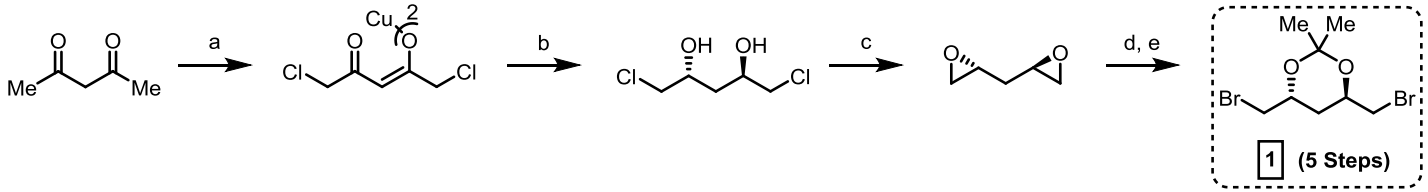


Key: (a) LiHMDS; (b) $(Boc)_2O$, DMAP; (c) 1,3-propanedithiol; (d) 1-cyclohexenecarboxylic acid, EDCI, DMAP; (e) pyrrolidine; (f) $NaBH_4$; (g) AllocCl, Et_3N; (h) $TsOH \bullet H_2O$, MeOH; (i) MnO_2; (j) $[Ph_3PCH_3]I$, tBuOK; (k) HF; (l) TESOTf, iPr_2EtN; (m) $NaBH_4$, S_8; (n) **3**, BOP-Cl, iPr_2EtN; (o) K_2CO_3, MeOH; (p) MnO_2; (q) $NaBH_4$; (r) 4-triethylsiloxy-3-penten-2-one; (s) Grubbs **I** catalyst; (t) Amberlyst 15

Graphical Summary of Previous Syntheses of Roxaticin

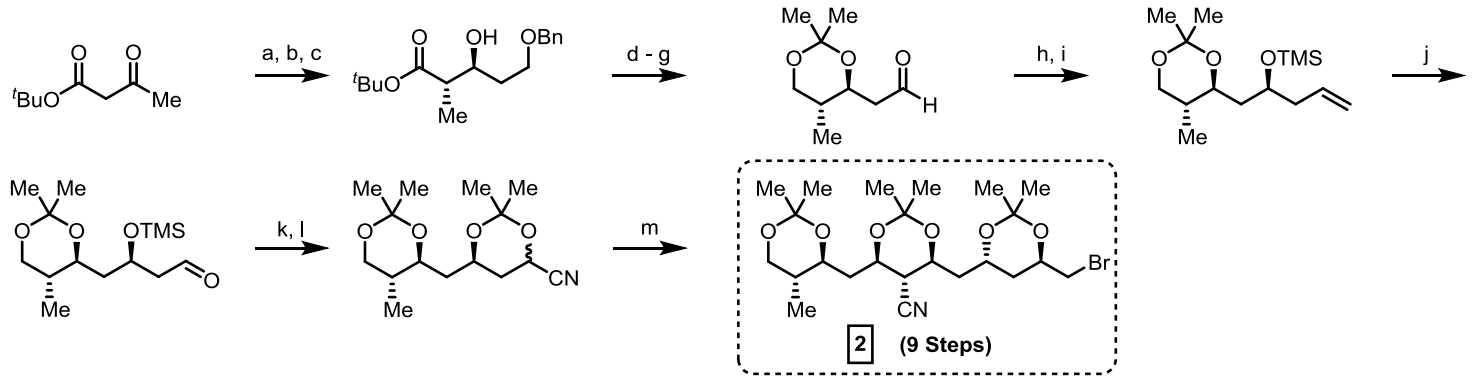
A. Rychnovsky *et al. J. Am. Chem. Soc.* **1994**, *116,* 1753.

Fragment 1



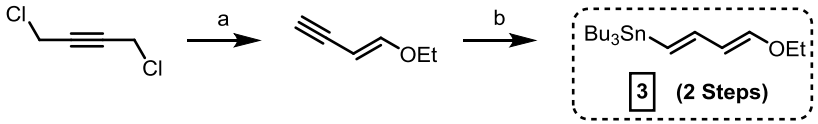
Key: (a) $AlCl_3$, $ClCH_2C(O)Cl$, 60 °C, $Cu(OAc)_2$; (b) H_3O^+, [((*S*)-BINAP)$RuCl_2$]$_2Et_3N$, H_2 1200 psi, 120 °C, MeOH, recrystallize; (c) KOH, Et_2O; (d) Li_2NiBr_4, 25 °C, THF; (e) 2,2-DMP, CSA, Acetone.

Fragment 2



Key: (a) NaH, *n*-BuLi, chloromethyl benzyl ether; (b) H_3O^+, [((*S*)-BINAP)$RuCl_2$]$_2Et_3N$, H_2 1620 psi, 45 °C, MeOH; (c) LHMDS, MeI; (d) $LiAlH_4$; (e) CSA, 2,2-DMP; (f) H_2, $Pd(OH)_2$/C; (g) Swern; (h) $Ipc_2BCH_2CH{=}CH_2$, NaOH, H_2O_2; (i) BSA, CH_3CN; (j) OsO_4, NMO, $NaIO_4$; (k) TMSCN; (l) 2,2-DMP, CSA; (m) **1**, $LiNEt_2$, THF.

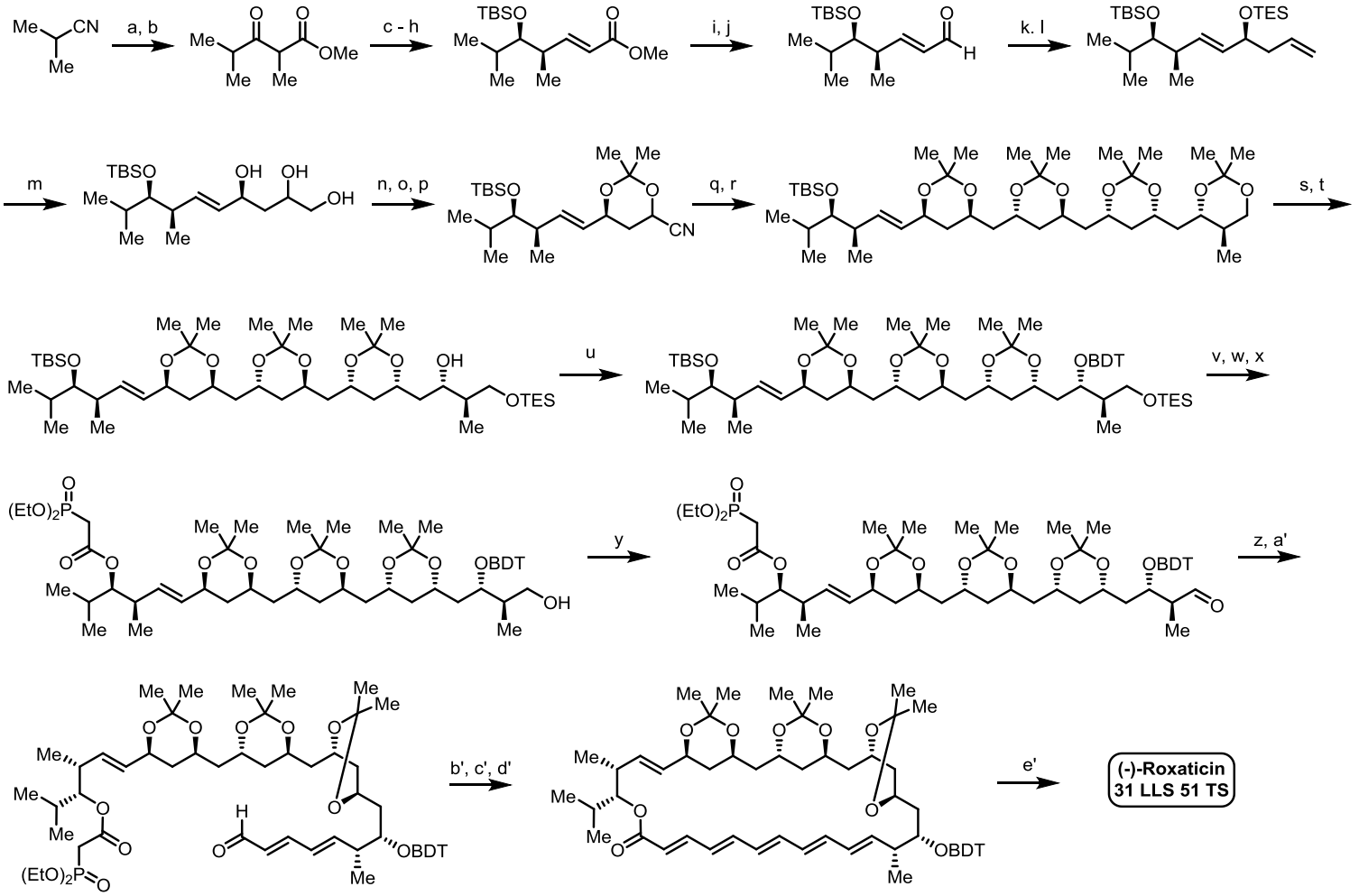
Fragment 3



Key: (a) KOH, EtOH. (b) Bu_3SnH, AIBN.

A. Rychnovsky *et al. J. Am. Chem. Soc.* **1994**, *116,* 1753. (Cont'd)

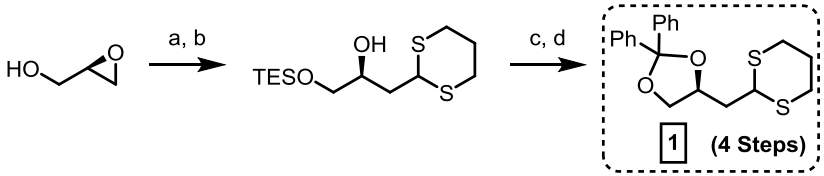
Longest Linear Sequence



Key: (a) Zn, methyl 2-bromopropionate, THF; (b) H_3O^+; (c) (R-BINAP)$RuCl_2$, H_2, MeOH; (d) LAH,(80%), recrystallization (35%); (e) TBSOTf; (f) Dowex H^+, MeOH; (g) Swern; (h) $Ph_3P{=}CHCO_2CH_3$, CH_3CN, reflux; (i) DIBAL-H; (j) TPAP, NMO; (k) $Ipc_2BCH_2CH{=}CH_2$, NaOH, H_2O_2; (l) TESOTf, 2,6-lutidine; (m) OsO_4, NMO, HOAc, THF, H_2O; (n) $NaIO_4$; (o) K_2CO_3, $(CH_3)_2C(OH)CN$; (p) 2,2-DMP, CSA; (q) **2**, $LiNEt_2$; (r) LiDBB, THF, MeOH; (s) TESOTf, *I*-Pr_2NEt; (t) OsO_4, *t*-BuOH, $CDCl_3$, pyridine; (u) 1,3-benzodithiolyl tetrafluoroborate, pyridine; (v) TBAF, THF; (w) $(EtO)_2P(O)CH_2CO_2H$, BOP, DMAP; (x) MeOH, NH_3; (y) Dess-Martin; (z) **3**, *n*-BuLi, $MgBr_2$, THF, -78 °C; (a') MsCl, Et_3N; (b') **3**, *n*-BuLi, $MgBr_2$, THF, -78 °C; (c') MsCl, Et_3N; (d') LiCl, DBU; (e') Dowex H^+, MeOH.

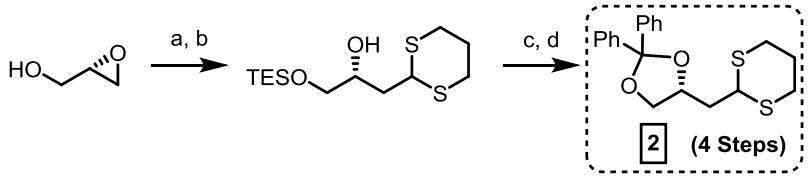
B. Mori *et al. Tetrahedron* **1995**, *51*, 5299; *Tetrahedron* **1995**, *51*, 5315.

Fragment 1



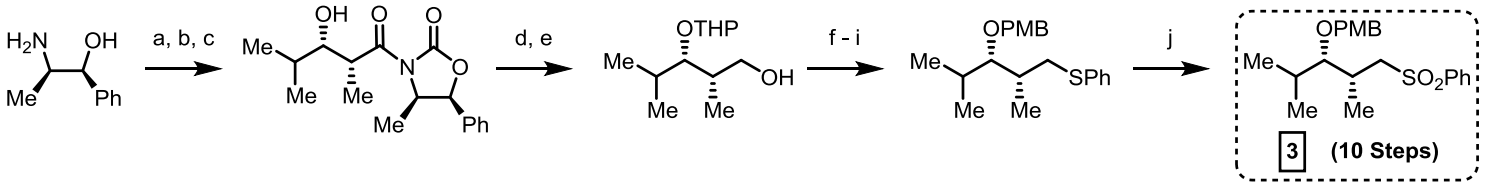
Key: (a) TESCl, Et_3N; (b) *n*-BuLi, 1,3-dithiane; (c) TBAF; (d) $Ph_2C(OMe)_2$.

Fragment 2



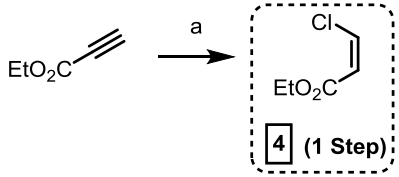
Key: (a) TESCl, Et_3N; (b) *n*-BuLi, 1,3-dithiane; (c) TBAF; (d) $Ph_2C(OMe)_2$.

Fragment 3



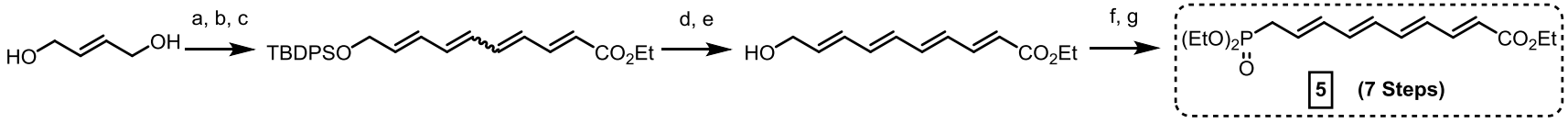
Key: (a) diphenyl carbonate, K_2CO_3; (b) *n*-BuLi, $CH_3CH_2C(O)Cl$; (c) Bu_2BOTf, Et_3N, Me_2CHCHO; (d) DHP, PPTS; (e) $LiAlH_4$; (f) MeOH, H^+; (g) TsCl, pyridine; (h) PhSNa; (i) PMBCl, KH; (j) *m*-CPBA.

Fragment 4



Key: (a) LiCl, HOAc, MeCN.

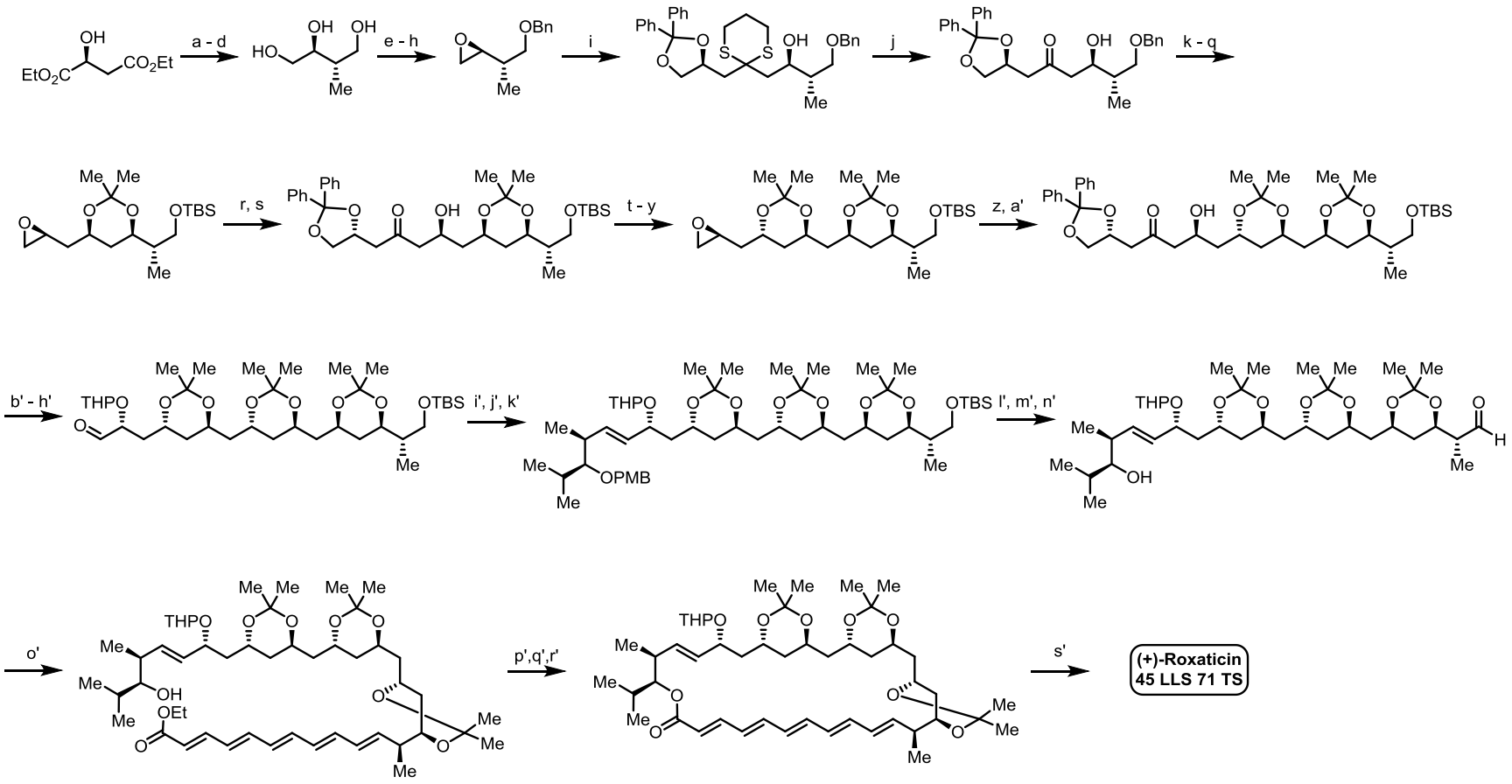
Fragment 5



Key: (a) TBDMPSCl, imidazole; (b) MnO_2; (c) allyl triphenylphosphonium bromide, *n*-BuLi, **4**, *t*-BuOK; (d) TBAF; (e) hv, I_2; (f) PBr_3; (g) $(OEt)_3P$.

B. Mori *et al. Tetrahedron* **1995**, *51*, 5299; *Tetrahedron* **1995**, *51*, 5315. (Cont'd)

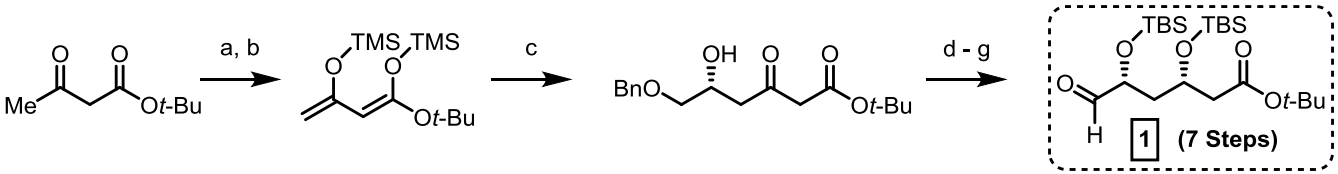
Longest Linear Sequence



Key: (a) LDA, MeI; (b) DHP, PPTS; (c) $LiAlH_4$; (d) MeOH, H^+; (e) $PhCH(OMe)_2$, TsOH; (f) DIBAL; (g) TsCl, pyridin; (h) *t*-BuOK, Et_2O-MeOH; (i) **1**, *n*-BuLi, THF; (j) $Hg(ClO_4)_2$; (k) $NaBH_4$, Et_2BOMe; (l) $Me_2C(OMe)_2$; (m) H_2, $Pd(OH)_2$; (n) TBSCl, imidazole; (o) Li, NH_3; (p) TsCl; (q) *t*-BuOK, Et_2O-MeOH; (r) **2**, *n*-BuLi, THF; (s) MeI, $CaCO_3$; (t) $Me_4NBH(OAc)_3$; (u) $Me_2C(OMe)_2$, PPTS; (v) Li, NH_3; (w) PivCl; (x) MsCl; (y) *t*-BuOK, Et_2O-MeOH; (z) **2**, *n*-BuLi; (a') MeI, $CaCO_3$; (b') $Me_4NBH(OAc)_3$; (c') $Me_2C(OMe)_2$, PPTS; (d') Li, NH_3; (e') PivCl, pyridine; (f') DHP, PPTS; (g') $LiAlH_4$; (h') SO_3pyr; (i') **3**, n-BuLi; (j') Ac_2O, pyridine; (k') Na-Hg; (l') TBAF; (m') Dess-Martin; (n') DDQ; (o') **5**, $LiN(TMS)_2$; (p') LiOH, THF, H_2O; (q') 2,4,6-trichlorobenzoyl chloride, Et_3N; (r') DMAP, toluene; (s') Dowex 50Wx8, MeOH.

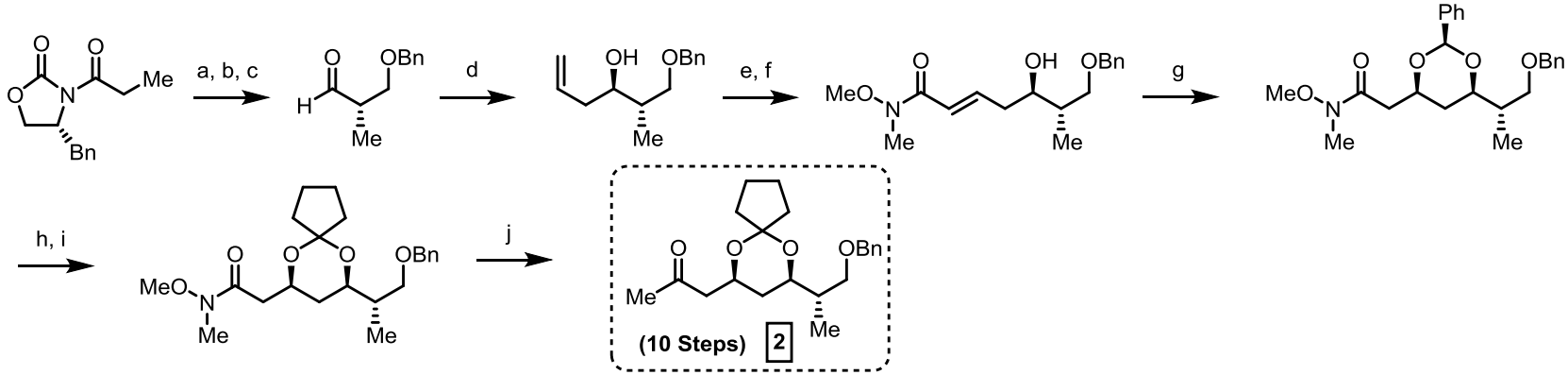
C. Evans *et al. J. Am. Chem. Soc.* **2003**, *125,* 10899.

Fragment 1



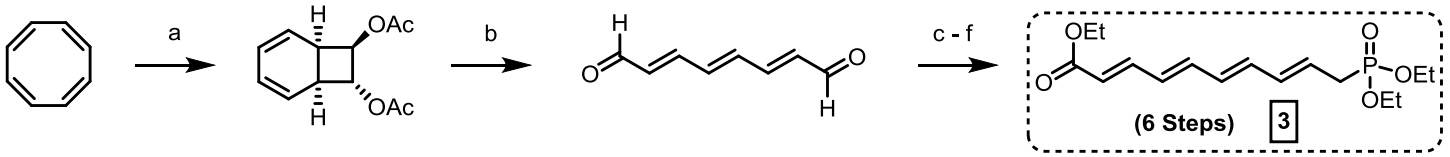
Key: (a) Et_3N, TMSCl, hexanes; (b) LDA, TMSCl, THF; (c) $[Cu((S,S)\text{-Ph-pybox})](SbF_6)_2$ (2 mol%), benzyloxyacetaldehyde, 99%ee; (d) Et_2BOMe, $NaBH_4$, MeOH, THF, -78 ^oC; (e) TBSCl, imidazole, CH_2Cl_2; (f) 2000 psi H_2, 10% Pd/C, EtOAc; (g) Dess-Martin, CH_2Cl_2.

Fragment 2



Key: (a) $TiCl_4$, NEt_3, $BnOCH_2Cl$, 0 ^oC, CH_2Cl_2; (b) $LiBH_4$, 0 ^oC, THF; (c) SO_3·pyr, DMSO, -10 ^oC, CH_2Cl_2; (d) allyltributyltin, $SnCl_4$, -78 ^oC, CH_2Cl_2; (e) TESCl, imidazole, CH_2Cl_2; (f) O_3, Ph_3P, N-MeO-N-Me(triphenylphosphoranylidene)-acetamide, TsOH, CH_2Cl_2; (g) cat. KHMDS, PhCHO, 0 ^oC, THF; (h) $Zn(OTf)_2$, EtSH, $NaHCO_3$, CH_2Cl_2; (i) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (j) MeLi, -78 ^oC, THF.

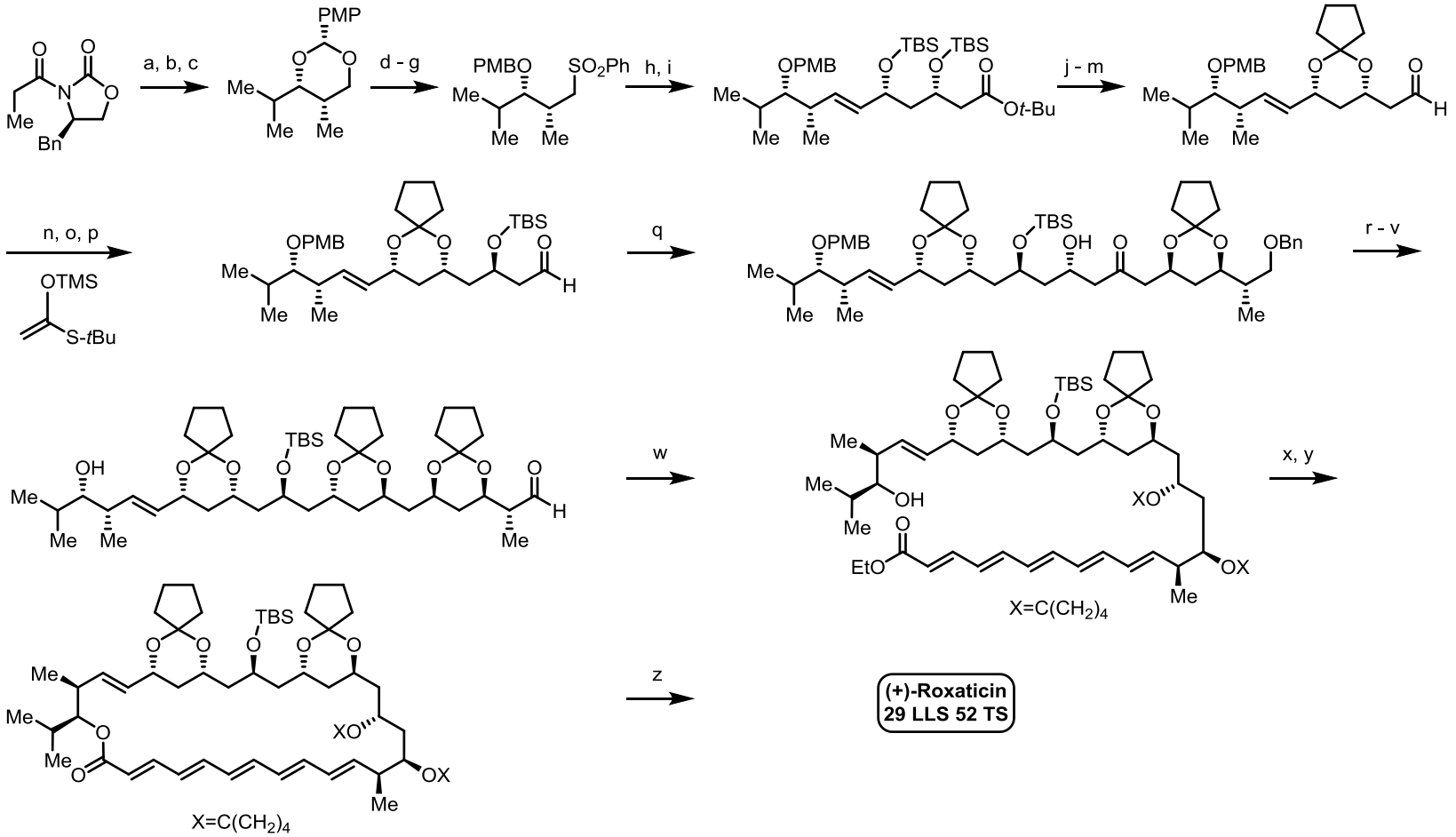
Fragment 3



Key: (a) $Hg(OAc)_2$, AcOH; (b) $LiAlH_4$, THF, 0 ^oC to rt, then O_2; (c) triethylphosphonoacetate, NaH, -78 ^oC to rt, THF; (d) $NaBH_4$, EtOH; (e) $SOBr_2$, 2,6-di-*tert*-butylpyridine, -20 ^oC, THF; (f) $(EtO)_3P$, toluene, 110 ^{o} C.

C. Evans *et al. J. Am. Chem. Soc.* **2003**, *125,* 10899. (Cont'd)

Longest Linear Sequence

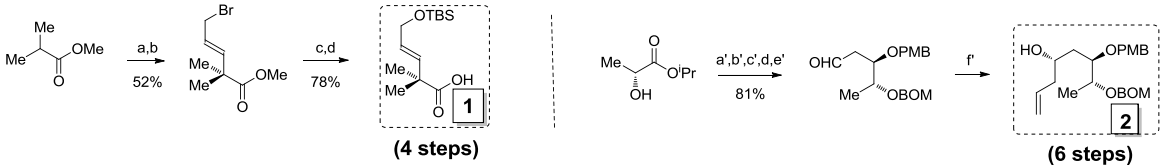


Key: (a) Bu_2BOTf, NEt_3, *i*-PrCHO, CH_2Cl_2, -78 °C, CH_2Cl_2; (b) $LiBH_4$, MeOH, THF, -78 °C; (c) cat. TsOH, *p*-MeOPhCH(OMe)$_2$, CH_2Cl_2; (d) DIBAl-H, CH_2Cl_2, -78 °C; (e) MsCl, NEt_3, CH_2Cl_2; (f) PhSLi, THF, -78 °C to 23 °C; (g) *m*-CPBA, CH_2Cl_2 $Zn(OTf)_2$; (h) *n*-BuLi, BF_3OEt_2, **1**, -78 °C, THF; (i) Na/Hg, Na_2HPO_4, -40 °C to 23 °C, MeOH; (j) HFpyr, THF; (k) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (l) $LiAlH_4$, THF; (m) Dess-Martin, CH_2Cl_2; (n) BF_3OEt_2, -90 °C, toluene; (o) TBSOTf, 2,6-lutidine, -78 °C, CH_2Cl_2; (p) DIBAl-H, -78 °C, toluene; (q) BuBOTf, NEt_3, -78 °C to 100 °C, **2**, Et_2O; (r) $Me_4NBH(OAc)_3$, -25 °C, CH_3CN, AcOH; (s) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (t) LiDBB, -78 °C, THF; (u) Dess-Martin, CH_2Cl_2; (v) DDQ, H_2O, CH_2Cl_2; (w) **3**, LiHMDS, -78 °C, THF; (x) LiOH, THF, H_2O, MeOH; (y) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, 23 °C, toluene; (z) PPTS, MeOH.

Graphical Summary of Previous Syntheses of Bryostatins

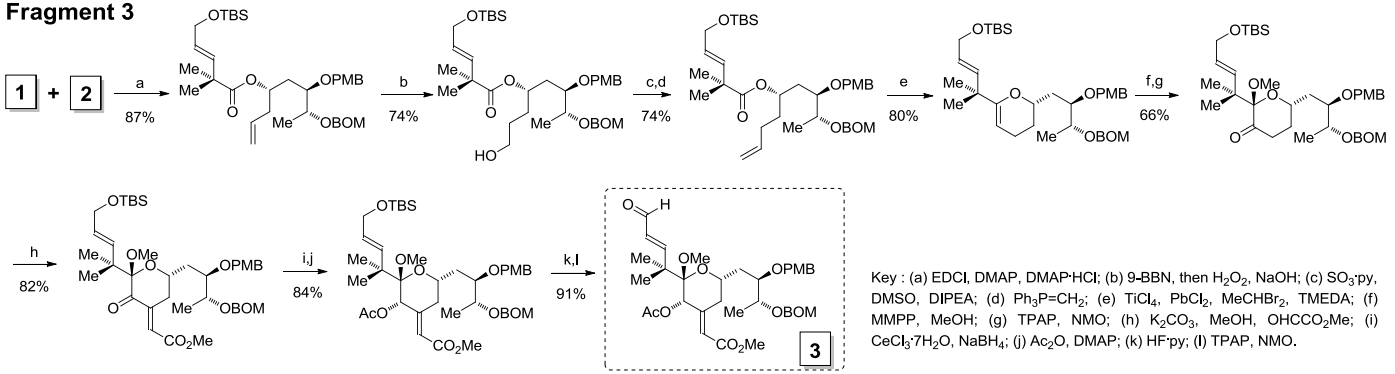
A. Keck *et al. J. Am. Chem. Soc.* **2011**, *133*, 744.

Fragments 1,2



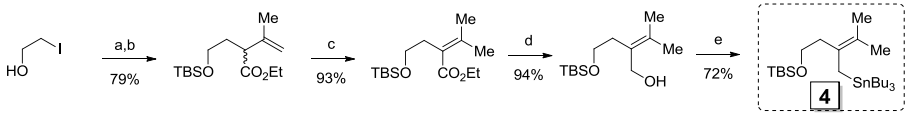
Key : (a) LDA, allylbromide; (b) NBS, benzoyl peroxide; (c) 2,6-di-^{t}Bu-4-Me-pyridine, AgOTf, TBSOH; (d) NaOH, EtOH, H_2O.
(a') BOMCl; (b') DIBAL; (c') allyl-$SnBu_3$,$MgBr{\cdot}OEt_2$; (d') PMBBr, KH; (e') O_3, $NaHCO_3$;(f') allyl-$SnBu_3$,$MgBr_2{\cdot}OEt_2$

Fragment 3



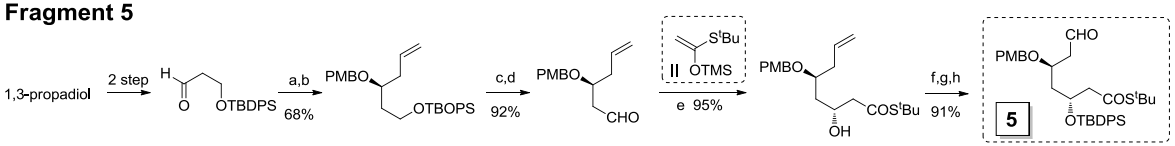
Key : (a) EDCI, DMAP, DMAP·HCl; (b) 9-BBN, then H_2O_2, NaOH; (c) SO_3·py, DMSO, DIPEA; (d) $Ph_3P{=}CH_2$; (e) $TiCl_4$, $PbCl_2$, $MeCHBr_2$, TMEDA; (f) MMPP, MeOH; (g) TPAP, NMO; (h) K_2CO_3, MeOH, $OHCCO_2Me$; (i) $CeCl_3{\cdot}7H_2O$, $NaBH_4$; (j) Ac_2O, DMAP; (k) HF·py; (l) TPAP, NMO.

Fragment 4



Key : (a) TBSCl, Imid. (b) ethyl 2,2-dimethylacrylate, LDA, -78 °C; (c) t-BuOK; (d) DIBAL;
(e) n-BuLi, -78 °C; MsCl, -78 °C; Bu_3SnLi, -78 °C to rt.

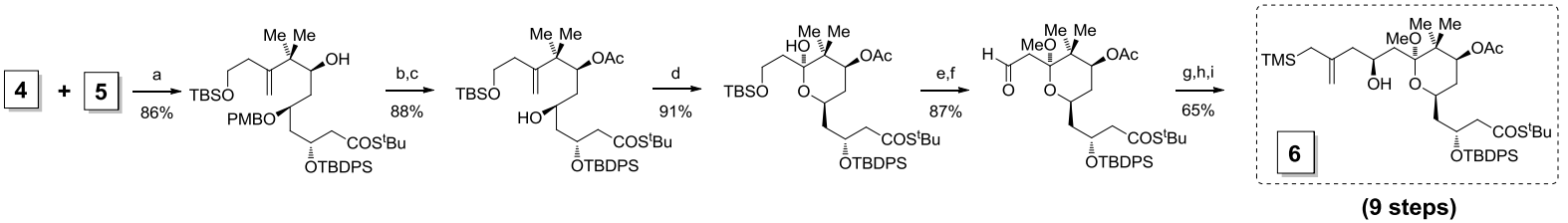
Fragment 5



Key : (a) (*S*)-(-)-1,1'-bi-2-napthol, $Ti(Oi\text{-}Pr)_4$, 4 A MS, -20 °C; (b) $PMBOC(NH)CCl_3$, CSA; (c) TBAF; (d) SO_3·py, DIPEA, DMSO, -5 °C; (e) $TiCl_2(O\textit{i}\text{-}Pr)_2$; (f) TBDPSCl, imid.;
(g) OsO_4, NMO, t-BuOH/THF/H_2O; (h) $Pb(OAc)_4$.

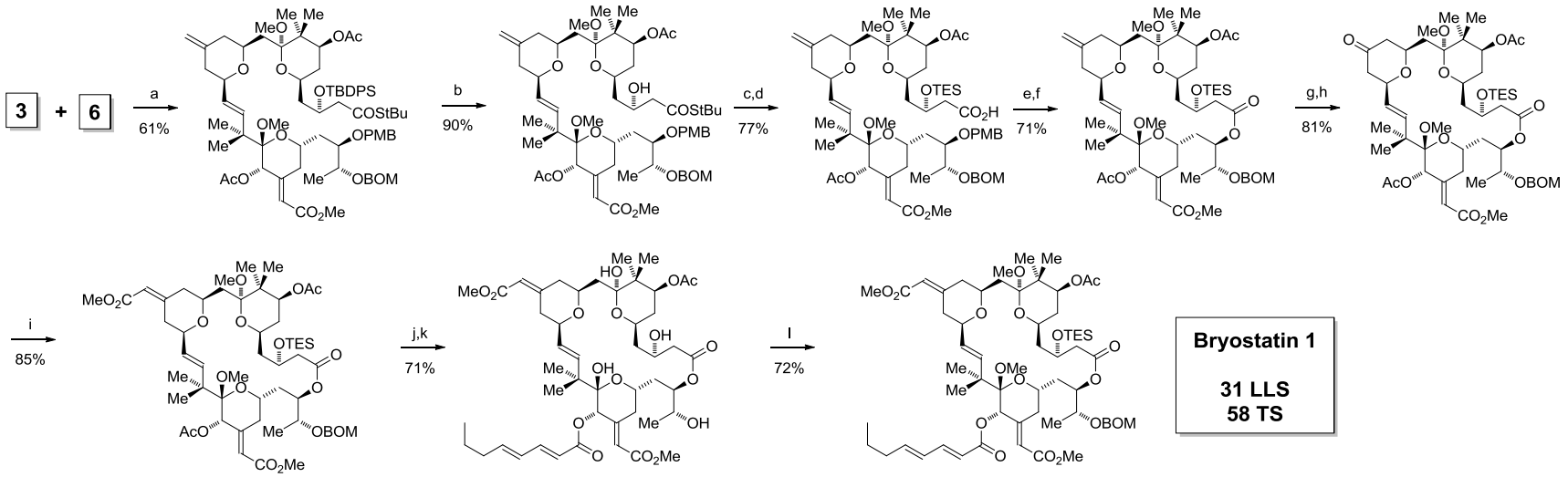
A. Keck *et al. J. Am. Chem. Soc.* **2011**, *133,* 744. (Cont'd)

Fragment 6



Key : (a) Me_2AlCl, -78 °C; (b) Ac_2O, DMAP, Et_3N; (c) DDQ; (d) O_3, -78 °C; DMS; (e) CSA; (f) SO_3·py, DIPEA, DMSO, -5 °C; (g) trimethyl(2-tributylstannylmethyl)allylsilane, reflux; (h) SO_3.py, DIPEA, DMSO, -15 °C; (i) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, -42 °C.

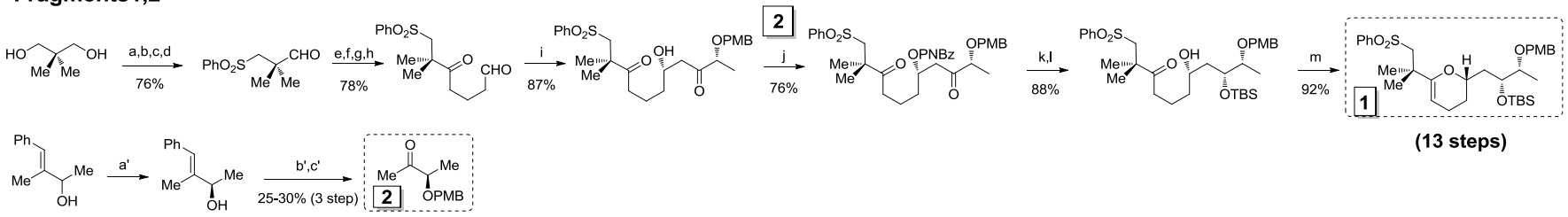
End Game



Key : (a) TMSOTf, Et_2O, -78 °C; (b) HF·py; (c) LiOH, H_2O_2, THF/H_2O; (d) TESCl, DMAP; (e) DDQ; (f) 2,4,6,-Cl_3PhCOCl, TEA then DMAP; (g) AD mix-α; (h) $NaIO_4$; (i) [(*R*)-BINOL]P(O)CH_2CO_2Me, NaHMDS, -78 °C to 0 °C; (j) K_2CO_3,MeOH; (k) $(C_8H_{11}O)_2O$, py, DMAP; (l) $LiBF_4$.

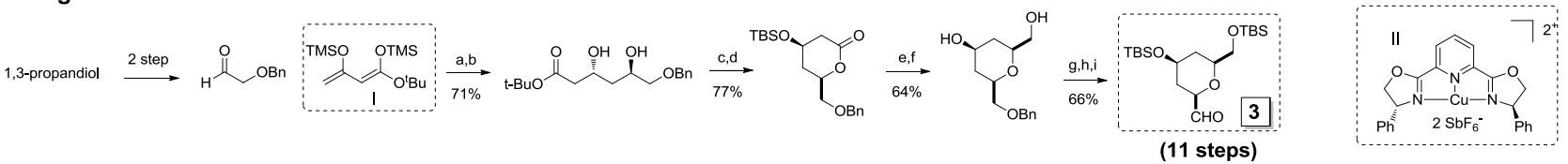
B. Evans *et al. Angew. Chem. Int. Ed.* **1998**, *37*, 2354; *J. Am. Chem. Soc.* **1999**, *121,* 7540.

Fragments1,2



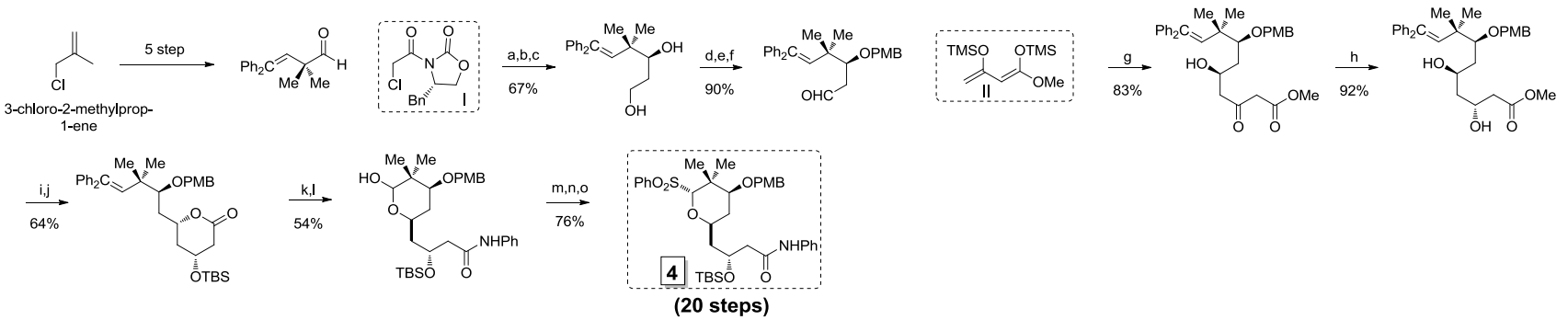
Key: (a) TsCl, py; (b) PhSH, NaH, 80 °C; (c) m-CPBA; (d) $(COCl)_2$, DMSO, TEA, -78 °C - 0 °C; (e) $BrMg(CH_2)_3CHCH_2$; (f) $(COCl)_2$, DMSO, TEA, -78 °C- -50 °C; (g) $K_2OsO_4(OH_2)_2$, quinuclidine, $K_3Fe(CN)_6$, K_2CO_3; (h) $NaIO_4$, $NaHCO_3$; (i) **2**, (-)-DIPCl, TEA, -78; then aldehyde, -70 °C; (j) SmI_2, p-NO_2PhCHO, 0 °C; (k) TBSOTf,2,6-lutidine, -15; (l) LiOH, 2:2:1 THF/MeOH/H_2O; (m) CSA, PhH, 80 °C.
(a') L-(+)-DIPT, $Ti(Oi\text{-}Pr)_4$, t-BuO_2H, -20 °C; (b') NaH, PMBBr, catalytic n-Bu_4NI; (c') O_3, 78 °C, then Me_2S.

Fragment 3



Key : (a) **I, II**, -90 °C; (b) $Me_4NHB(OAc)_3$, AcOH/MeCN, -35 °C; (c) F_3CCO_2H; (d) TESCl, imid.; (e) $PMBOCH_2Li$, - 78 °C- -50 °C;(f) $BF_3.OEt_2$, Et_3SiH, -20 °C; (g) TBSCl, imd., DMAP; (h) H_2, Pd/C, AcOH, EtOAc; (i) $(COCl)_2$, DMSO, TEA, -78 °C- -50 °C.

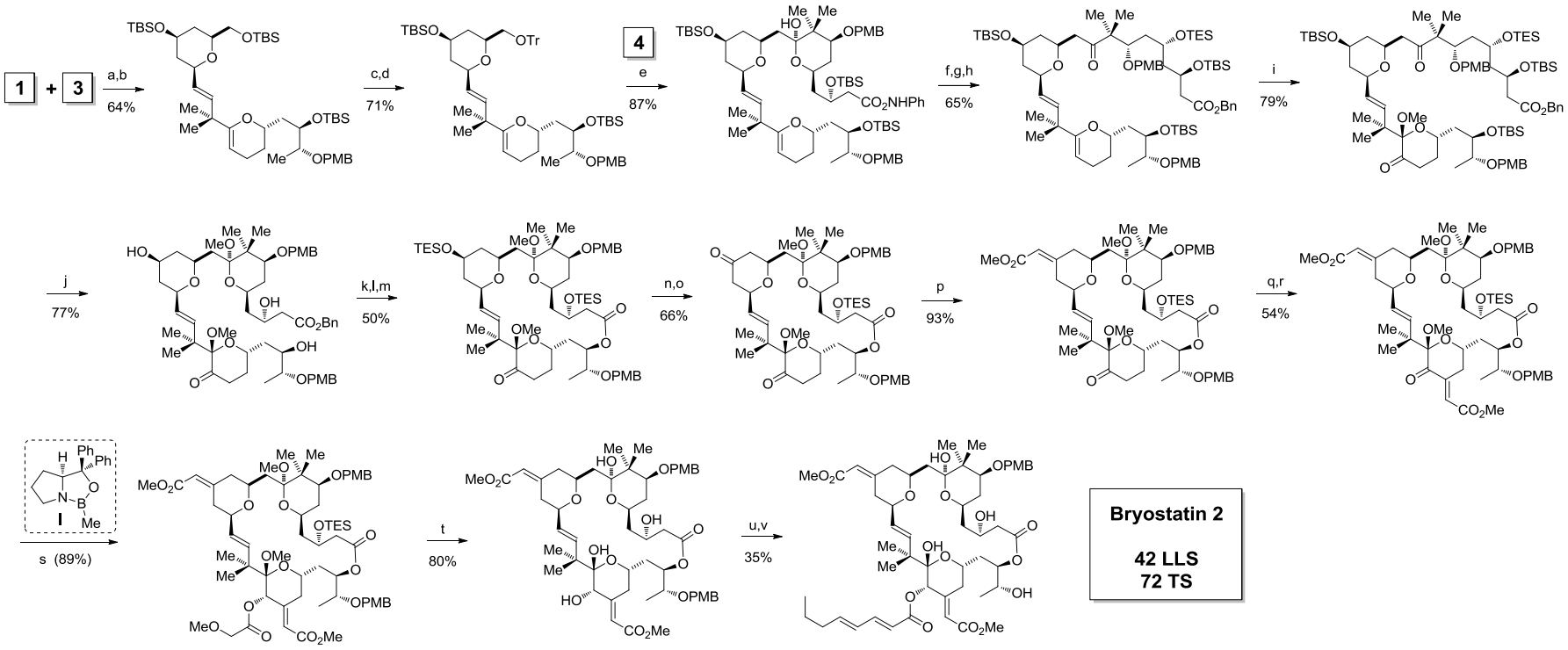
Fragment 4



Key: (a) **I**, Bu_2BOTf, i-Pr_2NEt, then aldehyde, -78 °C - 0 °C; (b) Zn, 2:1 THF/AcOH; (c) $LiBH_4$, MeOH, 0 °C; (d) $PMPCH(OME)_2$, PPTS, (e) DIBAl-H, 0 °C; (f) $(COCl)_2$, DMSO, NEt_3, -78 °C; (g) $TiCl_2(Oi\text{-}Pr)_2$, -78 °C, then **II**, 78 °C; (h) $Me_4NHB(OAc)_3$, AcOH/MeCN, -35 °C; (i) PPTS, PhH, 80 °C; (j) TBSOTf, 2,6-lutidine, -10 °C; (k) Me_3Al, $HCl.H_2NPh$; (l) O_3, -78 °C, then Me_2S; (m) Ac_2O, py; (n) PhSTMS, ZnI_2, n-Bu_4NI; (o) m-CPBA, $NaHCO_3$, EtOAc..

B. Evans *et al. Angew. Chem. Int. Ed.* **1998**, *37*, 2354; *J. Am. Chem. Soc.* **1999**, *121,* 7540. (Cont'd)

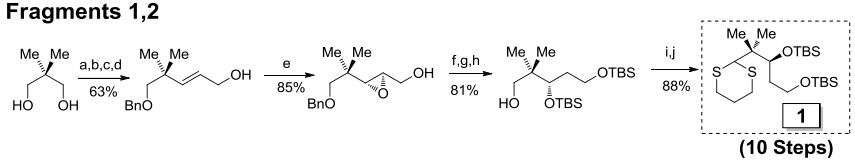
End Game



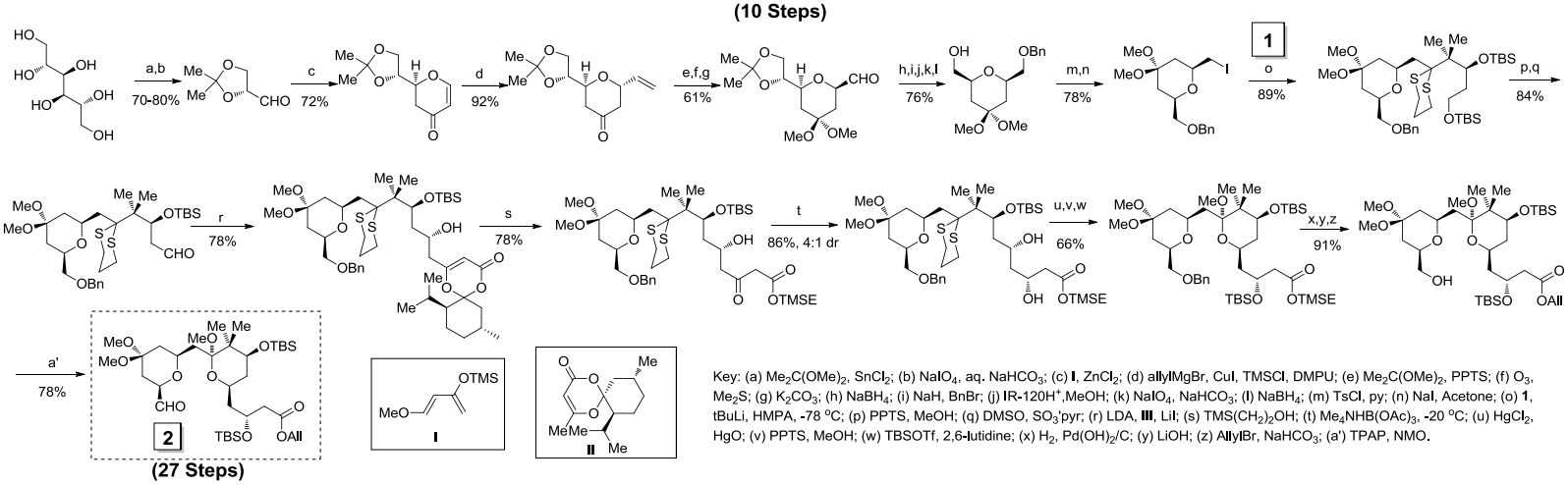
Key : (a) n-BuLi, THF, -78 °C then **3**, -78°C - -50°C; Ac_2O, DMAP; (b) Mg, $HgCl_2$, EtOH; (c) TBAF, -15 °C; (d) Tf_2O, 2,6-lutidine, -10 °C; (e) **4**, n-BuLi, -78 °C, then HMPA, then **triflate**, -78 °C; (f) TESCl, imid.; (g) Boc_2O, DMAP; (h) BnOLi, -30 °C; (i) (i) m-CPBA, MeOH, -20 °C, (ii) $ClCH_2CO_2H$, MeOH, 0 °C, (iii) Dess-Martin periodinane, py; (j) HF.pyr; (k) TESCl, DMAP, 10 °C; (l) 1,4-cyclohexadiene, 10% Pd/C, EtOAc; (m) 2,4,6 -trichlorobenzoyl chloride, DIPEA, then DMAP; (n) PPTS, 2:1 MeOH/$(MeO)_3CH$, -30 °C; (o) Dess-Martin periodinane, pyr; (p) [(R)-BINOL]$POCH_2CO_2Me$, NaHMDS, -78 °C, then ketone, -15 °C; (q) KHMDS, -78 °C, then $OHCCO_2Me$, -78 °C; (r) $Et_3NSO_2NCO_2Me$; (s) **I**, BH_3·SMe, then MeOH, then MAc_2O, py, DMAP; (t) (i)PPTS, 3:1 THF/H_2O, (ii) Na_2CO_3, MeOH, (iii) pTsOH; (u) (*E,E*)-2,4-octadienoic acid, DIC, DMAP; (v) DDQ.

C. Yamamura *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2290.

Fragments 1,2

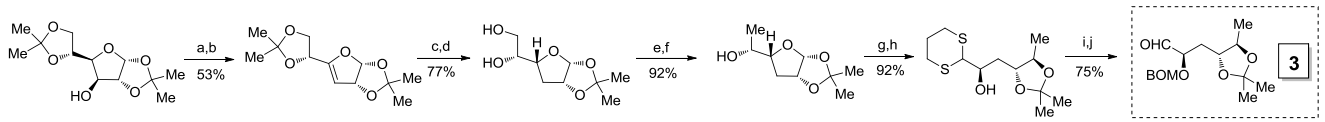


Key: (a) BnCl, NaH; (b) $(COCl)_2$, DMSO, Et_3N; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (d) $LiAlH_4$; (e) (-)-DET, $Ti(OiPr)_4$, TBHP; (f) RedAl-H; (g) TBSCl, imidazole; (h) H_2, Pd-black, EtOH; (i) $(COCl)_2$, DMSO, Et_3N; (j) Propane-1,3-dithiol, $MgBr_2.OEt_2$.

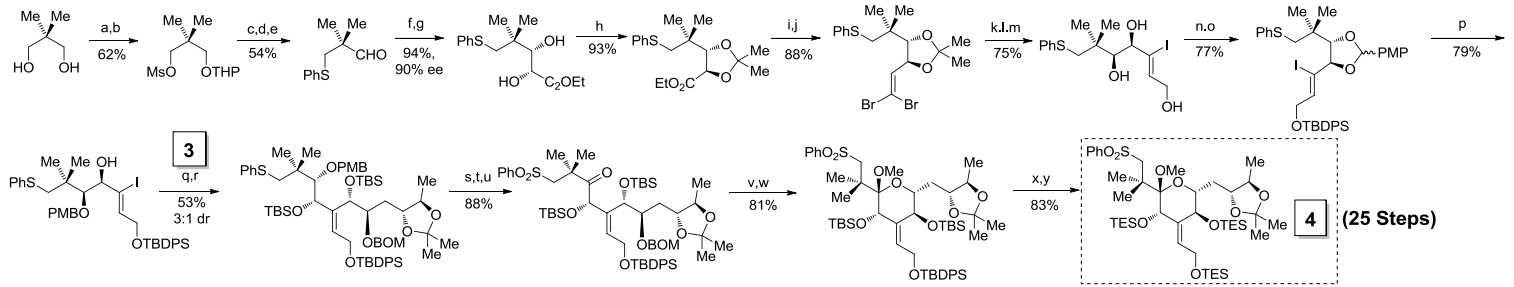


Key: (a) $Me_2C(OMe)_2$, $SnCl_2$; (b) $NaIO_4$, aq. $NaHCO_3$; (c) I, $ZnCl_2$; (d) allylMgBr, CuI, TMSCl, DMPU; (e) $Me_2C(OMe)_2$, PPTS; (f) O_3, Me_2S; (g) K_2CO_3; (h) $NaBH_4$; (i) NaH, BnBr; (j) IR-120H$^+$,MeOH; (k) $NaIO_4$, $NaHCO_3$; (l) $NaBH_4$; (m) TsCl, py; (n) NaI, Acetone; (o) 1, tBuLi, HMPA, -78 °C; (p) PPTS, MeOH; (q) DMSO, SO_3'pyr; (r) LDA, III, LiI; (s) $TMS(CH_2)_2OH$; (t) $Me_4NHB(OAc)_3$, -20 °C; (u) $HgCl_2$, HgO; (v) PPTS, MeOH; (w) TBSOTf, 2,6-lutidine; (x) H_2, $Pd(OH)_2$/C; (y) LiOH; (z) AllylBr, $NaHCO_3$; (a') TPAP, NMO.

Fragments 3,4



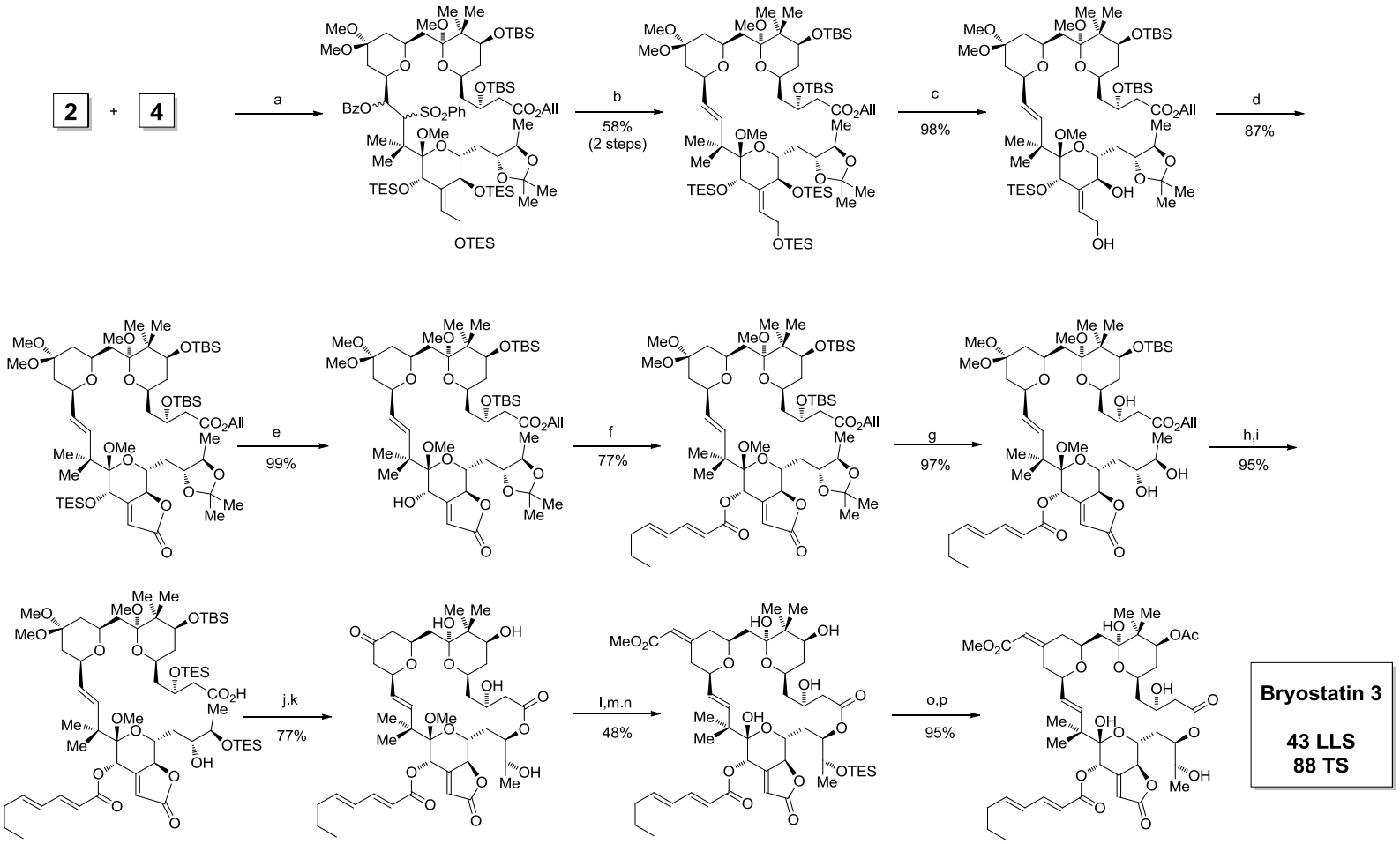
Key: (a) TsCl, py; (b) KOH, 60 °C; (c) H_2, 10% Pd/C; (d) HCl, MeOH/H_2O; (e) TsCl, Py; (f) LAH; (g) propane-1,3-dithiol, conc. HCl, $CHCl_3$; (h) $Me_2C(OMe)_2$, CSA; (i) DIPEA, then BOMCl; (j) 10% aq Acetone, $NaHCO_3$, MeI.



Key: (a) MsCl, py; (b) DHP, p-TsOH; (c) PhSNa, 18-Cr-6, 90 °C; (d) AcOH, THF/H_2O; (e) SO_3.py, DMSO, Et_3N; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH; (g) DHQPHN, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2C_3, $Me_2SO_2NH_2$, 0 °C; (h) $Me_2C(OMe)_2$, p-TsOH; (i) DIBAL-H, -78 °C; (j) Ph_3P, CBr_4, 0 °C; (k) n-BuLi, $(CH_2O)_n$; (l) Red-Al then I_2; (m) F_3CCO_2H; (n) TBDPSCl, imid.; (o) $PMPCH(OMe)_2$, PPTS; (p) DIBAL-H, 0 °C; (q) MeLi, -30 °C, then t-BuLi, -90 °C, then 3; (r) TBSOTf, 2,6-lutidine; (s) m-CPBA, Na_2HPO_4; (t) DDQ; (u) Dess-Martin periodiane; (v) H_2, $Pd(OH)_2$-C, EtOH, then $Me_2C(OMe)_2$, PPTS; (w) TBSOTf, TMSOMe, $Me_2C(OMe)_2$, 4A MS; (x) TBAF; (y) TESOTf, 2,6-lutidine.

C. Yamamura *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2290. (Cont'd)

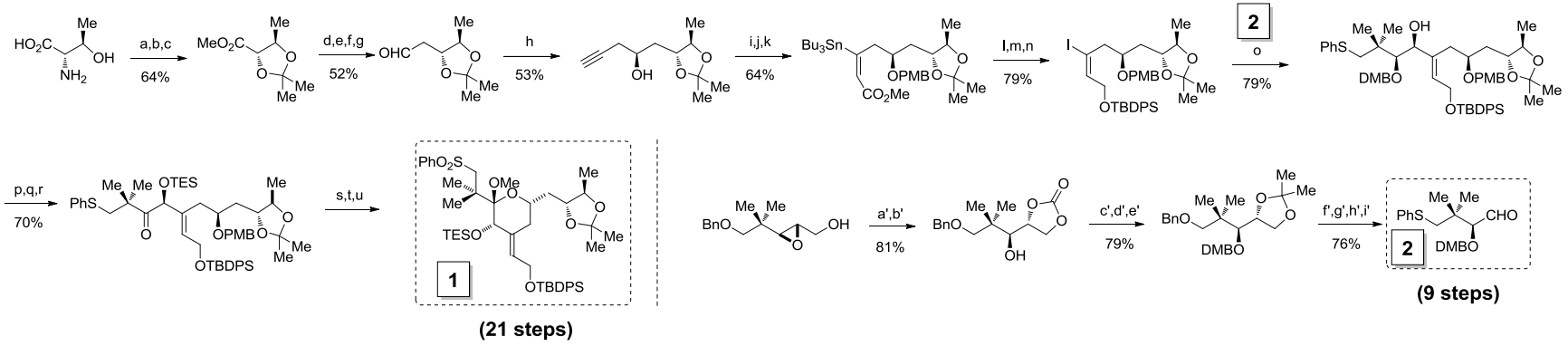
End Game



Key: (a) **4**, PhLi, then **2**, then BzCl, DMAP, -78 to 0 °C; (b) 5% Na/Hg, -35 °C; (c) TBAF, AcOH, 0 °C; (d) TPAP, NMO; (e) TBAF, AcOH, 0 °C; (f) (E,E)-2,4-octadienoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP; (g) CSA, MeOH; (h) TESCl, Et_3N, DMF, -30 °C; (i) $[Ph(PPh_3)_4]$, morpholine; (j) 2,4,6-trichlorobenzoyl chloride, Et_3N, then DMAP; (k) 46% aq. HF, H_2O; (l) [(*R*)-BINOL]P(O)CH_2CO_2Me, NaH, 0 °C; (m) TFA, H_2O, CH_2Cl_2; (n) TESCl, DMAP, 0 °C; (o) Ac_2O, py; (p) 46% aq. HF, MeCN.

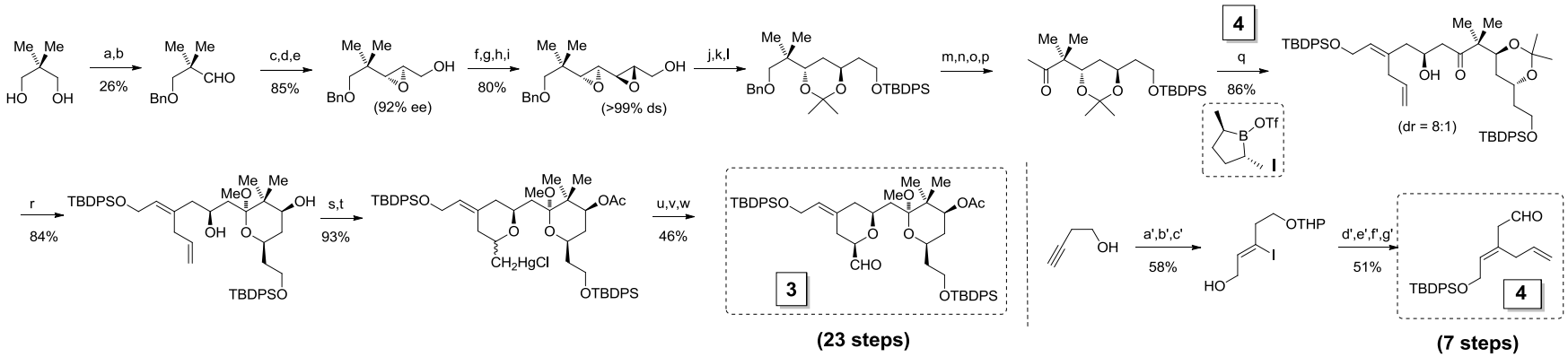
D. Masamure *et al. J. Am. Chem. Soc.* **1990**, *112,* 7407.

Fragments 1, 2



Key : (a) $NaNO_2$, H_2SO_4, H_2O; (b) MeOH, AcCl; (c) $(MeO)_2CMe_2$, p-TsOH; (d) DIBAL-H; (e) $Ph_3P{=}CH_2$; (f) Sia_2BH, H_2O_2; (g) PCC; (h) Allenyl-ZnBr; (i) NaH, PMBCl; (j) t-BuLi, $ClCO_2Me$; (k) n-$Bu_3SnCu.LiBr.Me_2S$; (l) DIBAL-H; (m) TBDPSCl, imid.; (n) I_2; (o) n-BuLi, then **2**; (p) TEOTf, 2,6-Lutidine; (q) DDQ; (r) DMSO, Ac_2O, TEA; (s) MoO_5.HMPA. H_2O; (t) DDQ, SiO_2; (u) TMSOTf, TMSOMe.
(a') PhNCO, TEA; (b') $BF_3.OEt_2$, 10 aq. H_2SO_4; (c') K_2CO_3, MeOH; (d') $(MeO)_2CMe_2$, PPTS; (e') NaH, m,p-dimethoxylbenzyl chloride; (f') Raney Ni, H_2; (g') MsCl, TEA, PhSNa; (h') HCl, MeOH; (I') $NaIO_4$, pH7.

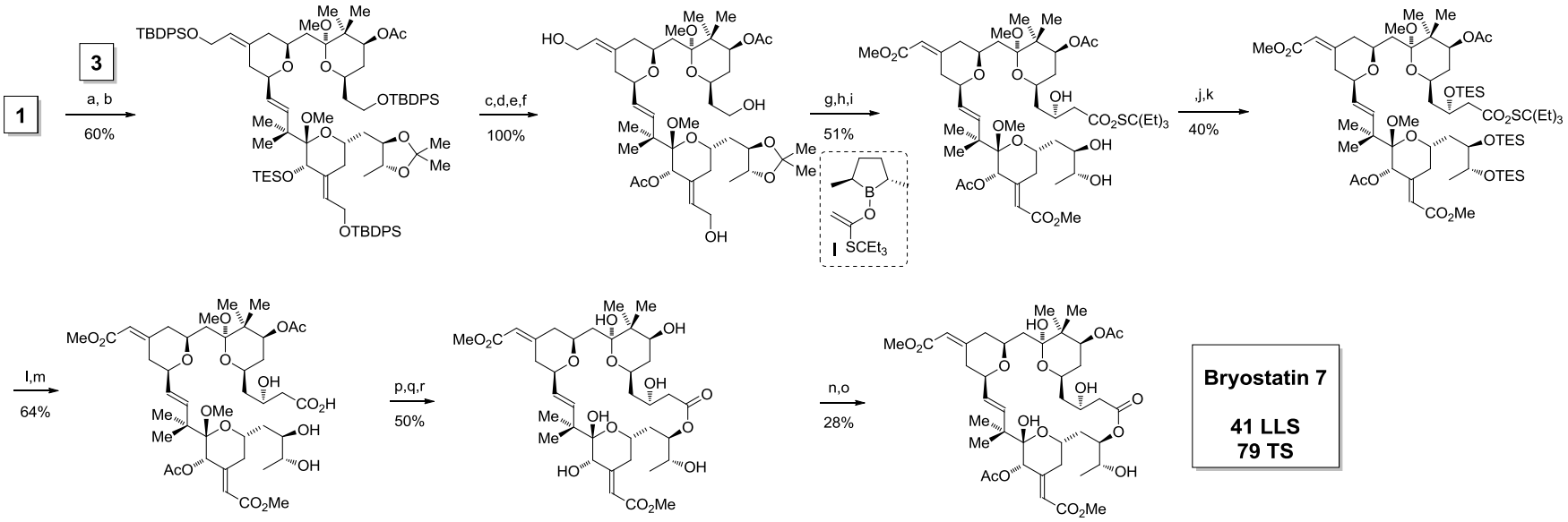
Fragments 3, 4



Key : (a) NaH, DMF, BnCl; (b) CrO_3, Py; (c) $(EtO)_2(P{=}O)CH_2CO_2Et$, NaH; (d) DIBAL-H; (e) (-)-DET, $Ti(O^iPr)_4$, ^tBOOH; (f) Swern oxid.; (g) $Ph_3P{=}CHCHO$; (h) $NaBH_4$, MeOH ; (i) (+)-DET, $Ti(O^iPr)_4$, ^tBOOH; (j) RedAl-H; (k) TBDPSCl, imid.; (l) PPTS, $(MeO)_2CMe_2$; (m) Na, liquid NH_3; (n) Swern oxid.; (o) MeLi; (p) Swern oxid.; (q) (R,R)-borolane triflate(**I**), DIPEA, then **4**; (r) $(MeO)_3CH$, MeOH, PPTS; (s) $Hg(OAc)_2$, MeOH, then KCl; (t) Ac_2O, Py, DMAP; (u) $NaBH_4$, O_2; (v) Swern oxid.; (w) Al_2O_3.
(a') DHP, PPTS; (b') nBuLi; HCHO; (c') RedAl-H, then I_2; (d') TBDPSCl, imid.; (e') Ally-MgBr, CuI; (f') PPTS, EtOH; (g') $(py)_2CrO_3$.

D. Masamure *et al. J. Am. Chem. Soc.* **1990**, *112,* 7407. (Cont'd)

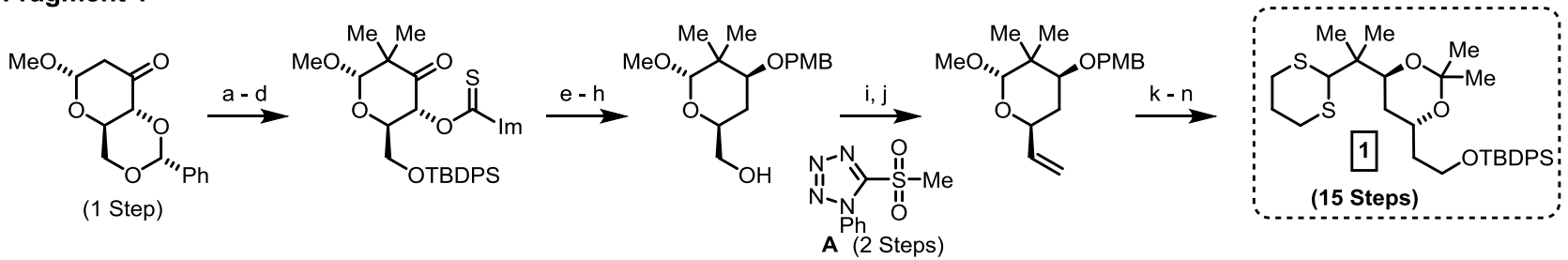
End Game (Bryostatin 7, Masamune)



Key : (a) PhLi, -78°C; **3**; BzCl, DMAP, -78°C to 25°C; (b) Na-Hg, $NaHPO_4$, -20°C; (c) TBAF; (d) TBSCl, imid.; (e) Ac_2O, Py, DMAP; (f) TBAF; (g) MnO_2, NaCN, AcOH; (h) Swern oxid.; (i) boron enolate(**I**), DIPEA; (j) CSA. MeOH; (k) TESOTf, 2,6-lutidine; (**I**) $Hg(O_2CCF_3)_2$, $NaHPO_4$; (m) HF·Py; (n) DCC, PPTS, Py; (o) K_2CO_3, MeOH; (p) TBSCl, TEA, DMAP; (q) Ac_2O, Py; (r) HF, MeCN.

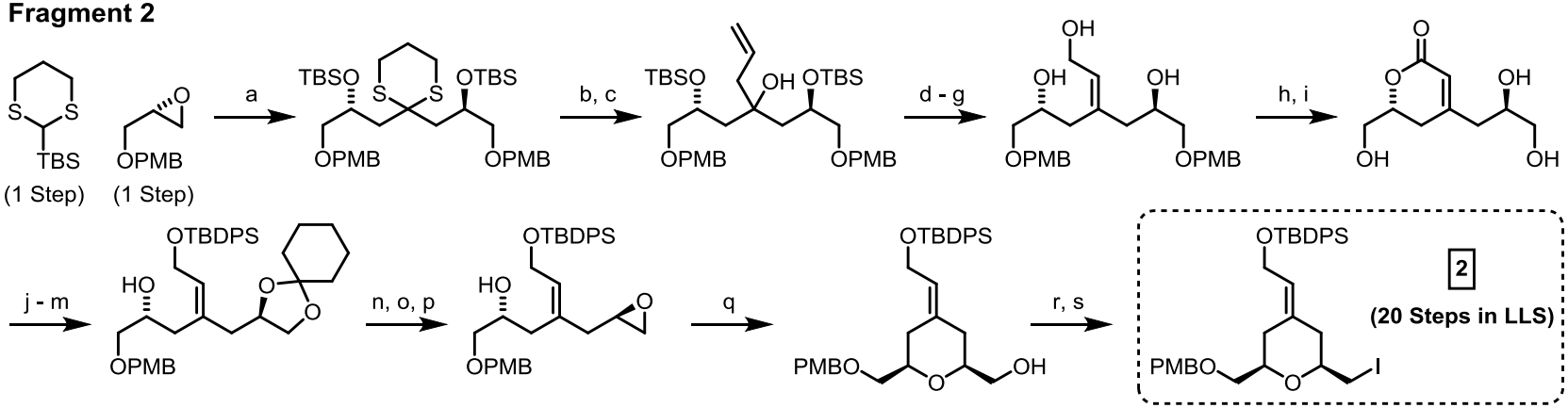
E. Hale *et al. Org. Lett.* **2001**, *3*, 3791; *Org. Lett.* **2003**, *5*, 503; *Org. Lett.* **2006**, *8*, 4477.

Fragment 1



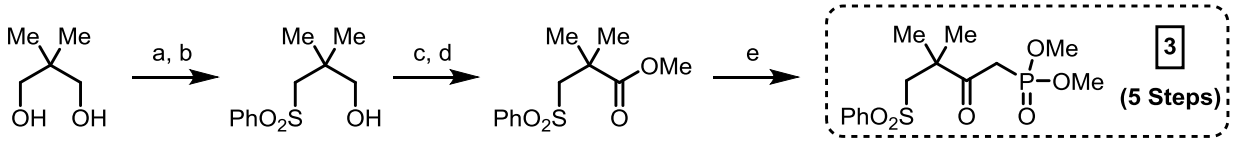
Key: (a) KH, then MeI; (b) H_2, $Pd(OH)_2$/C; (c) TBDPSiCl, imidazole; (d) $Im_2C{=}S$; (e) Bu_3SnH, AIBN; (f) Me_3Al, IPA; (g) $PMBOC(=NH)CCl_3$, PPTS; (h) TBAF; (i) TPAP, NMO, 4A MS; (j) **A**, KHMDS. (k) Catecholborane, $(PPh_3)_3RhCl$, then NaOH (aq.), H_2O_2; (l) 1,3-Propanedithiol, $BF_3{\bullet}OEt_2$; (m) TBDPSiCl, imidazole; (n) $Me_2C(OMe)_2$, PPTS.

Fragment 2



Key: (a) *t*BuLi, HMPA, then TBSCl; (b) $Hg(ClO_4)_2{\bullet}xH_2O$, $CaCO_3$; (c) AllylMgBr; (d) OsO_4, $NaIO_4$; (e) $(CF_3CO)_2O$, Et_3N, DMAP; (f) *i*Bu_2AlH; (g) TBAF; (h) MnO_2; (i) TFA, anisole; (j) Cyclohexanone, *p*TsOH; (k) $PMBOC(=NH)CCl_3$, PPTS; (l) $NaBH_4$, $CeCl_3{\bullet}7H_2O$; (m) TBDPSiCl, imidazole; (n) 1,3-Propanedithiol, $BF_3{\bullet}OEt_2$; (o) MsCl, collidine; (p) NaH, imidazole; (q) CSA; (r) TsCl, Pyr; (s) NaI.

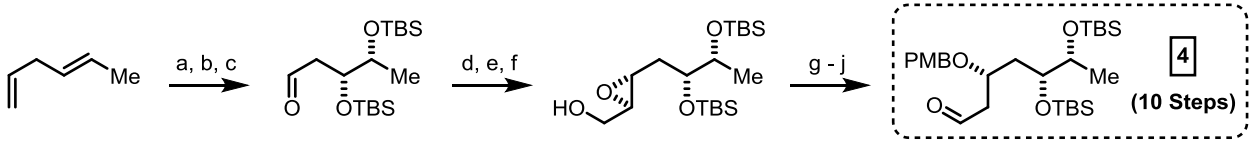
Fragment 3



Key: (a) PhSSPh, PBu_3; (b) Oxone; (c) $RuCl_3{\bullet}xH_2O$, $NaIO_4$; (d) K_2CO_3, MeI; (e) $(MeO)_2P(O)Me$, *n*BuLi.

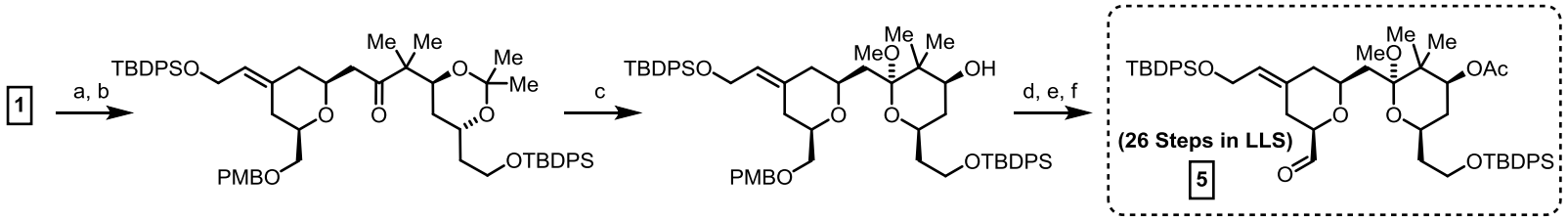
E. Hale *et al. Org. Lett.* **2001**, *3*, 3791; *Org. Lett.* **2003**, *5*, 503; *Org. Lett.* **2006**, *8*, 4477. (Cont'd)

Fragment 4



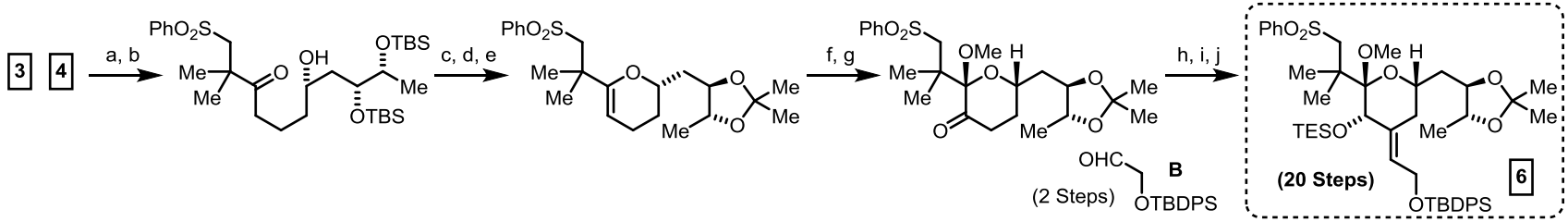
Key: (a) AD-mix-β; (b) TBSCl, imidazole; (c) OsO_4, $NaIO_4$; (d) $Ph_3P{=}CH_2CO_2Et$; (e) DIBAL; (f) (-)-DET, $Ti(OiPr)_4$, $tBuO_2H$, 4A MS; (g) Red-Al; (h) $PMPCH(OMe)_2$, PPTS; (i) DIBAL; (j) $(COCl)_2$, DMSO, Et_3N.

Fragment Union 1



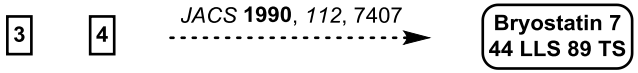
Key: (a) *t*BuLi, HMPA, then **2**; (b) $Hg(ClO_4)•xH_2O$, $CaCO_3$; (c) PPTS, $(MeO)_3CH$, MeOH; (d) Ac_2O, Pyr, DMAP; (e) DDQ; (f) TPAP, NMO, 4A MS.

Fragment Union 2



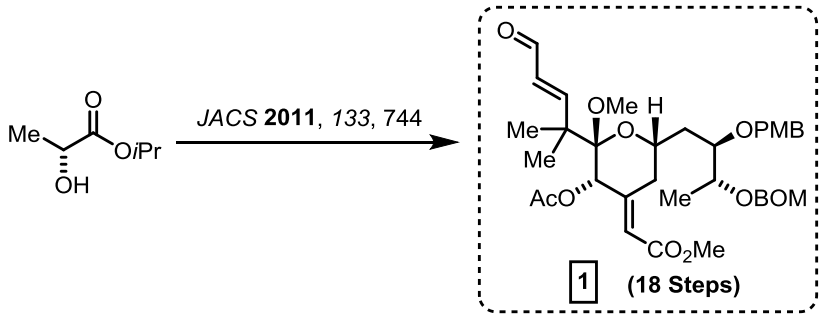
Key: (a) LiCl, iPr_2NEt; (b) $Pd(OH)_2/C$, H_2; (c) CSA; (d) TBAF; (e) $Me_2C(OMe)_2$, PPTS; (f) DMDO, $Me_2C(OMe)_2$, PPTS, 4A MS, MeOH; (g) PDC; (h) *n*BuLi, **B**; (i) $NaBH_4$, $CeCl_3•7H_2O$; (j) TESOTf, 2,6-lutidine.

End Game

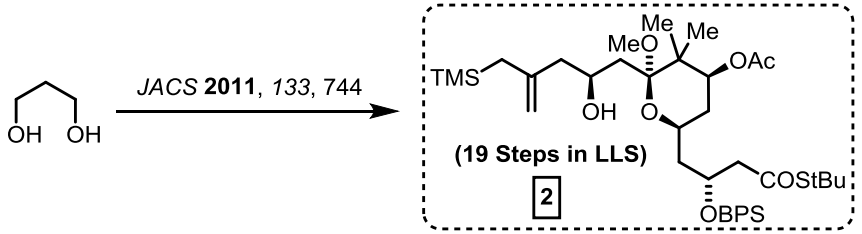


F. Keck *et al. ACS Chem. Biol.* **2013**, *8*, 767.

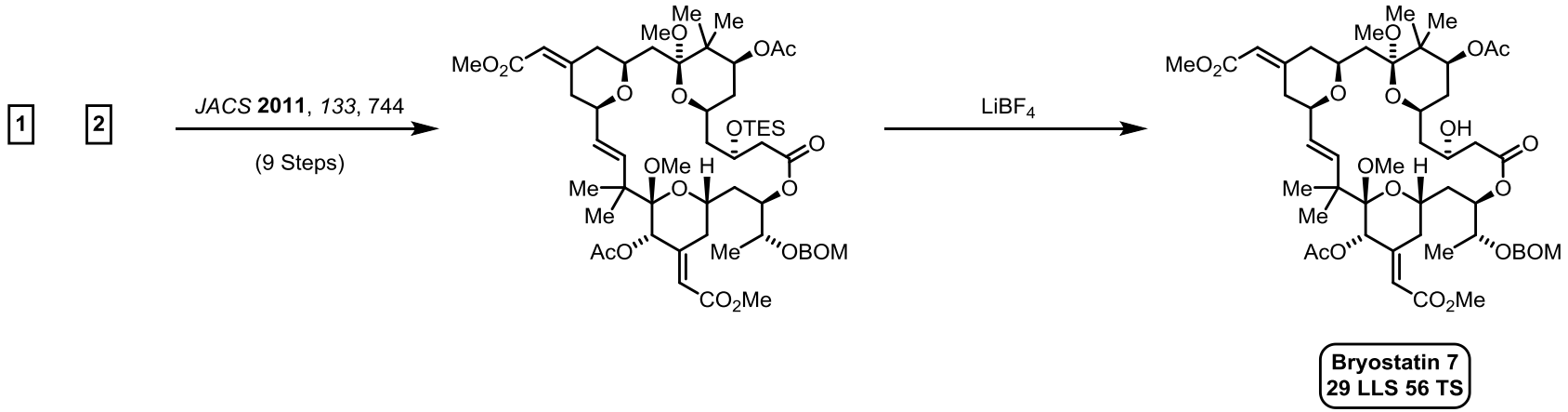
Fragment 1



Fragment 2

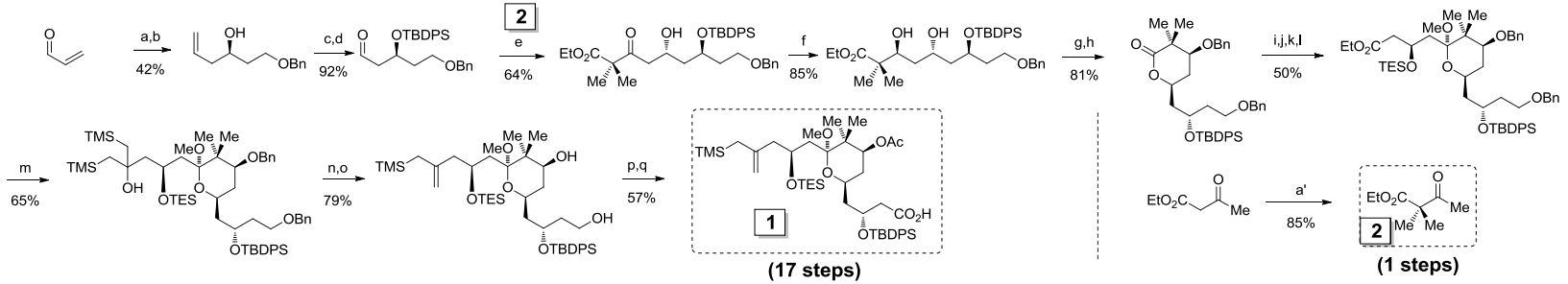


Fragment Union



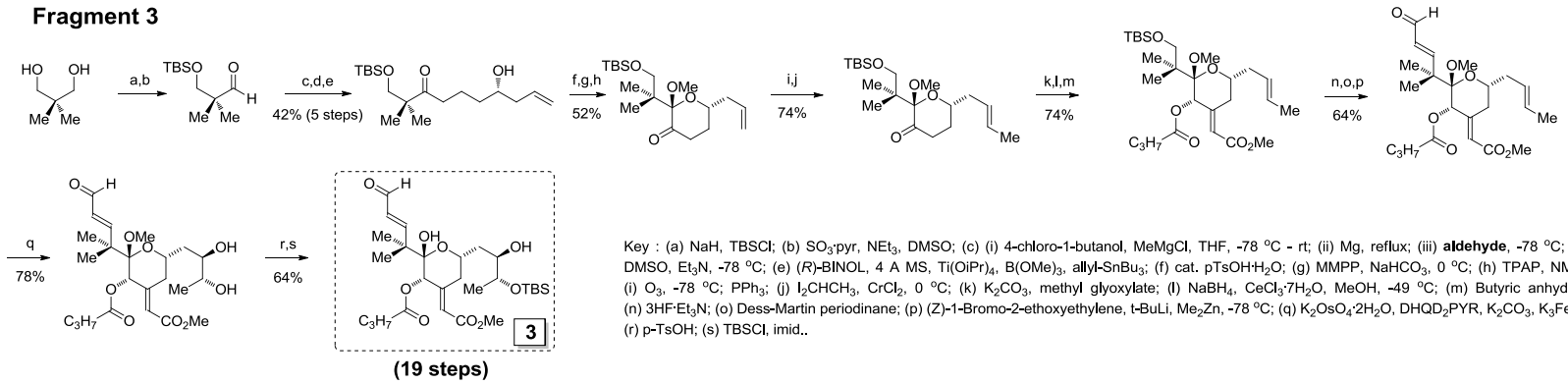
G. Wender *et al. J. Am. Chem. Soc.* **2011**, *133,* 9228.

Fragments 1,2



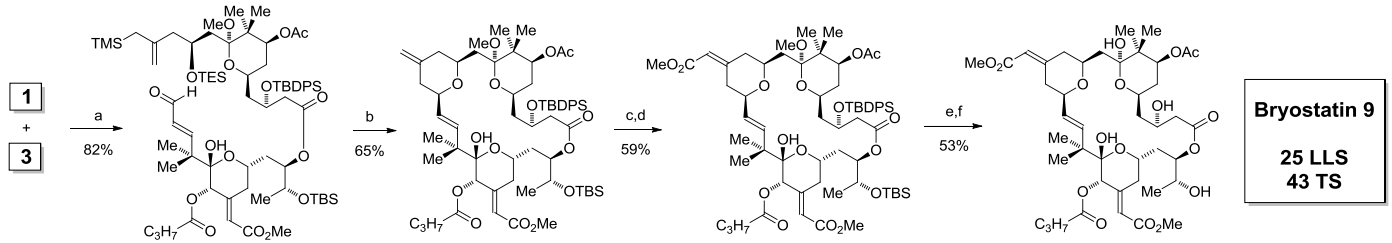
Key : (a) chloroacetic acid, NaOH, benzylalcohol; (b) $Ti(OiPr)_4$, (*R*)-BINOL, allyltributyltin; (c) TBDPSCl, imid.; (d) O_3; PPh_3; (e) Ketone **2**, (+)-Ipc_2BCl, Et_3N, then **aldehye**; (f) $Me_4NBH(OAc)_3$,1:1 HOAc:MeCN,-15 °C; (g) CSA, PhH, reflux; (h) BnBr, NaHMDS; (i) Ethyl acetoacetate, LDA, -78 °C; (j) PPTS, MeOH, 40 °C; (k) $NaBH_4$, EtOH, -15 °C; (l) TESCl, imid.; (m) $CeCl_3{\cdot}2LiCl$, $TMSCH_2MgCl$; (n) NaHMDS, THF, 0 °C; (o) Lithium naphthalenide, -30°C - -10 °C; (p) TEMPO, $PhI(OAc)_2$, 4:1 MeCN/H_2O; then NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, 0 °C; (q) Ac_2O, DMAP. (a') MeI, K_2CO_3.

Fragment 3



Key : (a) NaH, TBSCl; (b) $SO_3{\cdot}$pyr, NEt_3, DMSO; (c) (i) 4-chloro-1-butanol, MeMgCl, THF, -78 °C - rt; (ii) Mg, reflux; (iii) **aldehyde**, -78 °C; (d) $(COCl)_2$, DMSO, Et_3N, -78 °C; (e) (*R*)-BINOL, 4 A MS, $Ti(OiPr)_4$, $B(OMe)_3$, allyl-$SnBu_3$; (f) cat. $pTsOH{\cdot}H_2O$; (g) MMPP, $NaHCO_3$, 0 °C; (h) TPAP, NMO, 4 A MS; (i) O_3, -78 °C; PPh_3; (j) I_2CHCH_3, $CrCl_2$, 0 °C; (k) K_2CO_3, methyl glyoxylate; (l) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -49 °C; (m) Butyric anhydride, DMAP; (n) $3HF{\cdot}Et_3N$; (o) Dess-Martin periodinane; (p) (Z)-1-Bromo-2-ethoxyethylene, t-BuLi, Me_2Zn, -78 °C; (q) $K_2OsO_4{\cdot}2H_2O$, $DHQD_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, 4 °C; (r) p-TsOH; (s) TBSCl, imid..

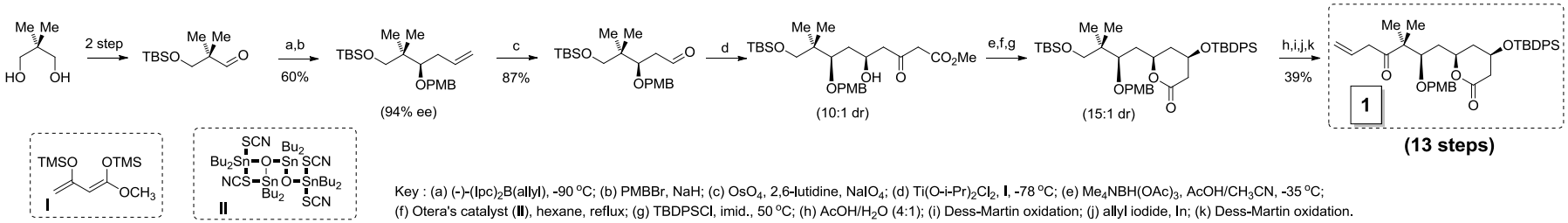
End Game (Bryostatin 9, Wender)



Key : (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, $PhCH_3$; then alcohol **3**, DMAP; (b) PPTS, MeOH; (c) O_3, -78 °C; then thioure; (d) [(R)-BINOL]-$P(O)CH_2CO_2Me$, NaHMDS, -78 °C to 4 °C (e) HF·py; (f) PPTS, 20% H_2O in THF.

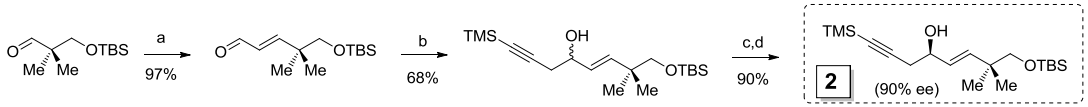
H. Trost *et al. Nature* **2008**, *456,* 485.

Fragment 1



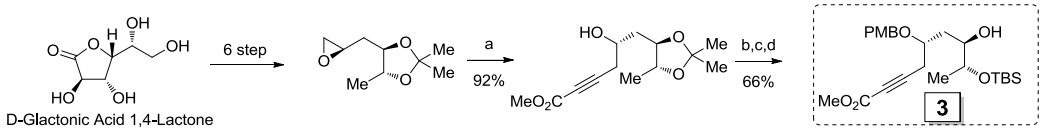
Key : (a) (-)-(Ipc)$_2$B(allyl), -90 °C; (b) PMBBr, NaH; (c) OsO_4, 2,6-lutidine, $NaIO_4$; (d) Ti(O-i-Pr)$_2$Cl$_2$, **I**, -78 °C; (e) $Me_4NBH(OAc)_3$, AcOH/CH_3CN, -35 °C; (f) Otera's catalyst (**II**), hexane, reflux; (g) TBDPSCl, imid., 50 °C; (h) AcOH/H_2O (4:1); (i) Dess-Martin oxidation; (j) allyl iodide, In; (k) Dess-Martin oxidation.

Fragment 2



Key : (a) (Z)-1-bromo-2-ethoxyethene, t-BuLi, $(CH_3)_2Zn$; **aldehyde**, -78 °C; $NaHSO_4$, rt; (b) (3-bromo-1-propynyl)-trimethylsilane, indium powder, InF_3, 65 °C; (c) Dess-Martin periodinane, $NaHCO_3$; (d) (*S*)-2-methyl-CBS-oxazaborolidine, catecholborane, -78 °C.

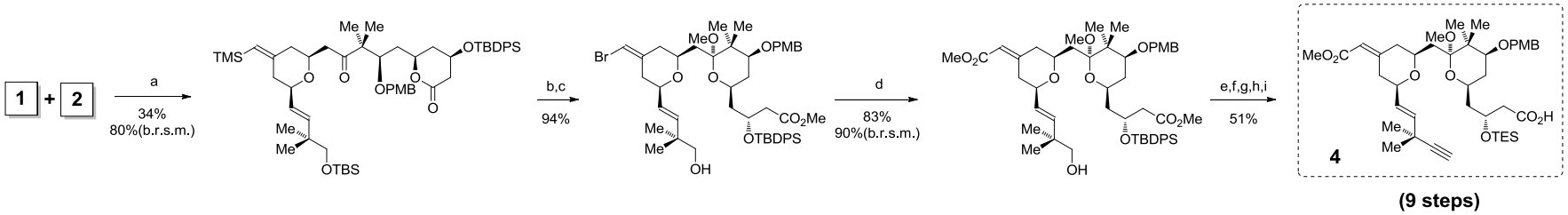
Fragment 3



Key : (a) n-BuLi, methyl propionate, $BF_3{\cdot}OEt_2$, -78 °C; (b) $Cu(OTf)_2$, $PMBOC(NH)CCl_3$, -10 °C; (c) PPTS, MeOH; (d) TBSOTf, 2,6-lutidine.

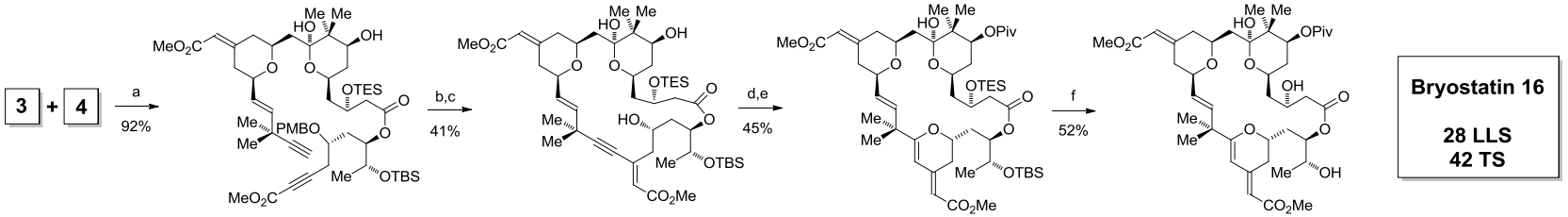
H. Trost *et al. Nature* **2008**, *456,* 485. (Cont'd)

Fragment 4



Key : (a) $CpRu(CH_3CN)_3PF_6$; (b) NBS; (c) CSA, MeOH, 0 °C; (d) $PdCl_2(CH_3CN)_2$, dppf, CO (1 atm), MeOH, TEA, 80 °C; (e) Dess-Martin periodinane, $NaHCO_3$; (f) Ohira-Bestmann reagent, K_2CO_3, MeOH; (g) TBAF, AcOH; (h) $(CH_3)_3SnOH$, 80 °C; (i) TESOTf, 2,6-lutidine, -10 °C to 0 °C.

End Game (Bryostatin 16, Trost)

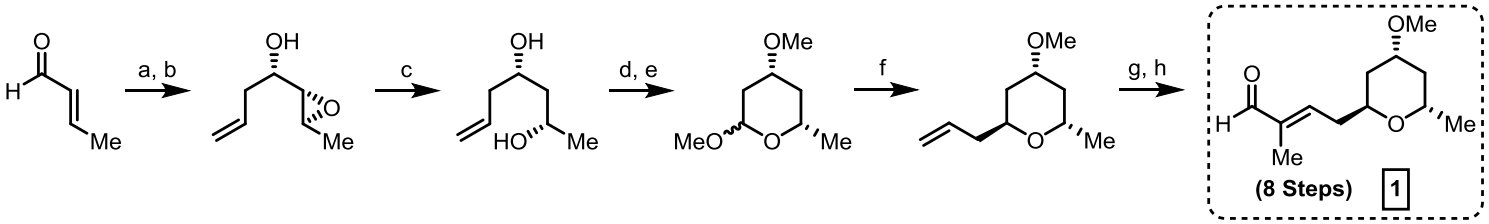


Key : (a) **4**, 2,4,6-trichlorobenzoyl chloride, TEA, then **3**, DMAP; (b) DDQ; (c) $Pd(OAc)_2$, TDMPP; (d) $AuCl(PPh_3)$, $AgSbF_6$, $NaHCO_3$, 0 °C to rt; (e) Piv_2O, DMAP, DCM, 50 °C; (f) TBAF.

Graphical Summary of Previous Syntheses of Swinholide Fragments

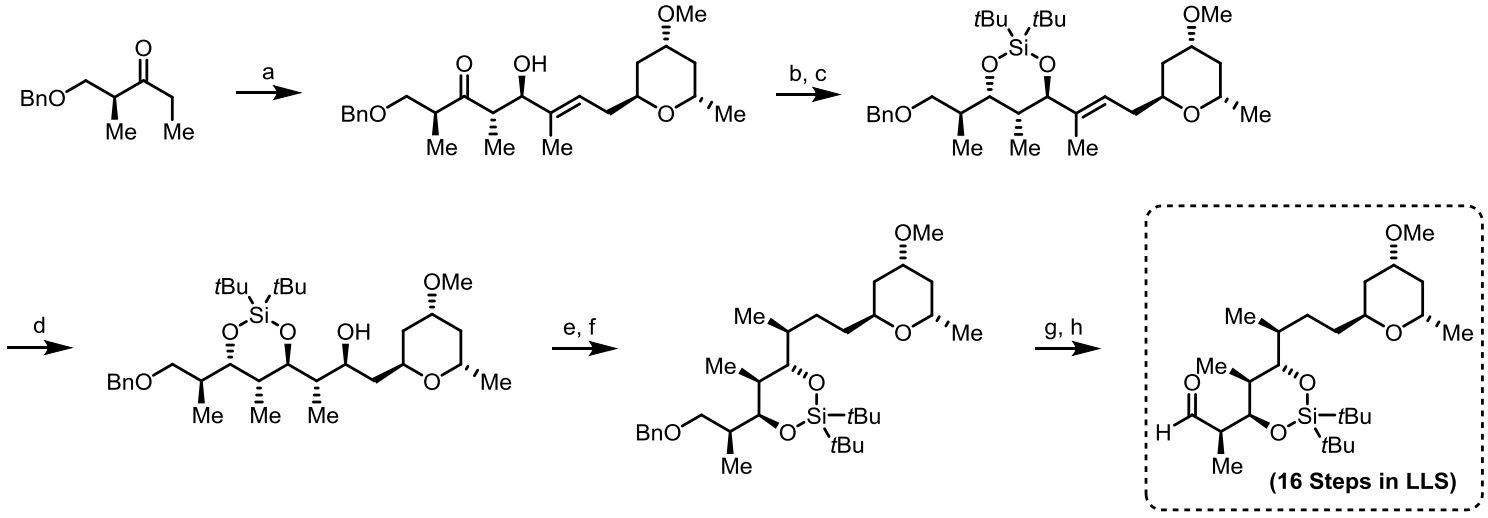
A. Paterson *et al. Tetrahedron* **1995**, *51*, 9393.

Fragment 1



Key: (a) allyl bromide, Zn, DMF; (b) (+)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, 4Å MS, CH_2Cl_2, then DMS; (c) Red-Al, THF; (d) O_3, MeOH, then DMS, 1M HCl; (e) NaH, MeI, THF; (f) allyl-TMS, Me_3SiOTf, MeCN; (g) O_3, CH_2Cl_2, MeOH, $NaHCO_3$, then DMS; (h) Ph_3P=C(Me)CHO, toluene.

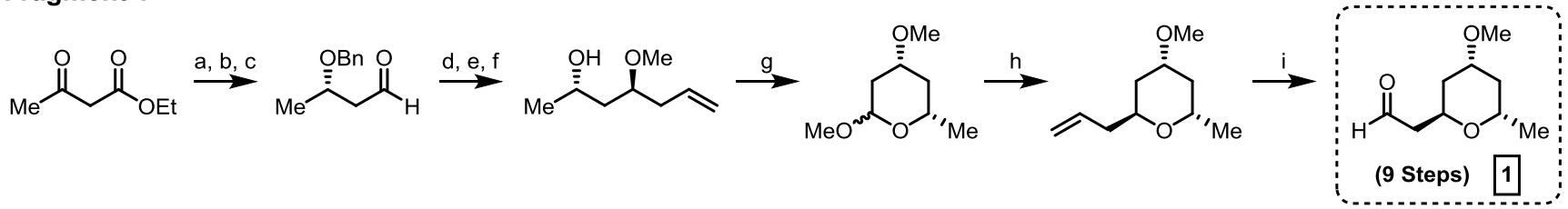
Fragment Union



Key: (a) (*c*-C_6H_{11})$_2$BCl, Et_3N, Et_2O, then **1**, then H_2O_2, pH7 buffer, MeOH; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN; (c) *t*$Bu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2; (d) Thexylborane, THF, then H_2O_2/NaOH; (e) (Imid)$_2$C=S, THF; (f) *n*Bu_3SnH, toluene; (g) H_2, Pd/C, EtOH; (h) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N.

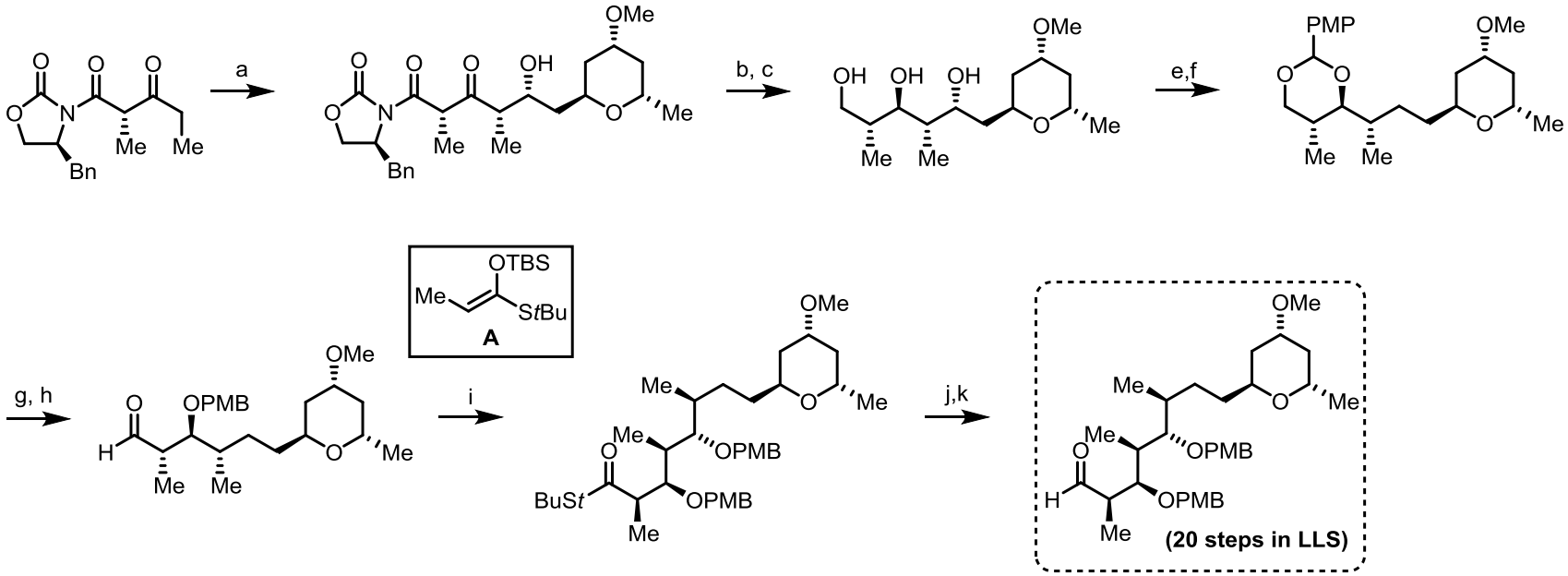
B. Keck *et al. J. Org. Chem.* **1999***, 64,* 4482.

Fragment 1



Key: (a) RuBINAP, H_2; (b) $CCl_3C(NH)OBn$, H^+; (c) DIBAL, CH_2Cl_2; (d) $TiCl_4$, then allyl-$Sn(Ph)_3$; (e) KH, MeI; (f) Li/NH_3; (g) O_3, MeOH, then DMS, 1M HCl; (h) allyl-TMS, TMSOTf; (i) O_3, CH_2Cl_2, then PPh_3.

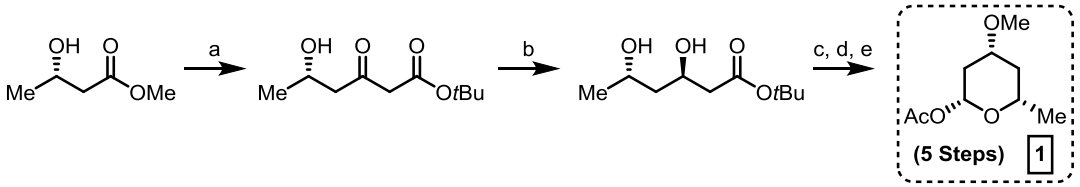
Fragment Union



Key: (a) **1**, $TiCl_4$, *i*Pr_2NEt; (b) $Me_4NBH(OAc)_3$; (c) $LiBH_4$, Et_2O; (d) PMBOMe, DDQ; (e) TCDI, THF; (f) Bu_3SnH, toluene; (g) DIBAL, CH_2Cl_2; (h) Dess-Martin periodinane, CH_2Cl_2; (i) **A**, $BF.OEt_2$, CH_2Cl_2; (j) $Cl_3CC(NH)OPMB$, CSA; (k) DIBAL.

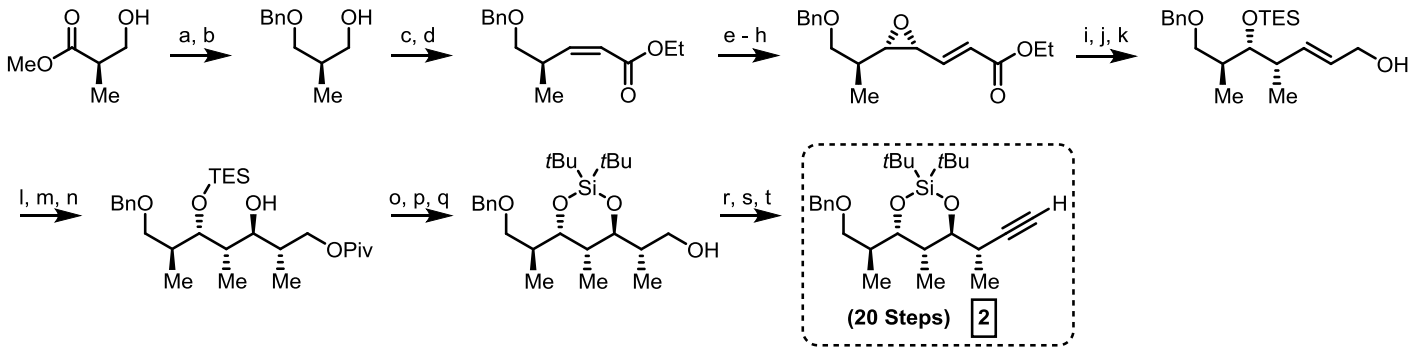
C. Miyashita *et al. Org. Lett.* **2003**, *5*, 3579; *Org. Lett.* **2005**, *7,* 2929.

Fragment 1



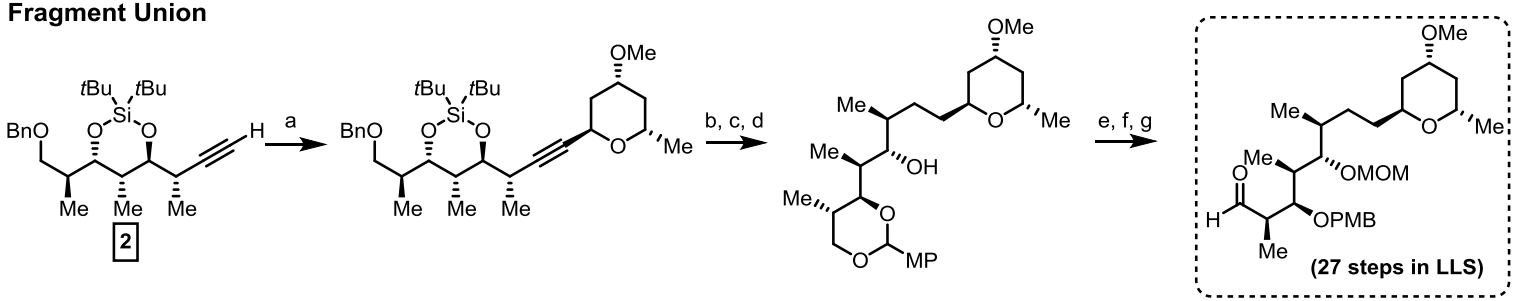
Key: (a) CH_3CO_2tBu, LDA, THF; (b) $Me_4NBH(OAc)_3$, AcOH, CH_3CN; (c) PPTS, $ClCH_2CH_2Cl$; (d) MeI, Ag_2O, 4A MS, Et_2O, CH_2Cl_2; (e) DIBAL, CH_2Cl_2, then pyridine, DMAP, $(CH_3CO)_2O$.

Fragment 2



Key: (a) $BnOC(=NH)CCl_3$, TfOH, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (d) di-*o*-tolyl ethoxycarbonyl-methyl phosphate, NaH, THF; (e) DIBAL, THF; (f) *m*-CPBA, CH_2Cl_2; (g) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (h) triethyl phosphonoacetate, NaH, THF; (i) $(CH_3)_3Al$, CH_2Cl_2, then H_2O; (j) TESCl, DMAP, imidazole, CH_2Cl_2; (k) DIBAL, THF; (l) *m*-CPBA, CH_2Cl_2; (m) Me_3CuLi, Et_2O; (n) *t*-BuCOCl, pyridine, Ch_2Cl_2; (o) TBAF, THF; (p) $tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2; (q) DIBAL, THF; (r) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (s) Ph_3P, CBr_4, pyridine, CH_2Cl_2; (t) BuLi, THF.

Fragment Union

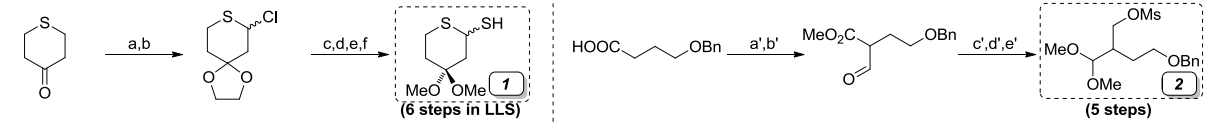


Key: (a) BuLi, Me_2AlOTf, then **1**, CH_2Cl_2; (b) H_2, $Pd(OH)_2/C$, AcOEt; (c) HF-Py, THF; (d) 4-$MeOC_6H_4CH(OMe)_2$, CSA, DMF; (e) MOMCl, iPr_2NEt, DCE; (f) DIBAL, CH_2Cl_2; (g) Dess-Martin periodinane, CH_2Cl_2.

Graphical Summary of Previous Syntheses of Erythromycins

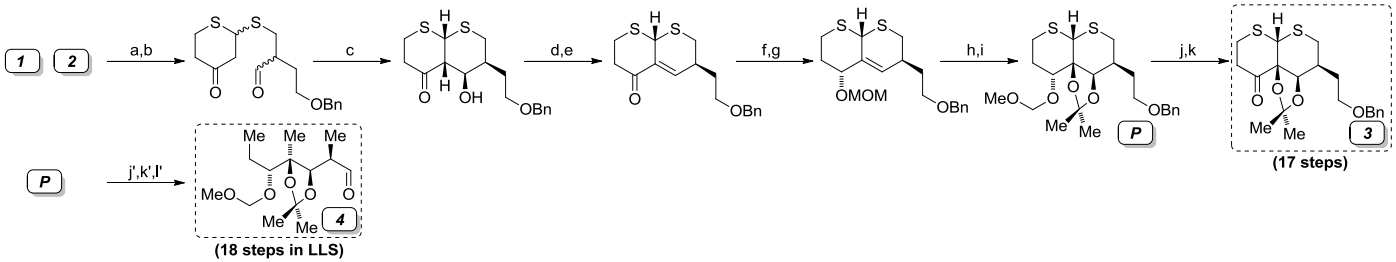
A. Woodward *et al. J. Am. Chem. Soc.* **1981**, *103*, 3210.

Fragment 1 and 2



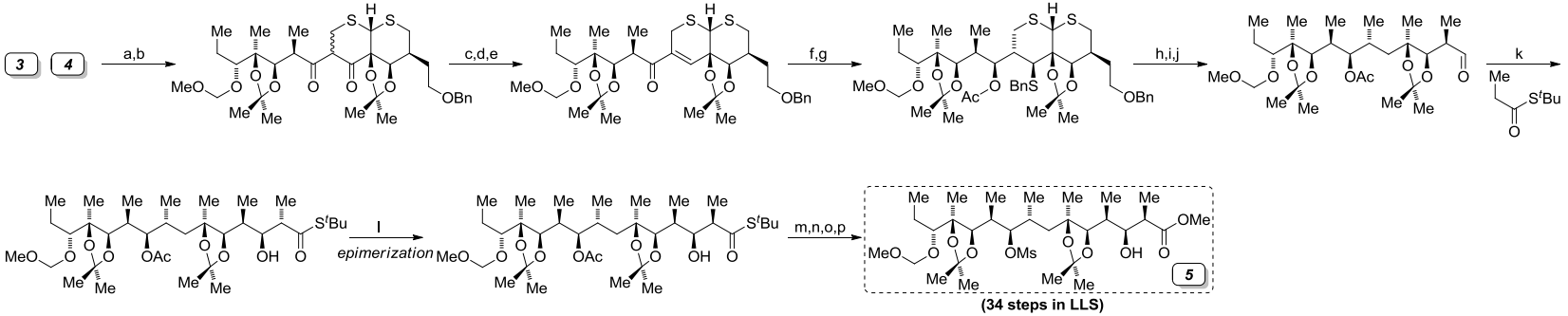
Key: (a) $HOCH_2CH_2OH$, TsOH; (b) NCS; (c) thiourea; (d) aq. NaOH; (e) aq. HCl; (f) $HC(OMe)_3$, TsOH
(a') conc. H_2SO_4, MeOH; (b') HCOOH, LDA; (c') conc. H_2SO_4, MeOH; (d') LAH; (e') MsCl, Py

Fragment Union, Fragment 3 and 4



Key: (a) NaH, DMSO; (b) AcOH; (c) D-Proline; (d) MsCl, Py; (e) alumina, EtOH; (f) $NaBH_4$; (g) MOMI, KH; (h) OsO_4, $NaHSO_4$, Py; (i) $Me_2C(OMe)_2$, TsOH; (j) TFA; (k) TFAA, DMSO
(j') Raney-Ni, H_2; (k') *o*-$NO_2C_6H_4SeCN$, PBu_3, then H_2O_2; (l') O_3, then Me_2S

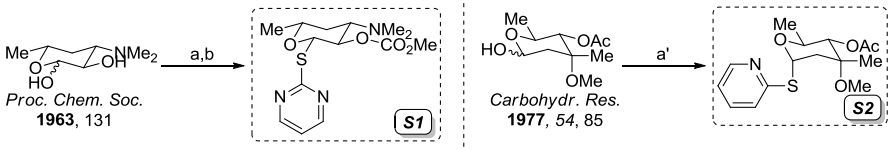
Fragment Union



Key: (a) mesityl-Li; (b) TFAA, DMSO, *i*Pr_2NEt; (c) KH, AcCl; (d) $NaBH_4$; (e) MsCl, Py; (f) BnSH, BuLi; (g) LAH; (h) Raney-Ni, H_2; (i) *o*-$NO_2C_6H_4SeCN$, PBu_3, then H_2O_2; (j) O_3, then Me_2S; (k) LDA; (l) *t*BuLi, then AcOH; (m) Na_2CO_3; (n) Bz_2O, Py; (o) MsCl, Py; (p) LiOH, H_2O_2

A. Woodward *et al. J. Am. Chem. Soc.* **1981**, *103*, 3210. (Cont'd)

Glycosidating Reagents S1 and S2

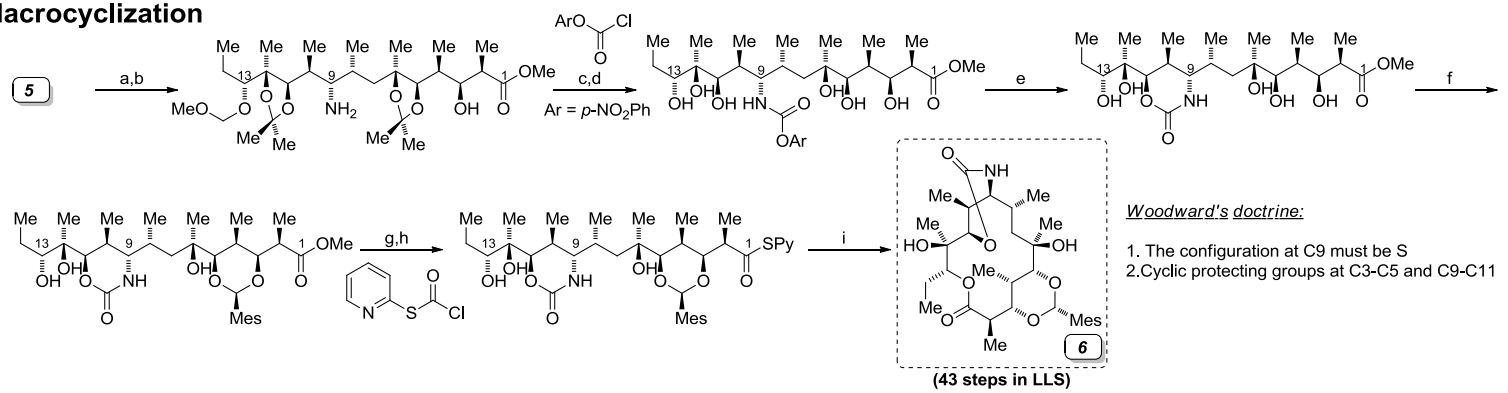


Proc. Chem. Soc. **1963**, 131

Carbohydr. Res. **1977**, *54*, 85

Key: (a) 2-mercaptopyrimidine, DEAD, PBu_3; (b) ClCOOMe, $NaHCO_3$
(a') $(2\text{-PyS})_2$, PBu_3

Macrocyclization

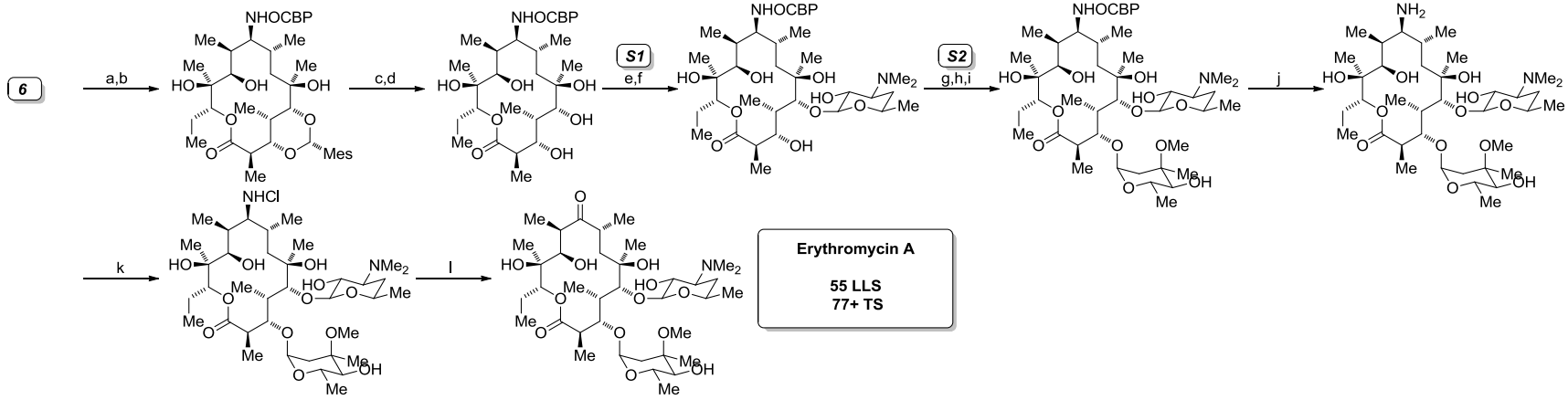


Woodward's doctrine:

1. The configuration at C9 must be S
2. Cyclic protecting groups at C3-C5 and C9-C11

Key: (a) LiN_3, HMPA; (b) PtO_2, H_2; (c) Na_2CO_3; (d) NH_2OH-HCl, KH_2PO_4; (e) TEA; (f) meityl-$CH(OMe)_2$, CSA; (g) EtSH,BuLi, HMPA; (h) TEA; (i) PPh_3, heat

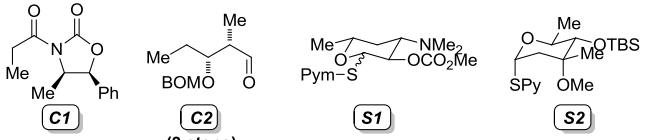
Glycosidation and End Game



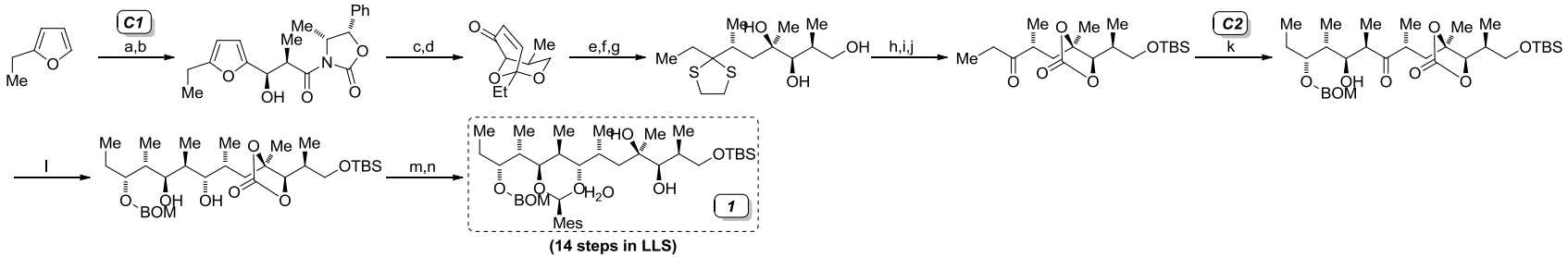
Key: (a) BPCOCl, TEA, DMAP; (b) NaOH, H_2O; (c) SiO_2, aq. TFA; (d) NH_2OH-HCl, KH_2PO_4; (e) AgOTf; (f) MeOH; (g) $ClCO_2Me$, $NaHCO_3$; (h) $Pb(ClO_4)_2$, MeCN; (i) MeOH; (j) Na-Hg/MeOH; (k) NCS, Py; (l) AgF, HMPA

B. Martin *et al. J. Am. Chem. Soc.* **1997**, *119*, 3193; *Tetrahedron* **2007**, *63*, 5709.

Chiral Auxiliary and Sugar

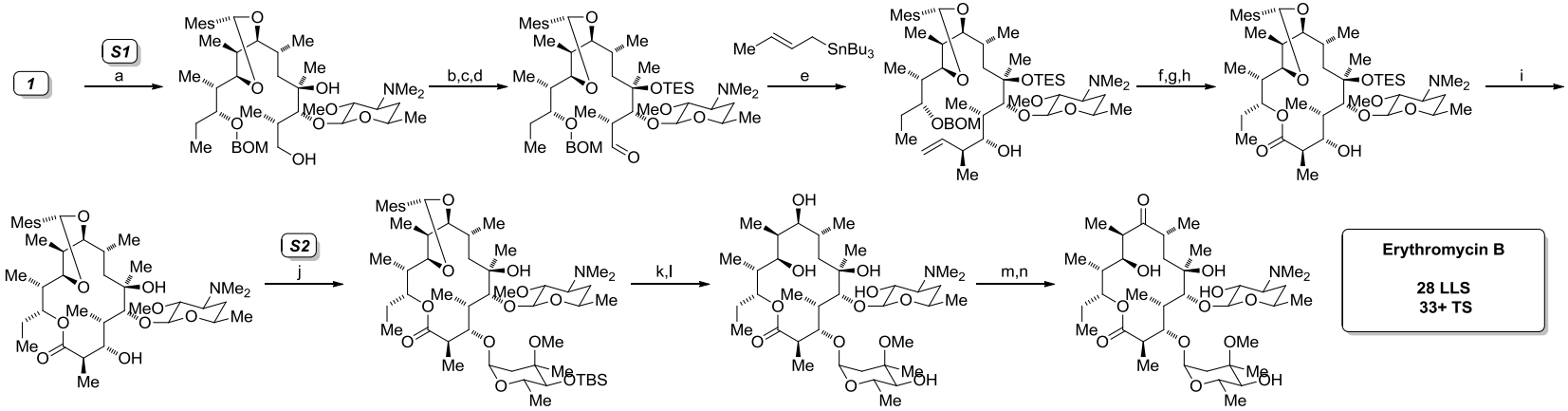


Functionalization of Furan



Key: (a) BuLi; (b) Bu_2BOTf; (c) $LiBH_4$; (d) Br_2; (e) $LiCuMe_2$; (f) MeLi-$CeCl_3$; (g) PPTS; (h) TBSCl; (i)CDI; (j) $Hg(ClO_4)_2$, $CaCO_3$; (k) LHMDS; (l) $Me_4NBH(OAc)_3$; (m) $Me_3C_6H_2CH(OMe)_2$, CSA; (n) $LiBH_4$

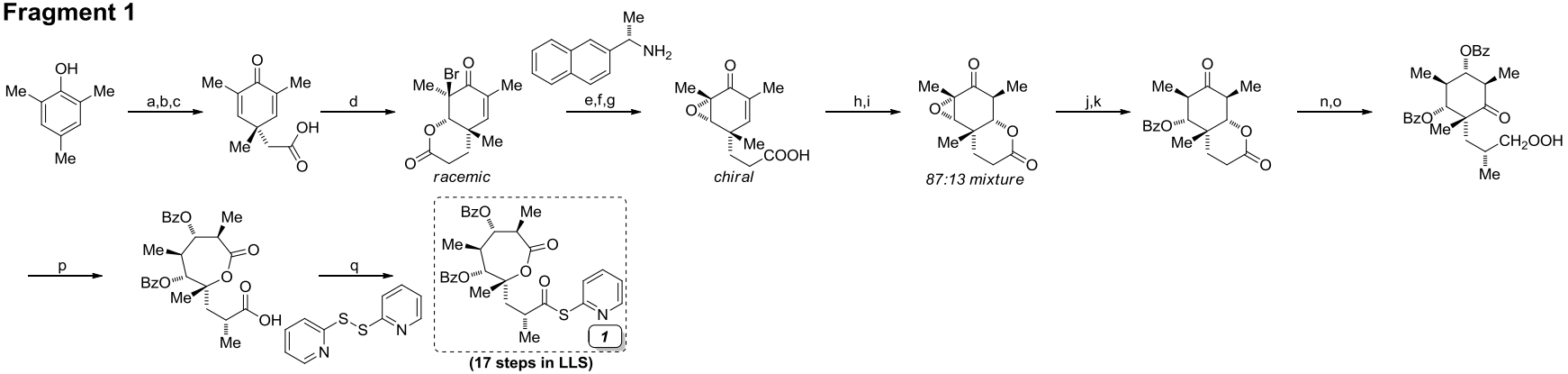
Glycosylation



Key: (a) AgOTf, 2,6-*t*Bu_2Py; (b) TBAF; (c) TESOTf, *i*Pr_2NEt; (d) $(COCl)_2$, DMSO, TEA; (e) BF_3-OEt_2; (f) OsO_4, Oxone, $NaHCO_3$; (g) Pd/C, $HClO_4$; (h) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (i) TBAF; (j) $Cu(OTf)_2$, CuO; (k) AcOH; (l) TBAF; (m) Dess-Martin Periodate; (n) MeOH, heating

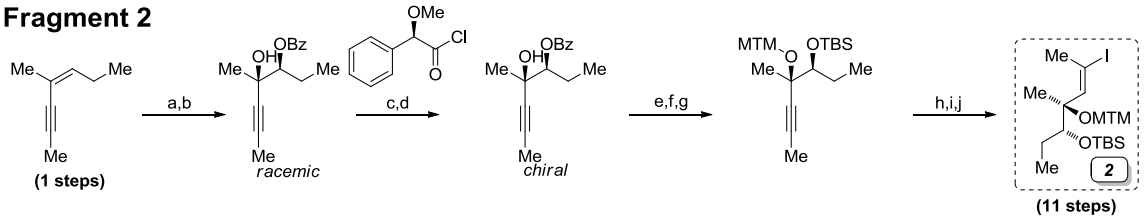
C. Corey *et al. J. Am. Chem. Soc.* **1979**, *101*, 7131.

Fragment 1



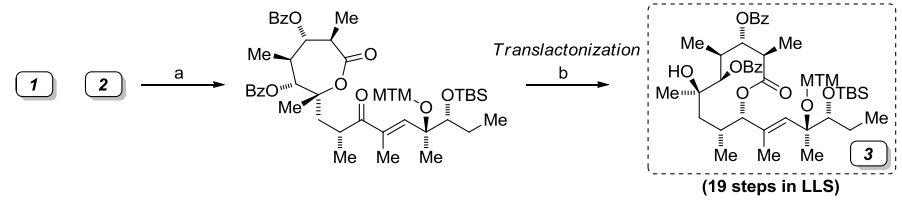
Key: (a) Allyl-Br, NaOMe; (b) BH_3•THF, H_2O_2, NaOH; (c) CrO_3, H_2SO_4; (d) Br_2, KBr; (e) KOH; (f) Amine, recrystallization; (g) MsOH; (h) Br_2, KBr; (i) Bu_3SnH, AIBN; (j) H_2, $Pd(OH)_2$/C, HOAc-THF; (k) BzCl, Py; (l) $Zn(BH_4)_2$,

Fragment 2



Key: (a) NMO, OsO_4, THF-H_2O; (b) BzCl, Py; (c) DMAP; (d) water associate P_{500}; (e) Ac_2O, DMSO, HOAc; (f) KOH, H_2O, MeOH; (g) TBSCl, DMAP, DMF; (h) Cy_2BH, then Et_3NO; (i) $Hg(OAc)_2$, NaCl; (j) I_2, Py

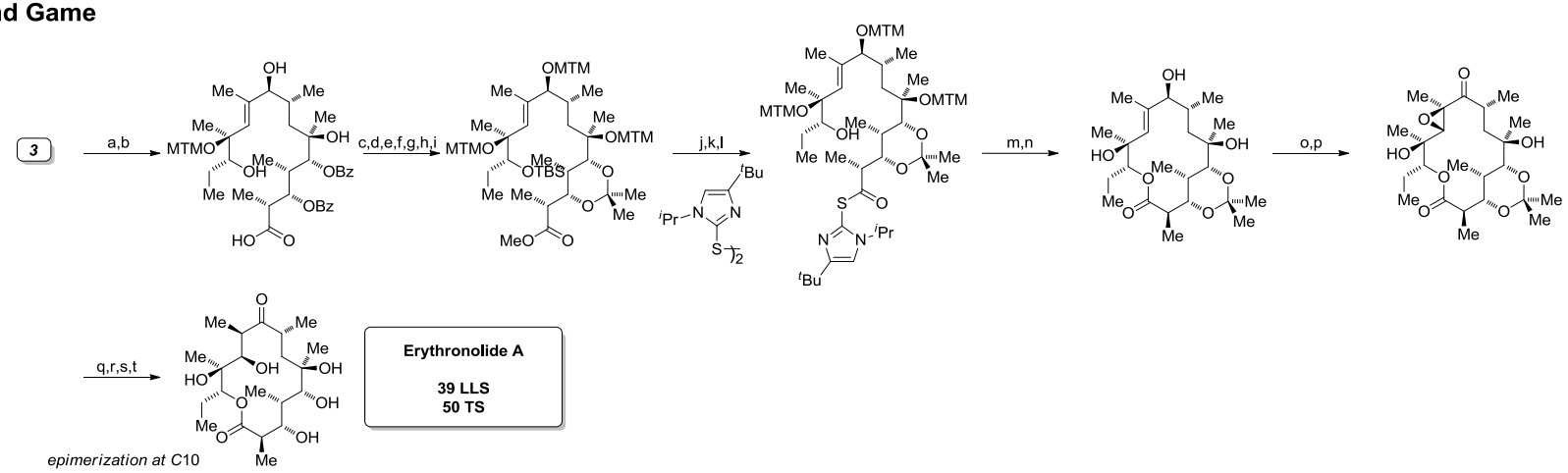
Coupling Fragment 1 and 2



Key: (a) BuLi, $MgBr_2$; (b) $Zn(BH_4)_2$

C. Corey *et al. J. Am. Chem. Soc.* **1979**, *101*, 7131. (Cont'd)

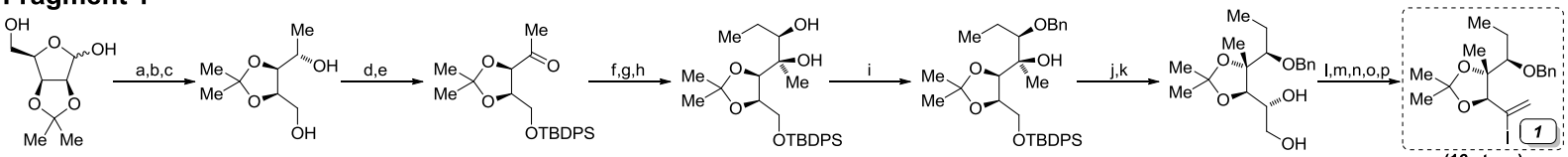
End Game



Key: (a) AcOH; (b) LiOH, H_2O_2; (c) KOH; (d) CH_2N_2; (e) $Me_2C(OMe)_2$, Amberlite-50; (f) Ac_2O, DMAP; (g) Ac_2O-DMSO-HOAc; (h) K_2CO_3; (i) Ac_2O-DMSO-HOAc; (j) NaOH, MeOH; (k) TBAF, THF; (l) PPh_3; (m) heating; (n) K_2CO_3, MeI, H_2O, THF; (o) mCPBA; (p) PCC; (q) Pd/C, H_2, (r) CH_2=C(Me)OMe, CSA; (s) Triton B methoxide; (t) PPTS, MeOH

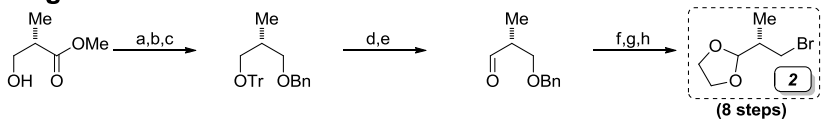
D. Kinoshita *et al. Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618.

Fragment 1



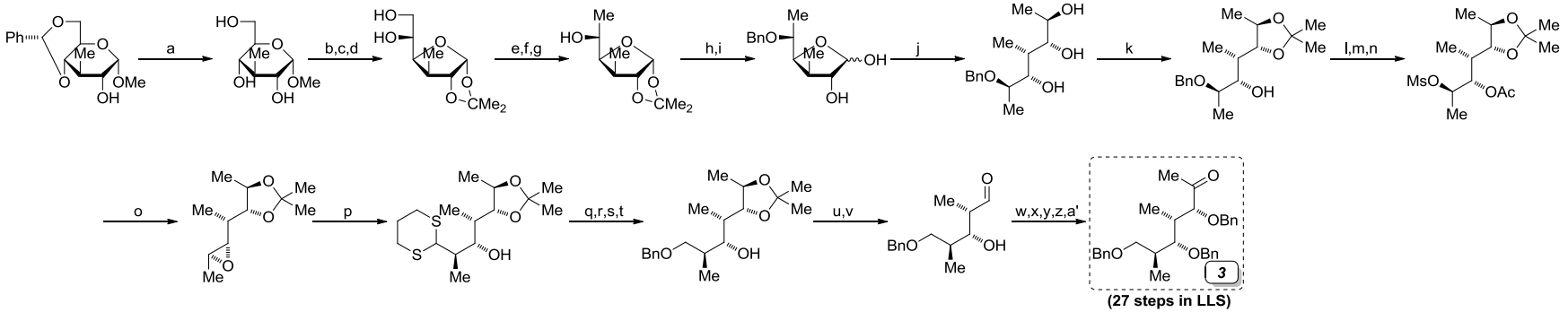
Key: (a) MeMgI; (b) $NaIO_4$; (c) $LiAlH_4$; (d) TBDPSCl, imidazole; (e) PCC; (f) vinylmagnesium bromide; (g) O_3, PPh_3; (h) EtMgBr; (i) NaH, BnBr; (j) $FeCl_3$, acetone; (k) TBAF; (l) $NaIO_4$; (m) MeMgI; (n) PCC; (o) NH_2NH_2-H_2O, TEA; (p) I_2, tetramethylguanidine

Fragment 2



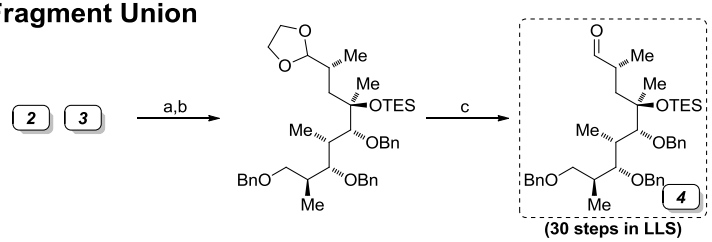
Key: (a) TrCl, TEA, DMAP; (b) LAH; (c) NaH, BnBr; (d) amberlyst^{-15}; (e) $(COCl)_2$, TEA, DMSO; (f) $HOCH_2CH_2OH$, TsOH; (g) H_2, Pd/C; (h) EtBr, PPh_3, DEAD

Fragment 3



Key: (a) HCl, MeOH; (b) TsOH, acetone; (c) HCl, H_2O; (d) $FeCl_3$, acetone; (e) TsCl, Py; (f) NaOH; (g) LAH; (h) NaH, BnBr; (i) HCl, H_2O; (j) MeMgBr; (k) $MeC(OMe)_2$, TsOH; (l) Ac_2O, DMAP; (m) H_2, Pd/C; (n) MsCl, Py; (o) LiOH, H_2O; (p) BuLi; (q) Ac_2O, TEA; (r) $HgCl_2$; (s) LAH; (t) NaH, BnBr; (u) HCl, H_2O; (v) $NaIO_4$; (w) $(EtS)_2CH_2$, BuLi; (x) NaH, BnBr; (y) $HgCl_2$; (z) MeMgBr; (a') PCC

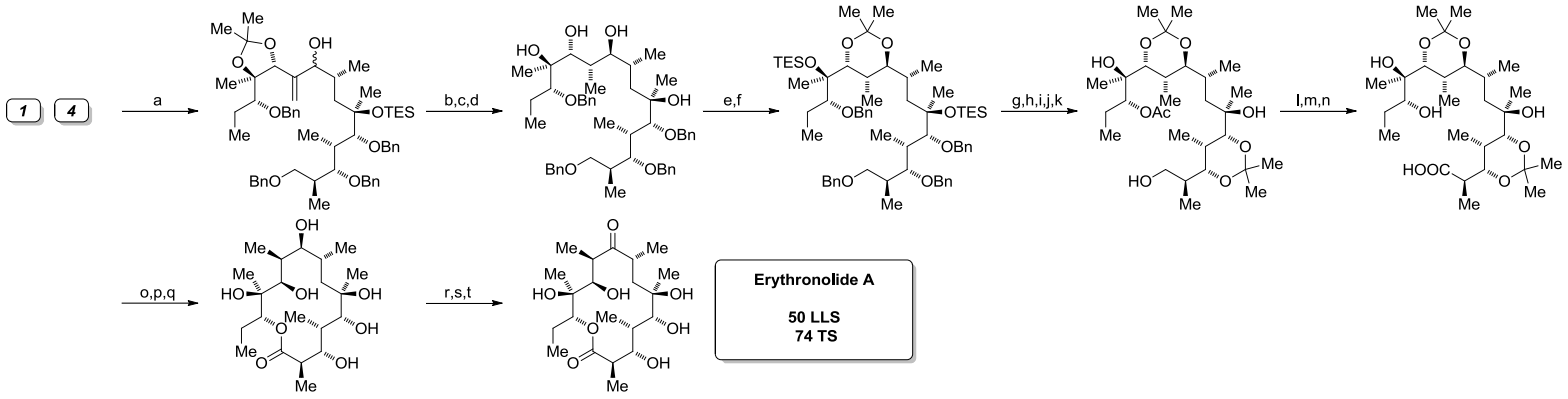
Fragment Union



Key: (a) Mg; (b) TESOTf, 2,6-lutidine; (c) $SnCl_2$, acetone

D. Kinoshita *et al. Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618. (Cont'd)

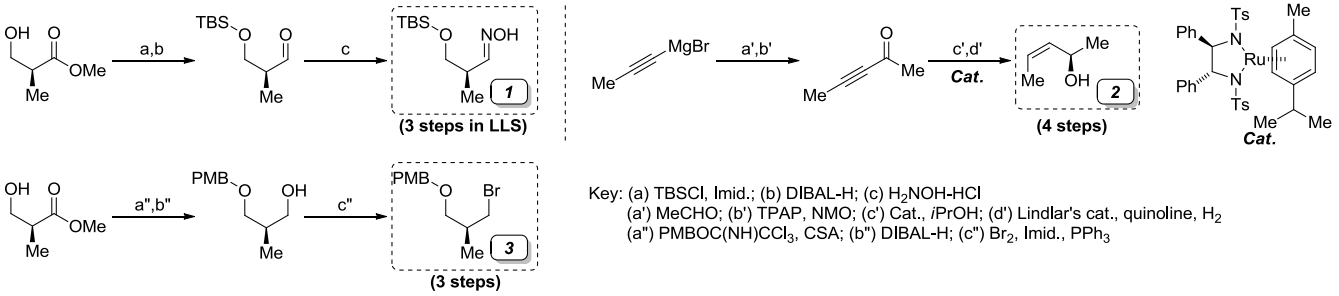
End Game



Key: (a) BuLi; (b) ClRh(PPh$_3$)$_3$, 50 atm H$_2$; (c) TBAF; (d) HCl, H$_2$O; (e) TsOH, acetone; (f) TESOTf, TEA; (g) Pd/C, H$_2$; (h) TBDPSCl, TEA; (i) TsOH, acetone; (j) Ac$_2$O, TEA; (k) TBAF; (l) (COCl)$_2$, TEA, DMSO; (m) NaClO$_2$; (n) LiOH, H$_2$O; (o) (2-pyr)$_2$S$_2$; (p) CuOAc; (q) AcOH; (r) PhCH(OMe)$_2$, CSA; (s) PCC; (t) H$_2$, Pd/C

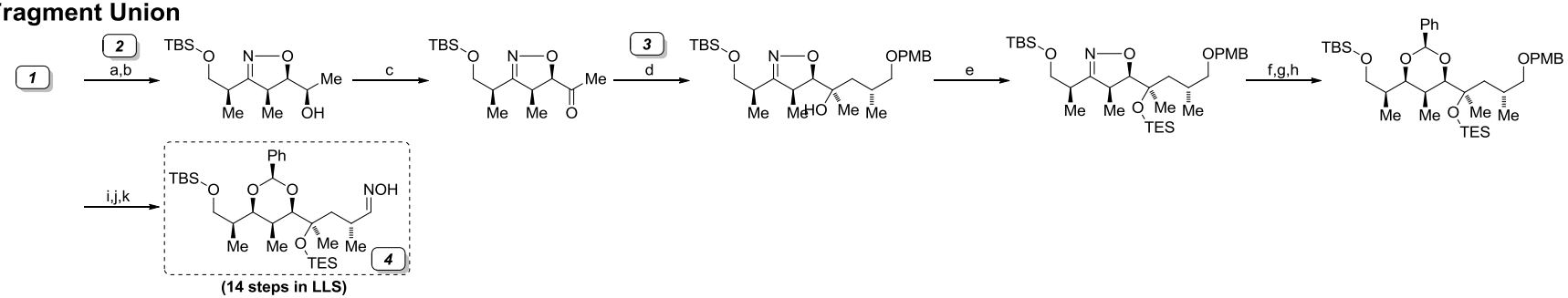
E. Carreira *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 4036; *J. Org. Chem.* **2009**, *74*, 8695.

Fragment 1, 2, 3



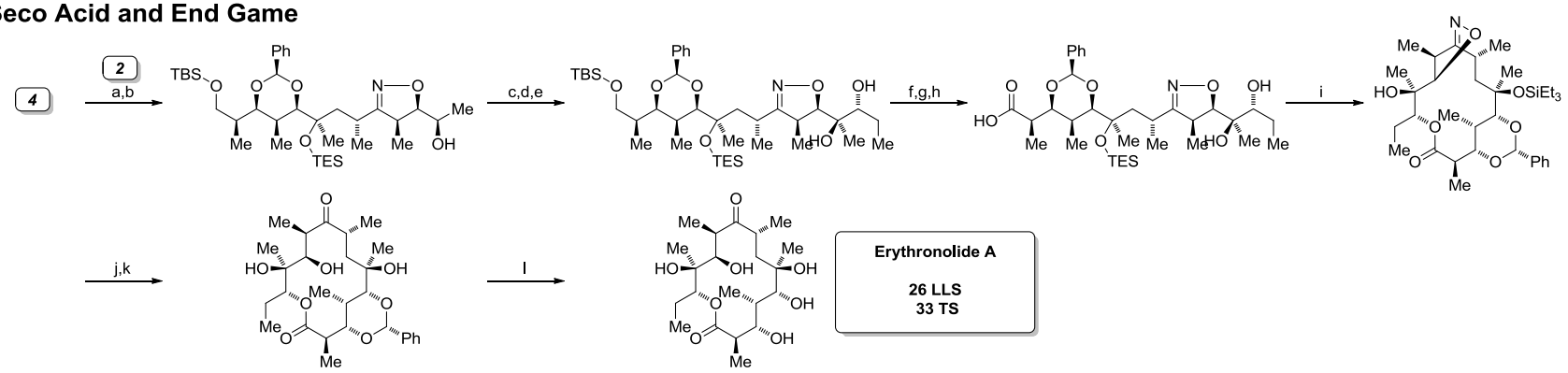
Key: (a) TBSCl, Imid.; (b) DIBAL-H; (c) H_2NOH-HCl
(a') MeCHO; (b') TPAP, NMO; (c') Cat., *i*PrOH; (d') Lindlar's cat., quinoline, H_2
(a") $PMBOC(NH)CCl_3$, CSA; (b") DIBAL-H; (c") Br_2, Imid., PPh_3

Fragment Union



Key: (a) *t*BuOCl; (b) *i*PrOH, ErMgBr; (c) TPAP, NMO; (d) THF; (e) TESOTf, 2,6-lutidine; (f) Raney-Ni, $B(OH)_3$, H_2; (g) $Zn(BH_4)_2$; (h) $PhCH(OMe)_2$, CSA; (i) DDQ; (j) TEMPO, NaOCl; (k) H_2NOH-HCl, Py

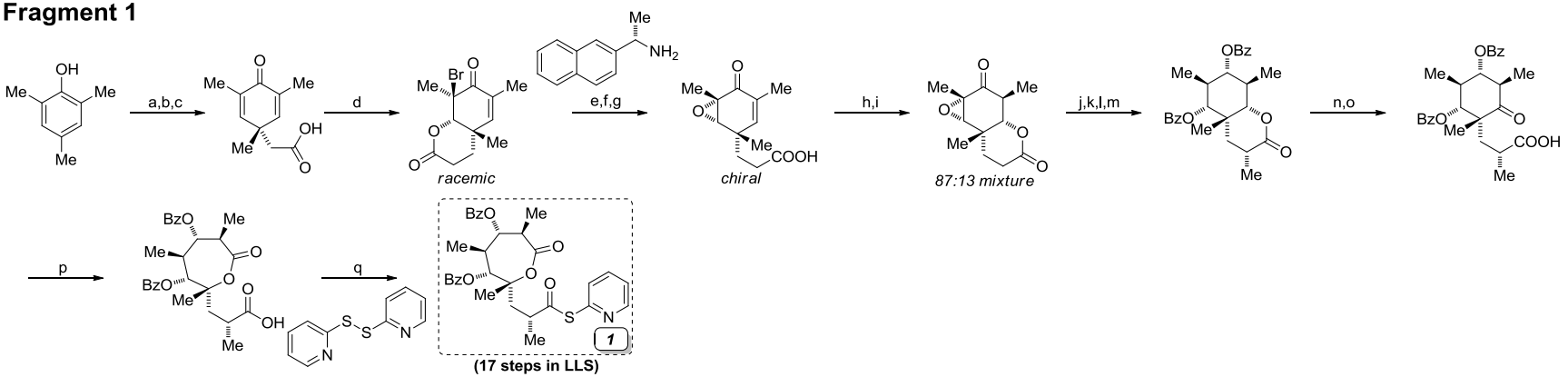
Seco Acid and End Game



Key: (a) *t*BuOCl; (b) *i*PrOH, ErMgBr; (c) TEMPO, NaOCl, KBr; (d) $PrPPh_3Br$, *t*BuLi; (e) $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, $MeSO_3NH_2$, K_2CO_3, K_2OsO_4; (f) HF-Py, Py; (g) TEMPO, NaOCl, KBr; (h) $NaClO_2$, 2-methyl-2-butene; (i) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (j) HF-NEt_3, NEt_3; (k) Raney-Ni, AcOH, H_2; (l) $Pd(OAc)_2$, MeOH, H_2

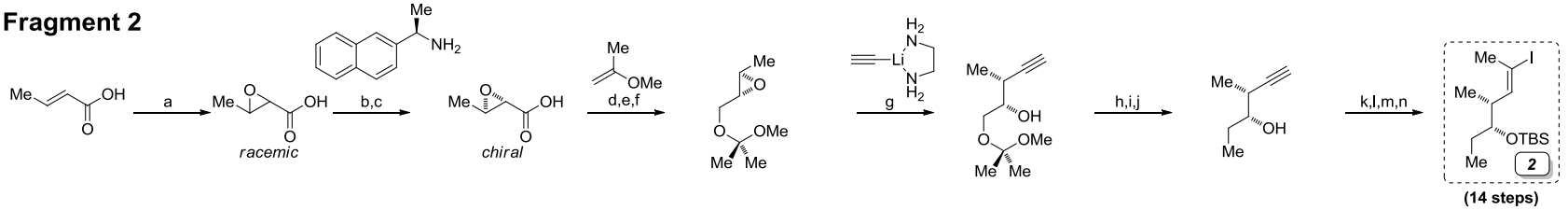
F. Corey *et al. J. Am. Chem. Soc.* **1978**, *100*, 5620.

Fragment 1



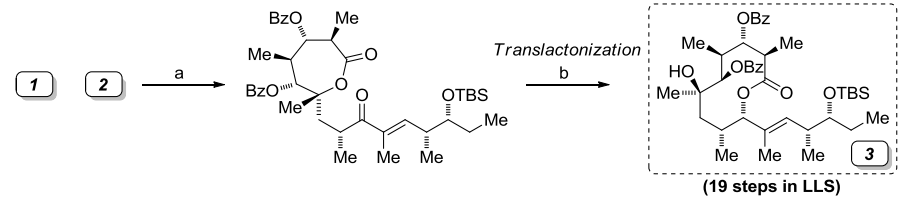
Key: (a) Allyl-Br, NaOMe; (b) BH_3•THF, H_2O_2, NaOH; (c) CrO_3, H_2SO_4; (d) Br_2, KBr; (e) KOH; (f) Amine, recrystallization; (g) MsOH; (h) Br_2, KBr; (i) Bu_3SnH, AIBN; (j) Al/Hg; (k) H_2, Raney-Ni; (l) BzCl, Py; (m) MeI, LDA, HMPA; (n) LiOH; (o) CrO_3, H_2SO_4; (p) AcOOH; (q) PPh_3

Fragment 2



Key: (a) H_2O_2, Na_2WO_4; (b) Amine, recrystallization; (c) MsOH; (d) $ClCO_2Et$, TEA; (e) $NaBH_4$; (f) $POCl_3$; (g) Lithium reagent; (h) Amberlite-50; (i) MsCl, Py; (j) Me_2CuLi; (k) TBSCl, Imidazole; (l) LDA, MeI; (m) Cp_2ZrHCl; (n) I_2, CCl_4

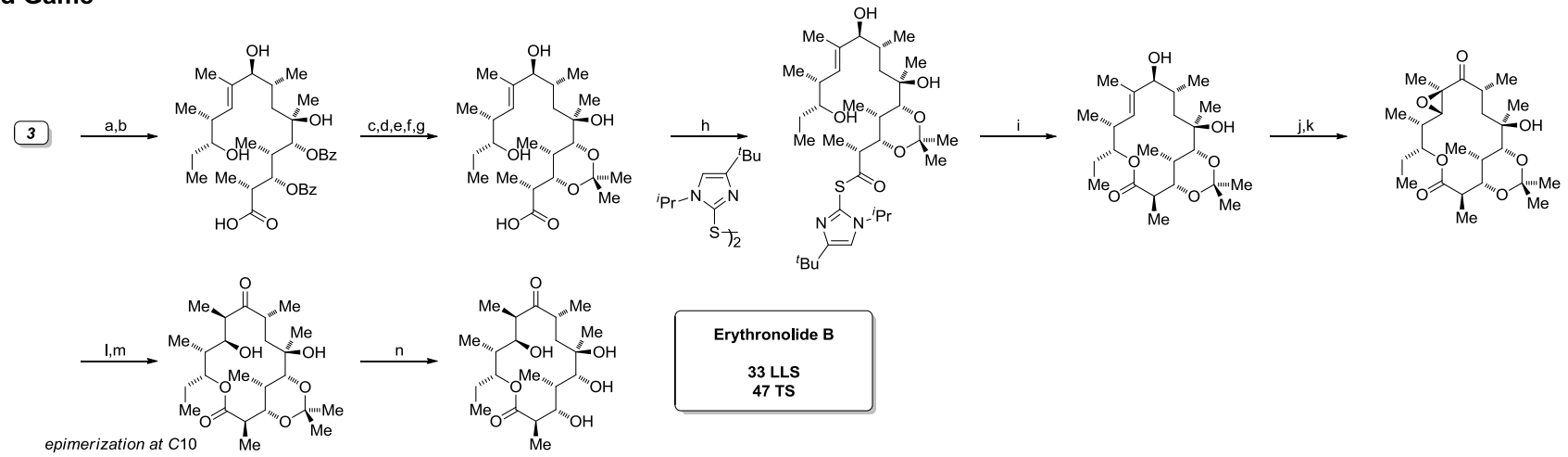
Coupling Fragment 1 and 2



Key: (a) BuLi, $MgBr_2$; (b) $Zn(BH_4)_2$

F. Corey *et al. J. Am. Chem. Soc.* **1978**, *100*, 5620. (Cont'd)

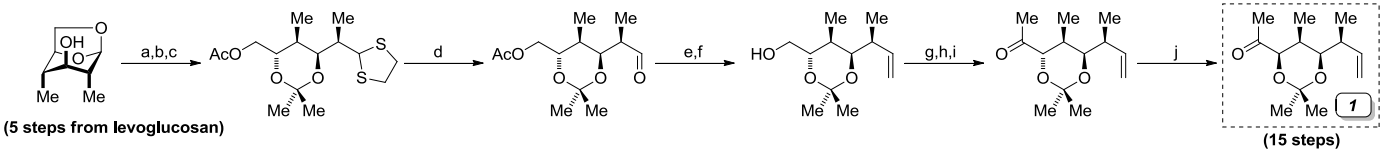
End Game



Key: (a) AcOH; (b) LiOH, H_2O_2; (c) KOH; (d) CH_2N_2; (e) HBr; (f) $Me_2C(OMe)_2$, Amberlite-50; (g) KOH; (h) PPh_3; (i) Heating; (j) MnO_2; (k) H_2O_2, NaOH; (l) H_2, Pd/C; (m) K_2CO_3; (n) HCl

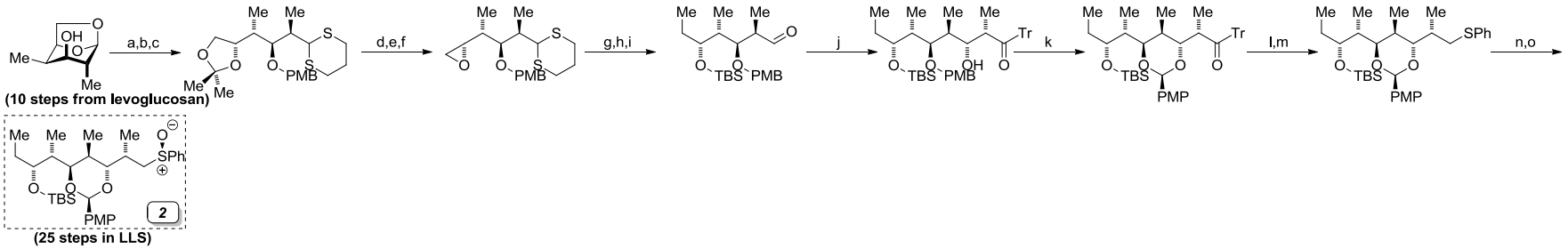
G. Kochetkov *et al. Tetrahedron Lett.* **1987**, *28*, 3835.

Fragment 1



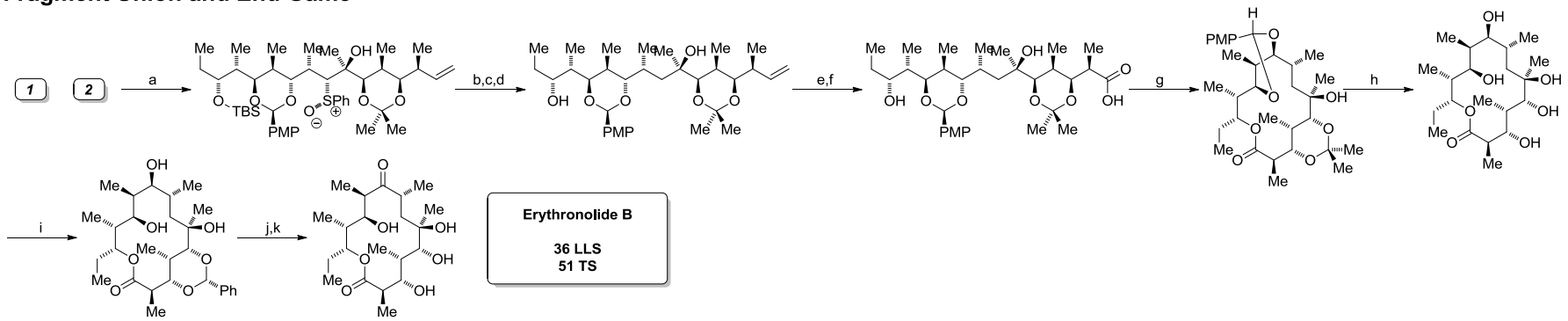
Key: (a) $HS(CH_2)_2SH$, BF_3OEt_2; (b) Ac_2O-Py; (c) DMP-Me_2CO, TsOH; (d) $HgCl_2$, $CaCO_3$; (e) $Ph_3P{=}CH_2$; (f) MeONa, MeOH; (g) $(COCl)_2$, DMSO, TEA; (h) MeMgCl; (i) $(COCl)_2$, DMSO, TEA; (j) K_2CO_3, MeOH

Fragment 2



Key: (a) $HS(CH_2)_2SH$, BF_3OEt_2; (b) DMP-Me_2CO, TsOH; (c) NaH, PMBCl; (d) AcOH, H_2O; (e) TsCl, Py; (f) K_2CO_3, MeOH; (g) MeMgCl, CuCl-Me_2S, THF; (h) *t*-$BuPh_2SiClO_4$, TEA; (i) $HgCl_2$-$CdCO_3$; (j) C_2H_5COTr, BuLi; (k) DDQ, 3A MS, DCM; (l) $LiBHEt_3$; (m) Ph_2S_2, PBu_3, Py; (n) MCPBA, FAA; (o) collidine

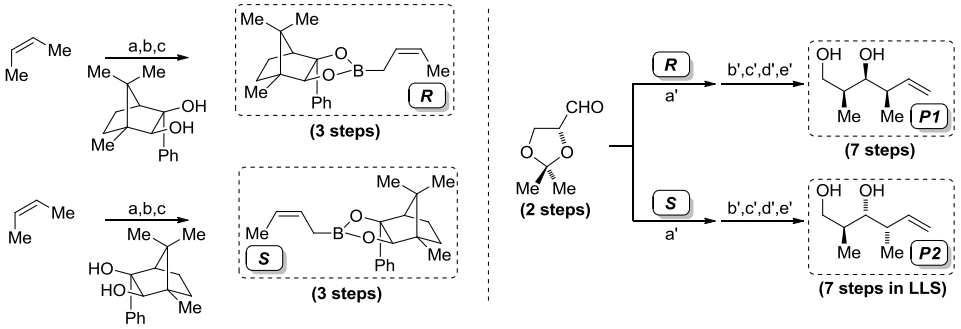
Fragment Union and End Game



Key: (a) LDA, THF; (b) TFAA, NaI, Me_2CO; (c) Na, NH_3; (d) TBAF, THF; (e) O_3; (f) mCPBA, pH = 7 buffer; (g) 2,2'-dithiobis(4-t-bu-l-i-pr-imidazole), PPh_3, $PhCH_3$; (h) TFA; (i) $PhCH(OEt)_2$, CSA; (j) PCC, 3A MS; (k) AcOH, H_2O

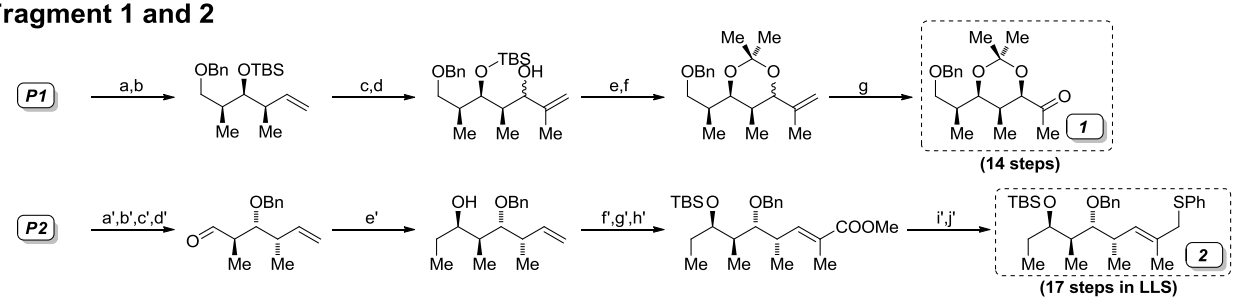
H. Mulzer *et al. J. Am. Chem. Soc.* **1991**, *113*, 910.

Chiral Auxiliary and Precursor 1,2



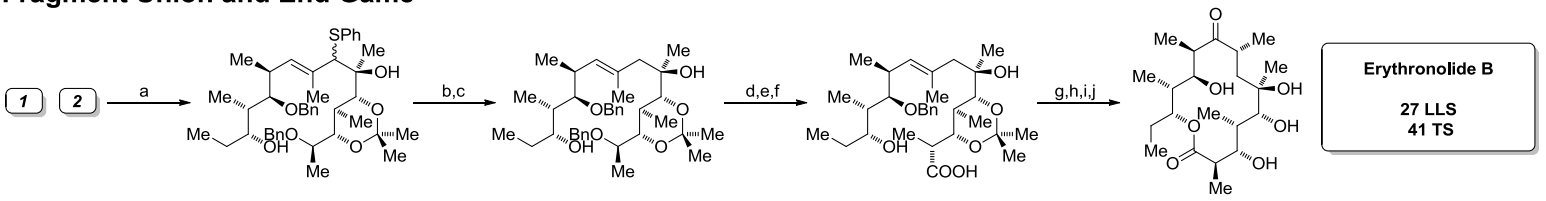
Key: (a) BuLi, *t*BuOK; (b) Cl-B(NMe$_2$)$_2$; (c) distillation
(a') -78 °C; (b') TsCl; (c') PPTS; (d') NaHCO$_3$; (e') Me$_2$CuLi

Fragment 1 and 2



Key: (a) NaH, BnBr; (b) TBSCl, Imid.; (c) O_3, PPh_3; (d) H_2C=C(Me)-MgBr; (e) TBAF; (f) DMP, H^+; (g) O_3, PPh_3
(a') TrCl, DMAP, Py; (b') NaH, BnBr; (c') HCOOH, then KOH; (d') $(COCl)_2$, DMSO, TEA; (e') EtMgBr; (f') TBSCl, TEA; (g') O_3, PPh_3; (h') Ph_3P-C(Me)COOMe; (i') DIBAL-H; (j') Bu_3P, $(PhS)_2$, Py

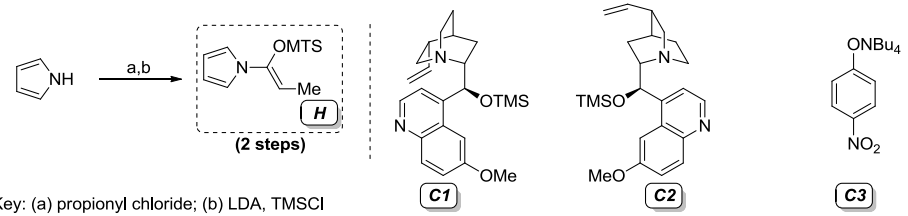
Fragment Union and End Game



Key: (a) BuLi, TMEDA, then BF_3; (b) Li/EtNH$_2$; (c) Ac_2O, DMAP, Py; (d) *t*BuOK; (e) PDC, DMF; (f) NaOH; (g) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (h) BH_3•SMe_2, then H_2O_2; (i) PCC; (j) 80% HOAc

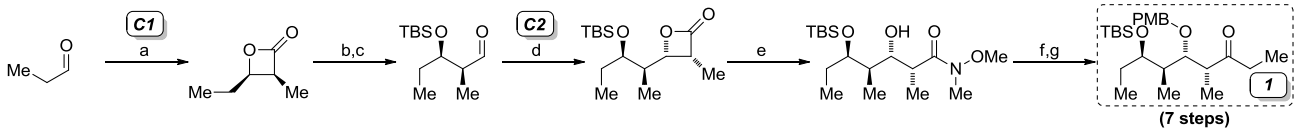
I. Nelson *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 2591.

Catalyst and Homologation Reagent



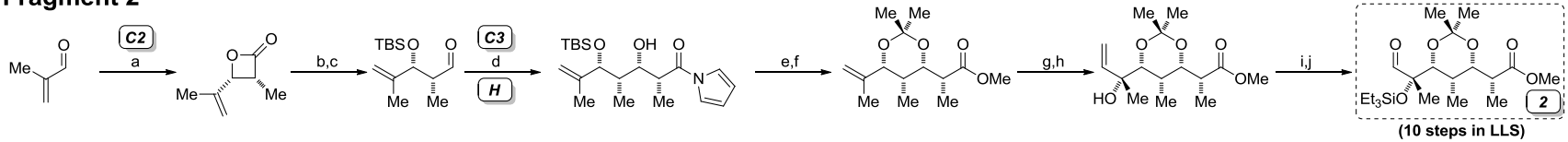
Key: (a) propionyl chloride; (b) LDA, TMSCl

Fragment 1



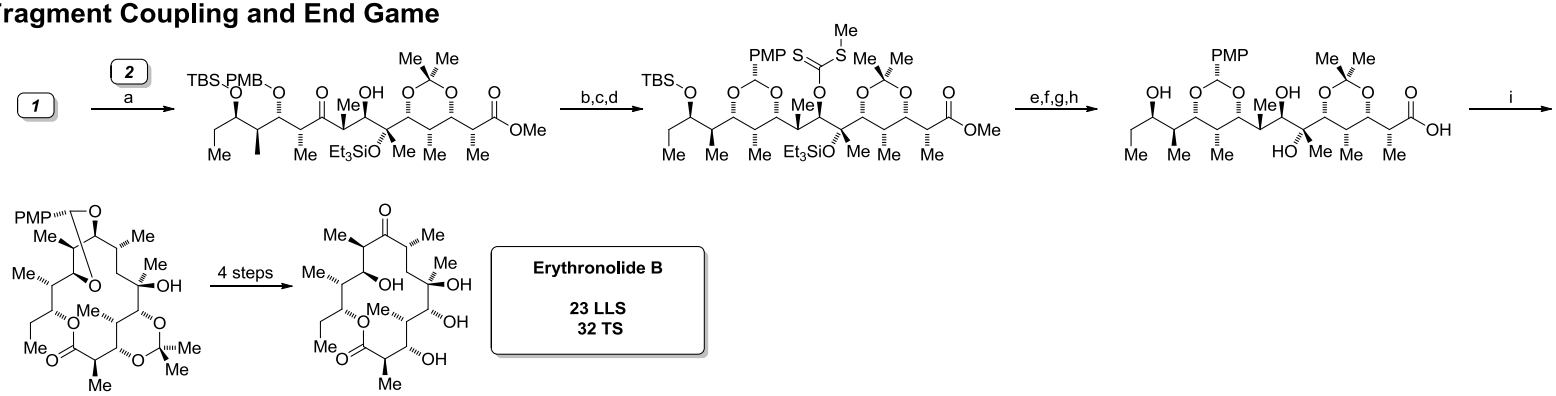
Key: (a) EtCOCl, *i*Pr$_2$NEt, LiClO$_4$; (b) EtSH, KHMDS; (c) DIBAL-H; (d) EtCOCl, *i*Pr$_2$NEt, LiI; (e) MeO(Me)NH$_2$Cl, Me$_2$AlCl; (f) EtMgBr; (g) PMBOC(NH)CCl$_3$, BF$_3$-OEt$_2$

Fragment 2



Key: (a) EtCOCl, *i*Pr$_2$NEt, LiI; (b) EtSH, KHMDS, TBSCl, NEt$_3$; (c) DIBAL-H; (d) 1N HCl; (e) Me$_2$C(OMe)$_2$, CSA; (f) NaOMe; (g) O$_3$, Me$_2$S; (h) EtMgBr; (i) O$_3$, Me$_2$S; (j) TESOTf, 2,6-lutidine

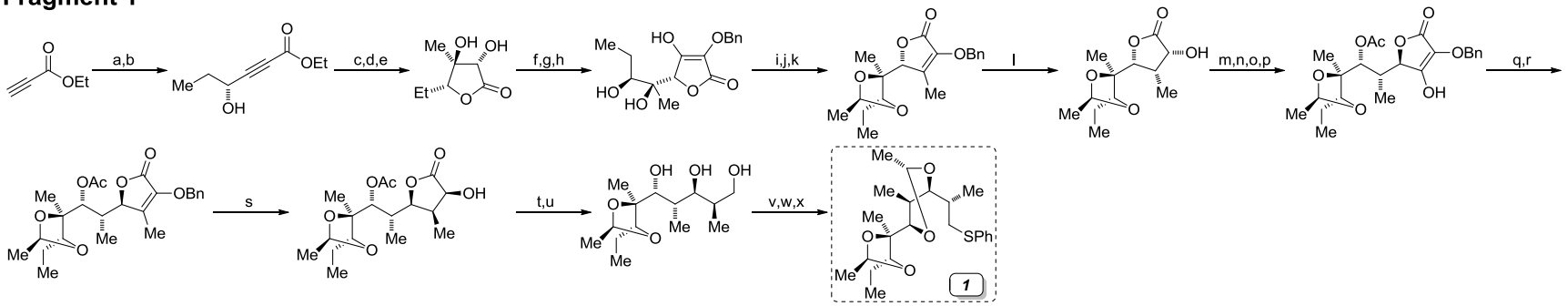
Fragment Coupling and End Game



Key: (a) LHMDS; (b) Zn(BH$_4$)$_2$; (c) DDQ; (d) KHMDS, CS$_2$, MeI; (e) AIBN, Bu$_3$SnH; (f) PMPCH(OMe)$_2$, CSA; (g) LiOH; (h) TBAF; (i) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP

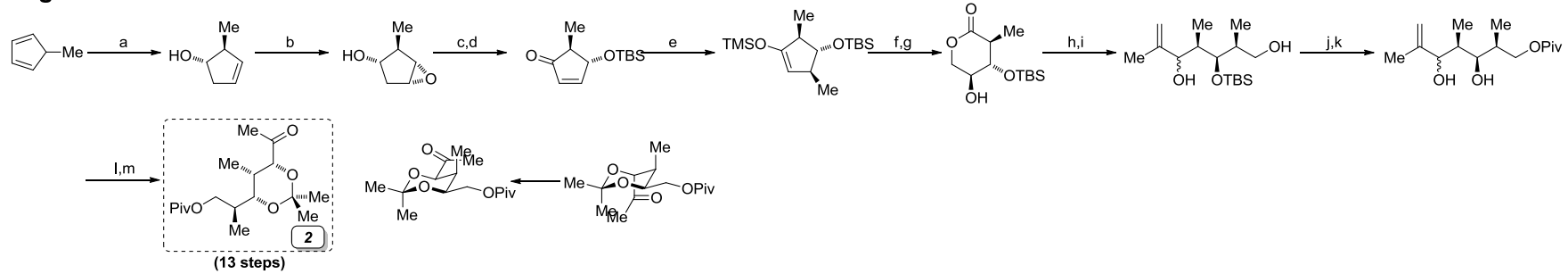
J. Stork *et al. J. Am. Chem. Soc.* **1987**, *109*, 1565.

Fragment 1



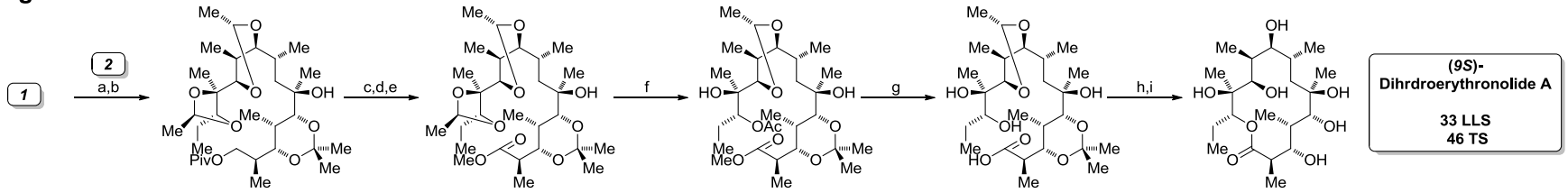
Key: (a) BuLi, propionyl chloride; (b) 9-BBN, (*R*)-pinene; (c) H_2C=C(Me)OMe, CSA; (d) dimethylthiocuprate, then acid; (e) OsO_4, NMO; (f) TMSCl, Imid.; (g) LHMDS, $EtOC(O)CH_2OBn$; (h) K_2CO_3; (i) $MeCH(COMe)_2$, CSA; (j) $(PhO)_2P(O)Cl$, Na_2CO_3, TBABr; (k) Me_2Zn, $Ni(acac)_2$; (l) H_2, Pd/C; (m) $TMSNMe_2$; (n) LHMDS, $EtOC(O)CH_2OBn$; (o) K_2CO_3; (p) Ac_2O, TEA, DMAP; (q) $(PhO)_2P(O)Cl$, Na_2CO_3, TBABr; (r) Me_2Zn, $Ni(acac)_2$; (s) Rh/Alumina, H_2; (t) LAH, HOAc, HIO_4; (u) $NaBH_4$; (v) $CH_3C(OEt)_3$, PPTS; (w) BH_3-THF; (x) $(PhS)_2$, PPh_3

Fragment 2



Key: (a) (*R*)-pinene, BH_3-THF, then H_2O_2; (b) $VO(acac)_2$; (c) CrO_3, H_2SO_4; (d) NEt_3, then TBSCl, DMAP; (e) $LiCuMe_2$, then TMSCl; (f) O_3, $NaBH_4$; (g) 2N HCl; (h) DIBAL-H; (i) 2-propenyl lithium; (j) TBAF; (k) PivCl, DMAP, TEA; (l) $Me_2C(OMe)_2$, PPTS; (m) O_3, PPh_3

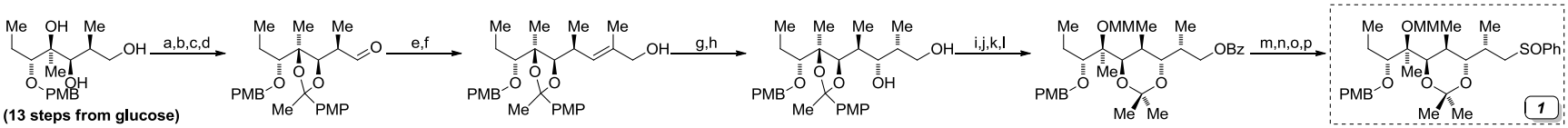
Fragment Union



Key: (a) 4,4'-dibutylbiphenyl, Li; (b) $MgBr_2$; (c) MeLi; (d) PDC; (e) Me_2SO_4; (f) O_3; (g) KOH, aq. MeOH; (h) DCC, DMAP, refluxing chloroform; (i) HCl

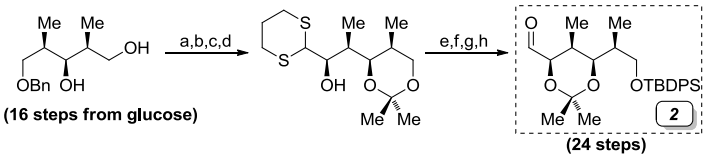
K. Yonemitsu *et al. Tetrahedron Lett.* **1987**, *28*, 4569.

Fragment 1



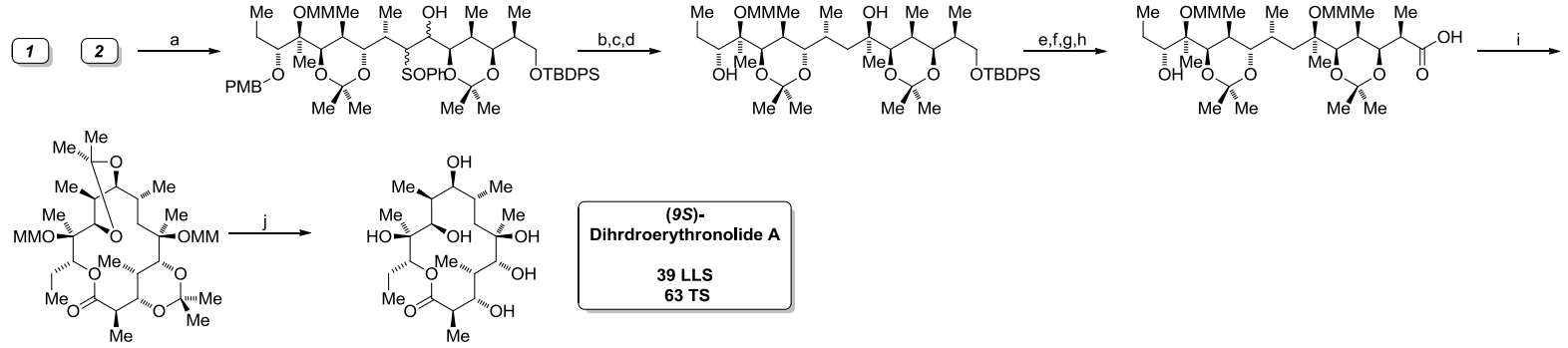
Key: (a) BzCl, Py; (b) $PMPCMe(OMe)_2$, CSA; (c) 1N KOH, MeOH; (d) $(COCl)_2$, DMSO, TEA; (e) $Ph_3P{=}CMeCO_2Et$, EDC; (f) LAH; (g) mCPBA; (h) $NaBH_3CN$, BF_3OEt_2; (i) BzCl, Py; (j) 4N HCl; (k) $CH_2{=}C(Me)OMe$, PPTS; (l) MMCl, *i*-Pr_2NEt; (m) 1N NaOH; (n) TsCl, TEA, DMAP; (o) PhSNa, EtOH; (p) $NaIO_4$

Fragment 2



Key: (a) $Me_2C(OMe)_2$, CSA; (b) 10% Pd-C, H_2; (c) PCC, 4A MS; (d) $HS(CH_2)_3SH$, BuLi; (e) TsOH; (f) TBDPSCl, imid.; (g) $CH_2{=}C(Me)OMe$, PPTS; (h) MeI, $NaHCO_3$

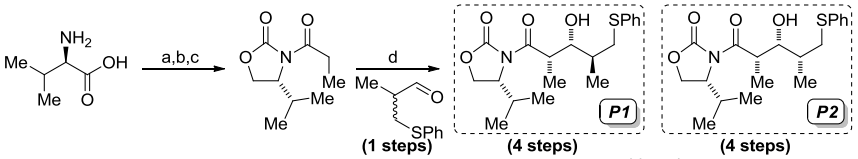
Fragment Union and Macrocyclization



Key: (a) LDA; (b) Raney Ni; (c) $(COCl)_2$, DMSO, TEA; (d) MeLi; (e) MMCl, *i*-Pr_2NEt; (f) TBAF; (g) Jones reagent; (h) 10% Pd/C, H_2; (i) 2,4,6-$Cl_3C_6H_2COCl$, TEA, then DMAP; (j) 50% HOAc

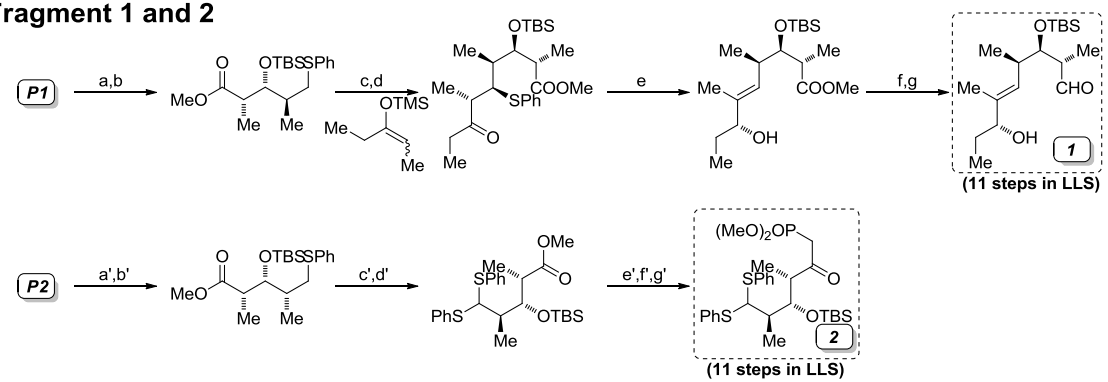
L. Paterson *et al. Tetrahedron Lett.* **1989**, *30*, 7463.

Precusor 1 and 2



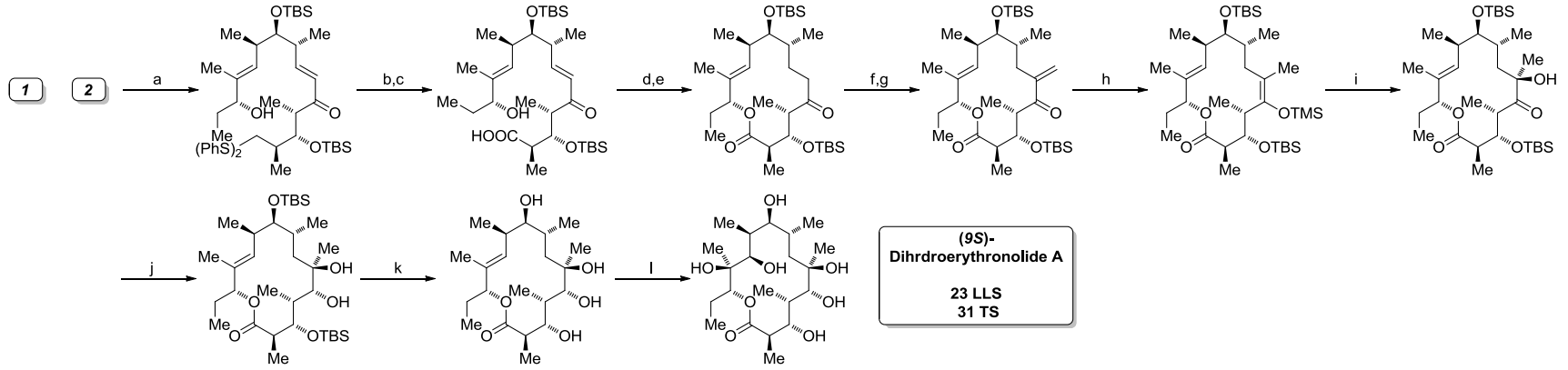
Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Bu_2BOTf, iPr_2NEt

Fragment 1 and 2



Key: (a) NaOMe; (b) TBSOTf, 2,6-lutidine; (c) NCS; (d) $ZnBr_2$; (e) $NaIO_4$; (f) (+)-*N*-methylephedrine, *N*-ethylaniline, LAH; (g) DIBAL-H
(*a*') NaOMe; (b') TBSOTf, 2,6-lutidine; (c') NCS; (d') $PhSSiMe_3$, $ZnBr_2$; (e') BuLi; (f') (+)-*N*-methylephedrine, *N*-ethylaniline, LAH; (g') DIBAL-H

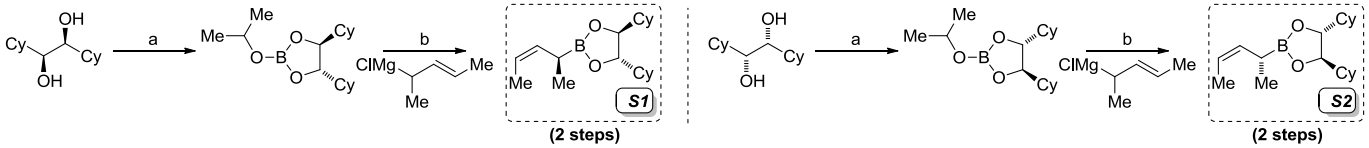
Fragment Union and Macrocyclization



Key: (a) iPr_2NEt, LiCl; (b) HgO, *aq.* HBF_4; (c) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4; (d) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (e) H_2, Rh/Al_2O_3; (f) LDA, CH_2O; (g) MsCl, TEA, then DBU; (h) L-selectride, then TMSCl; (i) OsO_4, NMO, quinuclidine; (j) $Zn(BH_4)_2$; (k) 40% *aq.* HF; (l) OsO_4, NMO, then $Na_2S_2O_5$

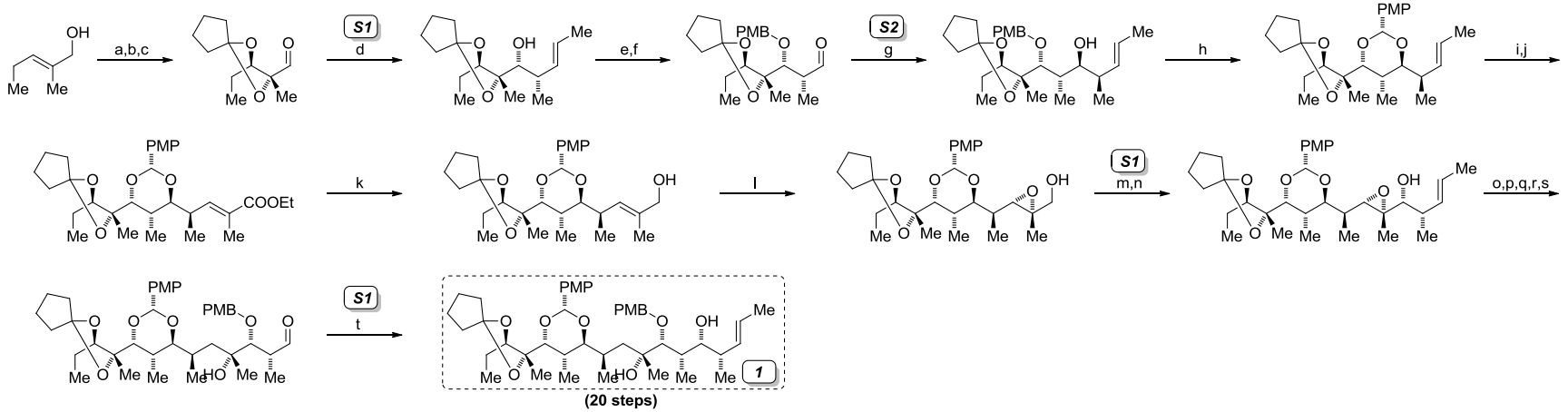
M. Hoffmann *et al. Angew. Chem. Int. Ed.* **1993**, *32*, 101.

Chiral Auxiliary



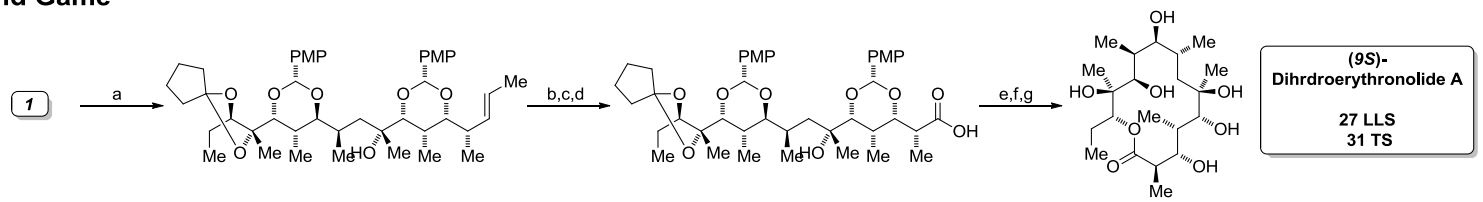
Key: (a) *i*PrOH; (b) THF, 0°C

Iterative Crotylation



Key: (a) (+)-dimethyl tartrate, $Ti(OiPr)_4$, tBu_2O_2; (b) $(COCl)_2$, TEA, DMSO; (c) $SnCl_4$, cyclopentanone; (d) 3d, benzene, 80°C; (e) NaH, PMBCl; (f) O_3, PPh_3; (g) pet. ether, 2d; (h) DDQ; (i) O_3, PPh_3; (j) $Ph_3PCH(CH_3)COOEt$; (k) LAH; (l) *t*BuOOH, (+)-dimethyl tartrate, $Ti(OiPr)_4$; (m) NMO, TPAP; (n) 10 kbar, pet. ether, 3d; (o) *i*PrMgCl; (p) LAH; (q) PMBCl, NaH; (r) NMO, OsO_4; (s) $NaIO_4$; (t) 10 kbar, pet. ether, 3d

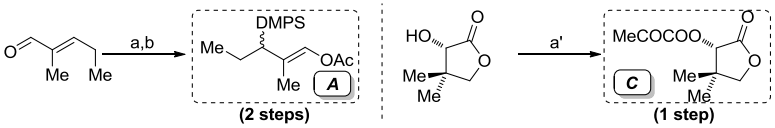
End Game



Key: (a) DDQ; (b) NMO, OsO_4; (c) $NaIO_4$; (d) CrO_3, acetone; (e) TNT, 2N HCl; (f) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (g) 2N HCl

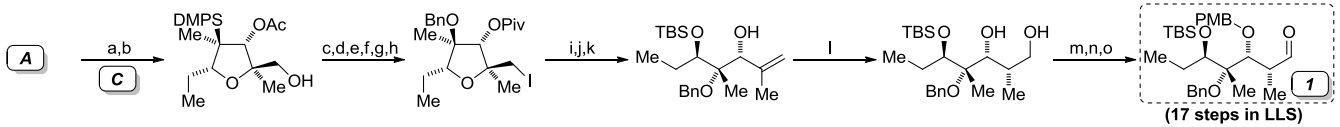
N. Woerpel *et al. J. Am. Chem. Soc.* **2003**, *125*, 6018.

Allylsilane and Auxillary Synthesis



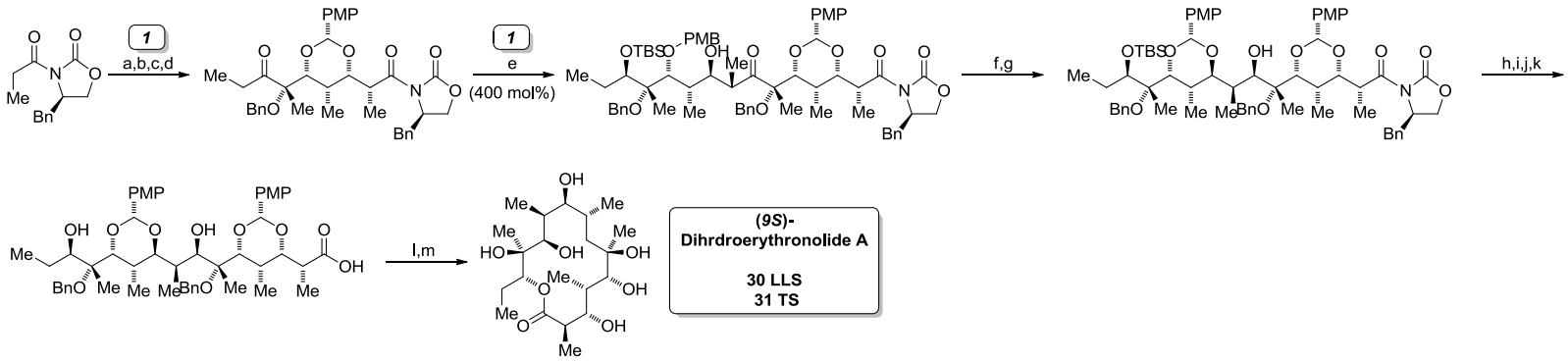
Key: (a) Li, then CuI, DMPSCl; (b) BuLi, Ac_2O
(a') MeCOCOCl, NEt_3, DMAP

Common Precursor 1



Key: (a) $TiCl_4$; (b) LAH; (c) NaH, PMBCl; (d) $PhMe_2CCOOH$; (e) NaH, BnBr; (f) CAN; (g) I_2, PPh_3; (h) Piv_2O, $Sc(OTf)_3$; (i) Zn, HOAc; (j) TBSOTf; (k) DIBAL-H; (l) HMDS, Pt(0), H_2O_2; (m) $MeOC_6H_4CH(OMe)_2$, PPTS; (n) DIBAL-H; (o) $(COCl)_2$, DMSO, TEA

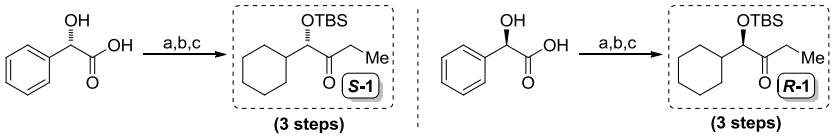
Fragment Union



Key: (a) $TiCl_4$, (-)-sparteine; (b) DDQ; (c) HF-Py, Py; (d) $(COCl)_2$, DMSO, TEA; (e) $Sn(OTf)_2$, TEA; (f) $Zn(BH_4)_2$; (g) DDQ; (h) NaH, CS_2, MeI; (i) AIBN, Bu_3SnH; (j) LiOOH; (k) TBAF; (l) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP; (m) H_2, $Pd(OH)_2/C$

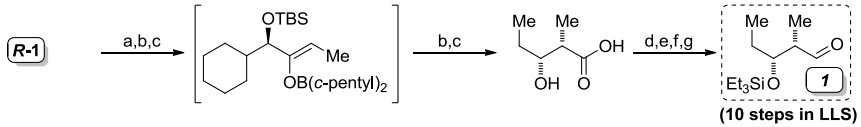
O. Masamune *et al. J. Am. Chem. Soc.* **1981**, *103*, 1568.

Auxiliary Preparation



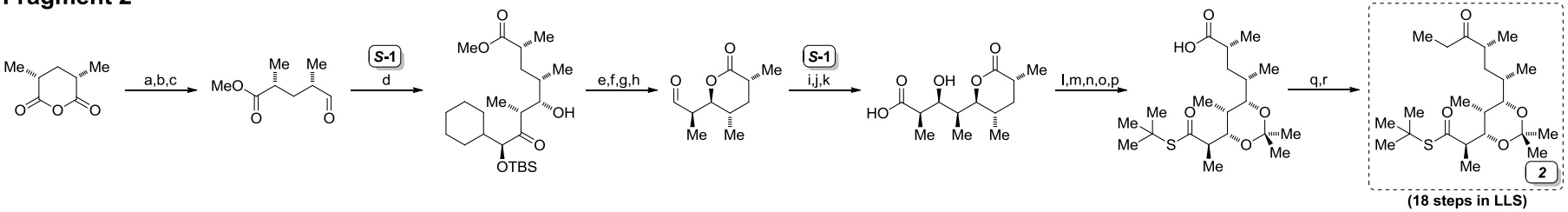
Key: (a) Rh/Al_2O_3; (b) EtLi, -78 °C; (c) TBSOTf, 2,6-lutidine

Fragment 1



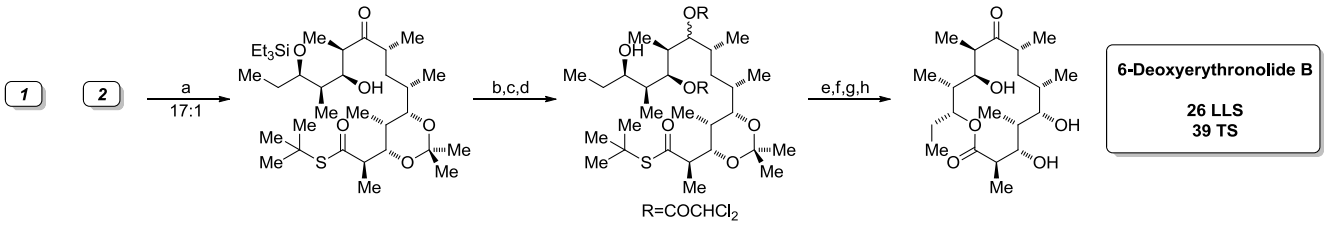
Key: (a) *c*-pentylBOTf, *i*Pr_2NEt, then acetyl aldehyde; (b) HF-MeCN; (c) $NaIO_4$; (d) CH_2N_2; (e) TESCl, DMAP; (f) DIBAL-H; (g) CrO_3•2Py

Fragment 2



Key: (a) lipase, MeOH; (b) $(COCl)_2$; (c) Pd-$BaSO_4$, H_2; (d) ***S*-1**, *c*-pentylBOTf, *i*Pr_2NEt; (e) HF-MeCN; (f) $NaIO_4$; (g) $(COCl)_2$; (h) Pd-$BaSO_4$, H_2; (i) ***S*-1**, *c*-pentylBOTf, *i*Pr_2NEt; (j) TBAF; (k) $NaIO_4$; (l) $ClCO_2Et$, Py; (m) TIS*t*Bu, HS*t*Bu; (n) KOH, H_2O; (o) TBDPSCl, DMF; (p) $MeC(OMe)=CH_2$, TFA; (q) $(COCl)_2$, Py; (r) $LiCuEt_2$

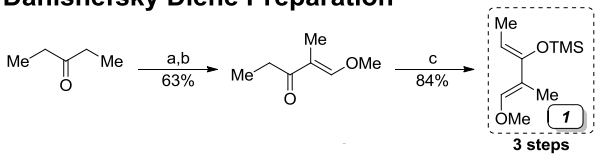
End Game



Key: (a) LHMDS; (b) $NaBH_4$, MeOH; (c) $(CHCl_2CO)_2O$, Py; (d) HOAc; (e) CuOTf, *i*Pr_2NEt; (f) KOH, H_2O/THF/MeOH; (g) PCC; (h) TFA, $MeCN/H_2O$

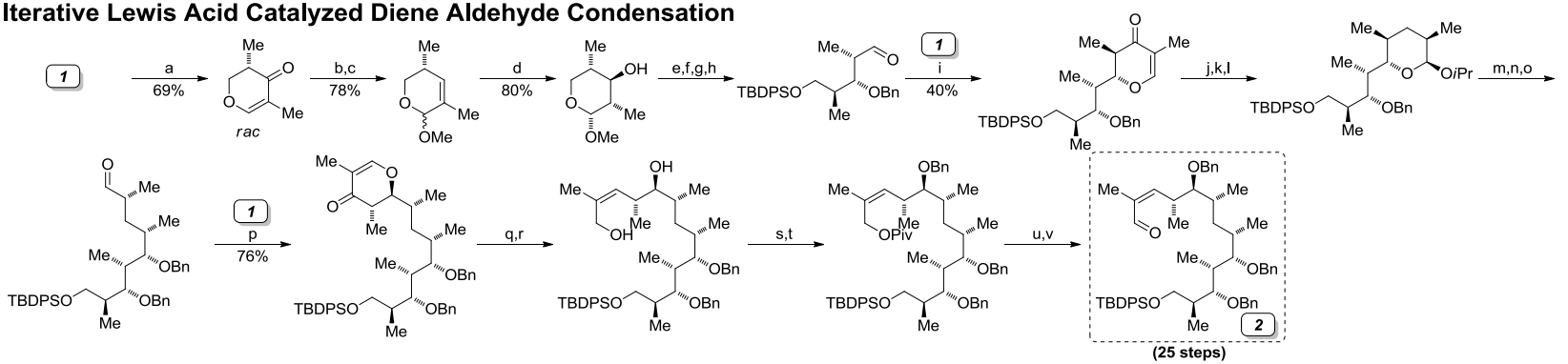
P. Danishefsky *et al. J. Org. Chem.* **1990**, *55*, 1636.

Danishefsky Diene Preparation



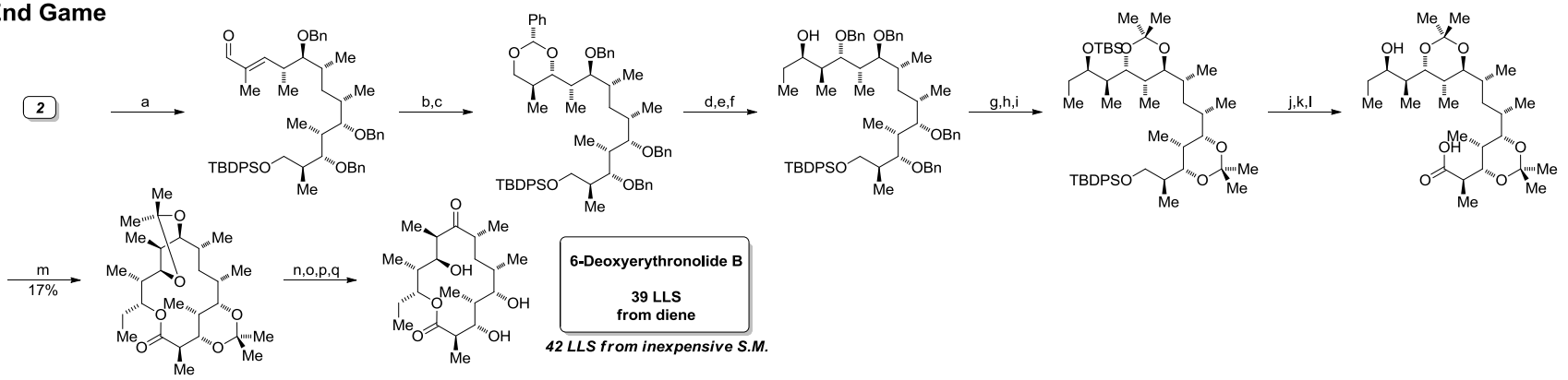
Key: (a) NaH, then ethyl formate; (b) TsOH, relux; (c) TMSOTf, TEA

Iterative Lewis Acid Catalyzed Diene Aldehyde Condensation



Key: (a) $ZnCl_2$, formaldehyde; (b) $CeCl_3$, $NaBH_4$; (c) TsOH; (d) $BH_3{\bullet}SMe_2$; (e) 1,3-propanedithiol, $TiCl_4$; (f) TBDPSCl, TEA; (g) NaH, BnBr, TBAI; (h) NBS, $NaHCO_3$; (i) $ZnCl_2$, $BF_3{\bullet}OEt_2$; (j) $CeCl_3$, $NaBH_4$; (k) TsOH, *i*PrOH; (l) Pd/Al_2O_3, H_2 (50 psi); (m) 1,3-propanedithiol, $TiCl_4$; (n) NaH, BnBr, TBAI; (o) NBS, acetone; (p) $ZnCl_2$, $BF_3{\bullet}OEt_2$; (q) $CeCl_3$, $NaBH_4$; (r) TsOH, then $LiBH_4$; (s) PivCl, TEA; (t) $BnC(NH)CCl_3$, TfOH; (u) LAH; (v) Dess-Martin periodate

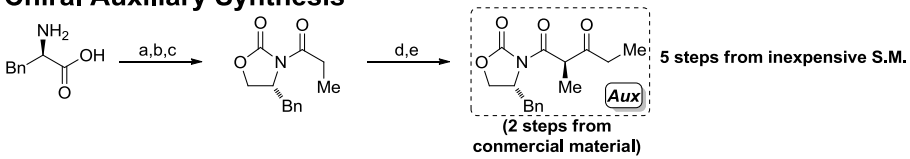
End Game



Key: (a) PhSH, BuLi; (b) $BH_3{\bullet}SMe_2$; (c) $PhCH(OMe)_2$, PPTS; (d) DIBAL-H; (e) Dess-Martin periodate; (f) EtMgBr; (g) TBSOTf, TEA; (h) Li/NH_3 (i) $(MeO)_2CH_2$, CSA; (j) TBAF, reflux; (k) $RuCl_2(PPh_3)_3$; (l) 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$; (m) TEA, 2,4,6-trichlorobenzoyl chloride, then DMAP; (n) CSA; (o) $(MeO)_2CH_2$, CSA; (p) PCC; (q) TFA, $MeCN/H_2O$

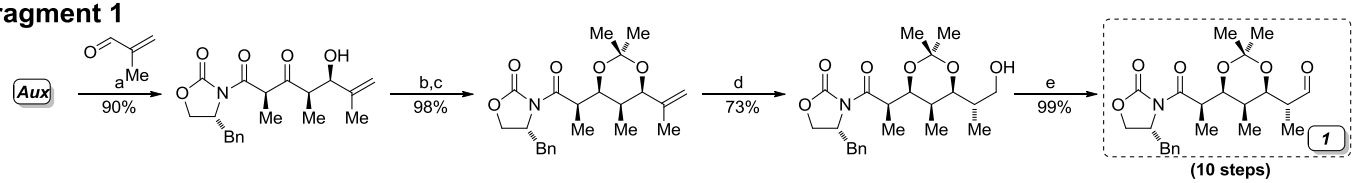
Q. Evans *et al. Tetrahedron Lett.* **1997**, *38*, 53; *J. Am. Chem. Soc.* **1998**, *120*, 5921.

Chiral Auxiliary Synthesis



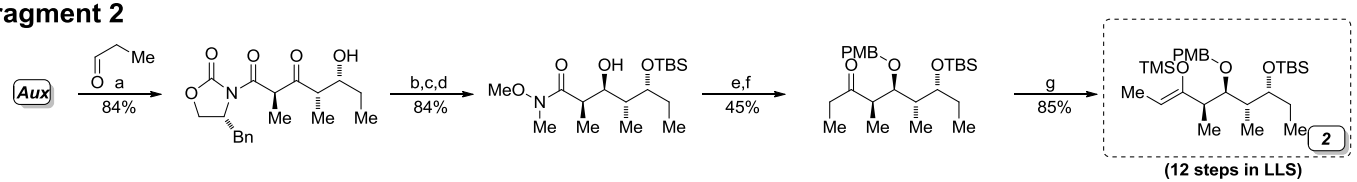
Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e) SO_3•Py, TEA, DMSO

Fragment 1



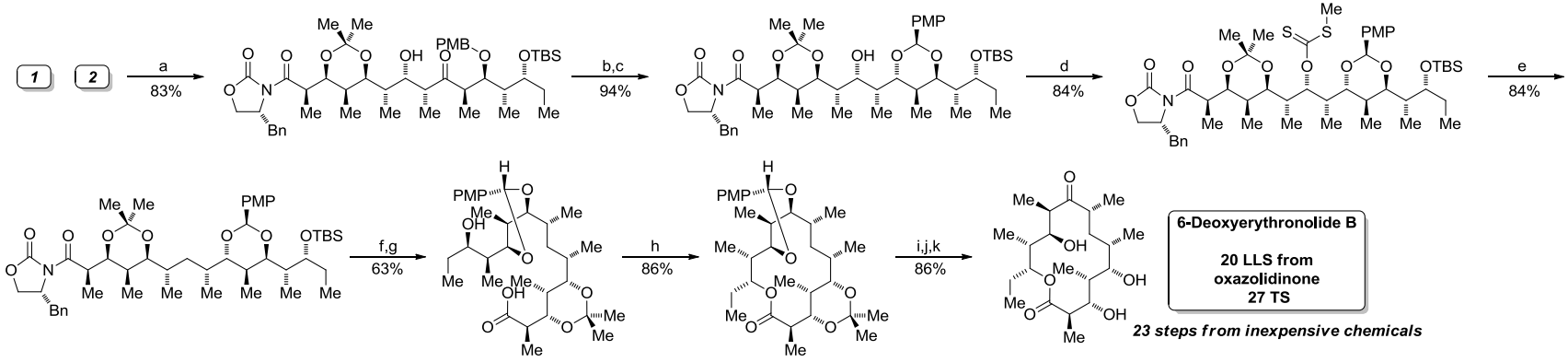
Key: (a) $TiCl_4$, iPr_2NEt, then methacrolein; (b) $Zn(BH_4)_2$; (c) $Me_2C(OMe)_2$, CSA; (d) 9-BBN; (e) $(COCl)_2$, TEA, DMSO

Fragment 2



Key: (a) $Sn(OTf)_2$, TEA, then propionaldehyde; (b) $NaBH(OAc)_3$, AcOH; (c) TBSOTf, 2,6-lutidine; (d) $AlMe_3$, (MeO)MeNH•HCl; (e) EtMgBr; (f) $Cl_3CC(NH)O$-(*p*-OMe)Bn, TfOH; (g) BuLi, $(PhMe_2Si)_2NH$, TMSOTf, 2,6-lutidine

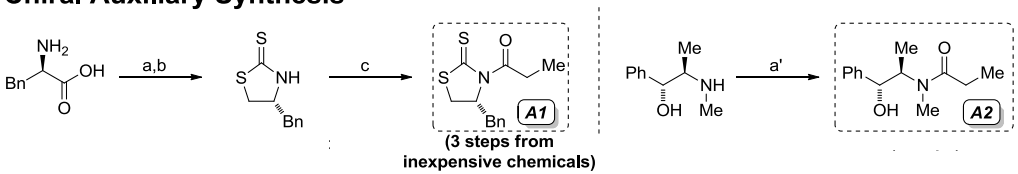
End Game



Key: (a) BF_3•OEt_2; (b) $Zn(BH_4)_2$; (c) DDQ; (d) NaH, then CS_2, then MeI; (e) AIBN, Bu_3SnH; (f) LiOOH; (g) TBAF; (h) TEA, 2,4,6-trichlorobenzoyl chloride, then DMAP (i) $Pd(OH)_2$/C, *i*PrOH; (j) PCC; (k) 1M HCl

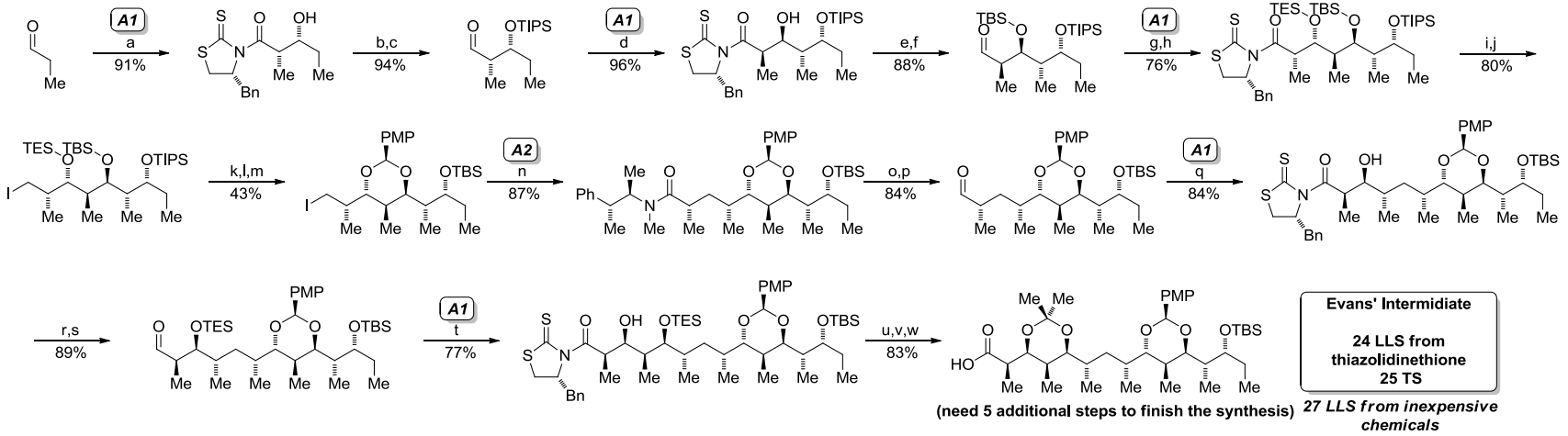
R. Crimmins *et al. Org. Lett.* **2006**, *8*, 2191.

Chiral Auxiliary Synthesis



Key: (a) $NaBH_4$, I_2; (b) KOH, CS_2, H_2O, reflux; (c) propionyl chloride, DMAP, TEA

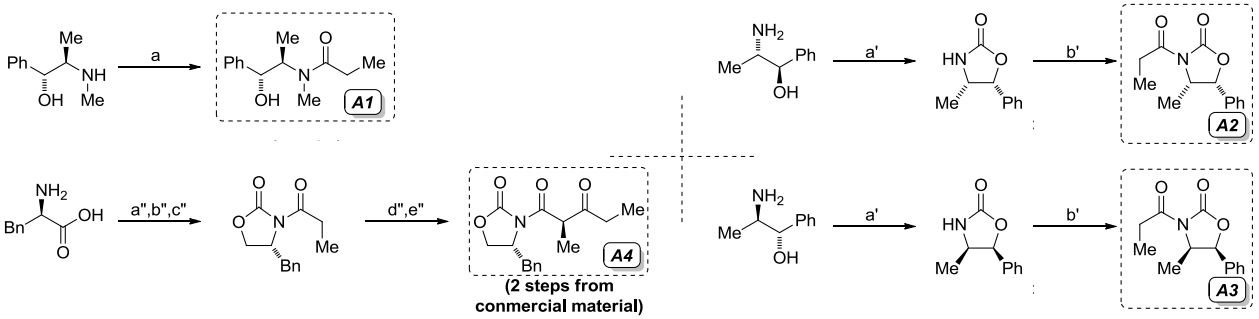
Iterative Aldol Addition



Key: (a) $TiCl_4$, iPr_2NEt, then propionaldehyde; (b) TIPSOTf, 2,6-lutidine; (c) DIBAL; (d) $TiCl_4$, (-)-sparteine, NMP; (e) TBSOTf, 2,6-lutidine; (f) DIBAL-H; (g) $TiCl_4$, iPr_2NEt; (h) TESOTf, 2,6-lutidine; (i) $LiBH_4$; (j) PPh_3, I_2; (k) TsOH, MeOH; (l) *p*-MeOPhCHO, CSA; (m) TBSOTf, 2,6-lutidine; (n) LDA, LiCl; (o) LDA, $BH_3 \bullet NH_3$; (p) Dess-Martin periodate; (q) $TiCl_4$, (-)-sparteine, NMP; (r) TESOTf, 2,6-lutidine; (s) DIBAL-H; (t) $TiCl_4$, (-)-sparteine, NMP; (u) HF-Py; (v) $(MeO)_2CMe_2$, CSA; (w) LiOH

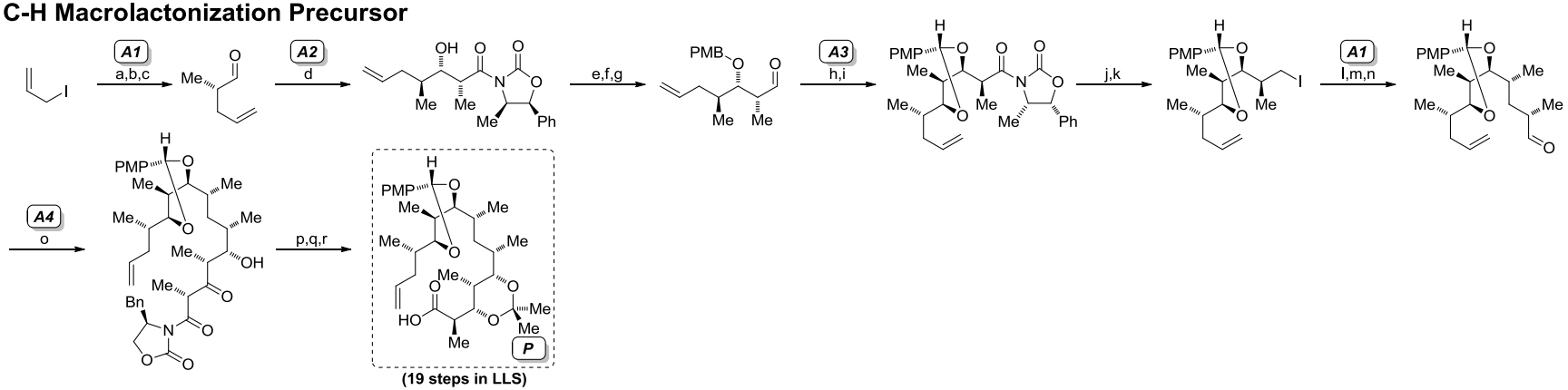
S. White *et al. Nature Chem.* **2009**, *1*, 547.

Chiral Auxiliary Synthesis



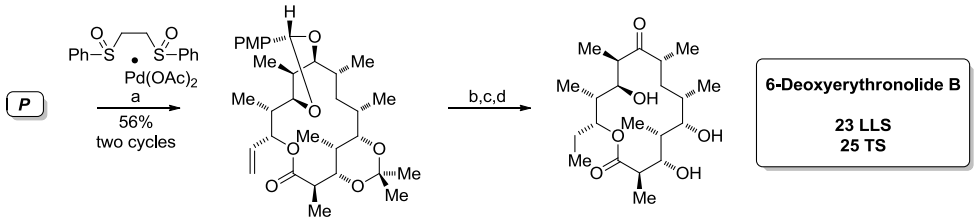
Key: (a) propionyl chloride, DMAP, TEA; (a') K_2CO_3, diethyl carbonate; (b') BuLi, then propionyl chloride; (a") $NaBH_4$, I_2; (b") K_2CO_3, diethyl carbonate; (c") BuLi, then propionyl chloride; (d") Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e") $SO_3 \cdot Py$, TEA, DMSO

C-H Macrolactonization Precursor



Key: (a) LDA, LiCl; (b) LDA, $BH_3 \bullet NH_3$; (c) $(COCl)_2$, DMSO, TEA; (d) Bu_2BOTf, iPr_2NEt; (e) $AlMe_3$, $(MeO)NHMe \bullet HCl$; (f) PMBBr, NaH; (g) DIBAL-H; (h) Bu_2BOTf, TEA; (i) DDQ; (j) LAH; (k) PPh_3, I_2, imidazole; (l) LDA, LiCl; (m) TBSOTf, 2,6-lutidine; (n) LDA, LiCl; (o) $Ti(OiPr)Cl_3$, TEA; (p) $Zn(BH_4)_2$; (q) $(MeO)_2CMe_2$, CSA; (r) LiOOH

End Game: C-H Macrolactonization

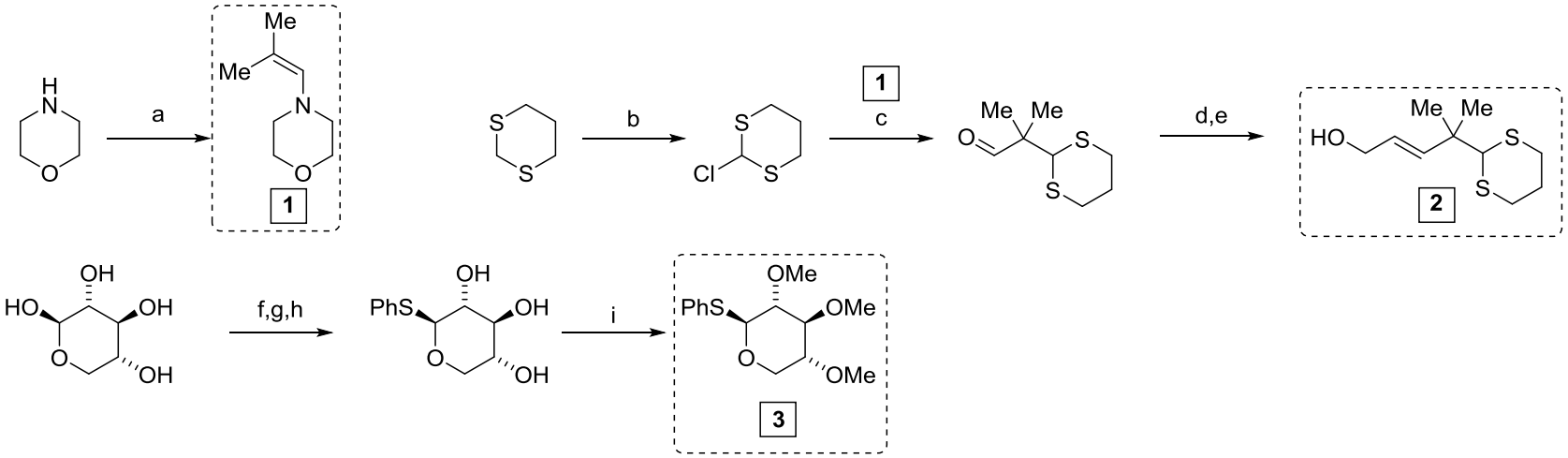


Key: (a) Cat., benzoquinone; (b) $Pd(OH)_2/C$, H_2; (c) TPAP, NMO; (d) 1M HCl

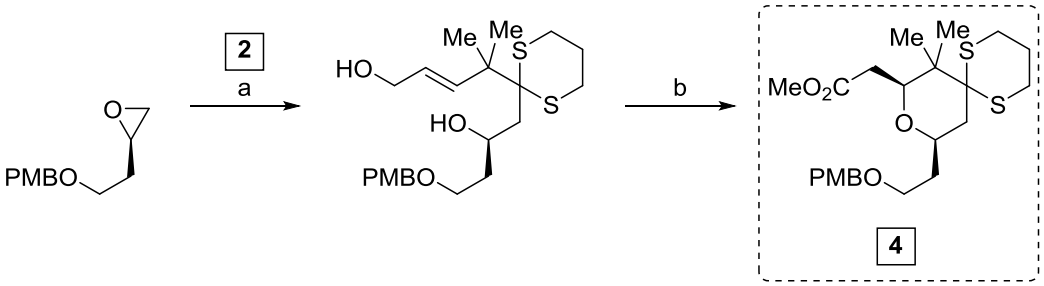
Graphical Summary of Previous Syntheses of Cyanolide A and Clavosolide A

A. Hong *et al. Org. Lett.* **2010**, *12*, 2880.

Starting Material Synthesis



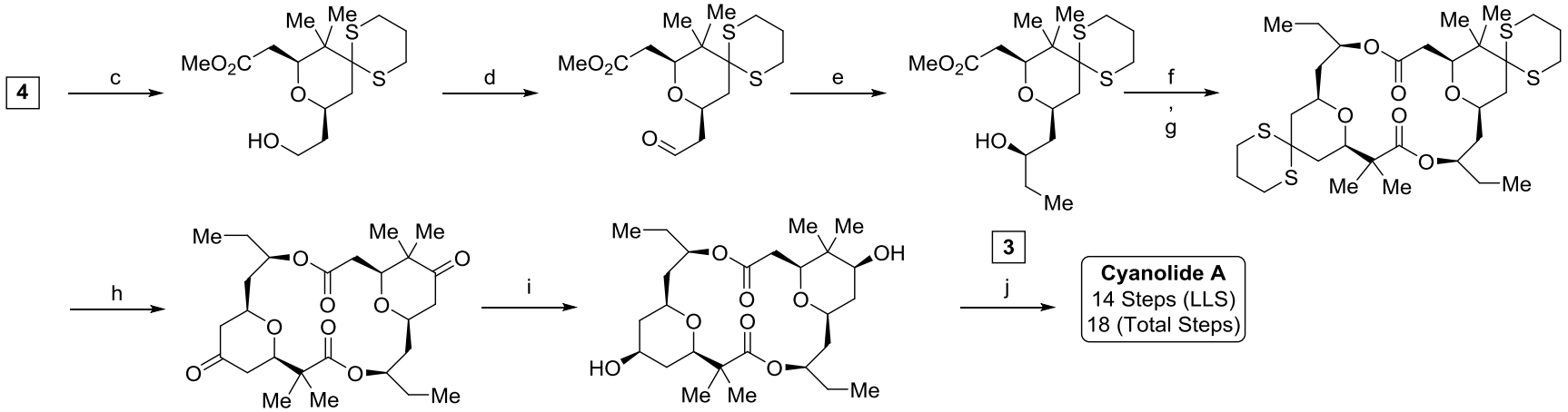
Key: (a) isobutyraldehyde, removal of H_2O; (b) N-chlorosuccinamide, benzene; (c) **1**, THF:Et_2O (1:1); (d) trimethyl phosphonoacetate, KO^{t}Bu, THF 0 °C; (e) DIBAL, toluene, -78 °C; (f) Ac_2O, pyridine, 0 °C to rt; (g) thiophenol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (h) NaOMe, MeOH, 25 °C, then Amberlite IR-120(H^+) resin; (i) NaH, MeI, DMF, rt.



Reagents: (a) **2**, ^{t}BuLi, HMPA/THF, -78 °C; (b) MnO_2, CH_2Cl_2, dimethyl triazolium iodide, DBU, MeOH, MnO_2, 4Å MS, 25 °C.

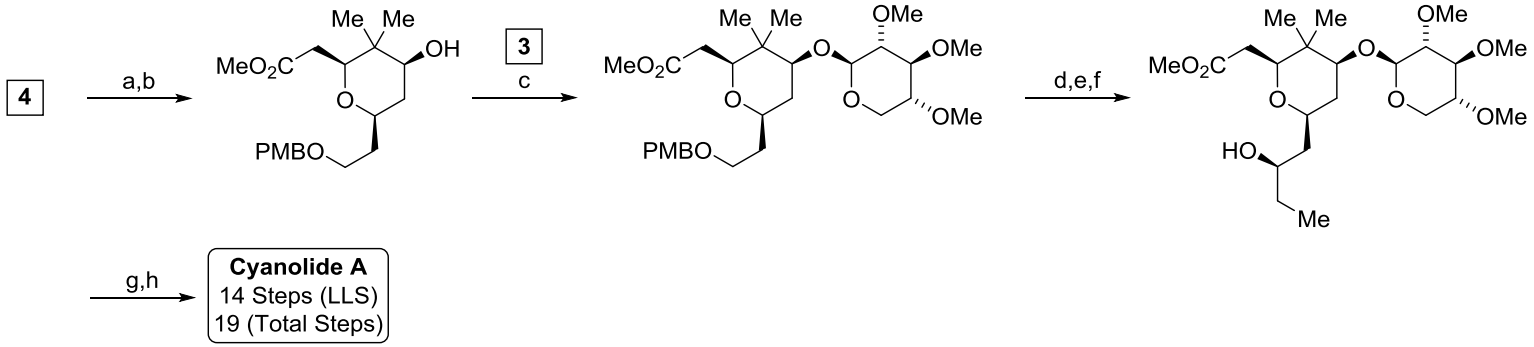
A. Hong *et al. Org. Lett.* **2010**, *12*, 2880. (Cont'd)

Dimerization-Glycosylation Route:



Key: (a) DDQ, H_2O:CH_2Cl_2 (1:10), 25 °C; (b) SO_3·pyr, Et_3N:DMSO:CH_2Cl_2 (1:1:10), 0 °C to 25 °C; (c) Et_2Zn, (+)-MIB, toluene:hexanes (1:2), 0 °C; (d) LiOH, THF:MeOH:H_2O (2:1:1), 25 °C; (g) MNBA, DMAP, toluene, 90 °C; (e) I_2, sat. aq. $NaHCO_3$:CH_3CN (1:1), 0 °C; (f) $NaBH_4$, MeOH, -40 to -20 °C; (g) **3**, MeOTf, Et_2O, 4Å MS, 25 °C.

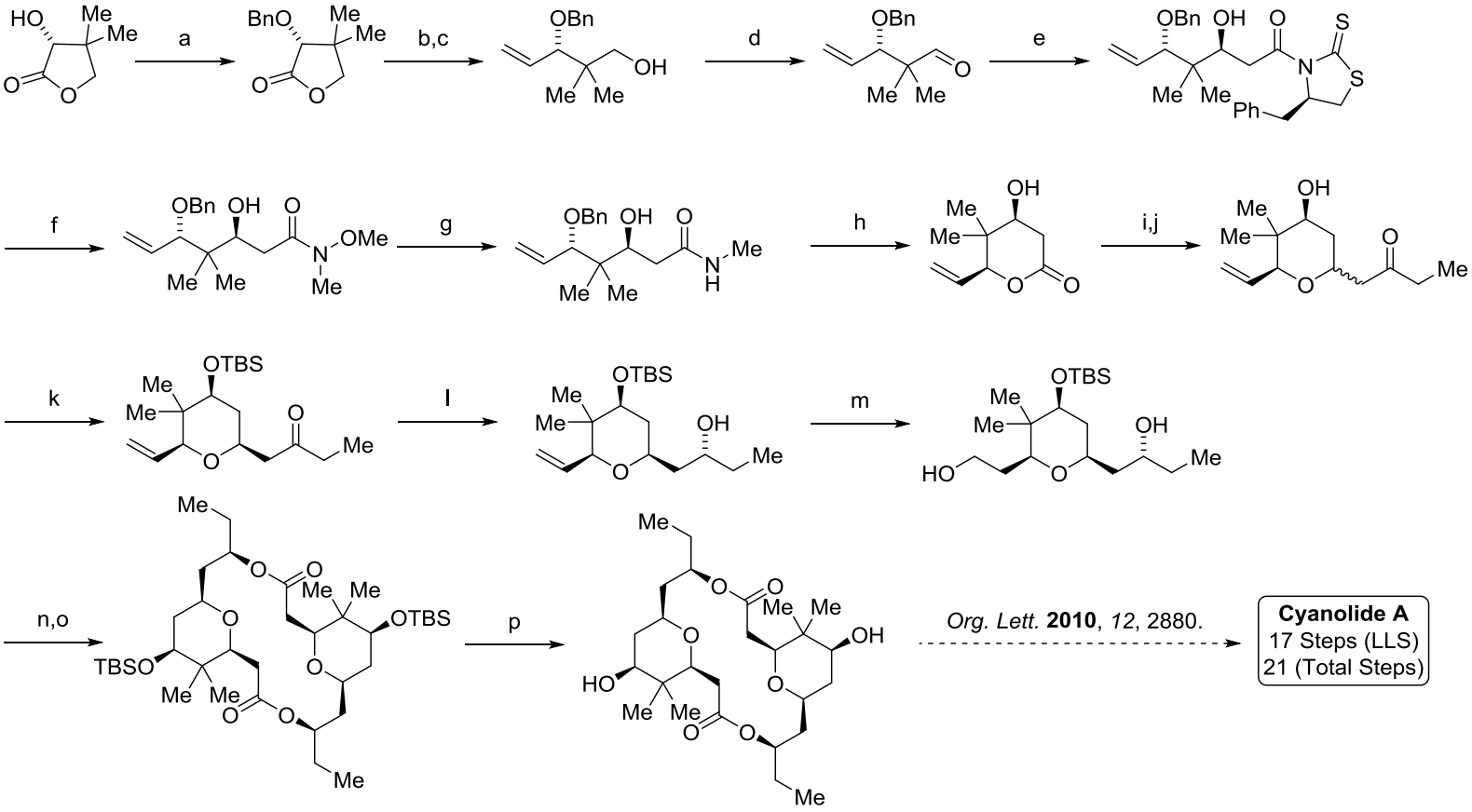
Glycosylation-Dimerization Route:



Key: (a) I_2, sat. aq. $NaHCO_3$:CH_3CN (1:1), 0 °C; (b) $NaBH_4$, MeOH, -40 to -20 °C; (c) **3**, MeOTf, Et_2O, 4Å MS, 25 °C; (d) DDQ, H_2O:CH_2Cl_2 (1:10), 25 °C; (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, 25 °C; (f) Et_2Zn, (+)-MIB, toluene:hexanes (1:2), 0 °C; (g) LiOH, THF:MeOH:H_2O (2:1:1), 25 °C; (h) MNBA, DMAP, toluene, 90 °C.

B. Pabbaraja *et al. J. Org. Chem.* **2011**, *76*, 1922.

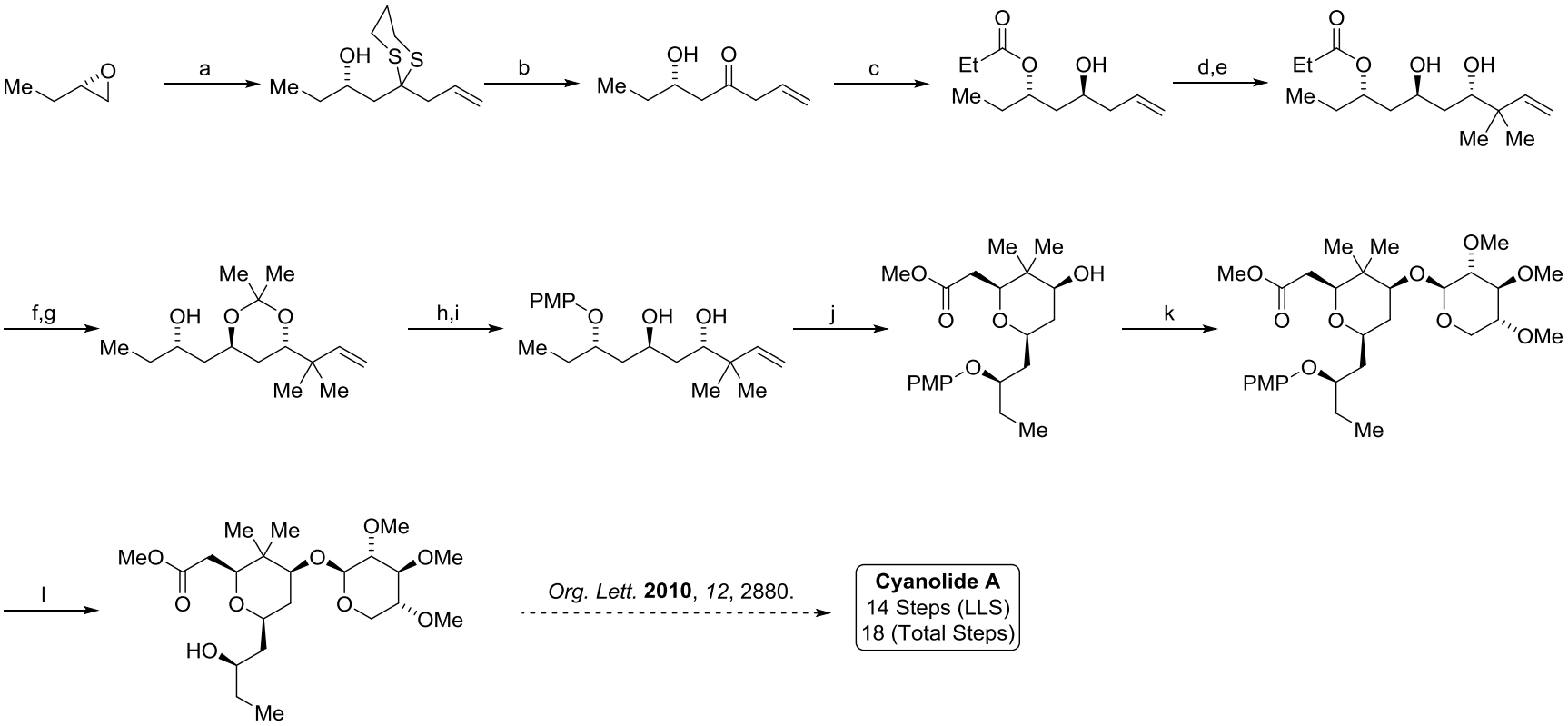
Linear Synthesis



Key: (a) Benzyl imidate, $BF_3{\cdot}Et_2O$, CH_2Cl_2:Cyclohexane (1:2); (b) DIBAL, CH_2Cl_2, -78 °C; (c) PPh_3CH_3I, ^tBuOK, THF, rt; (d) PCC, CH_2Cl_2, rt; (e) (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone, $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C to -78 °C; (f) $CH_3NHOCH_3{\xi}HCl$, imidazole, CH_2Cl_2, rt; (g) lithium naphthalenide, THF, -20 °C; (h) $Ba(OH)_2{\xi}8H_2O$, THF:H_2O (1:1), rt; (i) DIBAL, CH_2Cl_2, -78 °C; (j) 1-(triphenylphosphoranylidene)butan-2-one, benzene, reflux; (k) TBSCl, 2,6-lutidine, DMF, 0 °C to rt; (l) (*S*)-CBS, $BH_3{\xi}DMS$, THF, -30 °C; (m) $BH_3{\xi}DMS$, NaOH, H_2O_2, THF, 0 °C; (n) TEMPO, BAIB, CH_2Cl_2:H_2O (2:1) 0 °C to rt; (o) MNBA, DMAP, toluene, 90 °C; (p) 70% HF·pyr, THF, 0 °C to rt.

C. She *et al. Org. Biomol. Chem.* **2011**, *9*, 984.

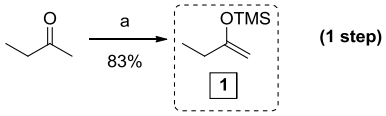
Linear Synthesis



Reagents: (a) 2-allyl-1,3-dithiane, ^{n}BuLi, THF, 0 °C; (b) I_2, $CaCO_3$, THF:H_2O (4:1), 0 °C; (c) SmI_2, EtCHO, THF, -10 °C; (d) O_3, CH_2Cl_2, -78 °C; (e) Zn, prenyl bromide, aq. NH_4Cl:THF (4:1), 0 °C; (f) 2,2-dimethoxypropane, TsOH (cat.), CH_2Cl_2, 0 °C; (g) $LiAlH_4$, THF, 0 °C; (h) 4-methoxyphenol, DIAD, PPh_3, THF, 25 °C; (i) 1 N HCl, MeOH, 0 °C; (j) $PdCl_2$ (cat.), $CuCl_2$, CH_3CN, MeOH, CO, 30 °C; (k) (3*R*,4*S*,5*R*)-3,4,5-trimethoxy-2-(phenylthio)tetrahydro-2*H*-pyran, MeOTf, 4Å MS, 25 °C; (l) CAN, CH_3CN:H_2O (4:1), 0 °C

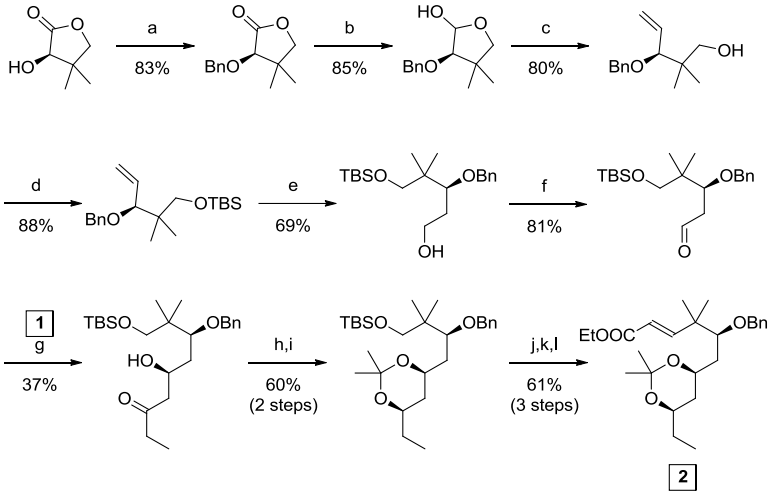
D. Reddy *et al. J. Org. Chem.* **2011**, *76*, 936.

Fragment 1

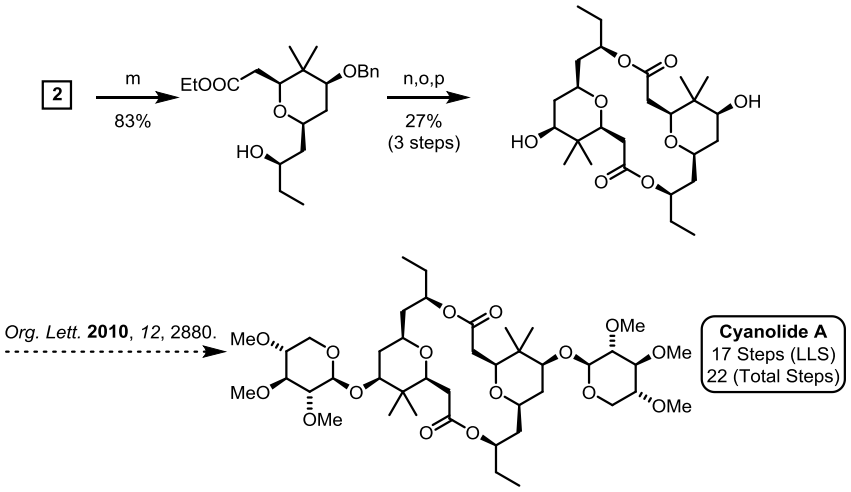


Key: (a) LDA, TMSCl, THF, -78 to 0 °C

Longest Linear Sequence



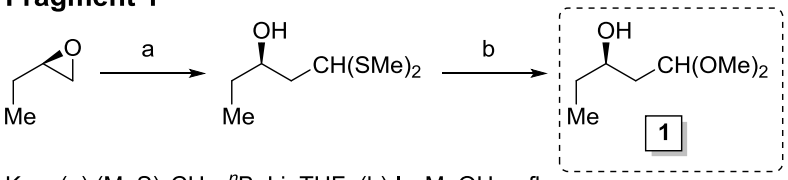
Reagents: (a) AgO, BnBr, DMF, 0 °C; (b) DIBAL, CH_2Cl_2, -78 °C; (c) methyl triphenylphosphonium bromide, THF, ^{n}BuLi in hexanes, 0 °C; (d) TBDMSCl, DMAP, pyridine, 0 °C; (e) BH_3·THF, THF, -20 °C to rt, then NaOH, H_2O_2; (f) $(COCl)_2$, CH_2Cl_2, DMSO, Et_3N, -78 °C; (g) **1**, BF_3·Et_2O, CH_2Cl_2, -78 °C; (h) catecholborane, THF, -10 °C; (i) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 25 °C; (j) TBAF, THF, 60 °C; (k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (l) $Ph_3PCHCOOEt$, toluene, reflux



Key: (m) PTSA, $CHCl_3$, reflux; (n) LiOH·H_2O, H_2O:MeOH:THF (1:1:2), 25 °C; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, reflux; (p) $Pd(OH)_2$, MeOH, H_2, rt.

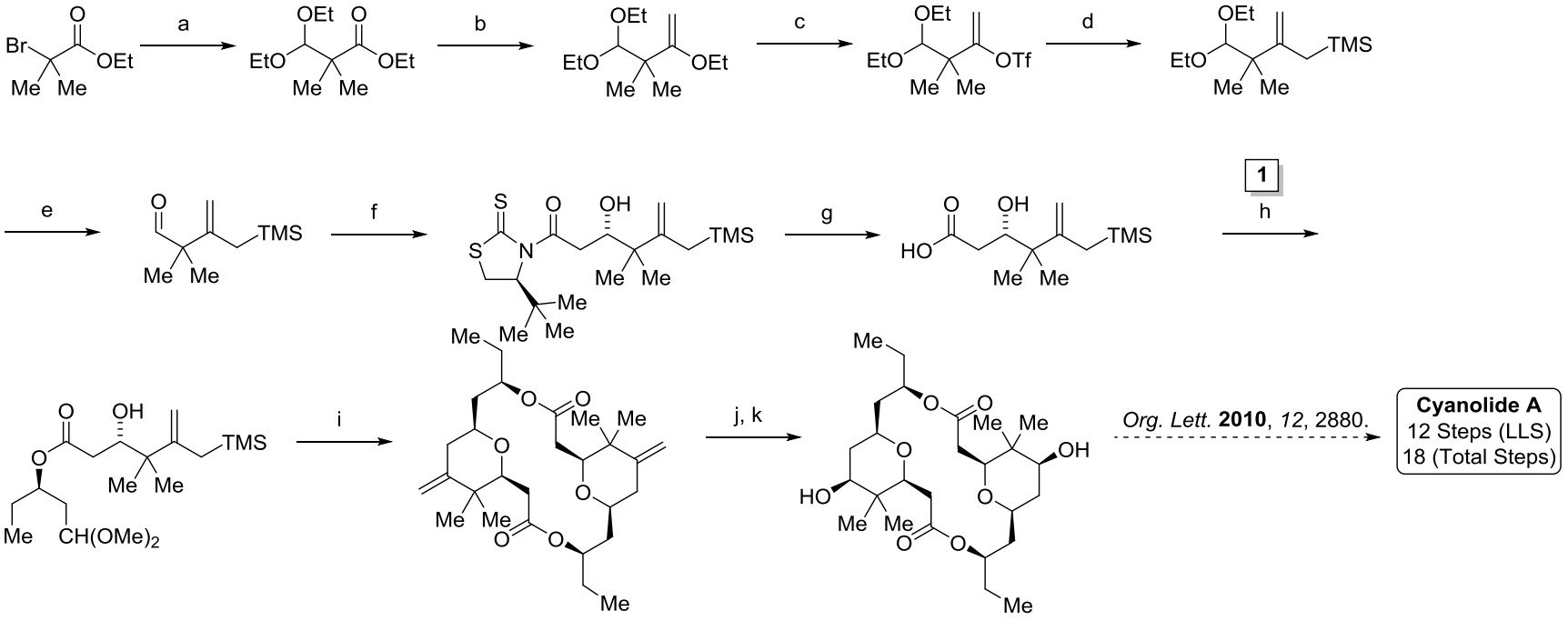
E. Rychnovsky *et al. J. Am. Chem. Soc.* **2011**, *133*, 9727.

Fragment 1



Key: (a) $(MeS)_2CH_2$, ^{n}BuLi, THF; (b) I_2, MeOH, reflux.

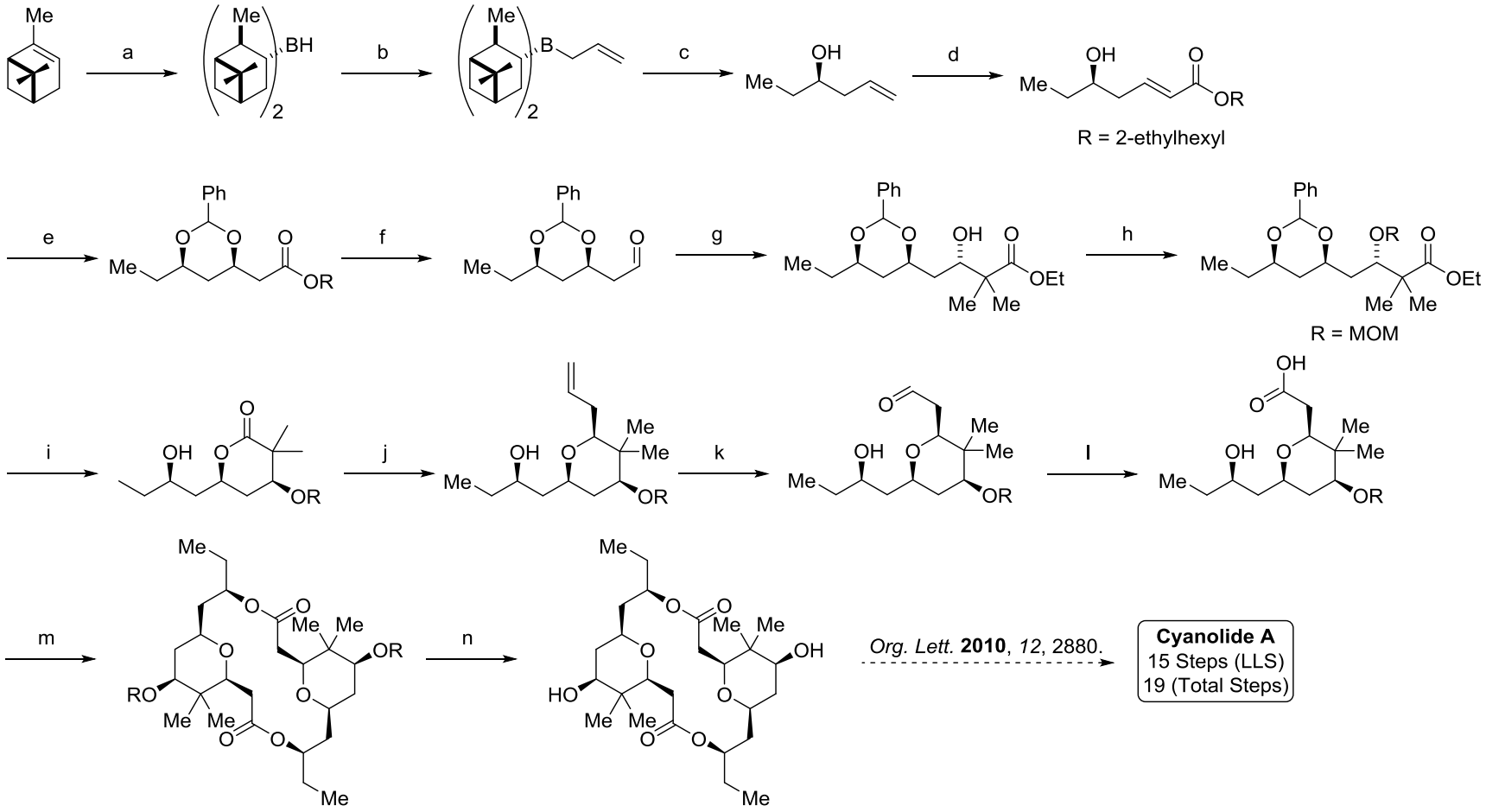
Linear Synthesis



Key: (a) Zn, ethylorthoformate, benzene; (b) $LiCH_2TMS$, pentane; (c) KHMDS, $PhNTf_2$, THF; (d) $ClMgCH_2TMS$, $Pd(PPh_3)_4$, LiCl, Et_2O ; (e) *p*TSA•H_2O, H_2O:acetone (1:1); (f) (*S*)-1-(4-(*tert*-butyl)-2-thioxothiazolidin-3-yl)ethanone, (-)-sparteine, $PhBCl_2$, CH_2Cl_2; (g) LiOH¬H $_2$O, H_2O:THF (1:2.6); (h) **1**, $Cl_3PhCOCl$, DMAP, Et_3N, benzene; (i) TMSOTf, CH_2Cl_2; (j) OsO_4, NMO, H_2O:acetone (1:3.15), then $NaIO_4$; (k) $NaBH_4$, MeOH.

F. Jennings *et al. J. Org. Chem.* **2011**, *76*, 8027.

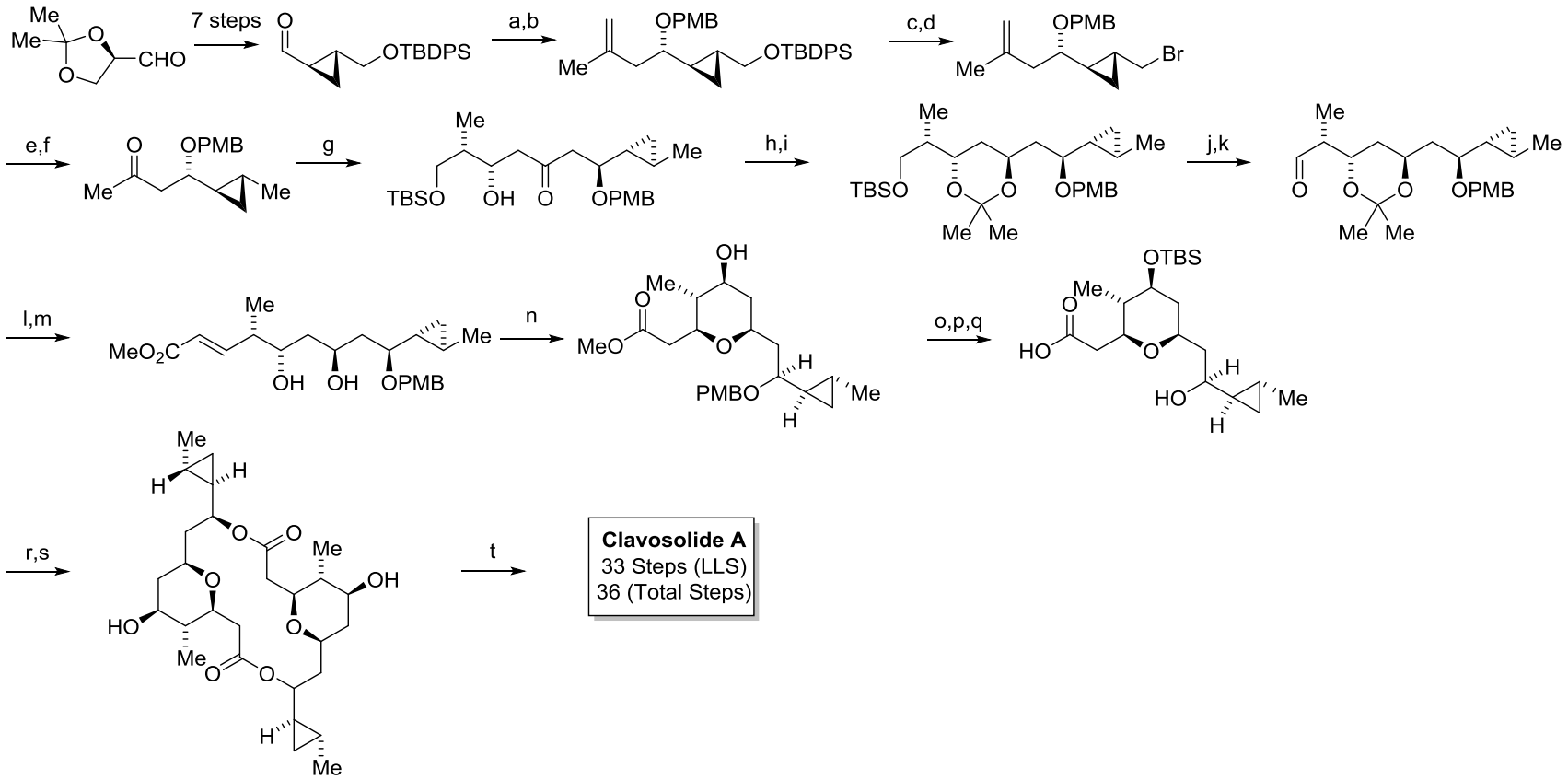
Linear Synthesis



Key: (a) BH_3·DMS, THF, 0 °C; (b) allylmagnesium bromide, Et_2O, -78 °C; (c) propanal, Et_2O, -78 °C; (d) 2-ethylhexyl acrylate, Grubbs' 2nd Generation, benzene, rt; (e) PhCHO, ^{t}BuOK, THF, 0 °C; (f) DIBAL, CH_2Cl_2, -78 °C; (g) BF_3·Et_2O, ((1-ethoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane, CH_2Cl_2, -78 °C; (h) MOMCl, DIPEA, CH_2Cl_2; (i) $Pd(OH)_2$, H_2, MeOH, rt, then TFA, THF, H_2O; (j) allylmagnesium bromide, THF, -78 °C, then TFA, CH_2Cl_2; (k) O_3, C Reagents: (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, -10 °C; (m) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, 125 °C; (n) $LiBF_4$, CH_3CN:H_2O, 60 °CH_2Cl_2, -78 °C; (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, -10 °C; (m) 2,4,6-trichloro-benzoyl chloride, DMAP, toluene, 125 °C; (n) $LiBF_4$, CH_3CN:H_2O, 60 °C.

G. Lee *et al. Org. Lett.* **2006**, *8*, 661.

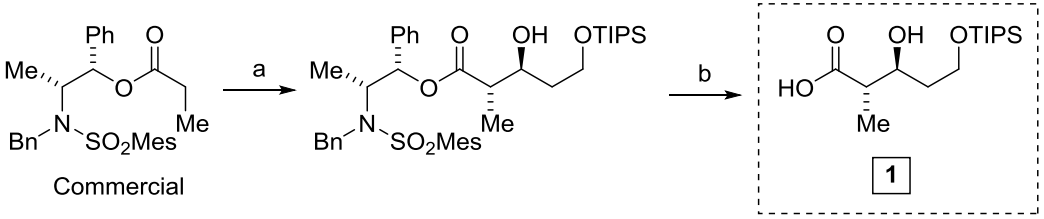
Linear Synthesis



Key: (a) isobutylene, TMEDA, ^{n}BuLi, (-)-(Ipc)$_2$BOMe, Et$_2$O; (b) PMBO(C=NH)CCl$_3$, TsOH; (c) TBAF, THF; (d) CBr$_4$, PPh$_3$, THF; (e) LAH, THF; (f) O$_3$, pyridine, MeOH; (g) (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanal, ^{i}Pr$_2$NEt, Bu$_2$BOTf, Et$_2$O; (h) Me$_4$NB(OAc)$_3$H, MeCN-AcOH; (i) 2,2-methoxypropane, PPTS, CH$_2$Cl$_2$; (j) TBAF, THF; (k) Dess-Martin periodinane, NaHCO$_3$; (l) MeO$_2$CCH$_2$P(O)(OMe)$_2$, LiCl, ^{i}Pr$_2$NEt, MeCN; (m) CSA, MeOH-H$_2$O; (n) NaH, THF; (o) TBSOTf, Et$_3$N, CH$_2$Cl$_2$; (p) DDQ, CH$_2$Cl$_2$-H$_2$O; (q) LiOH, THF-H$_2$O-MeOH; (r) 2,4,6-Cl$_3$PhCOCl, Et$_3$N, THF, then DMAP, toluene, reflux; (s) TBAF, THF; (t) (2*R*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yl 2,2,2-trichloroacetimidate, BF$_3$·OEt$_2$, 4 Å MS, CH$_2$Cl$_2$.

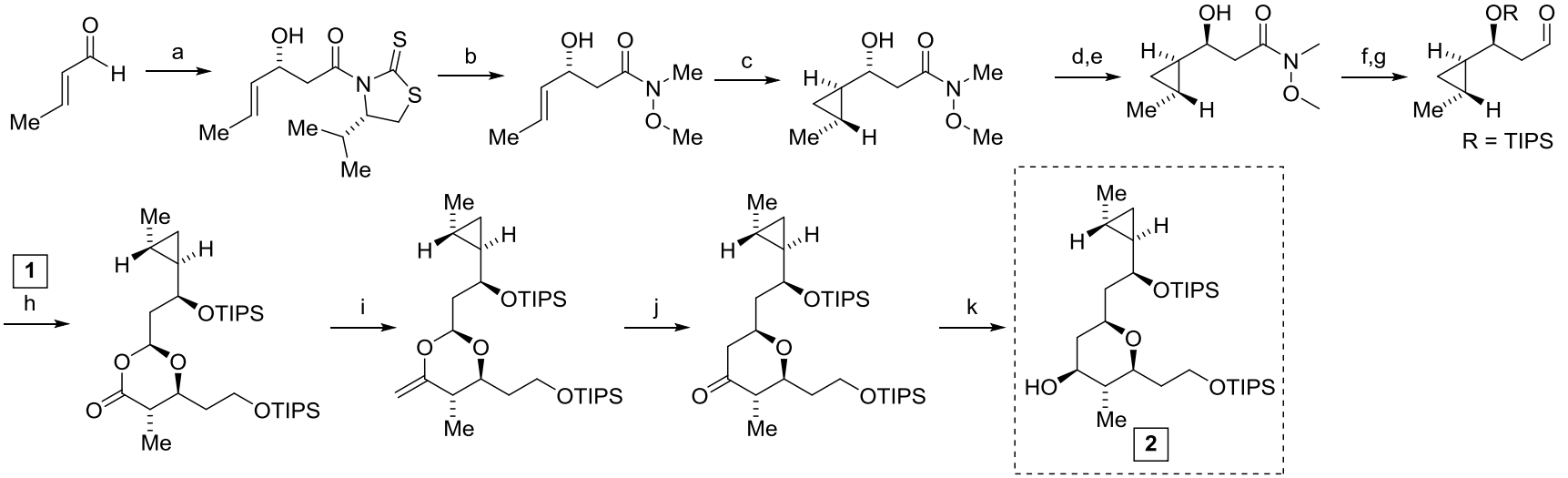
H. Smith *et al. Org. Lett.* **2006**, *8*, 3315.

Fragment 1



Key: (a) 3-((triisopropylsilyl)oxy)propanal, c-Hex$_2$BOTf, Et$_3$N, CH_2Cl_2; (b) LiOH, THF/H_2O.

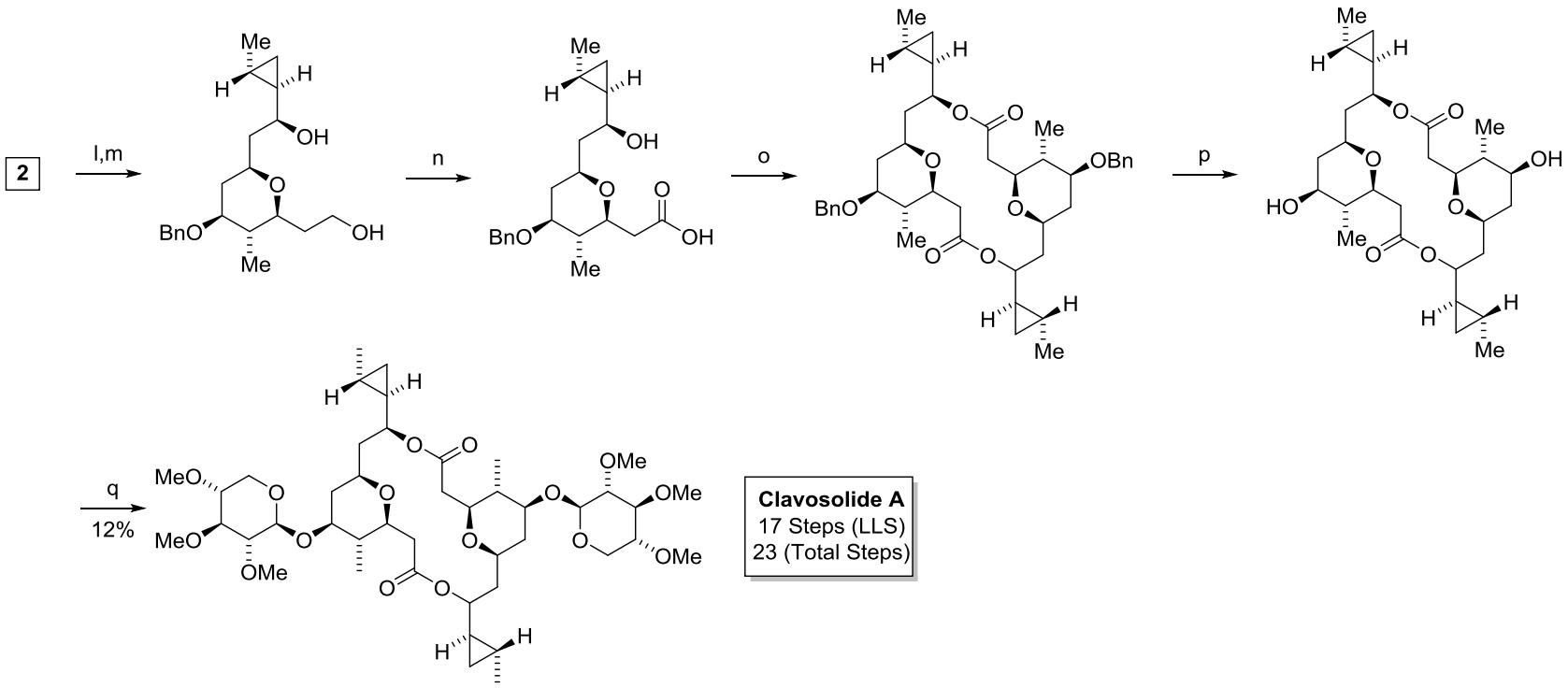
Fragment 2



Key: (a) (*S*)-1-(4-isopropyl-2-thioxothiazolidin-3-yl)ethanone, $TiCl_4$, DIPEA; (b) MeNH(OMe)-HCl, CH_2Cl_2, rt; (c) Et_2Zn, CH_2I_2, CH_2Cl_2; (d) AcOH, PPh_3, DIAD, $PhCH_3$; (e) K_2CO_3, MeOH; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (g) DIBAL, THF; (h) HMDS, **1**, CH_2Cl_2, then lactone, TMSOTf, DtBMP, CH_2Cl_2; (i) Cp_2TiMe_2, $Me_3CCOOEt$, THF, dark; (j) Me_2AlCl, 4 Å MS, CH_2Cl_2, rt; (k) $NaBH_4$, EtOH.

H. Smith *et al. Org. Lett.* **2006**, *8*, 3315. (Cont'd)

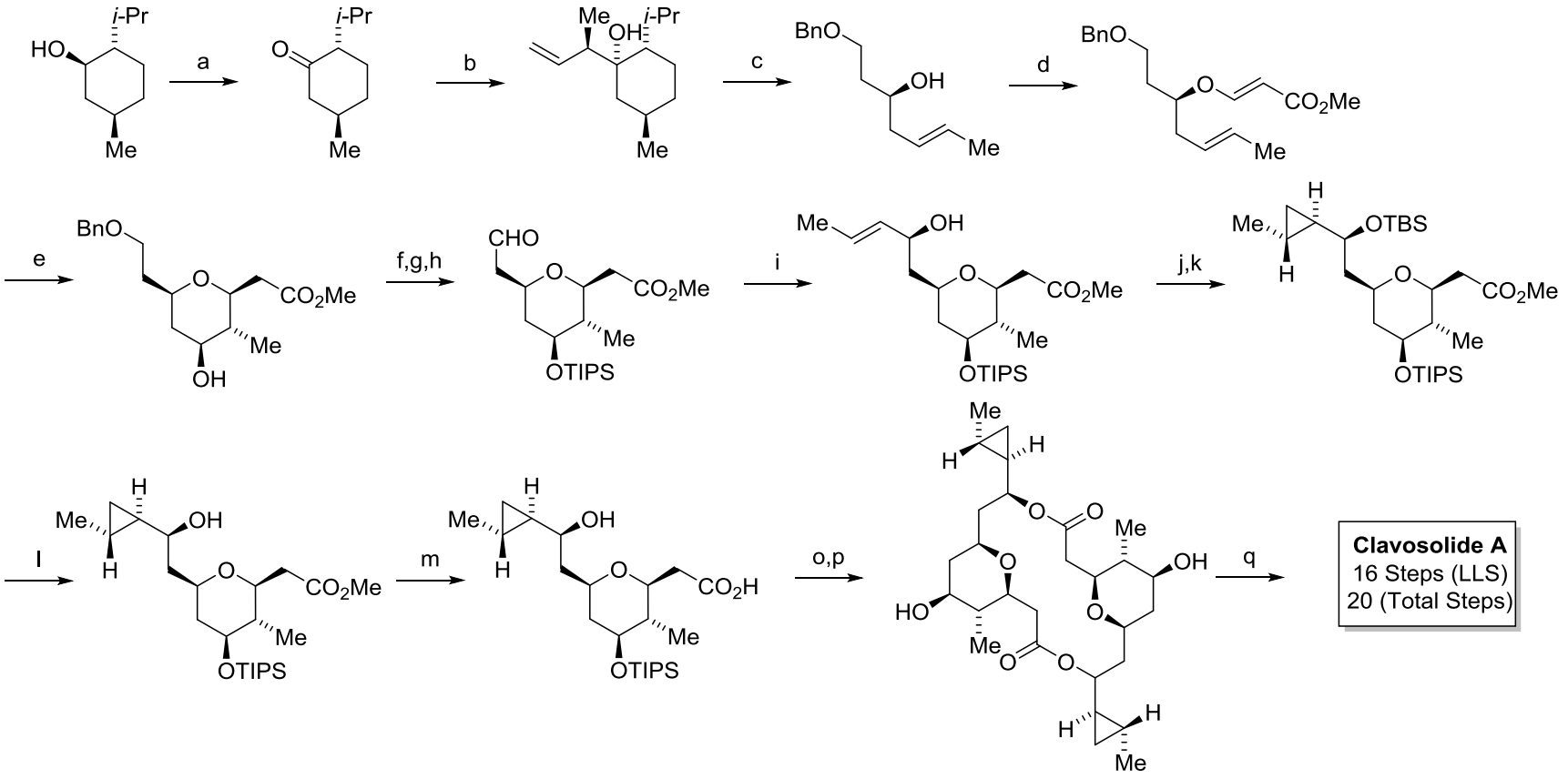
End Game



Reagents: (l) BnBr, NaH, TBAI, DMF, rt; (m) 1% HCl, EtOH; (n) TEMPO, NaOCl, KBr, TBAC, NaCl, $NaHCO_3$, CH_2Cl_2/H_2O, 0 ℃; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, then DMAP, toluene; (p) 10% Pd/C, H_2 (1 atm), EtOH; (q) (2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yl 2,2,2-trichloroacetimidate, TMSOTf, CH_2Cl_2, 4 Å MS.

I. Willis *et al*. *Org. Lett.* **2006**, *8*, 3319.

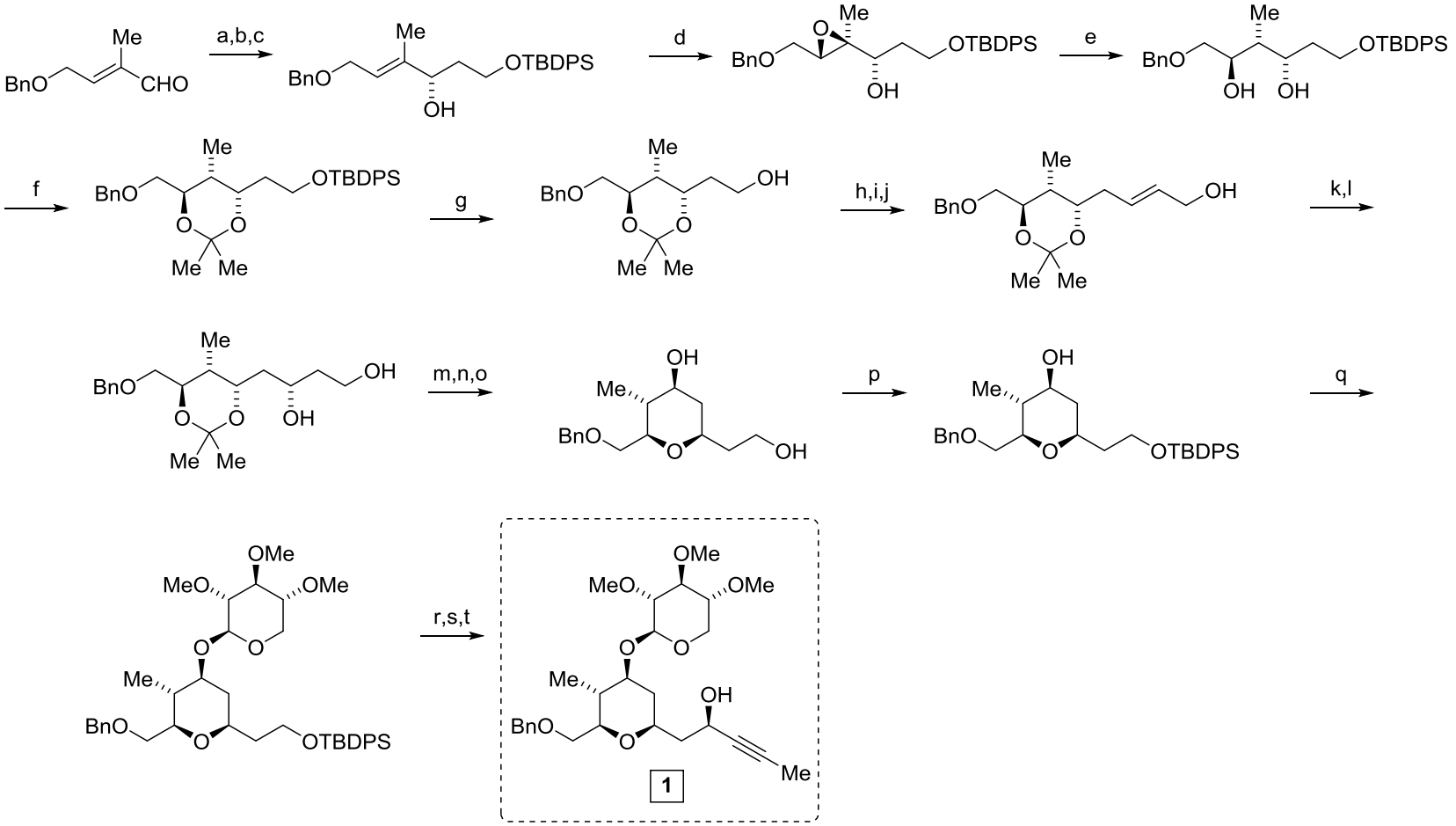
Linear Synthesis



Reagents: (a) IBX, ethyl acetate, reflux; (b) but-2-enylmagnesium chloride, THF; (c) $TsOH{\cdot}H_2O$, CH_2Cl_2, $BnOCH_2CH_2CHO$; (d) methyl propiolate, quinuclidine; (e) TFA, CH_2Cl_2; (f) K_2CO_3, MeOH; (f) TIPSCl, DMF, imidazole; (g) H_2, Pd/C, EtOH; (h) Dess-Martin periodinane; (i) $CrCl_2$, $NiCl_2$, DMF; (j) TBSOTf, imidazole, DMF; (k) CH_2ICl, Et_2Zn, CH_2Cl_2; (l) 1% v/v HCl, EtOH; (m) TMSONa, CH_2Cl_2; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux; (p) TBAF, THF; (q) (2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxy-2-(phenylthio)tetrahydro-2*H*-pyran, NBS, CH_3CN.

J. Chakraborty *et al. Tetrahedron*, **2008**, *64*, 5162.

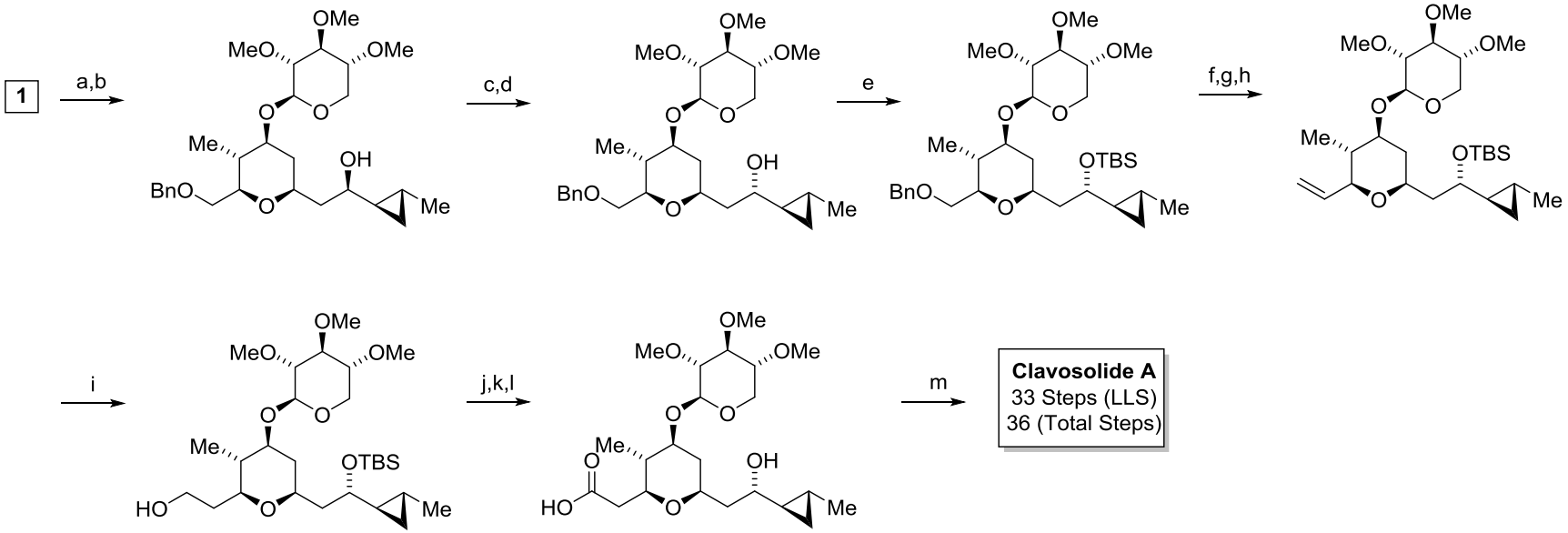
Fragment 1



Key: (a) EtOAc, LDA, THF; (b) LAH, Et_2O; (c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (d) (+)-DIPT, TBHP, $Ti(^iPrO)_4$, 4 Å MS, CH_2Cl_2; (e) Cp_2TiCl, cyclohexa-1,4-diene; (f) 2,2-dimethoxypropane, CSA, CH_2Cl_2; (g) TBAF, THF; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (i) $PH_3P{=}CHCO_2Et$, CH_2Cl_2; (j) DIBAL-H, CH_2Cl_2; (k) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2; (l) Red-Al, THF; (m) TBDPSCl, Et_3N, DMAP, DMF; (n) MsCl, Et_3N, DMAP, CH_2Cl_2; (o) CSA, MeOH; (p) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (q) (2*R*,3*R*,4*S*,5*R*)-3,4,5-trimethoxytetrahydro-2*H*-pyran-2-yl-2,2,2-trichloroacetimidate, TMSOTf, 4 Å MS, CH_2Cl_2; (r) TBAF, THF; (s) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (t) LDA, propyne, THF, then the aldehyde.

J. Chakraborty *et al. Tetrahedron*, **2008**, *64*, 5162. (Cont'd)

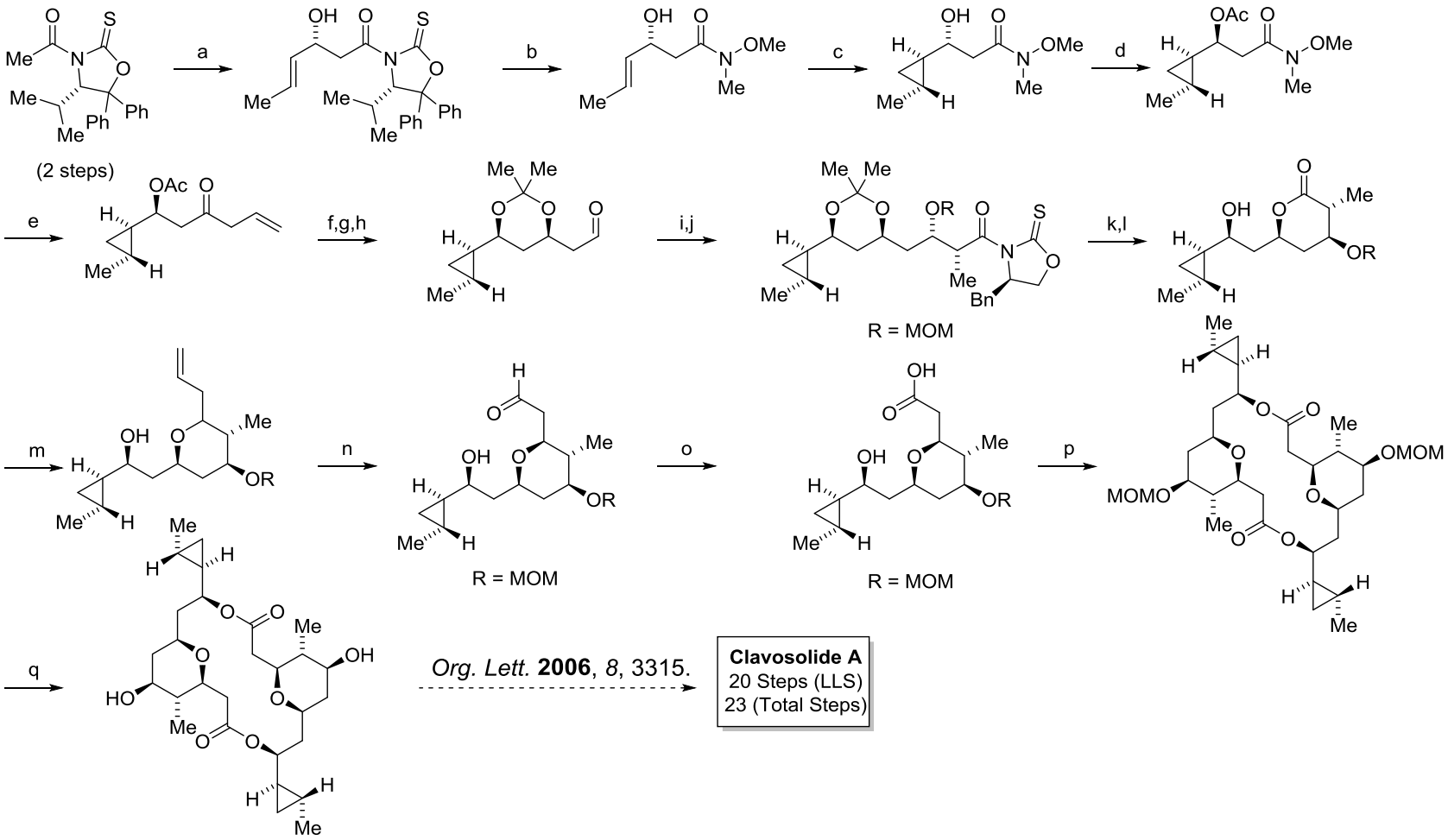
End Game and Dimerization



Key: (a) Red-Al, Et_2O; (b) CH_2I_2, Et_2Zn, CH_2Cl_2; (c) Dess-Martin periodinane, CH_2Cl_2; (d) LAH, THF; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2; (f) H_2, Pd-C, EtOAc; (g) Dess-Martin periodinane, CH_2Cl_2; (h) $Ph_3P{=}CH_2$, Et_2O; (i) $(chex)_2BH$, THF, then 30% H_2O_2, NaOH; (j) Dess-Martin periodinane, CH_2Cl_2; (k) $NaOCl_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, ^tBuOH; (l) CSA, MeOH-CH_2Cl_2 (1:1); (m) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene.

K. Jennings *et al. Org. Lett.* **2009**, *11*, 769.

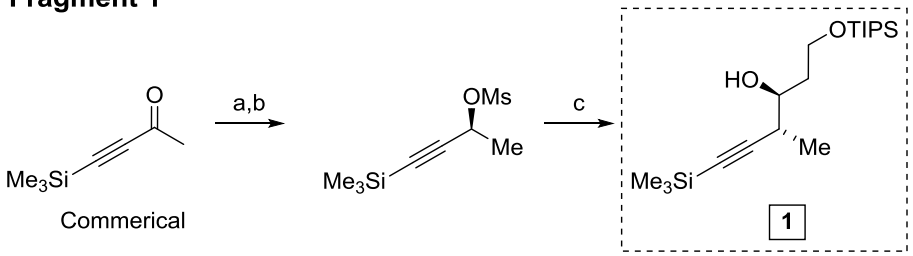
Linear Synthesis



Key: (a) $TiCl_4$, (-)-sparteine, NMP, (*E*)-crotonaldehyde, CH_2Cl_2; (b) imidazole, MeN(H)OMe·HCl, CH_2Cl_2; (c) Et_2Zn, CH_2I_2, CH_2Cl_2; (d) DIAD, PPh_3, HOAc, toluene; (e) allylmagnesium bromide, THF; (f) Et_2BOMe, $NaBH_4$, THF; (g) DMP, PPTS, CH_2Cl_2; (h) O_3, Sudan III, CH_2Cl_2; (i) $^nBu_2BOTf$, Et_3N, (*R*)-4-benzyl-3-propionyloxazolidin-2-one, CH_2Cl_2; (j) MOMCl, DIPEA, CH_2Cl_2; (k) BnOLi, THF; (l) TFA, THF; (m) (i) allylmagnesium bromide, THF; (ii) TFA then Et_3SiH; (n) O_3, Sudan III, CH_2Cl_2; (o) $NaOCl_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH; (p) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene; (q) 2-bromobenzo[*d*][1,3,2]dioxaborole, CH_2Cl_2.

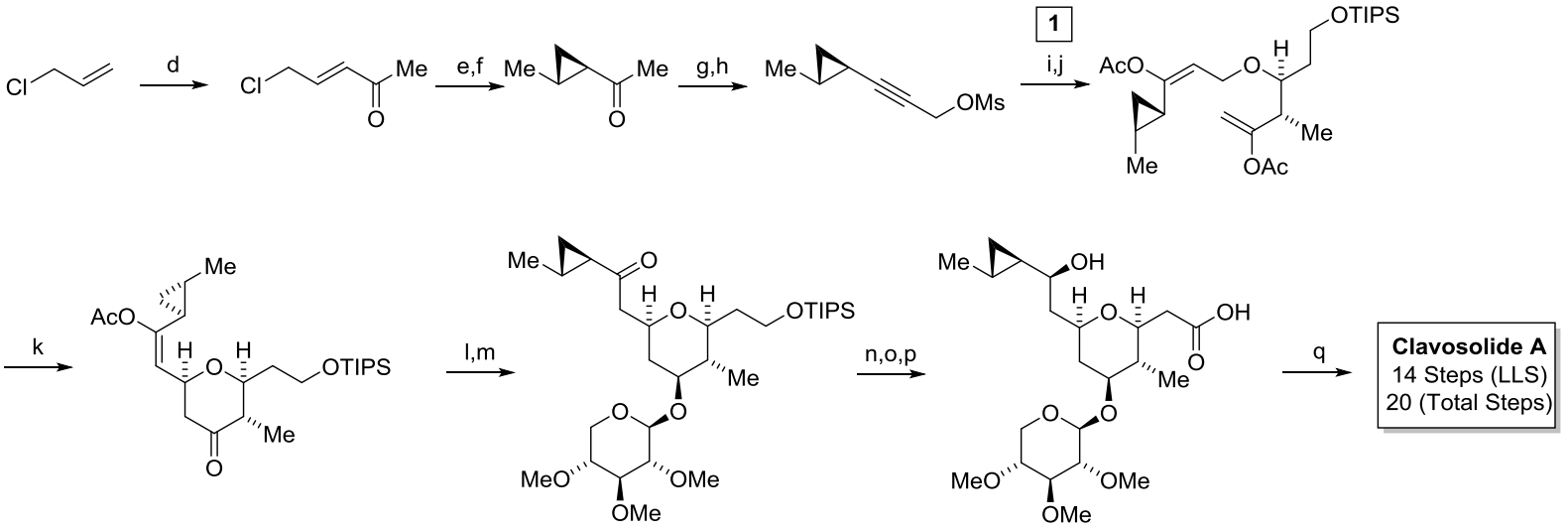
L. Floreancig *et al. Org. Lett.* **2012**, *14*, 5614.

Fragment 1



Key: (a) (*S*,*S*)-Noyori-TsDPEN, CH_2Cl_2, Et_3N, then formic acid; (b) MsCl, Et_3N, CH_2Cl_2; (c) 3-((triisopropylsilyl)oxy)propanal, Et_2Zn, $Pd(OAc)_2$, Ph_3P, CH_2Cl_2.

Linear Synthesis



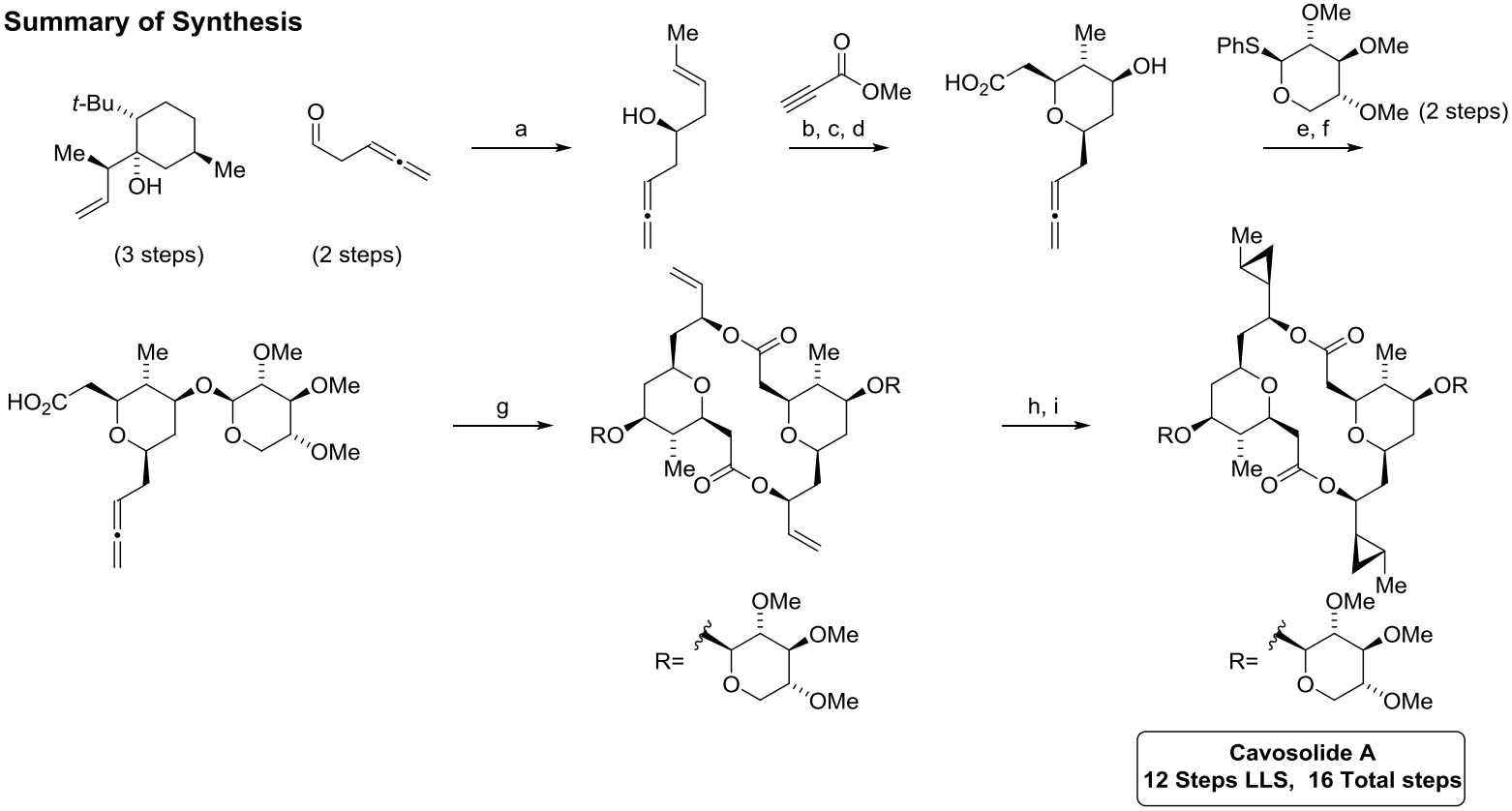
Key: (d) AcCl, $AlCl_3$, CH_2Cl_2, then Et_3N; (e) MeMgBr, CuI, (*R*)-TolBINAP, ^{t}BuOMe; (f) NaOH, H_2O; (g) LDA, THF, then $(EtO)_2P(O)Cl$, then LDA, then $(CH_2O)_n$; (h) MsCl, Et_3N, CH_2Cl_2; (i) NaH, 15-C-5, THF, then **1**; (j) $[(p\text{-cymene})RuCl_2]_2$, HOAc, Na_2CO_3, PhMe; (k) DDQ, $LiClO_4$, 2,6-Cl_2Py, DCE; (l) $NaBH_4$, MeOH, then K_2CO_3, MeOH; (m) (2*S*,3*R*,4*S*,5*R*)-3,4,5-trimethoxy-tetrahydro-2*H*-pyran-2-yl 2,2,2-trichloroacetimidate, TMSOTf, CH_2Cl_2; (n) $BH_3{\cdot}SMe_2$, (*R*)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-*c*][1,3,2]oxazaborole, THF; (o) HCl, EtOH; (p) TEMPO, NaOCl, KBr, Bu_4NCl, $NaHCO_3$, CH_2Cl_2, H_2O; (p) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene.

M. Breit *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 15530.

Synthesis of Starting Materials

Key: a) $AlMe_3$, TMSCl, CuBr (cat.), b) KOH, c) *E*-crotyl chloride, Mg, d) $(EtO_3)COMe$, $MeCH_2CO_2H$, e) DIBAL-H.

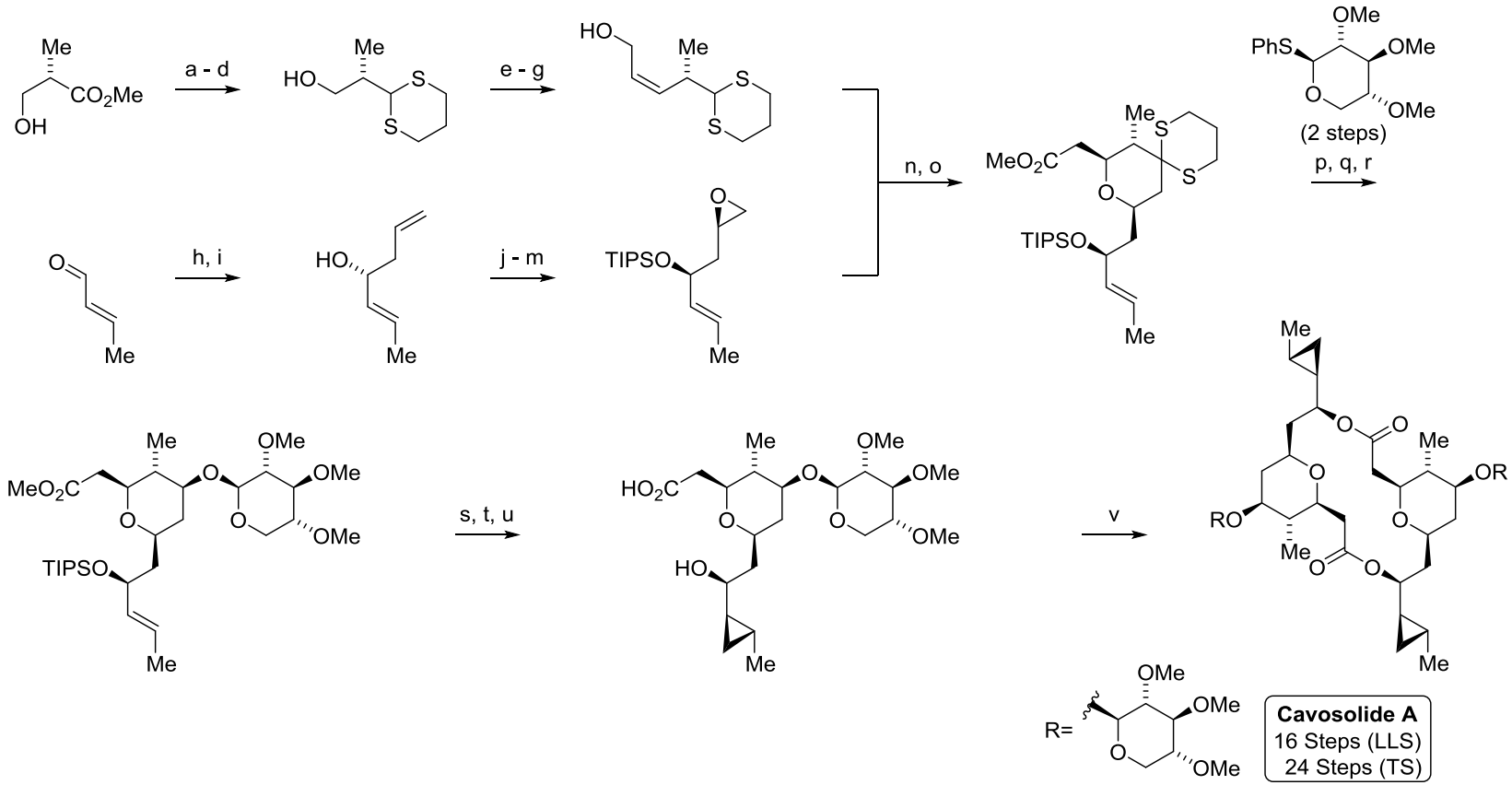
Summary of Synthesis



Key: a) *p*TsOH-H_2O, b) yneone, quinuclidine, TFA, c) K_2CO_3, MeOH, d) LiOH, H_2O, e) MeOTf, 4Å MS, sugar, f) LiOH, H_2O, g) $[Rh(cod)Cl]_2$, (*R*,*R*)-DIOP, Cs_2CO_3, h) Grubbs II, (*Z*)-2-butene, i) ICH_2Cl, Et_2Zn.

N. Kim, Hong *et al. Tetrahedron Lett.* **2015**, *56*, 3120.

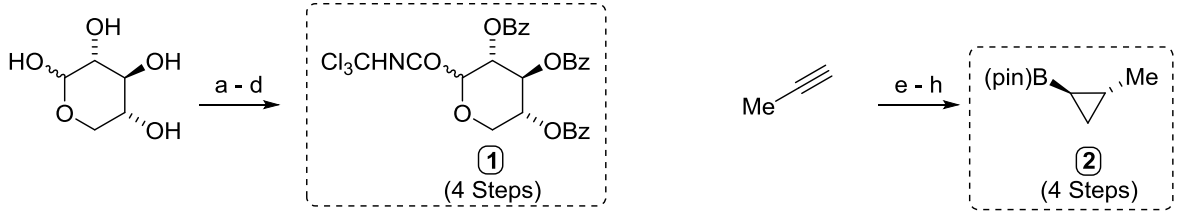
Synthesis



Key: a) TrCl, Et_3N; b) LAH; c) $(COCl)_2$, DMSO, *i*-Pr_2EtN; d) $HS(CH_2)_3SH$, BF_3-OEt_2; e) SO_3-pyridine, DMSO, *i*-Pr_2EtN; f) $(MeO)_2POCH_2CO_2Me$, KHMDS,18-crown-6; g) DIBAL-H; h) allyl bromide, Zn; i) (-)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, 4Å MS (resolution); j) Boc_2O, DMAP; k) NIS; l) K_2CO_3; m) NaH, TIPSOTf; n) *t*-BuLi, HMPA; o) MnO_2, then Me_2-triazolium I, DBU, MnO_2, 4Å MS, MeOH; p) I_2, $NaHCO_3$; q) $NaBH_4$; r) sugar, MeOTf, 4Å MS; s) $ClCH_2I$, Et_2Zn; t) TBAF; u) LiOH, H_2O; v) MNBA, DMAP.

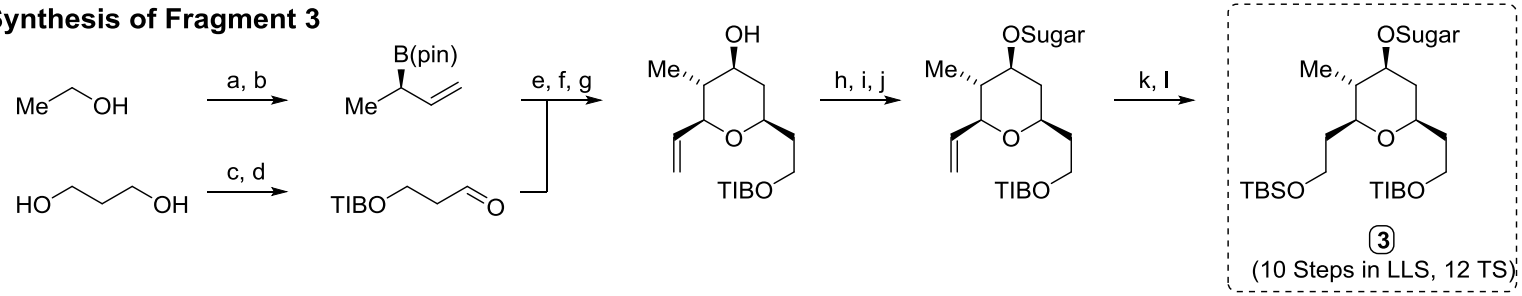
O. Aggarwal *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 2498.

Sugar and Boronate Synthesis



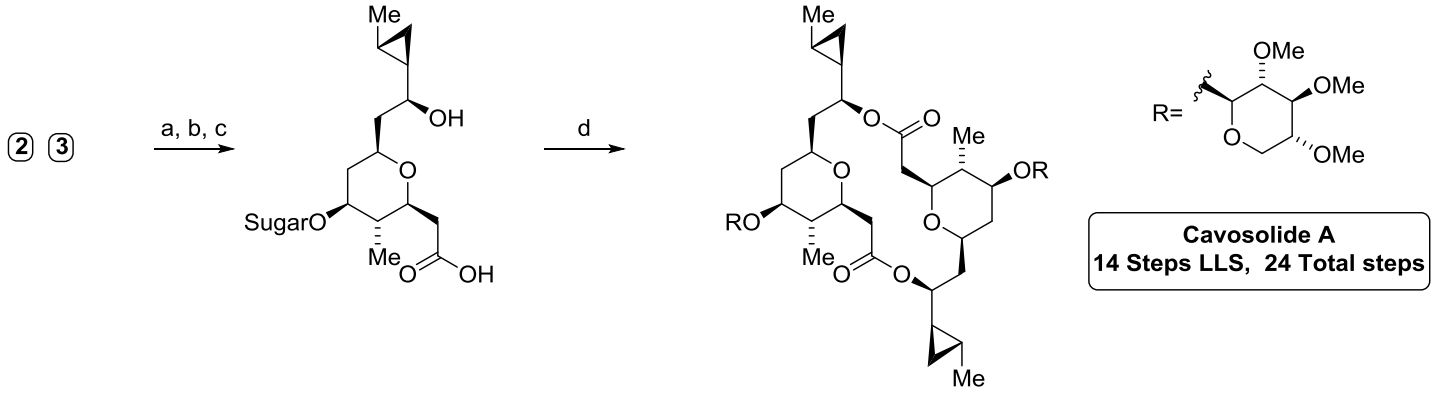
Key: a) BzCl, DMAP, pyr, b) HBr, AcOH, c) Ag_2CO_3, H_2O, acetone, d) DBU,$CNCCl_3$, e) HBBr-SMe_2, then NaOH, then HCl, f) diethanolamine, g) Me_4-D-tartaramide, h) Et_2Zn, CH_2I_2, tartaramide, then pinacol.

Synthesis of Fragment 3



Key: a) Cl(CO)N*i*Pr_2, Et_3N, b) *s*-BuLi, (–)-sparteine, then vinyl-B(pin), $MgBr_2$-Et_2O, c) TIB-Cl, NaH, d) TEMPO, KBr, $NaHCO_3$, NaClO, e) *n*-BuLi, TFAA, then aldehyde, f) acrolein, TFA, g) K_2CO_3, h) **1**, TMSOTf, 4Å MS, i) NaOMe, j) MeI, NaH, k) Cy_2BH, then H_2O_2, KOH, l) TBSCl, Et_3N.

Fragment Union and End Game

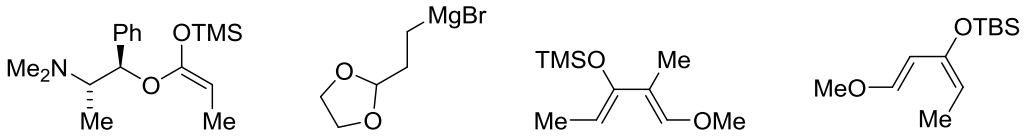


Key: a) *s*-BuLi, (+)-sparteine, then **2**, then NaOH, H_2O_2, b) HCl, c) TEMPO, KBr, $NaHCO_3$, NaOCl, d) 2,4,6-*i*Pr_3BzCl, Et_3N, then DMAP.

Graphical Summary of Previous Syntheses of Zincophorin

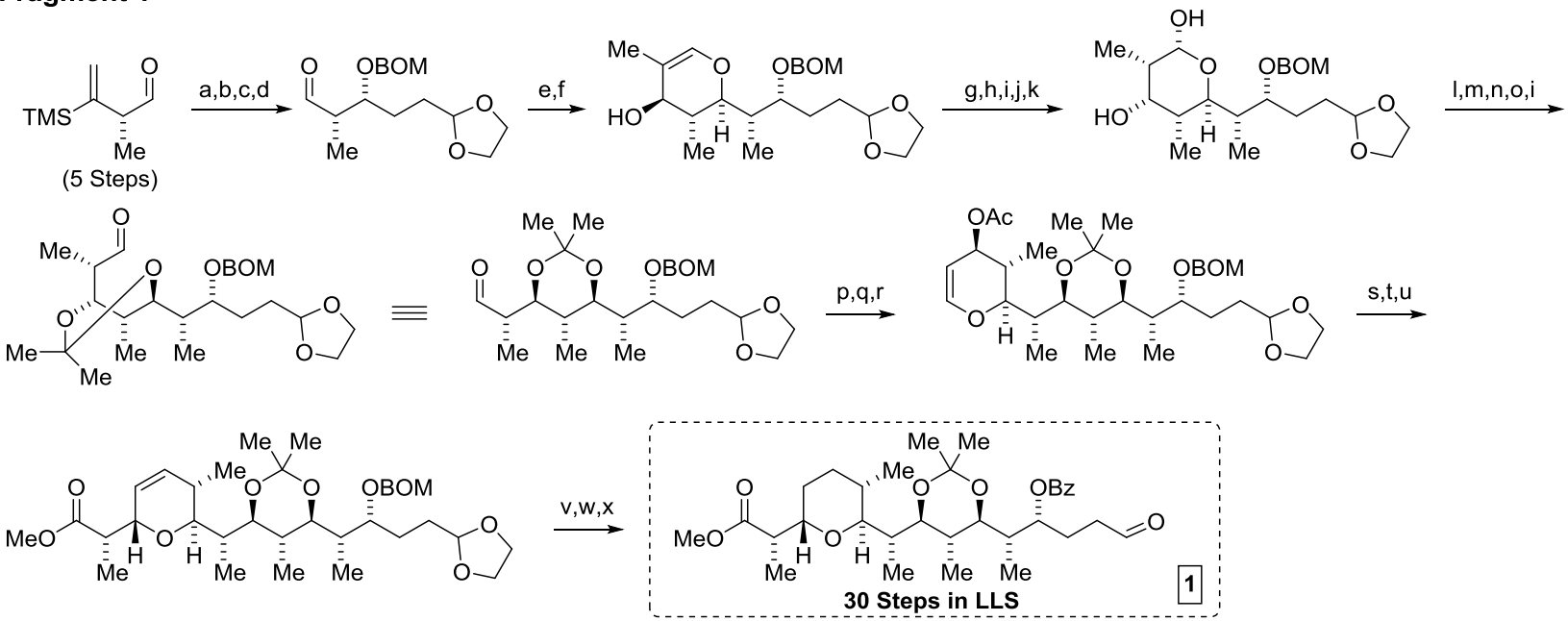
A. Danishefsky *et al. J. Am. Chem. Soc.* **1987**, *109*, 1572; *J. Am. Chem. Soc.* **1988**, *110*, 4368.

Reagents



A1 (2 steps) **S1** (2 steps to bromide) **S2** (3 steps) **S3** (4 steps)

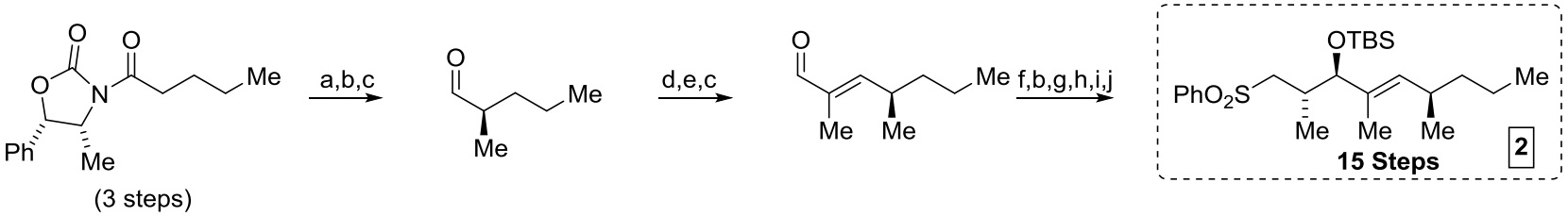
Fragment 1



Key: (a) **S1**; (b) NaH, HMPA, then H_2O; (c) BOMCl, *i*-Pr_2EtN; (d) Ozonolysis; (e) **S2**, $MgBr_2$; (f) $NaBH_4$, $CeCl_3$; (g) 3,4-$(OMe)_2PhCH_2Cl$, *p*-TsOH; (h) BH_3-THF, then H_2O_2, NaOH; (i) $(COCl)_2$, DMSO, then Et_3N; (j) L-Selectride; (k) DDQ; (l) $LiBH_4$; (m) TBDPSCl; (n) $Me_2C(OMe)_2$, PPTS; (o) TBAF; (p) **S3**; (q) $NaBH_4$, $CeCl_3$; (r) Ac_2O, DMAP ; (s) (*E*)-crotylsilane, BF_3-OEt_2; (t) OsO_4, $NaIO_4$; (u) CrO_3; (v) H_2, Pd-C; (w) BzCl, pyridine; (x) *p*-TsOH.

A. Danishefsky *et al. J. Am. Chem. Soc.* **1987**, *109*, 1572; *J. Am. Chem. Soc.* **1988**, *110*, 4368. (Cont'd)

Fragment 2



(3 steps)

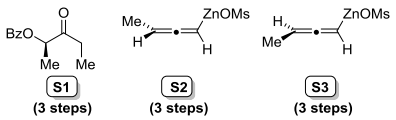
Key: (a) LDA, then MeI; (b) LAH; (c) $(COCl)_2$, DMSO, then Et_3N; (d) $Ph_3PC(Me)CO_2Et$; (e) DIBAL-H; (f) **A1**, $TiCl_4$; (g) *p*-TsCl, pyridine, DMAP; (h) TBSOTf, Et_3N; (i) KSPh; (j) PhSeSePh, H_2O_2.

Fragment Union and End Game

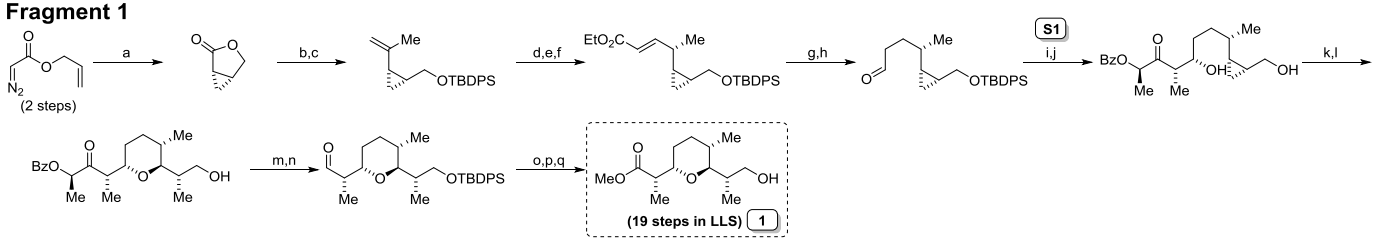
Key: (a) *n*-BuLi, $MgBr_2$; (b) Na/Hg; (c) 1M HCl/MeOH/THF; (d) 2.0 M LiOH in MeOH/THF, then 1N HCl; (e) CH_2N_2.

B. Cossy *Org. Lett.* **2003**, *5*, 4037; *J. Org. Chem.* **2004**, *69*, 4626.

Reagents

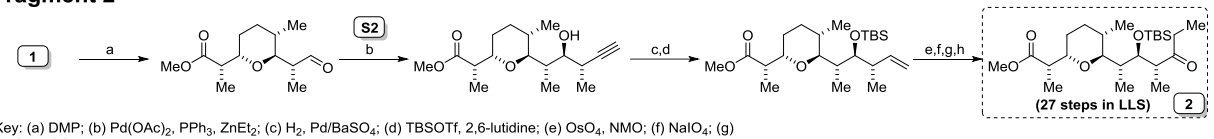


Fragment 1



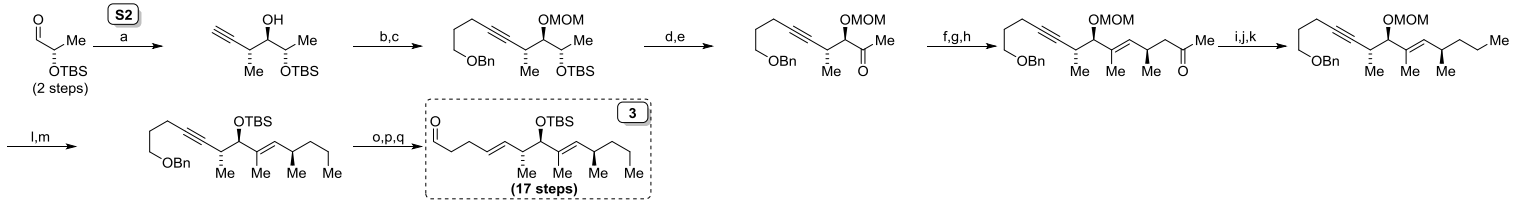
Key: (a) Rh_2(R-MEPY)$_4$; (b) MeLi, then TBDPSCl; (c) MsCl, NEt_3, DMAP; (d) BH_3-THF, H_2O_2; (e) PCC, 4A MS; (f) $(EtO)_2P(O)CH_2COOEt$; (g) H_2, PtO_2; (h) DIBAL-H; (i) Cy_2BCl, Et_2NMe; (j) HF-Py; (k) $Hg(TFA)_2$, KBr; (l) Bu_3SnH; (m) TBDPSCl, IM; (n) $LiBH_4$, then $NaIO_4$; (o) $NaClO_2$; (p) $TMSCHN_2$; (q) HF-Py

Fragment 2



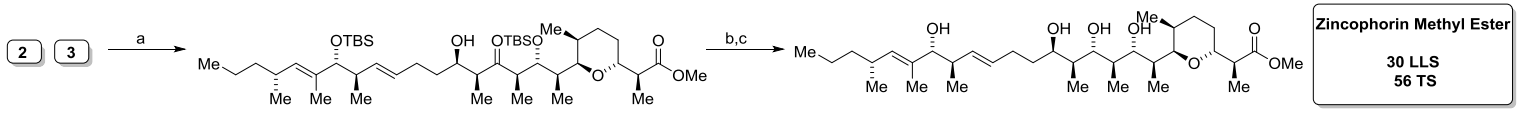
Key: (a) DMP; (b) $Pd(OAc)_2$, PPh_3, $ZnEt_2$; (c) H_2, Pd/$BaSO_4$; (d) TBSOTf, 2,6-lutidine; (e) OsO_4, NMO; (f) $NaIO_4$; (g) Et_2CuLi; (h) DMP

Fragment 3



Key: (a) $Pd(OAc)_2$, PPh_3, $ZnEt_2$; (b) MOMCl; (c) BuLi, RBr, HMPA; (d) TBAF; (e) DMP, Py; (f) (*Z*)-propenyl MgBr, $MgBr_2$-OEt_2; (g) diketene, DMAP; (h) Al_2O_3; (i) DIBAL-H; (j) MsCl, NEt_3; (k) LAH; (l) TsOH; (m) TBSOTf; (n) Li, NH_3; (o) DMP, Py.

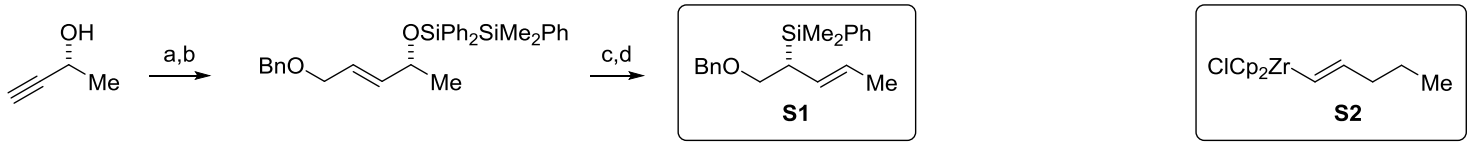
Fragment Union and End Game



Key: (a) $TiCl_4$; (b) $NaBH_4$; (c) HF-Py

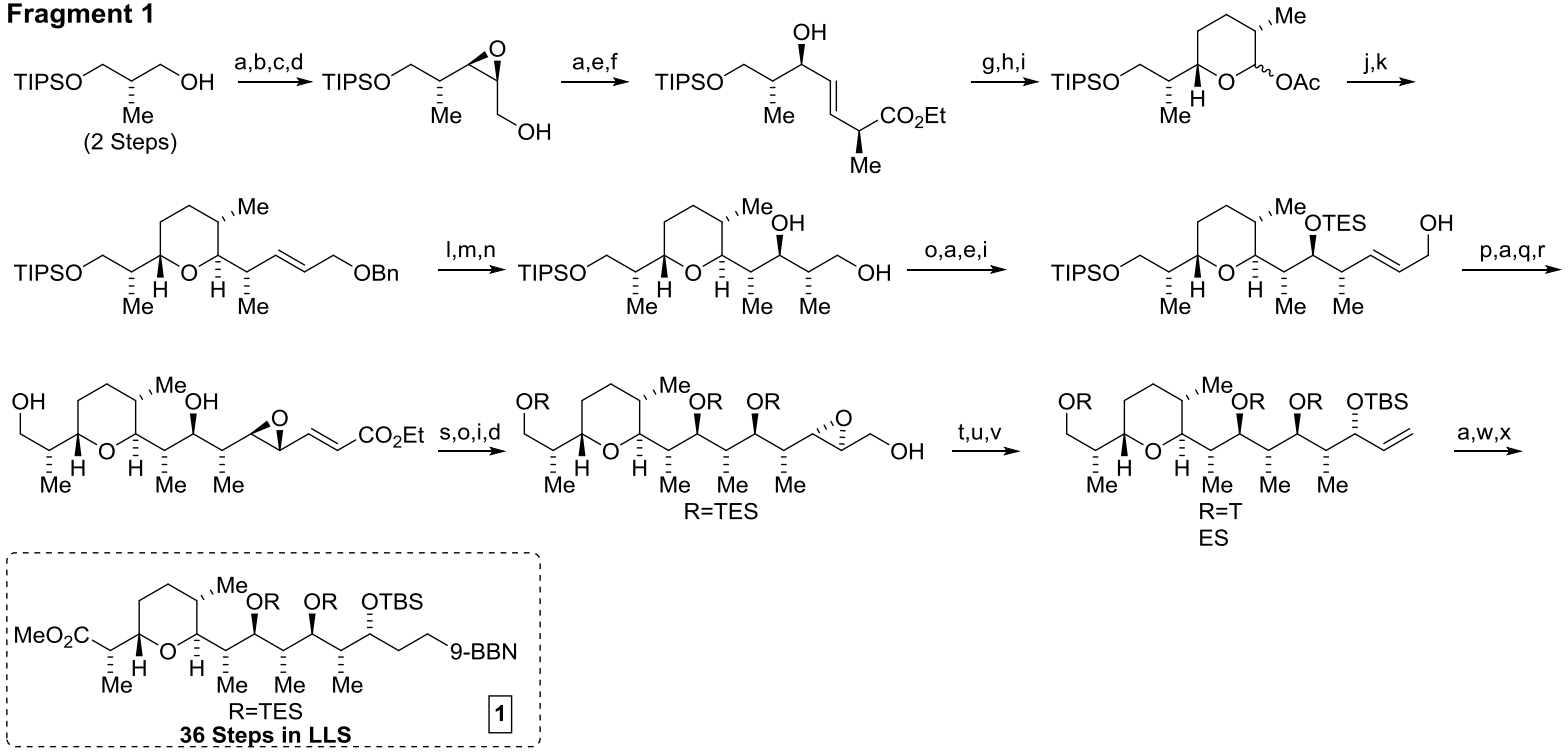
C. Miyashita *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 4341.

Starting Materials



Key: (a) ($SiClPh_2SiMe_2Ph$, Et_3N; (b) $Cp_2Zr(H)Cl$, then Me_2Zn, 4Å sieves, BOMCl; (c) $Pd(acac)_2$, *t*-$BuCH_2C(Me)_2NC$; (d) *n*-BuLi. (Fukuda, K.; Miyashita, M.; Tanino, K. *Tetrahedron Lett.* **2010**, *51*, 4523.)

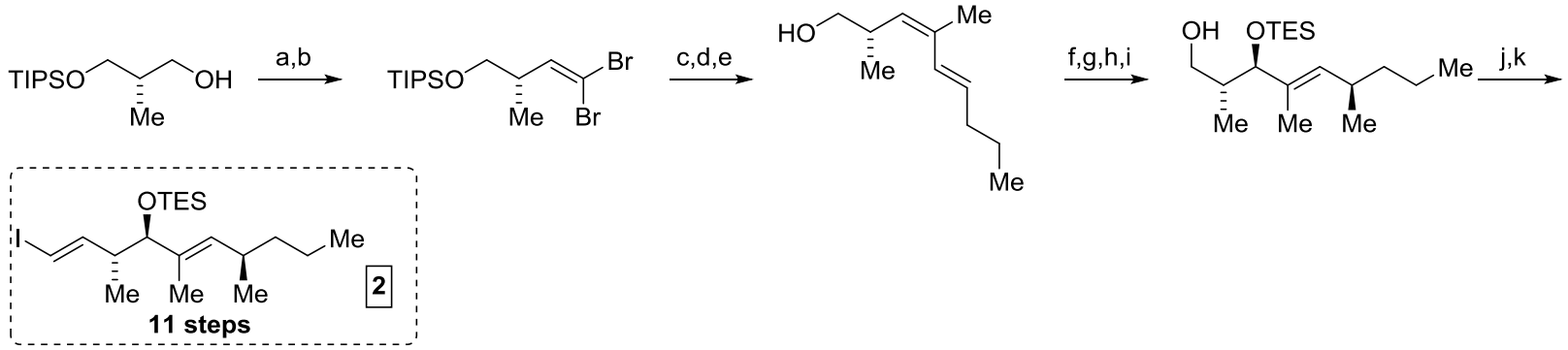
Fragment 1



Key: (a) $(COCl)_2$, DMSO, then Et_3N; (b) (*o*-Me-PhO)$_2$P(O)CH_2CO_2Et, NaH; (c) DIBAL-H; (d) MCPBA; (e) (*i*-PrO)$_2$P(O)CH_2CO_2Et, *t*-BuOK; (f) Me_2Zn-CuCN; (g) H_2, PtO_2; (h) Ti(O*i*-Pr)$_4$; (i) DIBAL-H, then Ac_2O, pyridine; (j) **S1**, TiCl(O*i*-Pr)$_4$; (k) TIPSOTf, 2,6-lutidine; (l) Ca, NH_3; (m) Ti(O*i*-Pr)$_4$, D-(–)-DIPT, *t*-BuOOH, 4Å sieves; (n) Me_2CuLi; (o) TESOTf, 2,6-lutidine; (p) Ti(O*i*-Pr)$_4$, D-(–)-DET, *t*-BuOOH, 4Å sieves; (q) (EtO)$_2$P(O)CH_2CO_2Et, NaH; (r) TBAF; (s) Me_3Al-D_2O; (t) PPh_3, I_2, imidazole; (u) BuLi; (v) TBSCl, DMAP; (w) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (x) $TMSCHN_2$ (y) 9-BBN.

C. Miyashita *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 4341. (Cont'd)

Fragment 2

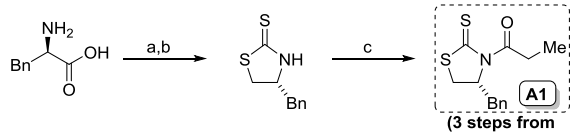


Fragment Union and End Game

Key: (a) aq. Cs_2CO_3, $AsPh_3$, [$PdCl_2$(dppf)]; (b) TEAF; (c) LiOH, H_2O/MeOH/THF.

D. Leighton *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308.

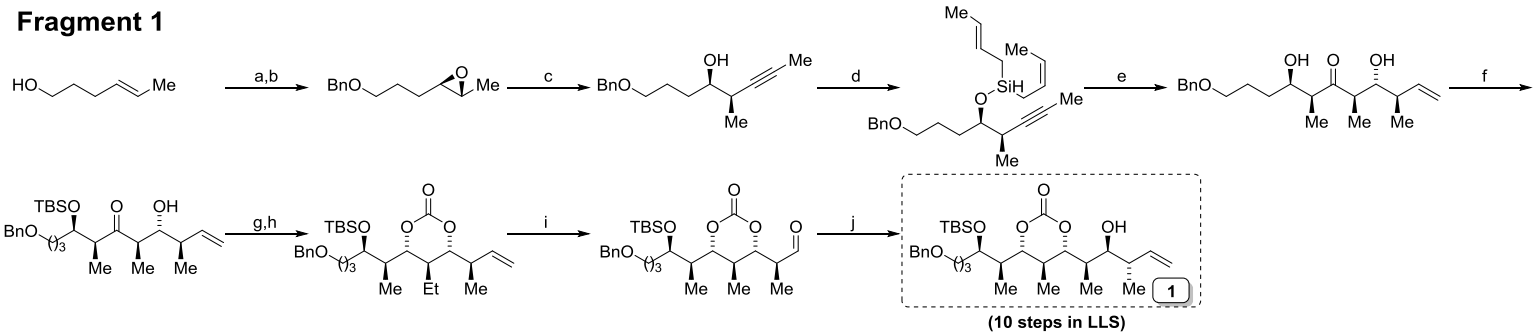
Chiral Auxiliary Synthesis



(3 steps from inexpensive chemicals)

Key: (a) $NaBH_4$, I_2; (b) KOH, CS_2, H_2O, reflux; (c) propionyl chloride, DMAP, TEA.

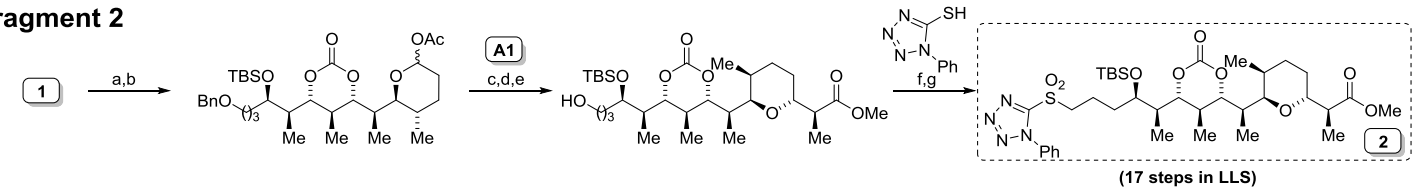
Fragment 1



(10 steps in LLS)

Key: (a) NaH, BnBr; (b) Shi epoxidation, oxone, Na_2EDTA; (c) Propyne, BuLi, $AlMe_3$; (d) dicrotylsilane, NaH; (e)$Rh(acac)(CO)_2$, then H_2O_2, KF; (f) TBSOTf, 2,6-lutidine; (g) DIBAL-H; (h) CDI; (i) OsO_4, NMO, then $NaIO_4$; (j) K-trifluorocrotylborate, TBAI.

Fragment 2

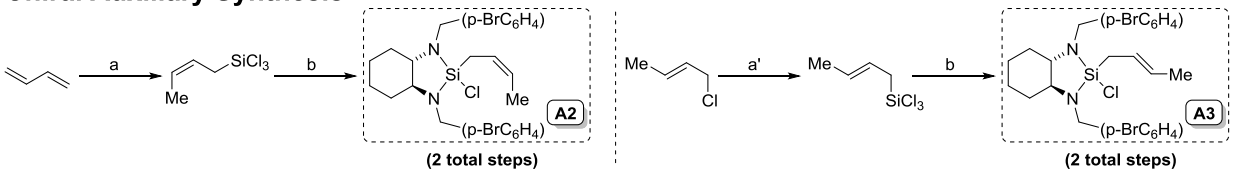


(17 steps in LLS)

Key: (a) $Rh(acac)(CO)_2$, PPh_3, CO/H_2; (b) Ac_2O, Py, DMAP; (c) $TiCl_4$, $SnCl_4$, iPr_2NEt; (d) DMAP, MeOH; (e) Pd/C; (f) DIAD, PPh_3; (g) $(NH_4)_6Mo_7O_{24}{}^{-4}H_2O$, H_2O_2.

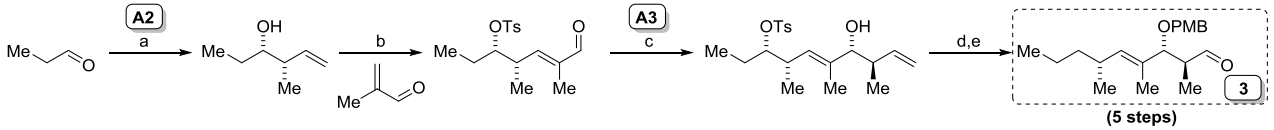
D. Leighton *et al. J. Am. Chem. Soc.* **2011**, *133*, 7308. (Cont'd)

Chiral Auxiliary Synthesis



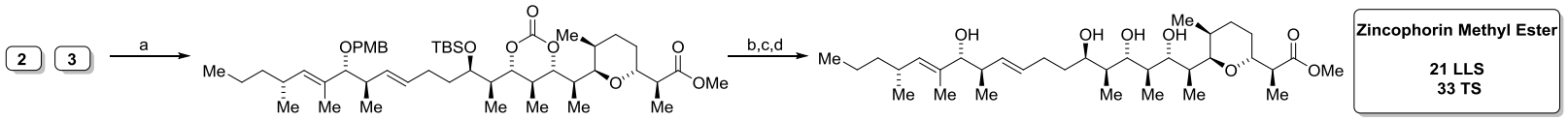
Key: (a) $HSiCl_3$, Pd; (b) diamine, DBU
(a') $HSiCl_3$, NEt_3, CuCl

Fragment 3



Key: (a) $Sc(OTf)_3$; (b) Hoveyda-Grubbs-II, then TsCl, Et_3N; (c) $Sc(OTf)_3$; (d) KHMDS, PMBBr, then $LiBEt_3H$; (e) OsO_4, $NaIO_4$, 2,6-lutidine.

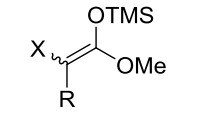
Fragment Union and End Game



Key: (a) KHMDS; (b) DDQ, pH = 7 buffer; (c) NaOMe; (d) HF, H_2O.

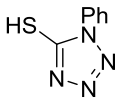
E. Guindon *et al. Tetrahedron* **2015**, *71*, 709.

Reagents

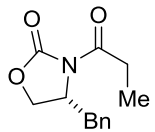


S1 X=Br, R=Me
S2 X=SePh, R=H

S1: 1 Step
S2: 2 Steps



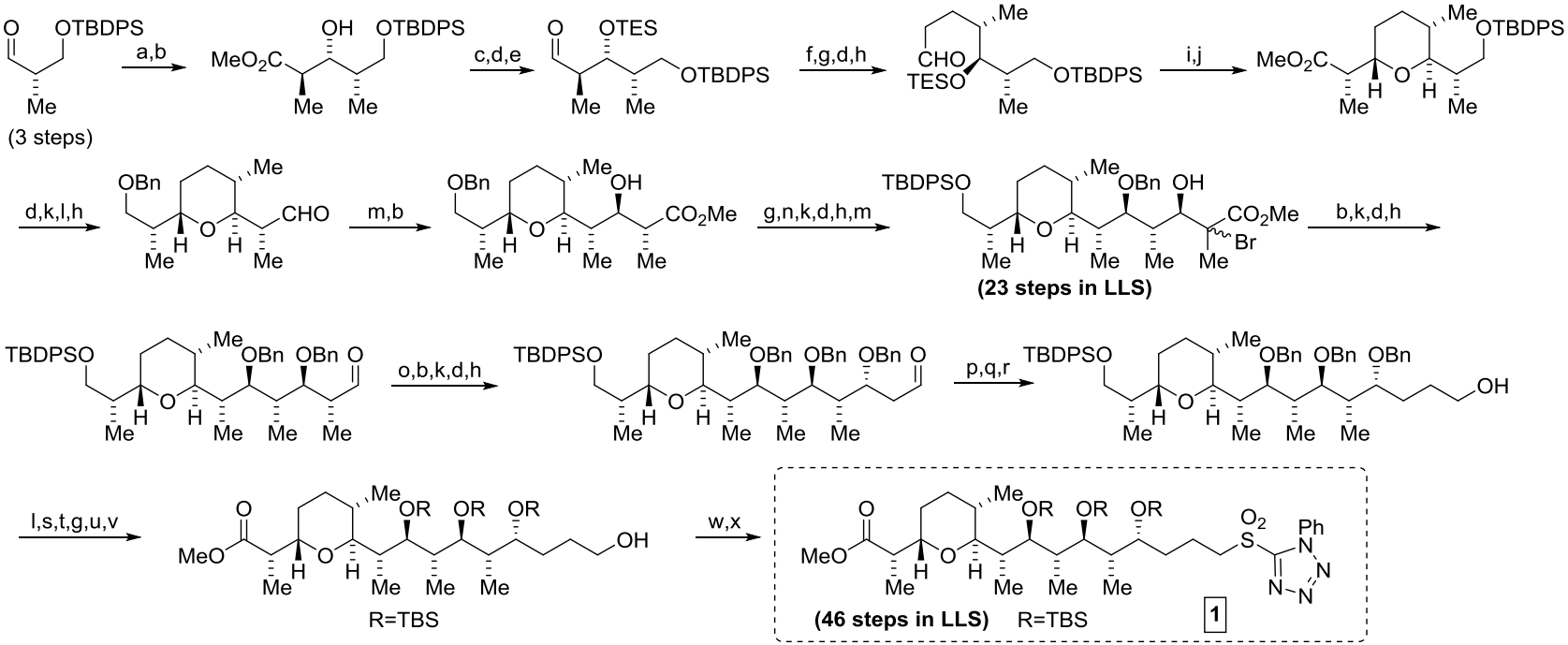
S3



A1

(3 Steps)

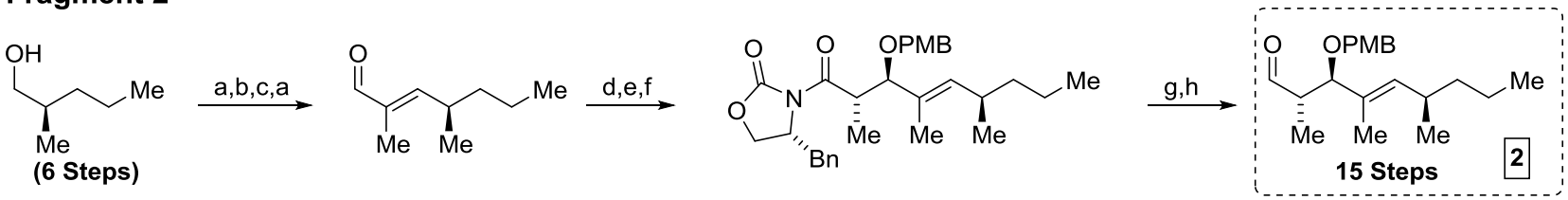
Fragment 1



Key: (a) BF_3OEt_2, **S1**; (b)Bu_2BOTf, DIEA, then Bu_3SnH, BEt_3, air; (c) TESOTf, 2,6- lutidine; (d) DIBAL-H; (e) $(COCl)_2$, DMSO, then Et_3N; (f) $Ph_3PC(H)=CO_2Me$; (g) H_2, Pd–C; (h) DMP, $NaHCO_3$; (i) $BiBr_3$, **S1**; (j) Ph_3SnH, BEt_3, air; (k) $BnO=CNHCl_3$, TfOH; (l) TBAF; (m) $TiCl_4$, **S1**; (n) TBDPSCl, Et_3N, DMAP; (o) BF_3OEt_2, **S2**; (p)$MePPh_3Br$, *n*-BuLi; (q) 9-BBN, then $NaOH/H_2O_2$; (r) PivCl, pyridine; (s) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene; (t) $TMSCHN_2$; (u) TBSOTf, 2,6-lutidine; (v) K_2CO_3; (w) DIAD, PPh_3, **S3**; (x) $(NH_4)_6Mo_7O_{24}$-$4H_2O$, H_2O_2.

E. Guindon *et al. Tetrahedron* **2015**, *71*, 709.

Fragment 2



Key: (a) $(COCl)_2$, DMSO, then Et_3N; (b) $Ph_3P{=}C(Me)CO_2Et$; (c) DIBAL-H; (d) $MgCl_2$, Et_3N, TMSCl, **A1**; (e) TFA; (f) $PMPOC(NH)CCl_3$ (g) $LiBH_4$; (h) DMP, $NaHCO_3$.

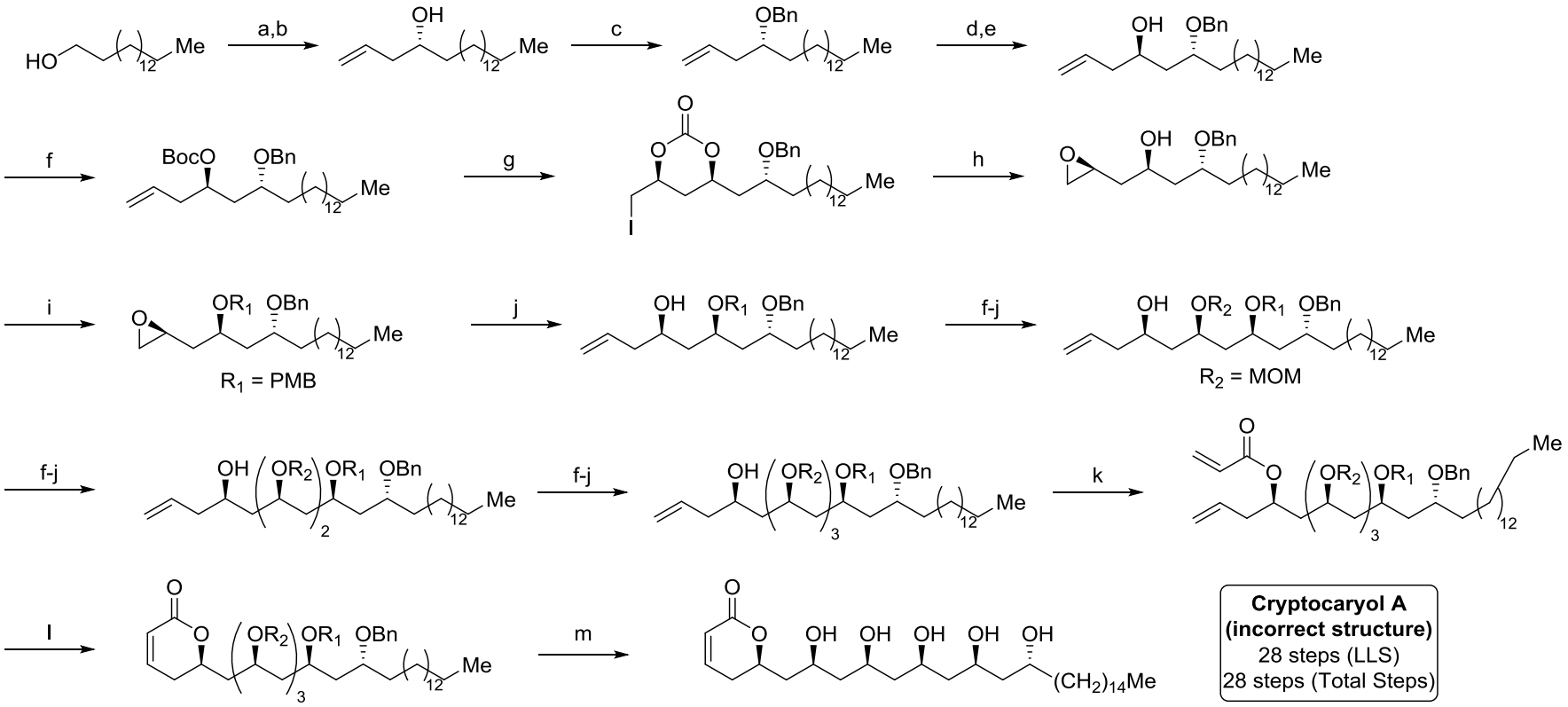
Fragment Union and End Game

Key: (a) KHMDS; (b) DDQ, pH 7 buffer; (c) TBAF.

Graphical Summary of Previous Syntheses of Cryptocaryol A

A. Mohapatra *et al. Eur. J. Org. Chem.* **2013**, 1051.

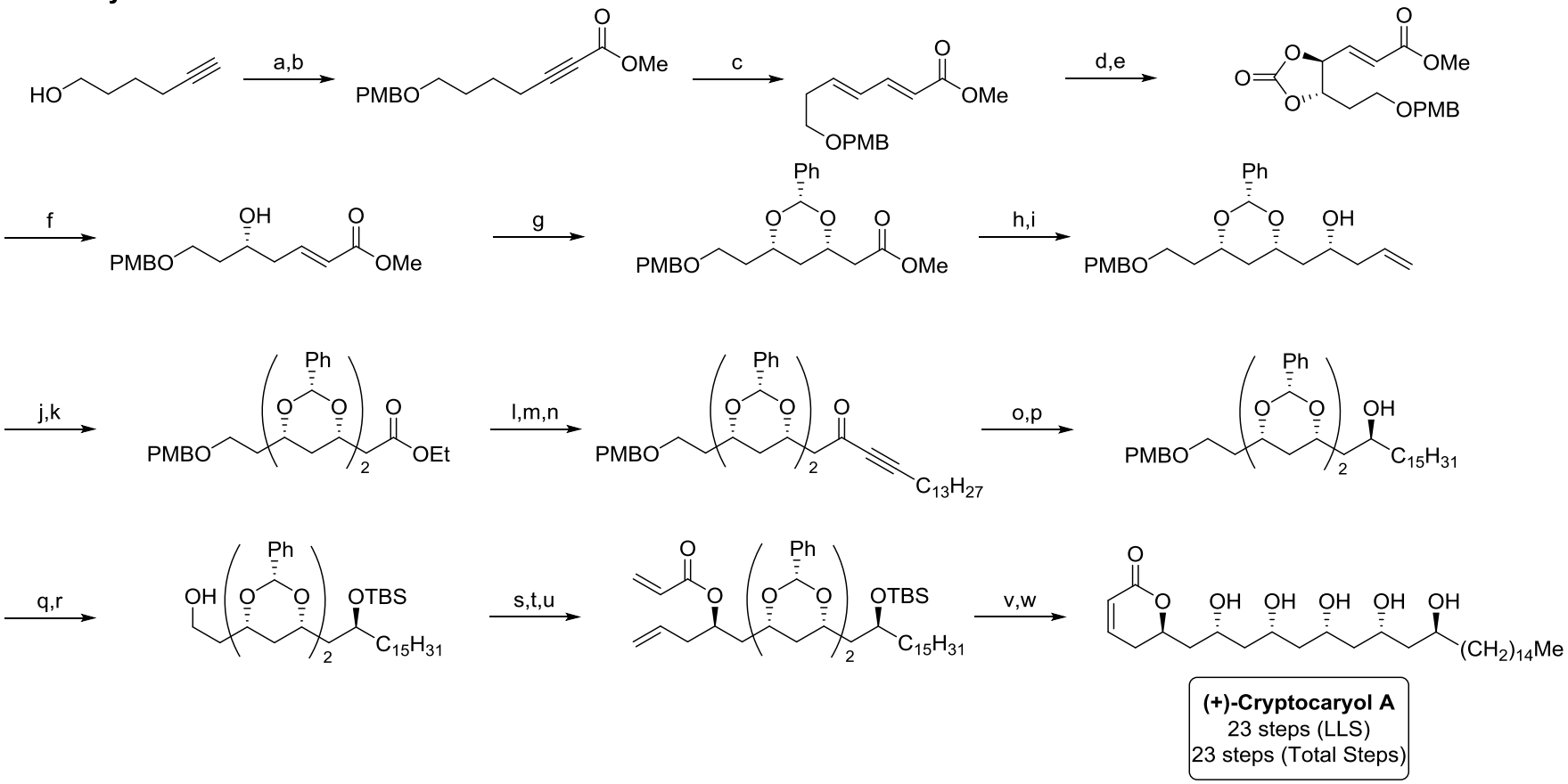
Linear Synthesis



Key: (a) PCC, CH_2Cl_2, rt; (b) $TiCl_4$, $Ti(OiPr)_4$, (*S*)-BINOL, Ag_2O, allyltributylstannane, -20 °C; (c) NaH, BnBr, THF, 0 °C; (d) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, rt; (e) allylTMS, $TiCl_4$, -78 °C; (f) Boc_2O, Et_3N, CH_2Cl_2, rt; (g) NIS, CH_3CN, -40 to 0 °C; (h) K_2CO_3, MeOH, rt; (i) first iteration: NaH, PMBCl, THF, DMF, 0 °C (subsequent iterations: NaH, MOMCl, THF, DMF, 0 °C); (j)vinylmagnesium bromide, CuI, THF, -20 °C; (k) acryloyl chloride, DIPEA, CH_2Cl_2, 0°C; (l) Grubbs I, CH_2Cl_2, reflux; (m) $TiCl_4$, CH_2Cl_2, rt.

B. O'Doherty *et al. J. Am. Chem. Soc.* **2013**, *135*, 9334.

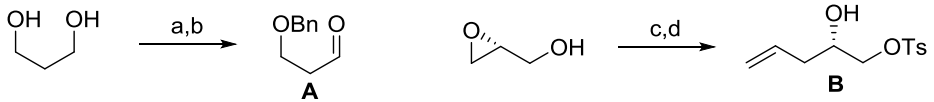
Linear Synthesis



Key: (a) PMBCl, NaH, TFAB, 0 °C; (b) $ClCO_2Me$, *n*-BuLi, THF, -78 to 0 °C; (c) PPh_3, PhOH, benzene, 50 °C; (d) AD-mix-α, *t*-BuOH/H_2O, 0 °C; (e) triphosgene, pyridine, DMAP, CH_2Cl_2, -78 °C; (f) $PdPPh_3$, Et_3N, HCO_2H, THF, reflux; (g)PhCHO, KO*t*Bu, THF, 0 °C; (h) DIBALH, CH_2Cl_2, -78 °C; (i) (*R,R*)-Leighton, $Sc(OTf)_3$, CH_2Cl_2, -10 °C, (j) ethyl acetate, Grubbs II, CH_2Cl_2; (k) PhCHO, KO*t*Bu, THF, 0 °C; (l) DIBALH, CH_2Cl_2, -78 °C; (m) 1-pentadecyne, *n*-BuLi, THF, -78 °C; (n) DMP, CH_2Cl_2, 0 °C; (o) (*R,R*)-Noyori, Et_3N, HCO_2H; (p) NBSH, Et_3N, CH_2Cl_2; (q) TBSCl, imidazole, DMF; (r) DDQ, CH_2Cl_2, H_2O, 0 °C; (s) DMP, CH_2Cl_2, 0 °C; (t) (*S,S*)-Leighton, $Sc(OTf)_3$, CH_2Cl_2, -10 °C; (u) acrylic acid, DCC, DMAP, CH_2Cl_2; (v) Grubbs I, CH_2Cl_2, reflux; (w) AcOH/H_2O = 4:1, 80 °C.

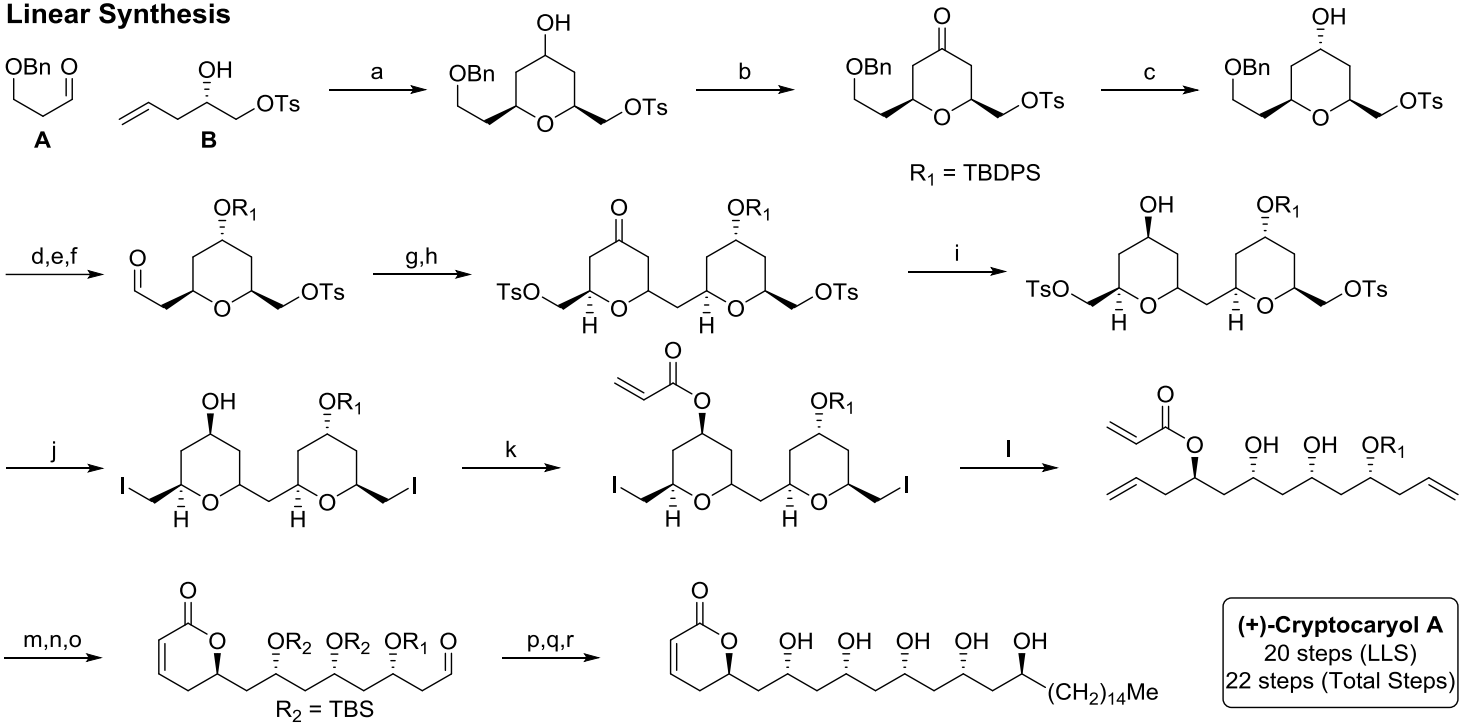
C. Cossy *et al. J. Org. Chem.* **2015**, *80*, 8668.

Starting Materials



Key: (a) NaH, BnBr, *n*-Bu_4NI, THF, rt, 7h; (b) PCC, NaOAc, 4 Å MS, CH_2Cl_2, rt, 3h; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 3 h; (d) Li_2CuCl_4, vinylmagnesium bromide, THF, -40 °C, 3h.

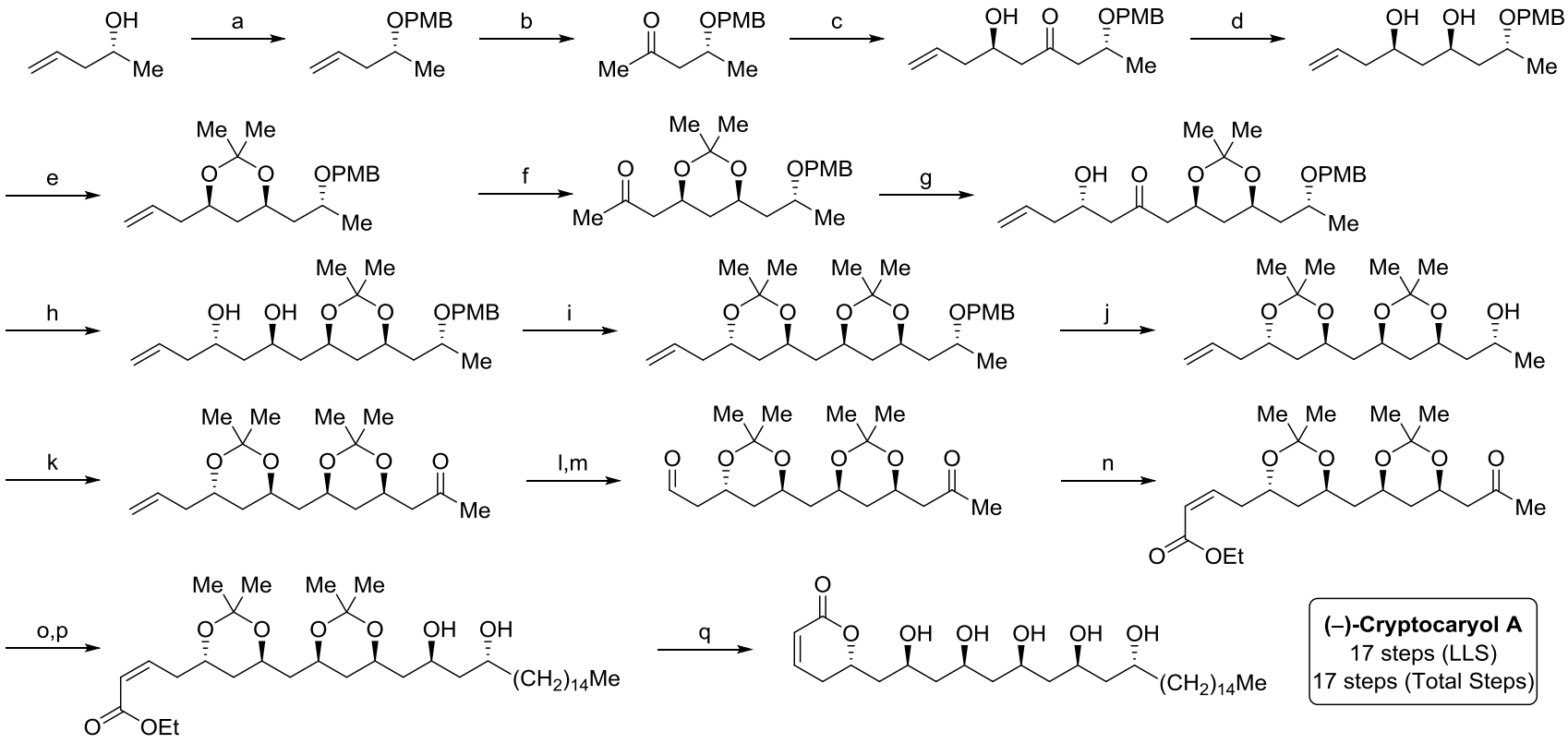
Linear Synthesis



Key: (a) TFA, CH_2Cl_2, rt, 3 then $NaHCO_3$, Et_3N; (b) DMP, CH_2Cl_2, rt 2.5 h; (c) L-Selectride, THF, -78 °C, 1 h; (d) TBDPSCl, imidazole, CH_2Cl_2, rt, 14 h; (e) H_2, Pd/C, MeOH, EtOAc, rt, 16 h; (f) TPAP, NMO, CH_2Cl_2, rt, 2 h; (g) **B**, TFA, CH_2Cl_2, rt, 3 h then Et_3N, $NaHCO_3$ (aq); (h) DMP, CH_2Cl_2, rt, 2h; (i) $NaBH_4$, MeOH, -40 °C, 1 h; (j) NaI, acetone, ∝w, 120 °C, 2 h; (k) acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, 0 °C to rt, 3.5 h; (l) Zn, THF/H_2O = 5:1, 70 °C, 1 h; (m) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 1 h; (n) Grubbs **I** (10 mol%), CH_2Cl_2, 45 °C, 2.5 h; (o) O_3, CH_2Cl_2, -78 °C then PPh_3; (p) (1) heptadecan-2-one, Cy_2BCl, Et_3N, pentane, 0 °C, 2 h (2) aldehyde, pentane, -78 °C to 40 °C, 4 h (3) MeOH/pH7 buffer/H_2O_2, -40 °C to rt, 16 h; (q) $Me_4NBH(OAc)_3$, CH_3CN/MeOH = 1:1, -20 °C, 7 h; (r) HF•CH_3CN, rt, 2.5 h.

D. Dias *et al. Org. Biomol. Chem.* **2015**, *13*, 3575.

Linear Synthesis



Key: (a) PMB trichloroacetimidate, CSA, CH_2Cl_2, rt; (b) $PdCl_2$, CuCl, O_2, DMF, H_2O, rt; (c) (1) Cy_2BCl, Et_3N, Et_2O, -30 °C (2) 3-butenal, -78 °C; (d) $LiBH_4$, Et_2BOMe, THF, MeOH, -78 °C; (e) 2,2-DMP, CSA, rt; (f)$PdCl_2$, CuCl, O_2, DMF, H_2O, rt; (g) (1) Cy_2BCl, Et_3N, Et_2O, -30 °C (2) 3-butenal, -78 °C; (h) $Me_4NHB(OAc)_3$, MeCN, AcOH, -30 to -20 °C; (i) 2,2-DMP, PPTS, rt; (j) DDQ, CH_2Cl, buffer, 0 °C; (k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (l) OsO_4, NMO, *t*-BuOH, THF, H_2O, rt; (m) $NaIO_4$, THF, H_2O; (n) ethyl 2-(bis(*o*-tolyloxy)phosphoryl)acetate, NaH, THF, -78 °C; (o) (1) Cy_2BCl, Et_3N, Et_2O, -30 °C (2) palmitaldehyde, CH_2Cl_2, -78 °C; (p) $Me_4NHB(OAc)_3$, MeCN, AcOH, -30 to -20 °C; (q) CSA, MeOH.