Supporting Information

Total Synthesis of 6-Deoxyerythronolide B via C-C Bond-Forming Transfer Hydrogenation

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Complete ref 5a:

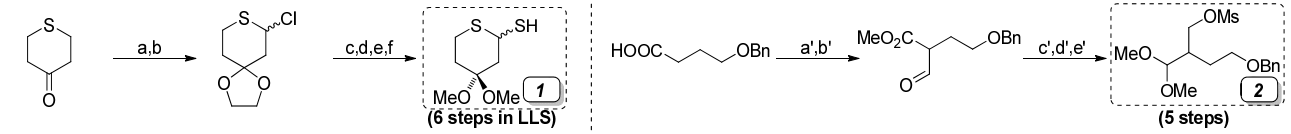
Woodward R. B.; Logusch, E; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. Chênevert, R. B.; Fliri, A.; Froble, K.; Gais, H. J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdales, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3215.

Graphical Summary of Prior Syntheses

Note: Our step count starts from commercial materials used stoichiometrically with a retail price below $50 / 1g.

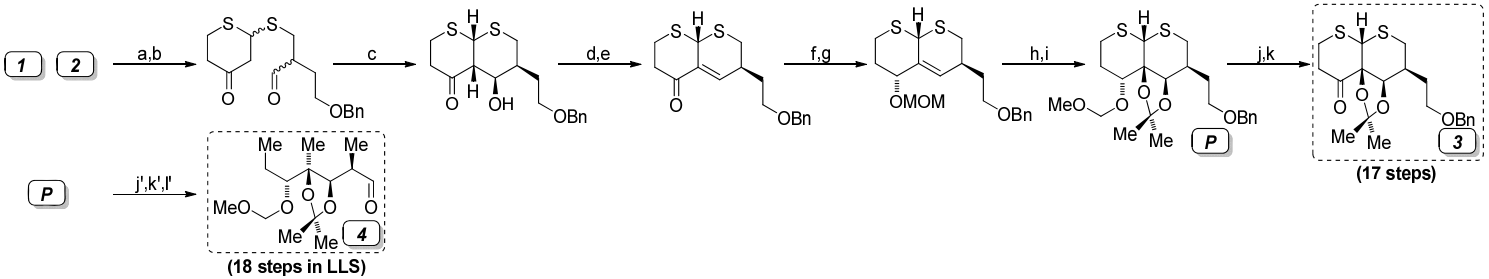
Erythromycin A (Woodward, *J. Am. Chem. Soc.* **1981**, *103*, 3210.)

Fragment 1 and 2



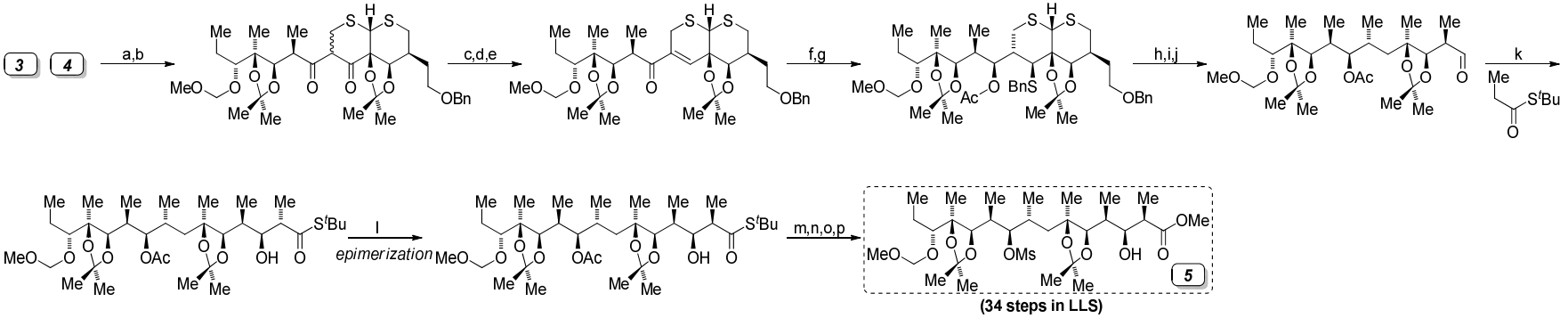
Key: (a) $HOCH_2CH_2OH$, TsOH; (b) NCS; (c) thiourea; (d) aq. NaOH; (e) aq. HCl; (f) $HC(OMe)_3$, TsOH
(a') conc. H_2SO_4, MeOH; (b') HCOOH, LDA; (c') conc. H_2SO_4, MeOH; (d') LAH; (e') MsCl, Py

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

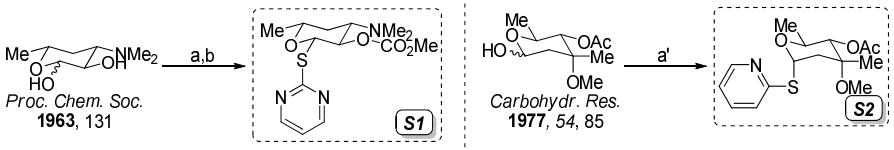
Fragment Union



Key: (a) mesityl-Li; (b) TFAA, DMSO, iPr_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

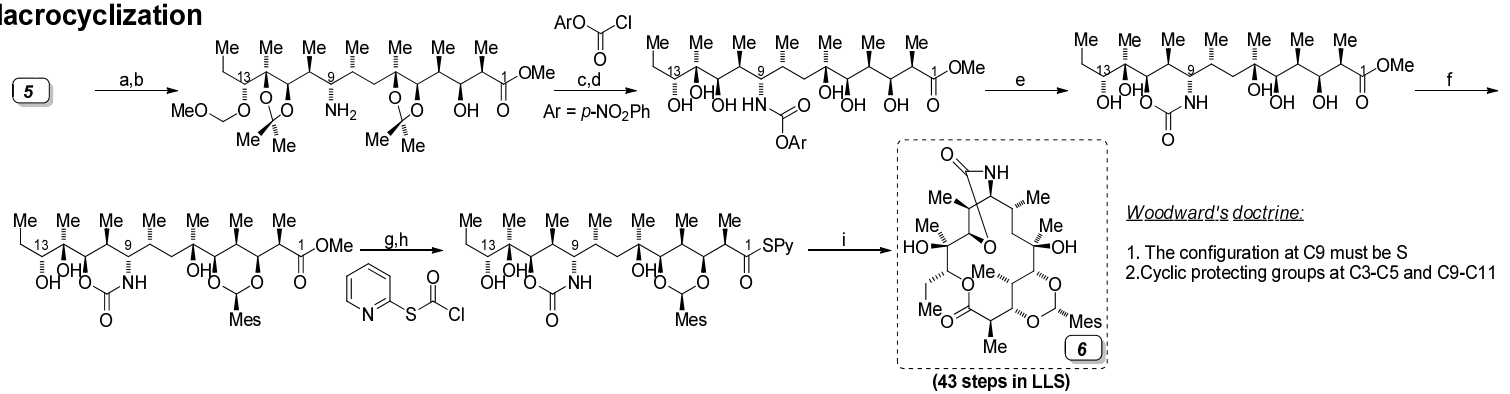
Erythromycin A (Woodward, *J. Am. Chem. Soc.* **1981**, *103*, 3210.) (*continued*)

Glycosidating Reagents S1 and S2



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

Macrocyclization

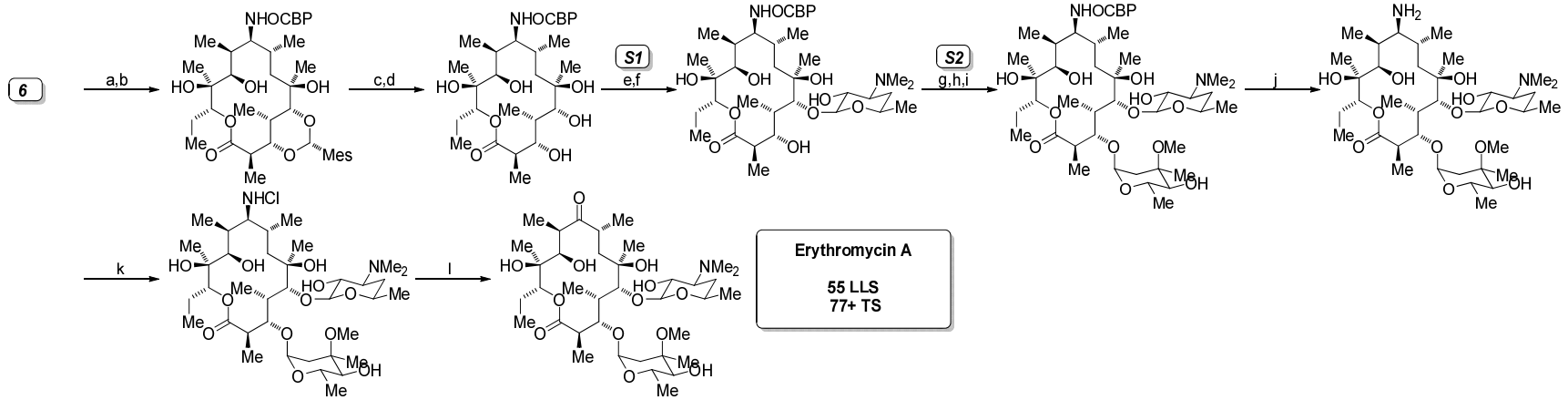


Woodward's doctrine:

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

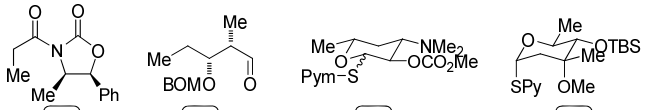
Glycosidation and End Game



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

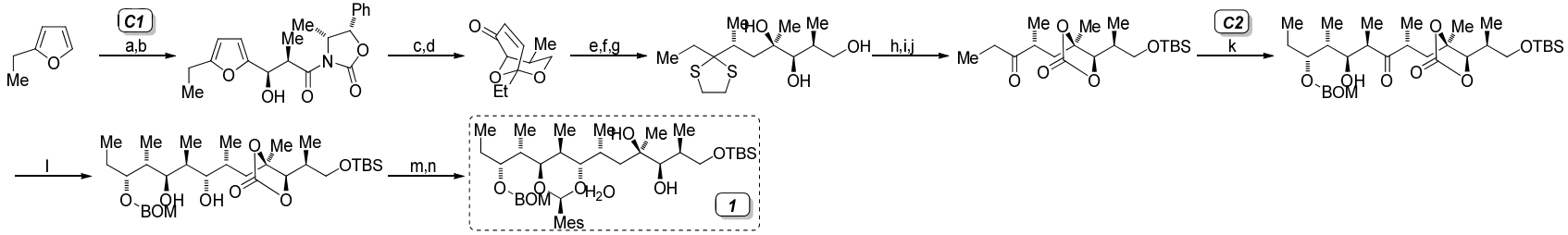
Erythromycin B (Martin, *J. Am. Chem. Soc.* **1997**, *119*, 3193; *Tetrahedron* **2007**, *63*, 5709.)

Chiral Auxiliary and Sugar



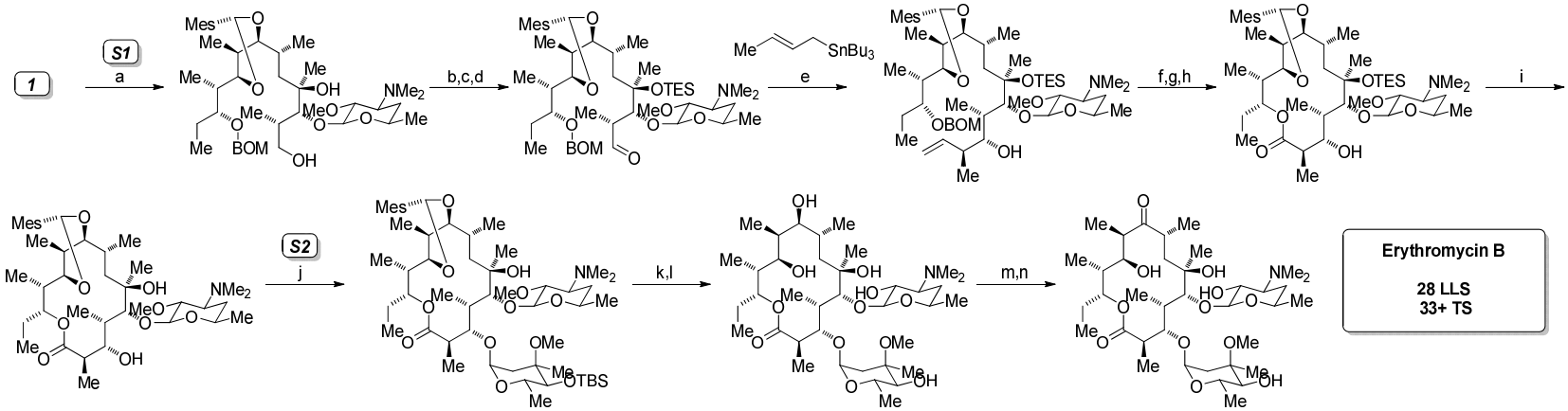
Sigma-Aldrich: $105.50/1g

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) $LiBH_4$

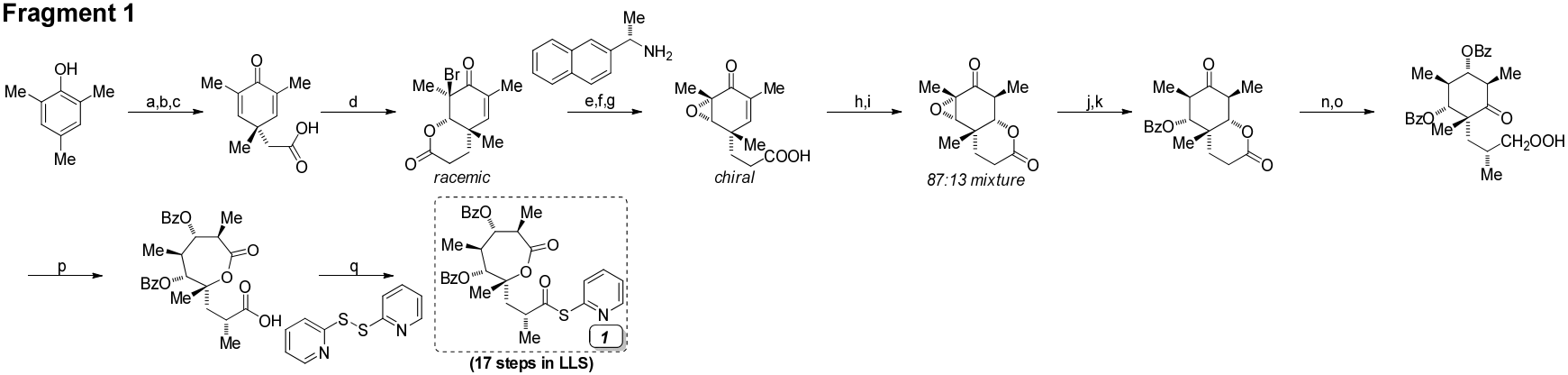
Glycosylation



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

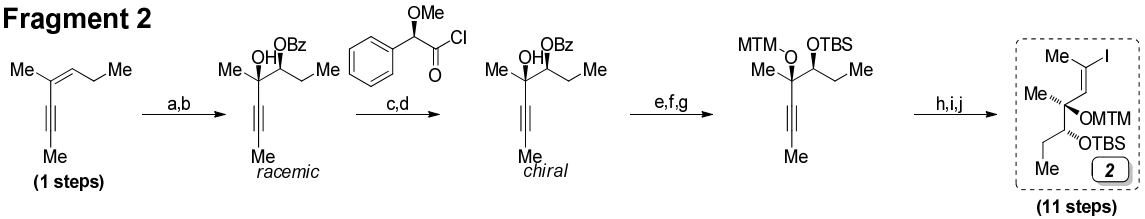
Erythronolide A (Corey, *J. Am. Chem. Soc.* **1979**, *101*, 7131.)

Fragment 1



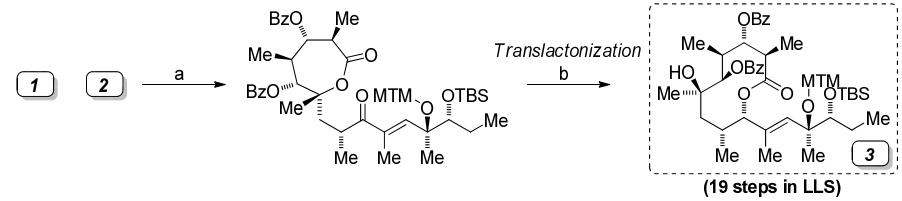
Key: (a) Allyl-Br, NaOMe; (b) BH_3•THF, H_2O_2, NaOH; (c) CrO_3, H_2SO_4; (d) Br_2, KBr; (e) KOH; (f) Amine, recrystallization; (g) MsOH; (h) Br_2, KBr; (i) Bu_3SnH, AIBN; (j) H_2, $Pd(OH)_2/C$, HOAc-THF; (k) BzCl, Py; (l) $Zn(BH_4)_2$,

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

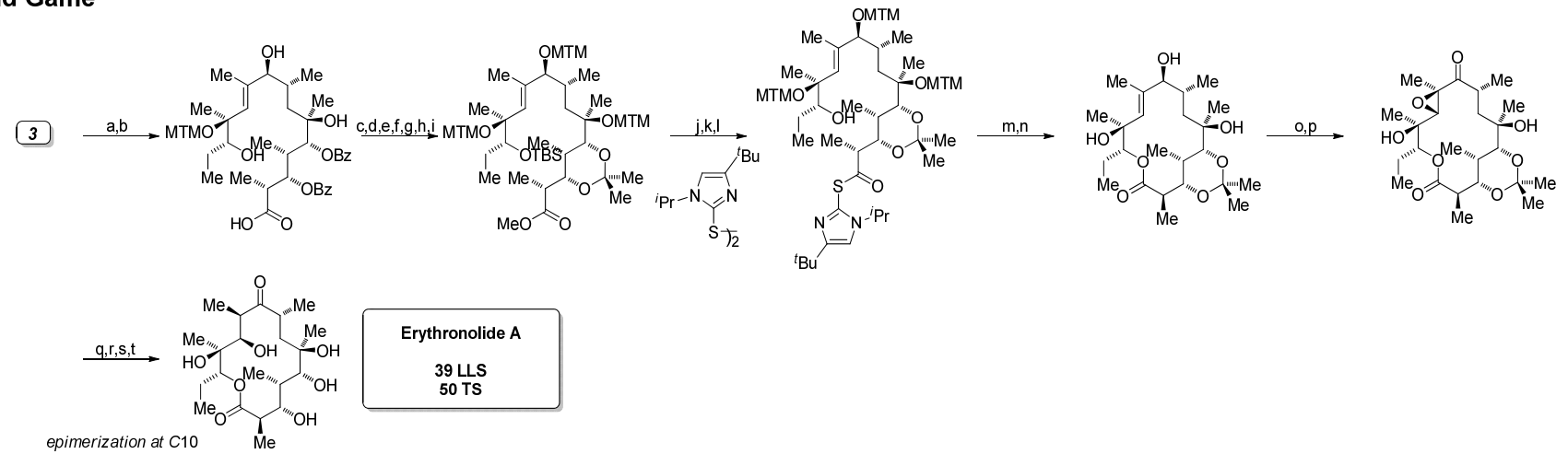
Coupling Fragment 1 and 2



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

Erythronolide A (Corey, *J. Am. Chem. Soc.* **1979**, *101*, 7131.) (*continued*)

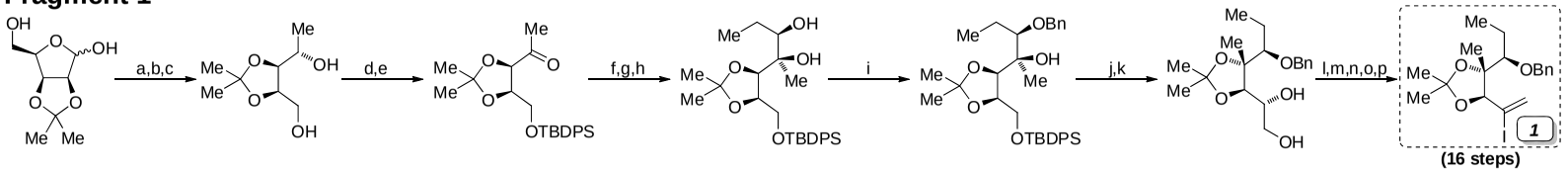
End Game



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_2C THF; (o) mCPBA; (p) PCC; (q) Pd/C, H_2, (r) CH_2=C(Me)OMe, CSA; (s) Triton B methoxide; (t) PPTS, MeOH

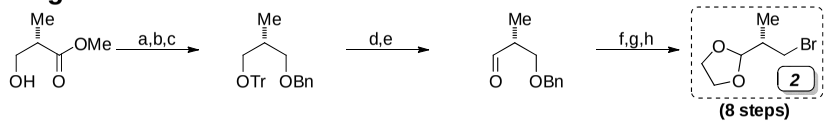
Erythronolide A (Kinoshita, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618.)

Fragment 1



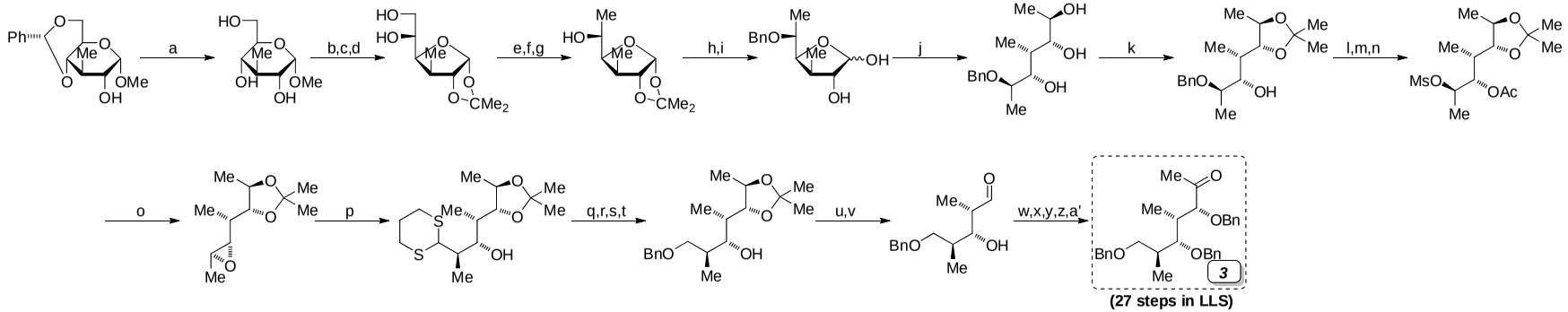
Key: (a) MeMgI; (b) $NaIO_4$; (c) $LiAlH_4$; (d) TBDPSCl, imidazole; (e) PCC; (f) vinylmagnesium bromide; (g) O_3, PPh_3; (h) EtMgBr; (i) NaH, BnBr; (j) $FeCl_3$, acetone; (k) TBAF; (l) $NaIO_4$; (m) MeMgI; (n) PCC; (o) NH_2NH_2-H_2O, TEA; (p) I_2, tetramethylguanidine

Fragment 2



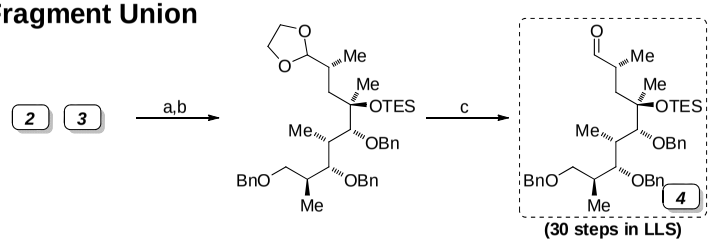
Key: (a) TrCl, TEA, DMAP; (b) LAH; (c) NaH, BnBr; (d) amberlyst^{-15}; (e) $(COCl)_2$, TEA, DMSO; (f) $HOCH_2CH_2OH$, TsOH; (g) H_2, Pd/C; (h) EtBr, PPh_3, DEAD

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

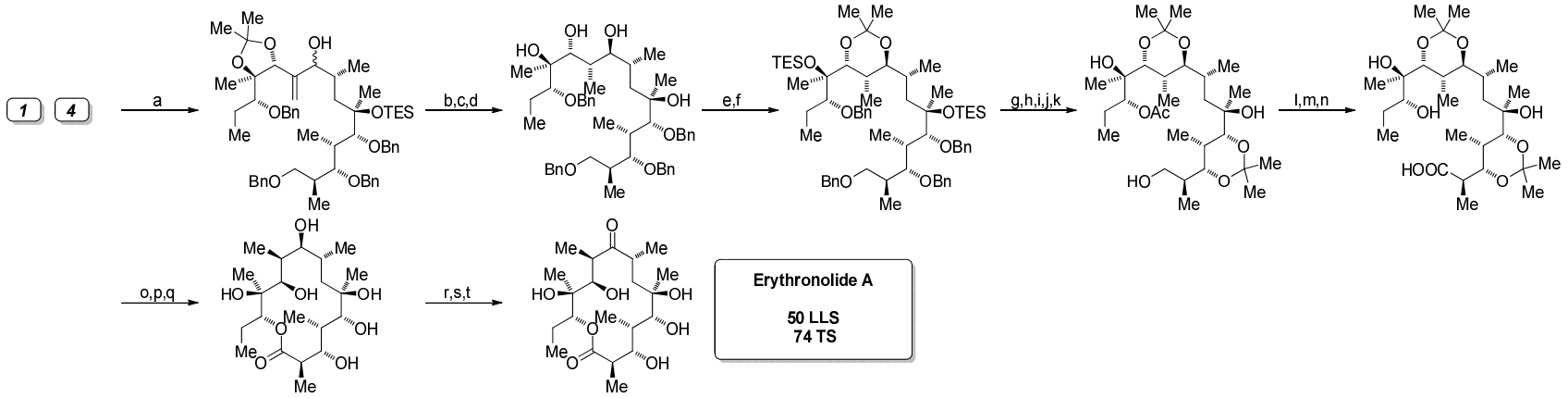
Fragment Union



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

Erythronolide A (Kinoshita, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618.) (*continued*)

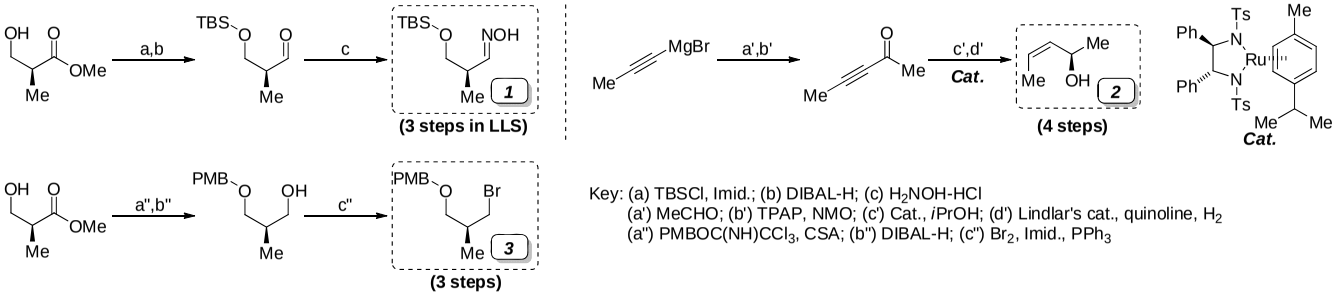
End Game



Key: (a) BuLi; (b) $ClRh(PPh_3)_3$, 50 atm H_2; (c) TBAF; (d) HCl, H_2O; (e) TsOH, acetone; (f) TESOTf, TEA; (g) Pd/C, H_2; (h) TBDPSCl, TEA; (i) TsOH, acetone; (j) Ac_2O, TEA; (k) TBAF; (l) $(COCl)_2$, TEA, DMSO; (m) $NaClO_2$; (n) LiOH, H_2O; (o) (2-pyr)$_2S_2$; (p) CuOAc; (q) AcOH; (r) $PhCH(OMe)_2$, CSA; (s) PCC; (t) H_2, Pd/C

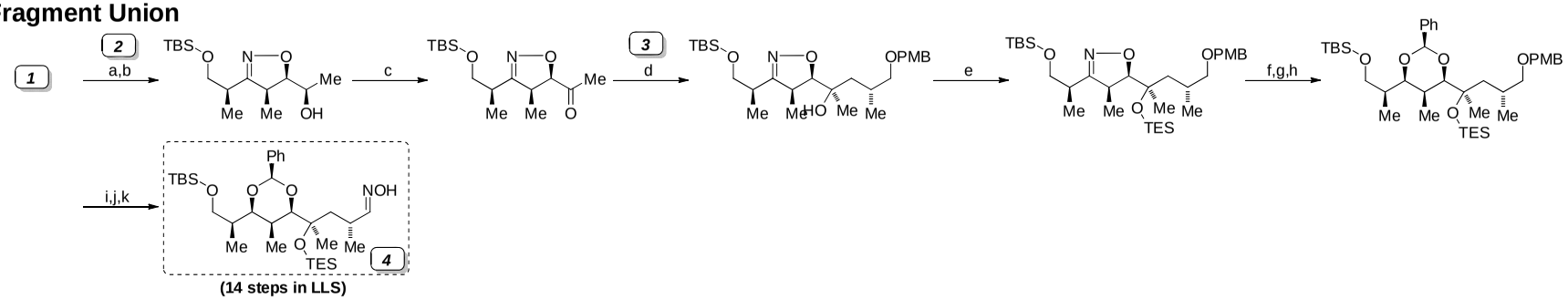
Erythronolide A (Carreira, *Angew. Chem. Int. Ed.* **2005**, *44*, 4036; Carreira, *J. Org. Chem.* **2009**, *74*, 8695.)

Fragment 1, 2, 3



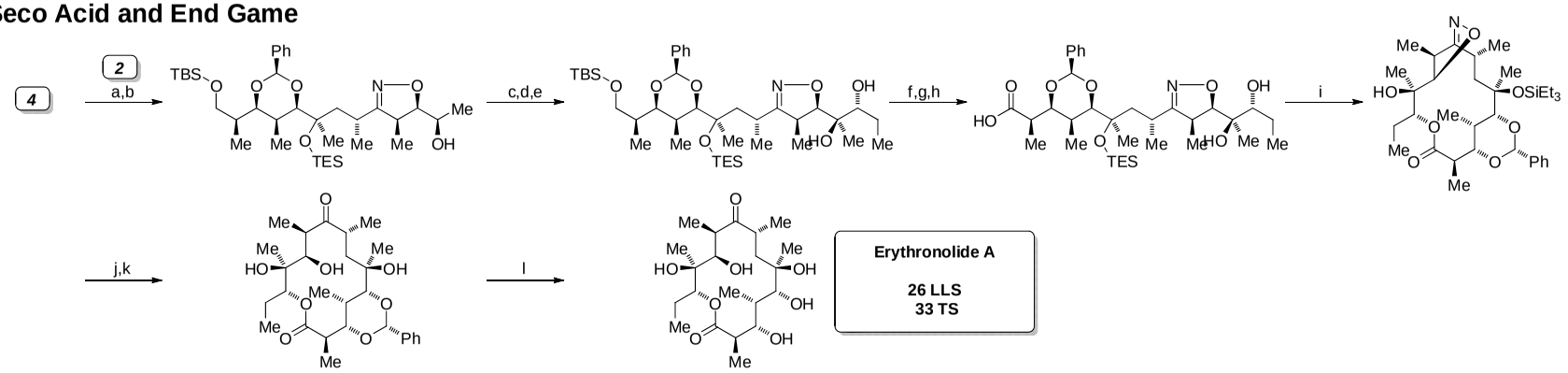
Key: (a) TBSCl, Imid.; (b) DIBAL-H; (c) H_2NOH-HCl
(a') MeCHO; (b') TPAP, NMO; (c') Cat., *i*PrOH; (d') Lindlar's cat., quinoline, H_2
(a'') $PMBOC(NH)CCl_3$, CSA; (b'') DIBAL-H; (c'') Br_2, Imid., PPh_3

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

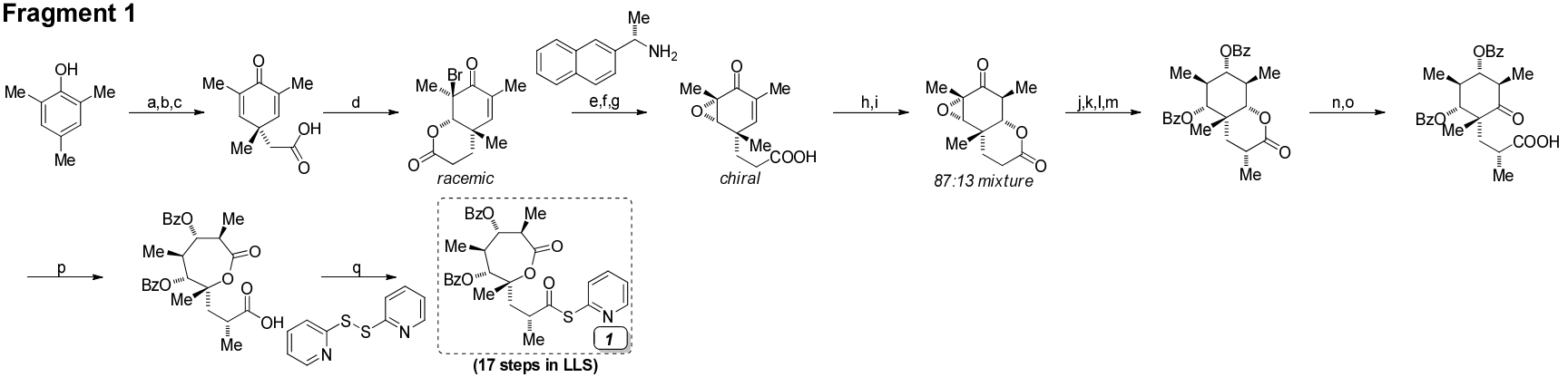
Seco Acid and End Game



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

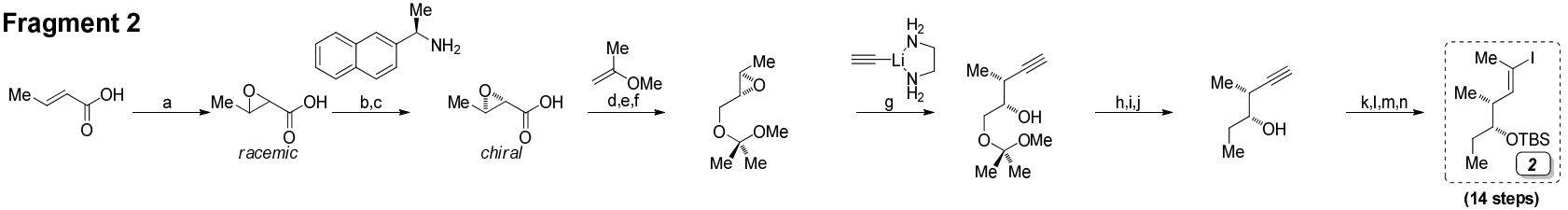
Erythronolide B (Corey, *J. Am. Chem. Soc.* **1978**, *100*, 5620.)

Fragment 1



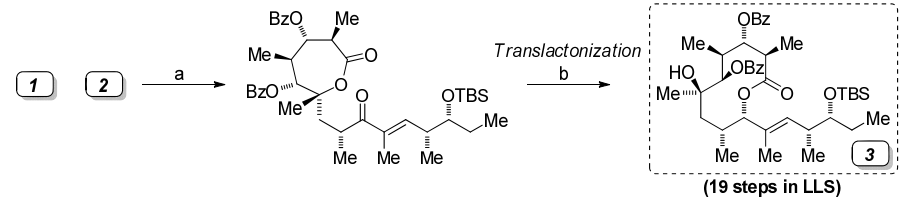
Key: (a) Allyl-Br, NaOMe; (b) BH_3•THF, H_2O_2, NaOH; (c) CrO_3, H_2SO_4; (d) Br_2, KBr; (e) KOH; (f) Amine, recrystallization; (g) MsOH; (h) Br_2, KBr; (i) Bu_3SnH, AIBN; (j) Al/Hg; (k) H_2, Raney-Ni; (l) BzCl, Py; (m) MeI, LDA, HMPA; (n) LiOH; (o) CrO_3, H_2SO_4; (p) AcOOH; (q) PPh_3

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

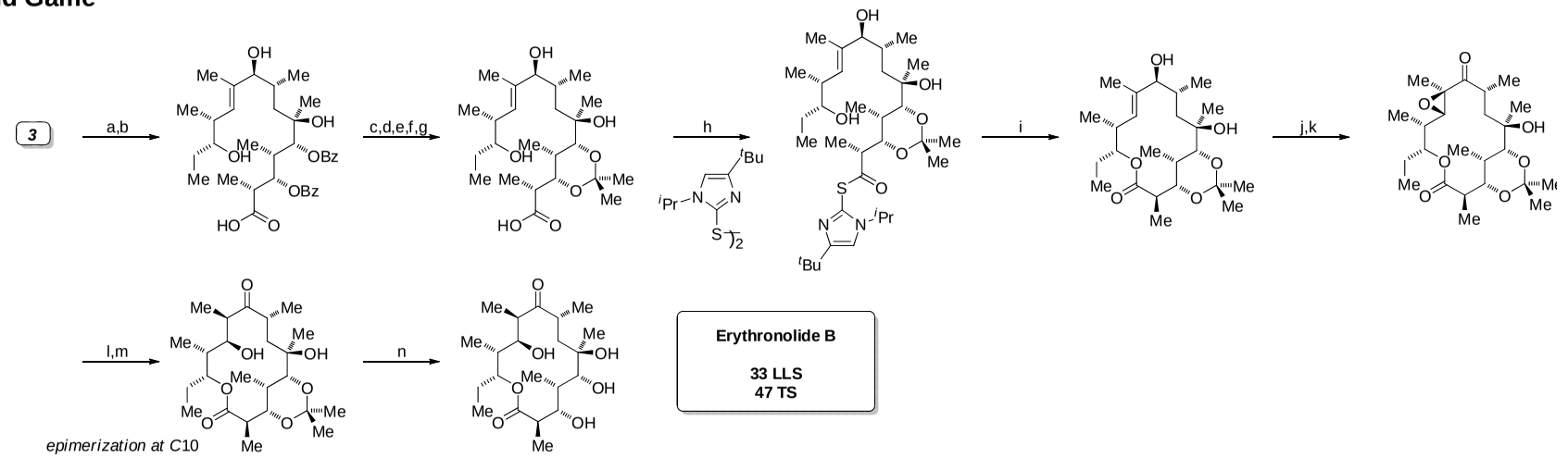
Coupling Fragment 1 and 2



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

Erythronolide B (Corey, *J. Am. Chem. Soc.* **1978**, *100*, 5620.) (*continued*)

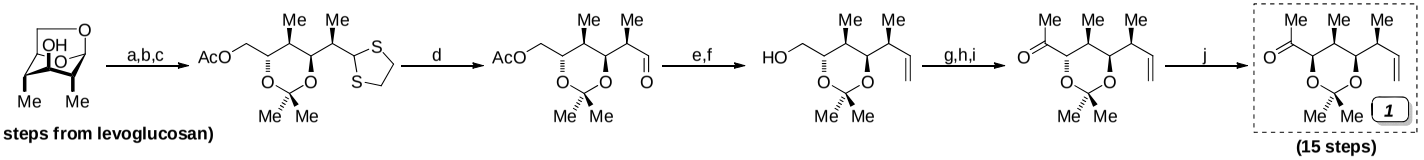
End Game



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

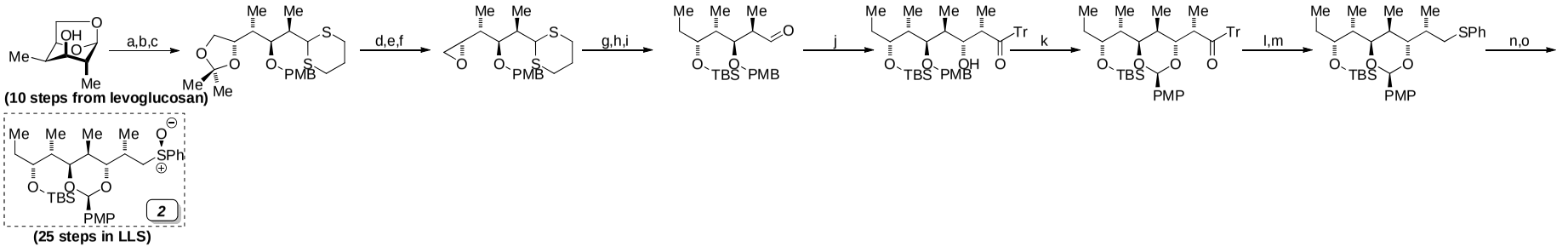
Erythronolide B (Kochetkov, *Tetrahedron Lett.* **1987**, *28*, 3835.)

Fragment 1



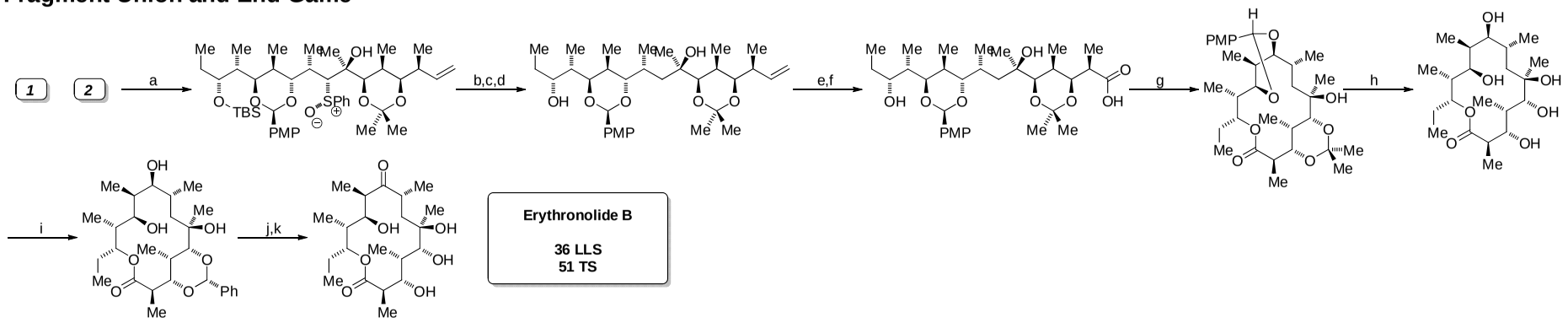
Key: (a) $HS(CH_2)_2SH$, BF_3OEt_2; (b) Ac_2O-Py; (c) DMP-Me_2CO, TsOH; (d) $HgCl_2$, $CaCO_3$; (e) $Ph_3P{=}CH_2$; (f) MeONa, MeOH; (g) $(COCl)_2$, DMSO, TEA; (h) MeMgCl; (i) $(COCl)_2$, DMSO, TEA; (j) K_2CO_3, MeOH

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

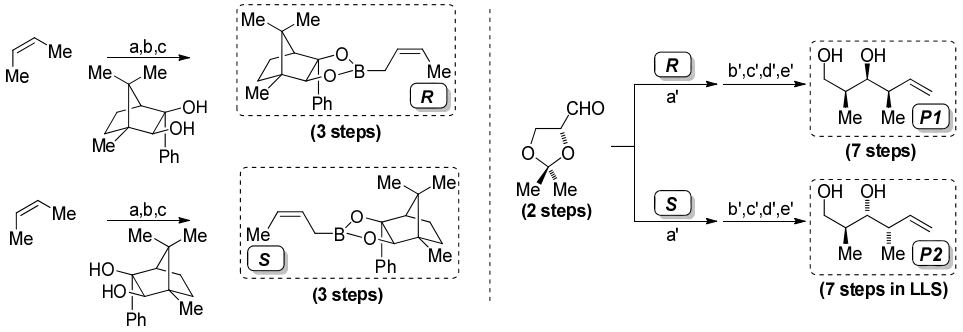
Fragment Union and End Game



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

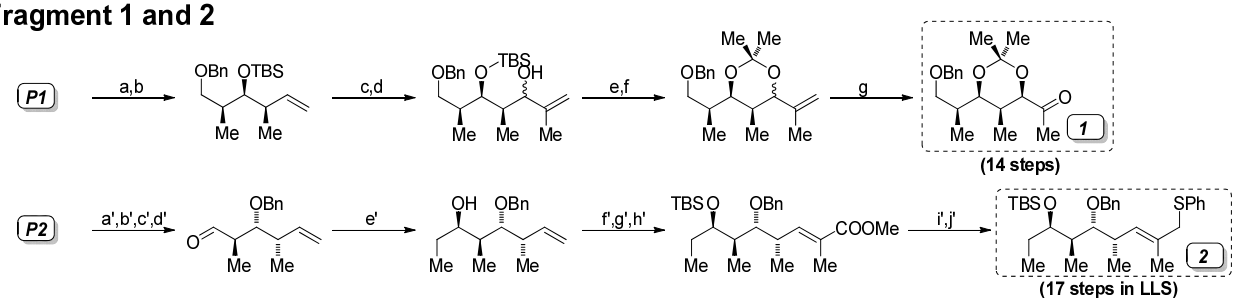
Erythronolide B (Mulzer, *J. Am. Chem. Soc.* **1991**, *113*, 910.)

Chiral Auxiliary and Precursor 1,2



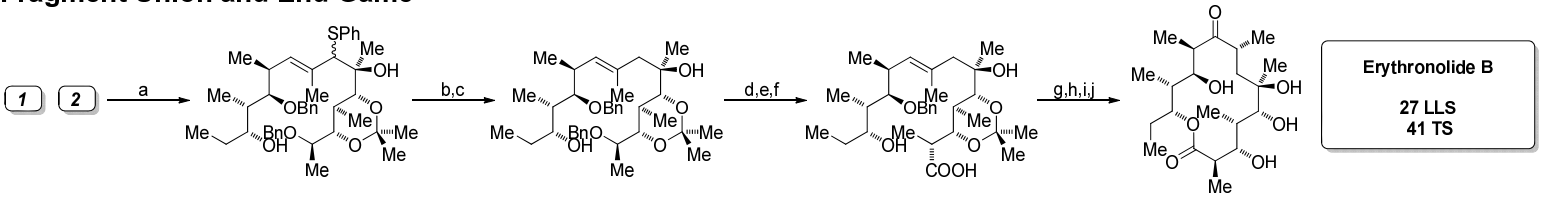
Key: (a) BuLi, *t*BuOK; (b) Cl-B(NMe$_2$)$_2$; (c) distillation
(a') -78 ^{o}C; (b') TsCl; (c') PPTS; (d') NaHCO$_3$; (e') Me$_2$CuLi

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

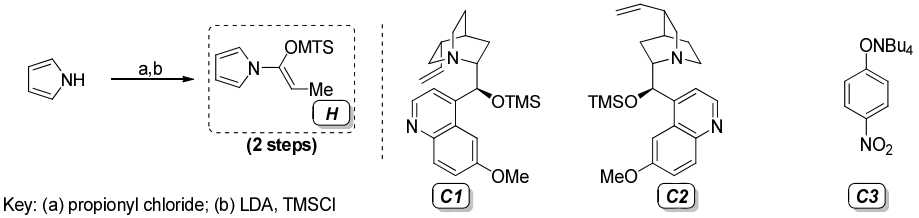
Fragment Union and End Game



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

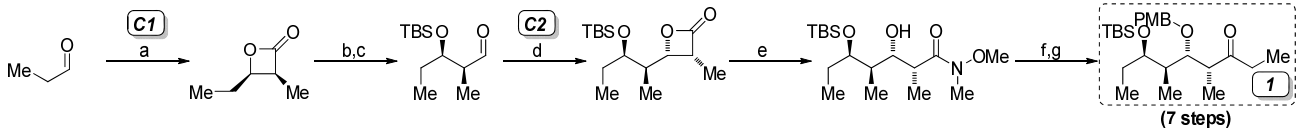
Erythronolide B (Nelson, *Angew. Chem. Int. Ed.* **2010**, *49*, 2591.)

Catalyst and Homologation Reagent



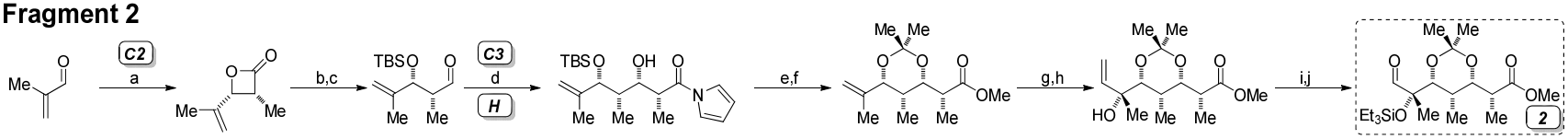
Key: (a) propionyl chloride; (b) LDA, TMSCl

Fragment 1



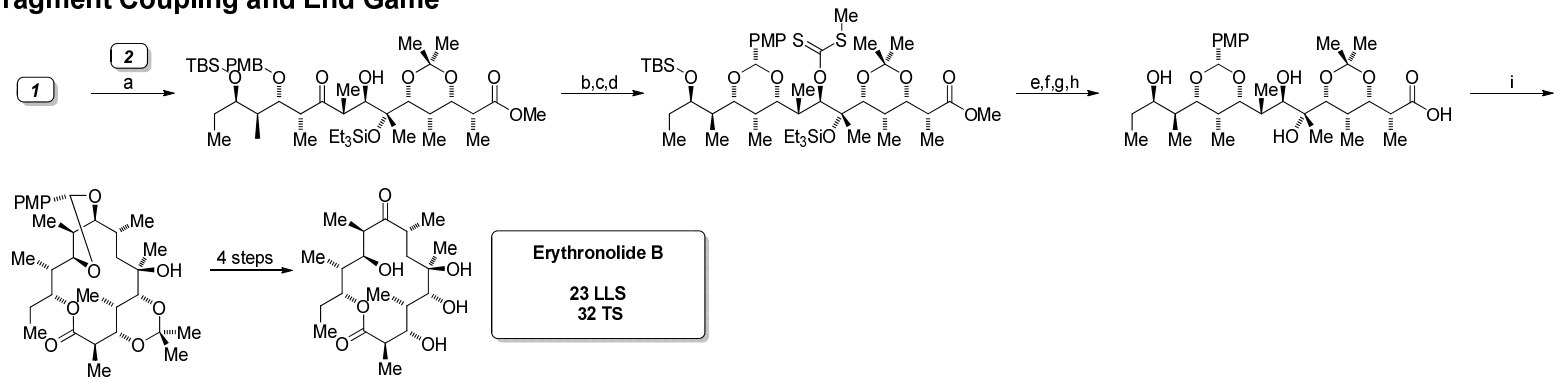
Key: (a) EtCOCl, *i*Pr_2NEt, $LiClO_4$; (b) EtSH, KHMDS; (c) DIBAL-H; (d) EtCOCl, *i*Pr_2NEt, LiI; (e) MeO(Me)NH_2Cl, Me_2AlCl; (f) EtMgBr; (g) PMBOC(NH)CCl_3, BF_3-OEt_2

Fragment 2



Key: (a) EtCOCl, *i*Pr_2NEt, LiI; (b) EtSH, KHMDS, TBSCl, NEt_3; (c) DIBAL-H; (d) 1N HCl; (e) $Me_2C(OMe)_2$, CSA; (f) NaOMe; (g) O_3, Me_2S; (h) EtMgBr; (i) O_3, Me_2S; (j) TESOTf, 2,6-lutidine

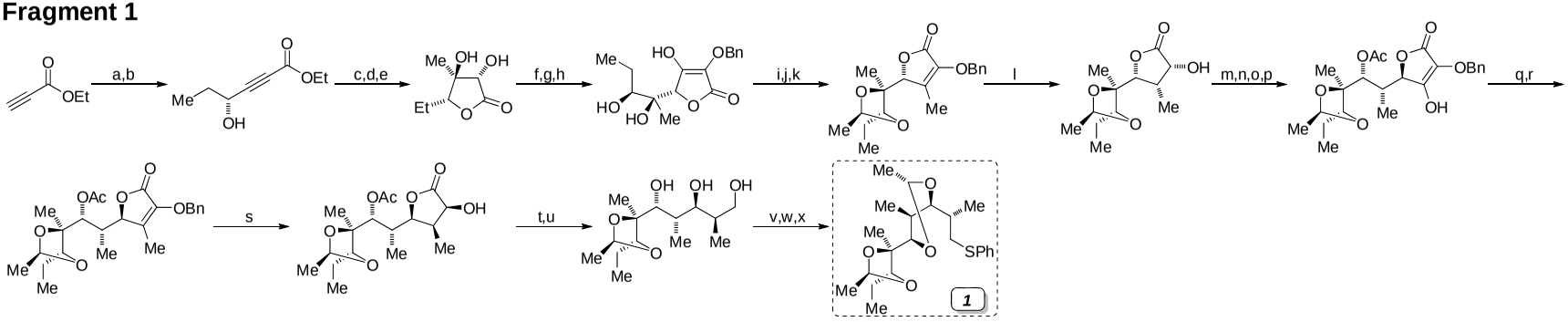
Fragment Coupling and End Game



Key: (a) LHMDS; (b) $Zn(BH_4)_2$; (c) DDQ; (d) KHMDS, CS_2, MeI; (e) AIBN, Bu_3SnH; (f) PMPCH$(OMe)_2$, CSA; (g) LiOH; (h) TBAF; (i) 2,4,6-trichlorobenzoyl chloride, TEA, then DMAP

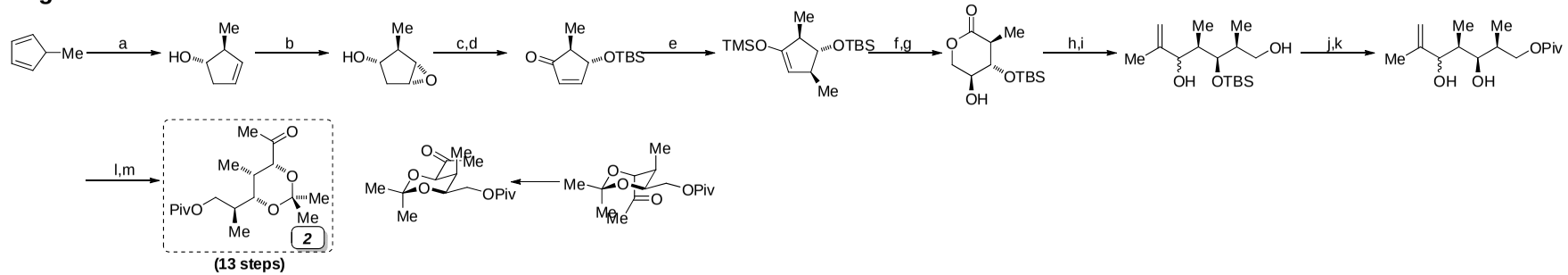
(9*S*)-Dihydroerythronolide A (Stork, *J. Am. Chem. Soc.* **1987**, *109*, 1565.)

Fragment 1



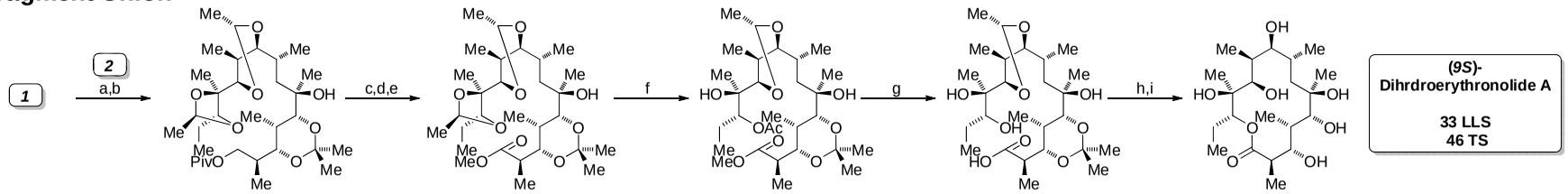
Key: (a) BuLi, propionyl chloride; (b) 9-BBN, (*R*)-pinene; (c) $H_2C{=}C(Me)OMe$, CSA; (d) dimethylthiocuprate, then acid; (e) OsO_4, NMO; (f) TMSCl, Imid.; (g) LHMDS, $EtOC(O)CH_2OBn$; (h) K_2CO_3; (i) $MeCH(COMe)_2$, CSA; (j) $(PhO)_2P(O)Cl$, Na_2CO_3, TBABr; (k) Me_2Zn, $Ni(acac)_2$; (l) H_2, Pd/C; (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

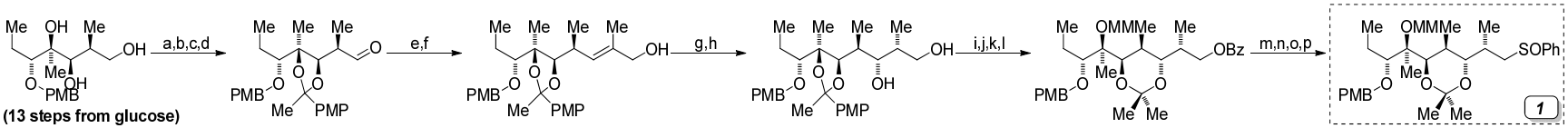
Fragment Union



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

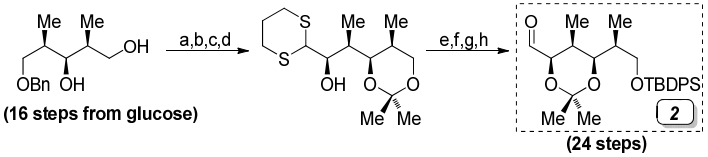
(9*S*)-Dihydroerythronolide A (Yonemitsu, *Tetrahedron Lett.* **1987**, *28*, 4569.)

Fragment 1



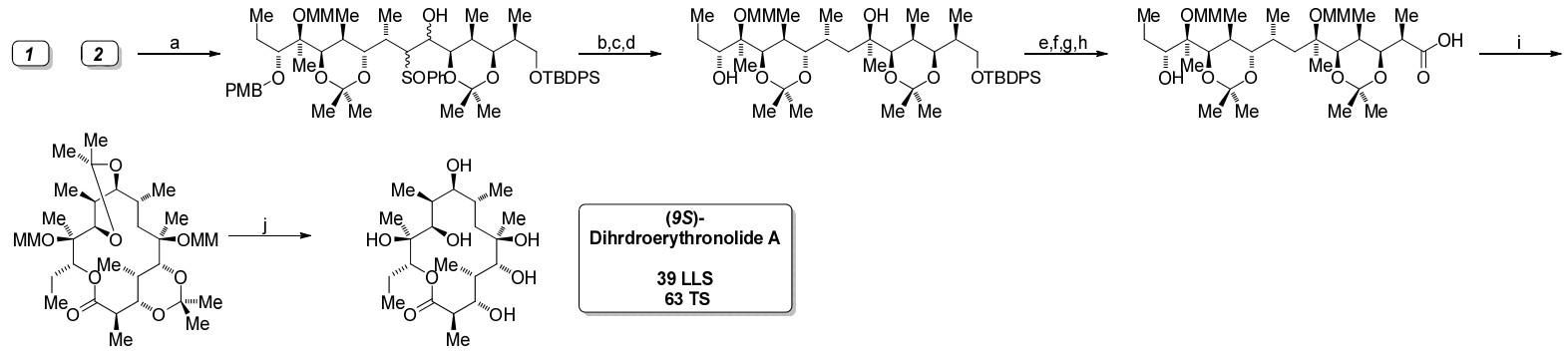
Key: (a) BzCl, Py; (b) $PMPCMe(OMe)_2$, CSA; (c) 1N KOH, MeOH; (d) $(COCl)_2$, DMSO, TEA; (e) $Ph_3P{=}CMeCO_2Et$, EDC; (f) LAH; (g) mCPBA; (h) $NaBH_3CN$, BF_3OEt_2; (i) BzCl, Py; (j) 4N HCl; (k) $CH_2{=}C(Me)OMe$, PPTS; (l) MMCl, *i*-Pr_2NEt; (m) 1N NaOH; (n) TsCl, TEA, DMAP; (o) PhSNa, EtOH; (p) $NaIO_4$

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, $NaHCO_3$

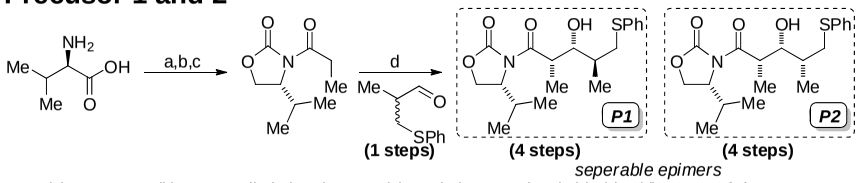
Fragment Union and Macrocyclization



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

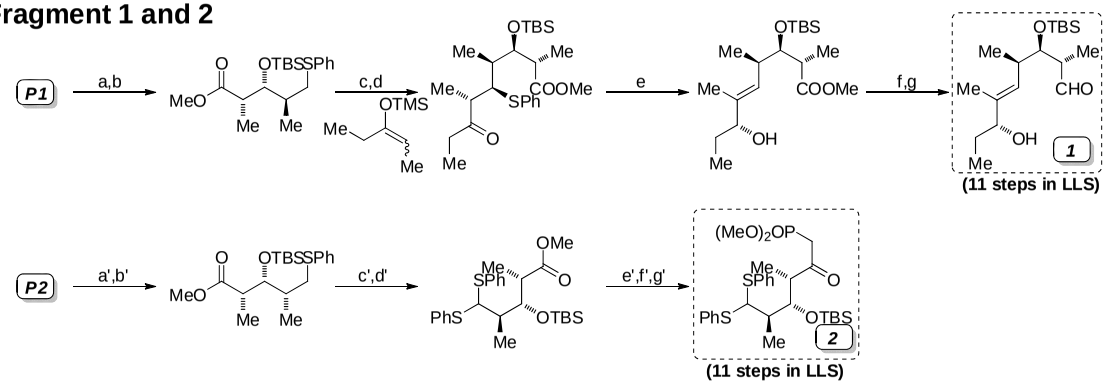
(9*S*)-Dihydroerythronolide A (Paterson, *Tetrahedron Lett.* **1989**, *30*, 7463.)

Precusor 1 and 2



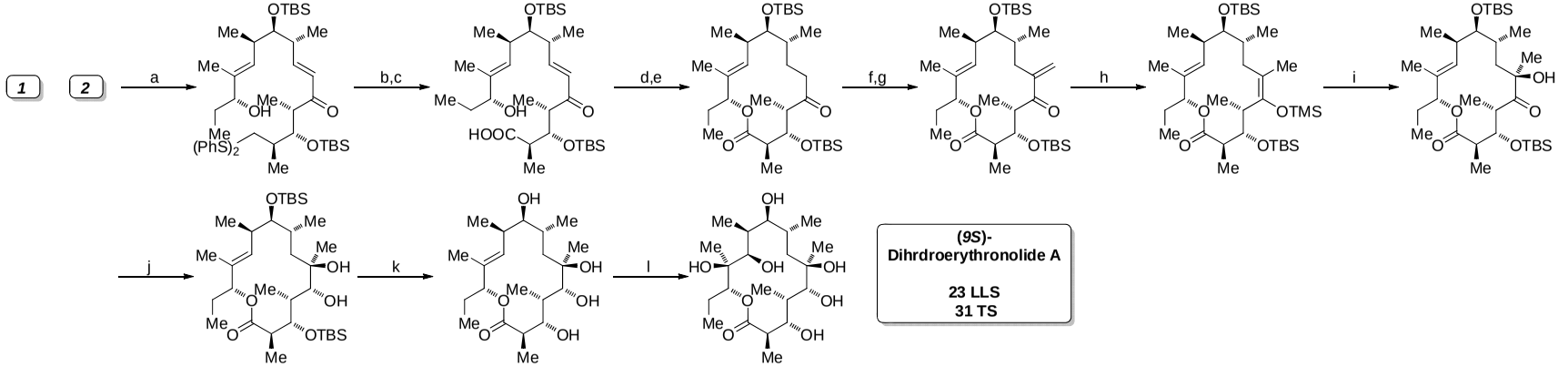
Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Bu_2BOTf, iPr_2NEt

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

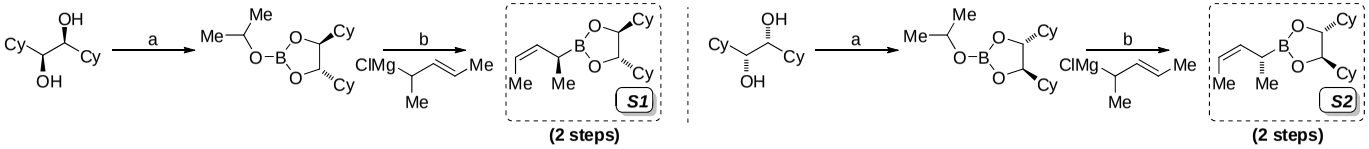
Fragment Union and Macrocyclization



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 $Na_2S_2O_5$

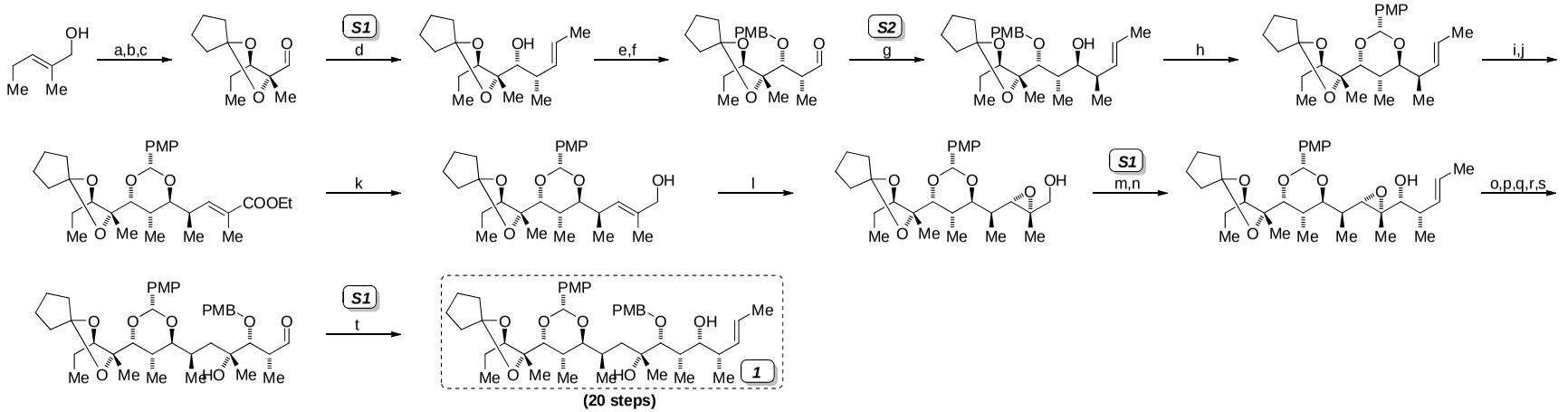
(9*S*)-Dihydroerythronolide A (Hoffmann, *Angew. Chem. Int. Ed.* **1993**, *32*, 101.)

Chiral Auxiliary



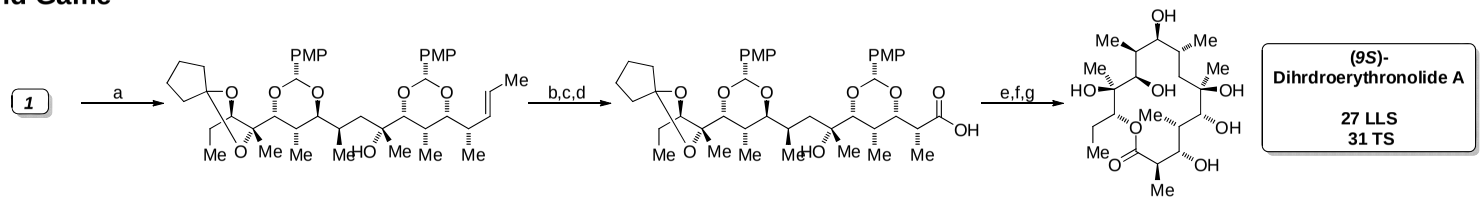
Key: (a) *i*PrOH; (b) THF, 0°C

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

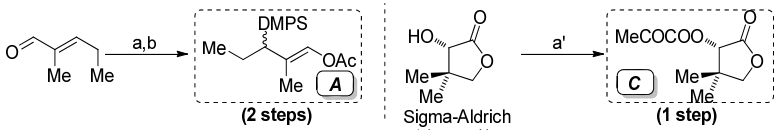
End Game



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

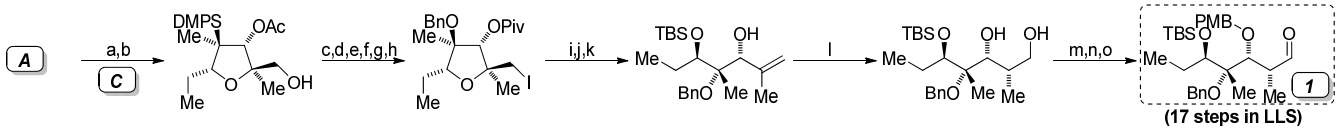
(9S)-Dihydroerythronolide A (Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 6018.)

Allylsilane and Auxillary Synthesis



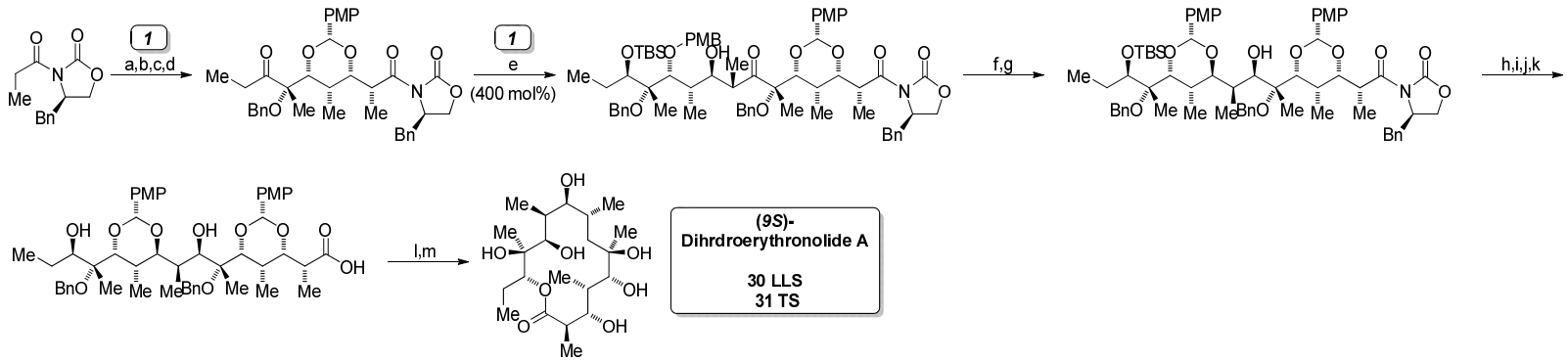
Key: (a) Li, then CuI, DMPSCl; (b) BuLi, Ac_2O
(a') MeCOCOCl, NEt_3, DMAP

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

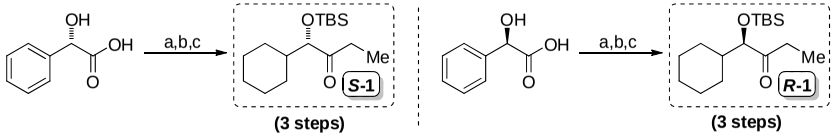
Fragment Union



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, $Pd(OH)_2/C$

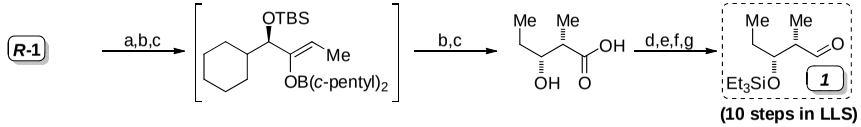
6-Deoxyerythronolide B (Masamune, *J. Am. Chem. Soc.* **1981**, *103*, 1568.)

Auxiliary Preparation



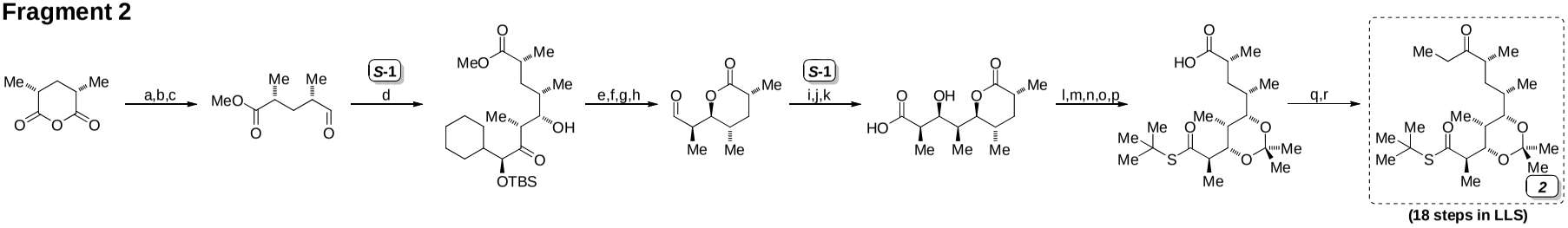
Key: (a) Rh/Al_2O_3; (b) EtLi, -78 °C; (c) TBSOTf, 2,6-lutidine

Fragment 1



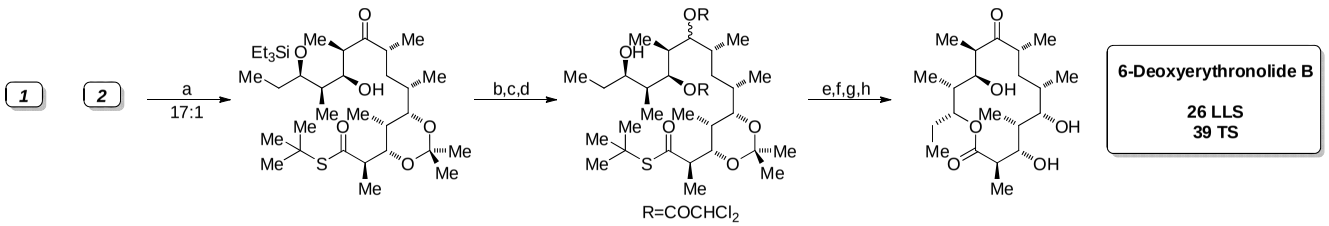
Key: (a) *c*-pentylBOTf, *i*Pr_2NEt, then acetyl aldehyde; (b) HF-MeCN; (c) $NaIO_4$; (d) CH_2N_2; (e) TESCl, DMAP; (f) DIBAL-H; (g) CrO_3•2Py

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) TlS*t*Bu, HS*t*Bu; (n) KOH, H_2O; (o) TBDPSCl, DMF; (p) $MeC(OMe)=CH_2$, TFA; (q) $(COCl)_2$, Py; (r) $LiCuEt_2$

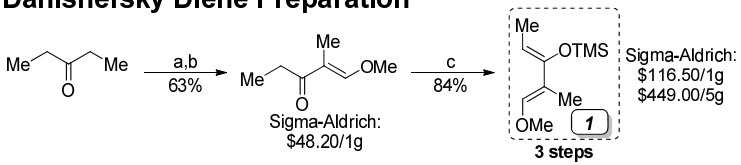
End Game



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

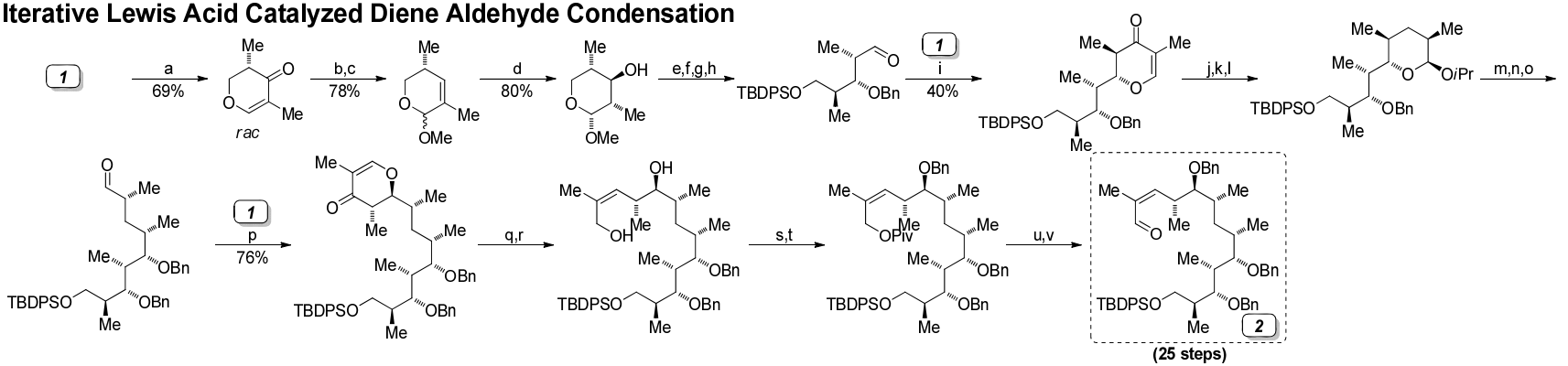
6-Deoxyerythronolide B (Danishefsky, *J. Org. Chem.* **1990**, *55*, 1636.)

Danishefsky Diene Preparation



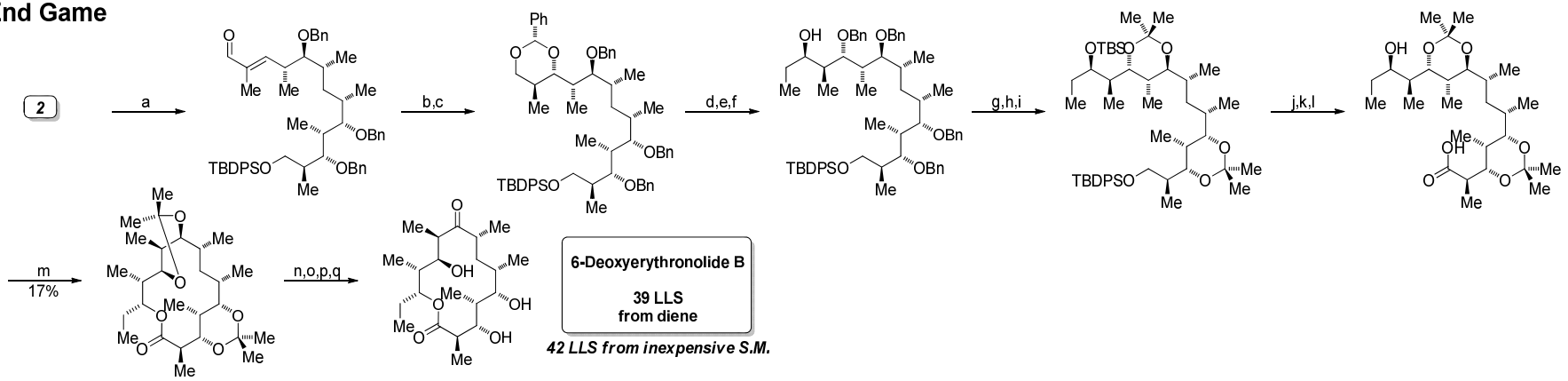
Key: (a) NaH, then ethyl formate; (b) TsOH, relux; (c) TMSOTf, TEA

Iterative Lewis Acid Catalyzed Diene Aldehyde Condensation



Key: (a) $ZnCl_2$, formaldehyde; (b) $CeCl_3$, $NaBH_4$; (c) TsOH; (d) BH_3•SMe_2; (e) 1,3-propanedithiol, $TiCl_4$; (f) TBDPSCl, TEA; (g) NaH, BnBr, TBAI; (h) NBS, $NaHCO_3$; (i) $ZnCl_2$, BF_3•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•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

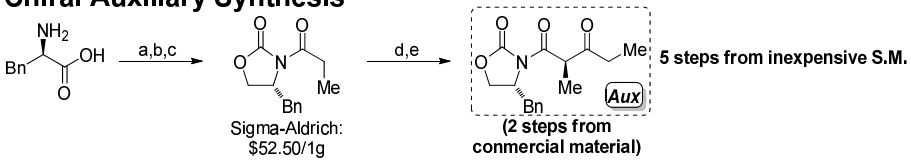
End Game



Key: (a) PhSH, BuLi; (b) BH_3•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, $MeCN/H_2O$

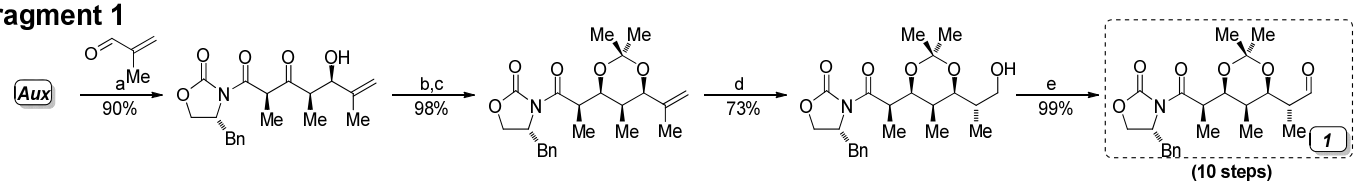
6-Deoxyerythronolide B (Evans, *Tetrahedron Lett.* **1997**, *38*, 53; *J. Am. Chem. Soc.* **1998**, *120*, 5921.)

Chiral Auxiliary Synthesis



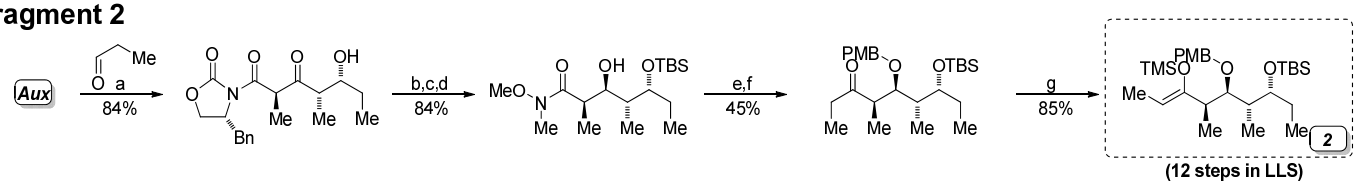
Key: (a) $NaBH_4$, I_2; (b) K_2CO_3, diethyl carbonate; (c) BuLi, then propionyl chloride; (d) Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e) SO_3•Py, TEA, DMSO

Fragment 1



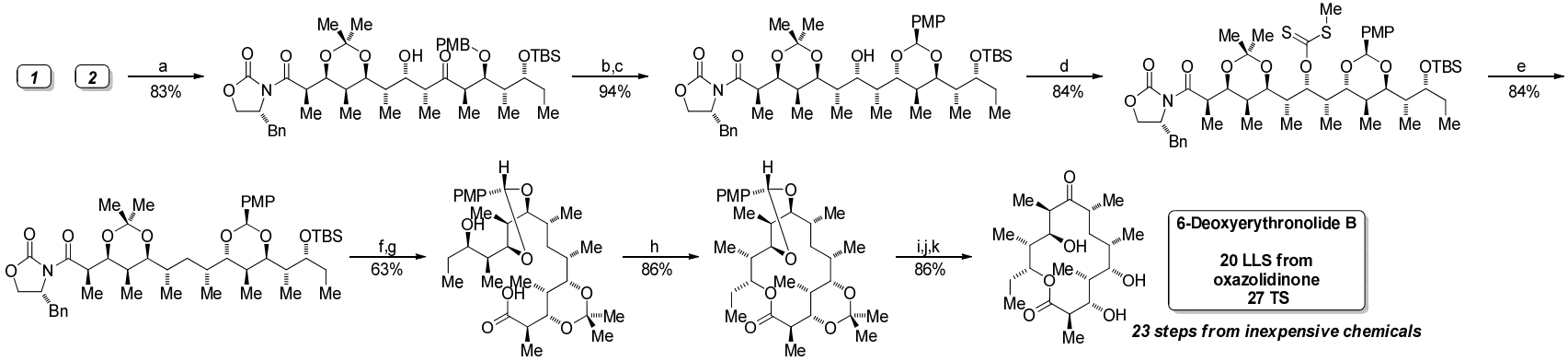
Key: (a) $TiCl_4$, iPr_2NEt, then methacrolein; (b) $Zn(BH_4)_2$; (c) $Me_2C(OMe)_2$, CSA; (d) 9-BBN; (e) $(COCl)_2$, TEA, DMSO

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

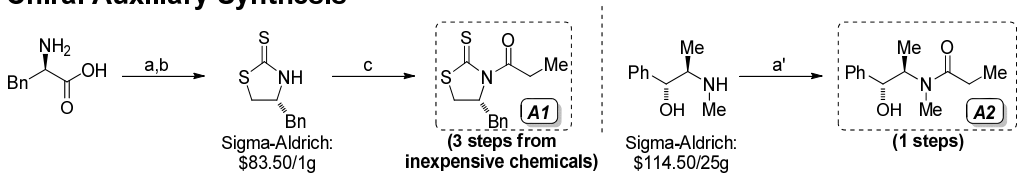
End Game



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

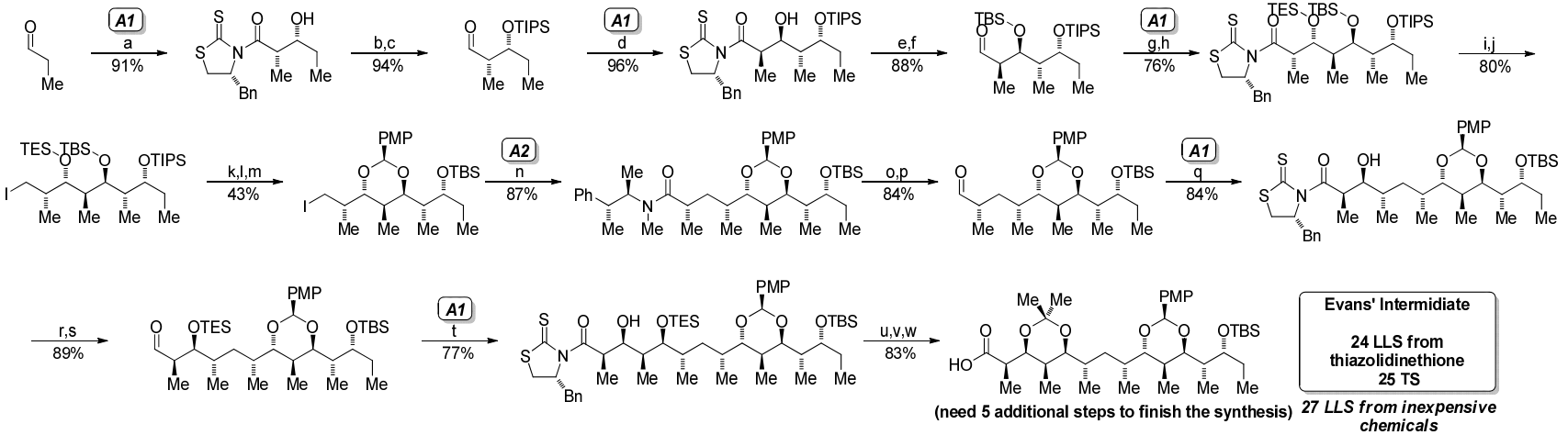
6-Deoxyerythronolide B (Crimmins, *Org. Lett.* **2006**, *8*, 2191.)

Chiral Auxiliary Synthesis



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

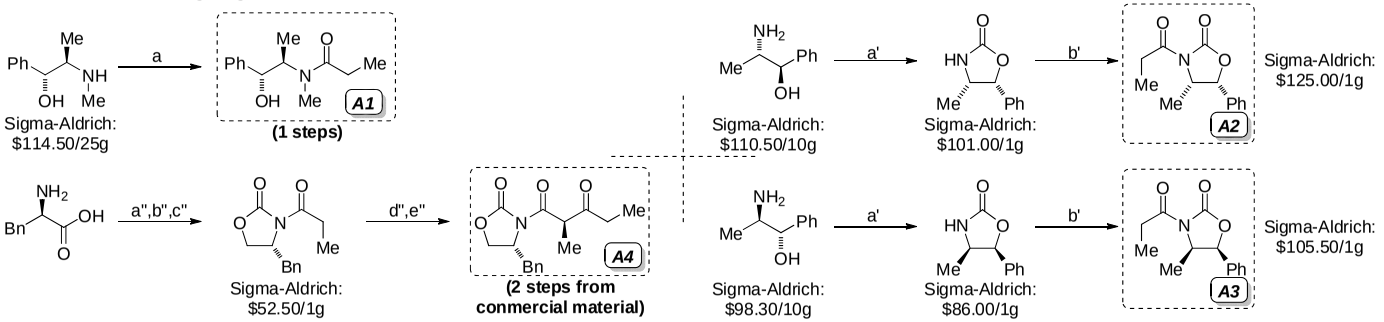
Iterative Aldol Addition



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

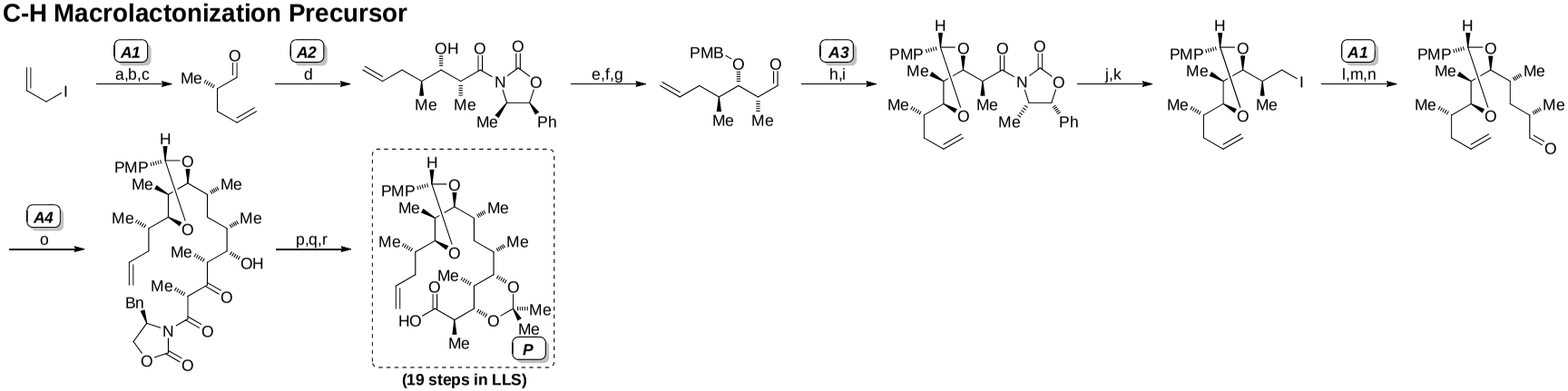
6-Deoxyerythronolide B (White, *Nature Chem.* **2009**, *1*, 547.)

Chiral Auxiliary Synthesis



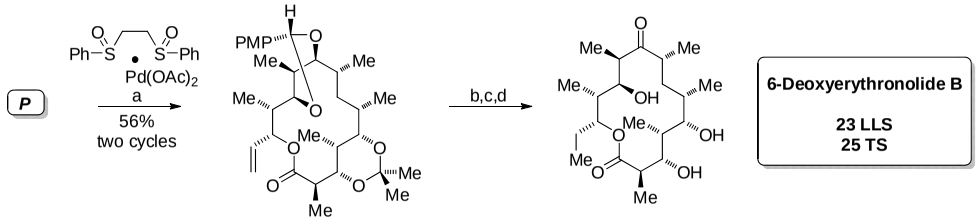
Key: (a) propionyl chloride, DMAP, TEA; (a') K_2CO_3, diethyl carbonate; (b') BuLi, then propionyl chloride; (a") $NaBH_4$, I_2; (b") K_2CO_3, diethyl carbonate; (c") BuLi, then propionyl chloride; (d") Cy_2BOTf, iPr_2NEt, then propionaldehyde; (e") SO_3·Py, TEA, DMSO

C-H Macrolactonization Precursor



Key: (a) LDA, LiCl; (b) LDA, BH_3•NH_3; (c) $(COCl)_2$, DMSO, TEA; (d) Bu_2BOTf, iPr_2NEt; (e) $AlMe_3$, (MeO)NHMe•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) $Ti(O/Pr)Cl_3$, 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

General Methods

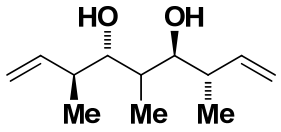
All reactions were run under an atmosphere of Argon. Tetrahydrofuran (THF), ether and toluene were distilled from sodium and benzophenone. Anhydrous solvents were transferred by an oven-dried syringe. Sealed tubes (13x100 mm) were purchased from Fischer Scientific and were dried in an oven overnight and cooled under a stream of nitrogen prior to use. Commercially available α-methylallyl acetate (Aldrich) was purified by distillation prior to use. Cesium carbonate was purchased from Alfa Aesar and was used directly without further purification. Isopropanol (Fisher) was purified by distillation prior to use. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M or M-H) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H-NMR 400 MHz and ^{13}C-NMR 100 MHz) spectra were recorded with a Varian Gemini spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3\delta_H$ (7.26 ppm) and $CDCl_3\delta_C$ (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).

Preparation of (*S*)-I

To a mixture of $[Ir(cod)Cl]_2$ (87.3 mg, 0.13 mmol, 100 mol%), (*S*)-SEGPHOS (159 mg, 0.26 mmol, 200 mol%), Cs_2CO_3 (169 mg, 0.52 mmol, 400 mol%), 4-CN-3-NO_2BzOH (100 mg, 0.52 mmol, 400 mol%) and allyl acetate (65 mg, 0.65 mmol, 500 mol%) in a sealed tube under an atmosphere of N_2 was added THF (2.6 mL, 0.05 M). The reaction mixture was stirred for 30 minutes at ambient temperature and heated for 1.5 hours at 80 ^oC. Upon cooling to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through a celite plug, washed with CH_2Cl_2 (50 mL) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 20% Et_2O/CH_2Cl_2) and concentrated *in vacuo*. The light yellow gum was dissolved in THF (3 mL). Rapid addition of hexanes (50 mL) to the stirred solution resulted in precipitation of a bright yellow powder, which was collected by gravity filtration. Removal of trace solvents *in vacuo* delivered (*S*)-**I** (228 mg, 0.221 mmol) in 85% yield.

Procedure and Spectral Data for Acid Fragment Synthesis (Fragment B)

(*3S,4S,6S,7S*)-3,5,7-Trimethylnona-1,8-diene-4,6-diol



7

An oven-dried sealed tube under an atmosphere of N_2 was charged with 2-methyl-1,3-propanediol (2.163 g, 24.0 mmol, 100 mol%), (*S*)-**I** (620.4 mg, 0.60 mmol, 2.5 mol%), Na_2CO_3 (5.088 g, 48.0 mmol, 200 mol%), H_2O (1.73 mL, 96.0 mmol, 400 mol%) and THF (24.0 mL, 1.0 M). Freshly distilled crotyl acetate (15.12 mL, 120.0 mmol, 500 mol%) was added and the mixture was allowed to stir at 70 ^oC for 96 hr. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:10) provides the title compound (2.427 g, 12.24 mmol) as an colorless viscous oil which solidified on standing in 51% yield, ≥ 99% ee, 6:1 dr.

TLC (SiO_2): R_f = 0.31 (ethyl acetate:hexanes, 1:3).

^{1}H NMR(400 MHz, $CDCl_3$): δ5.85-5.73 (m, 2H), 5.15-5.09 (m, 4H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.39-3.37 (m, 1H), 2.80 (s, 1H), 2.54 (d, J = 4.0 Hz, 1H), 2.46-2.40 (m, 1H), 2.31-2.25 (m, 1H), 1.89-1.86 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H).

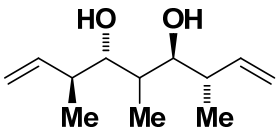
^{13}C NMR (100 MHz, $CDCl_3$): δ142.2, 141.0, 116.5, 116.0, 79.3, 73.9, 42.3, 42.0, 34.8, 17.2, 16.5, 10.7.

$[\alpha]_D^{27}$ = -19.0 (c = 0.41, CH_2Cl_2).

MP = 44-59 ^oC

FTIR (neat): υ 3389, 2970, 2931, 1638, 1459, 1417, 1376, 1325, 1242, 1130, 1085, 1041, 994, 971, 911, 812, 720, 674.

HRMS: (CI) Calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698, Found: 199.1696.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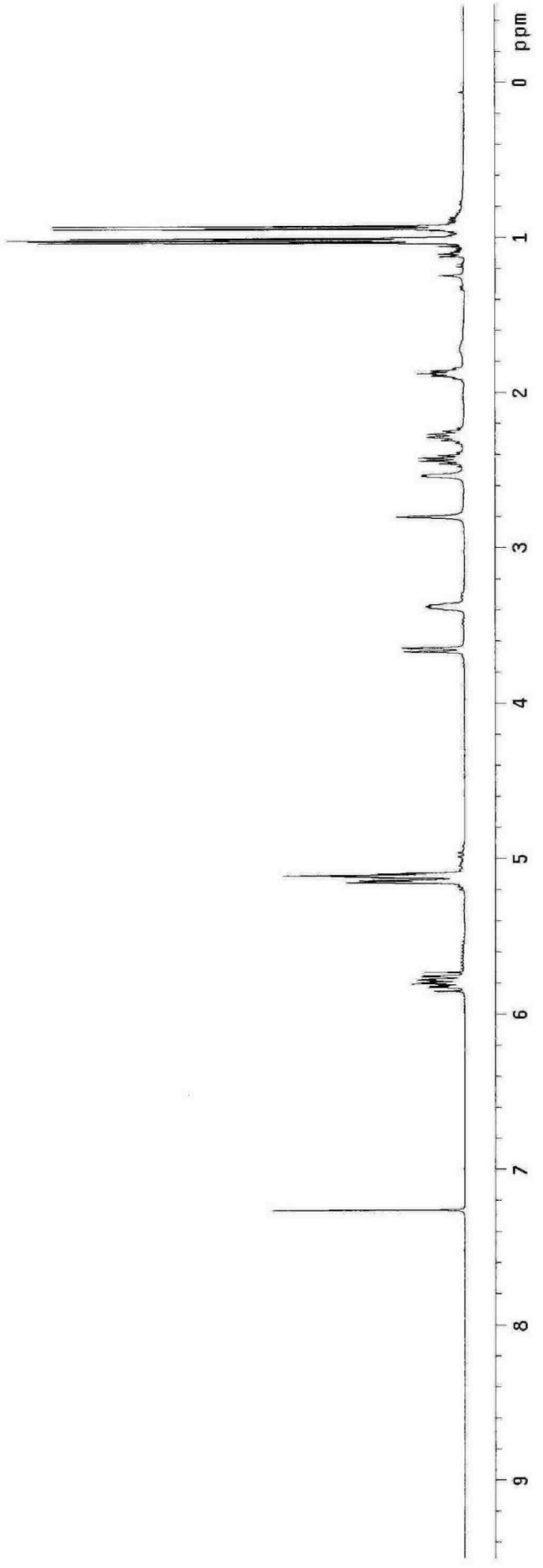
OH
Me
Me
Me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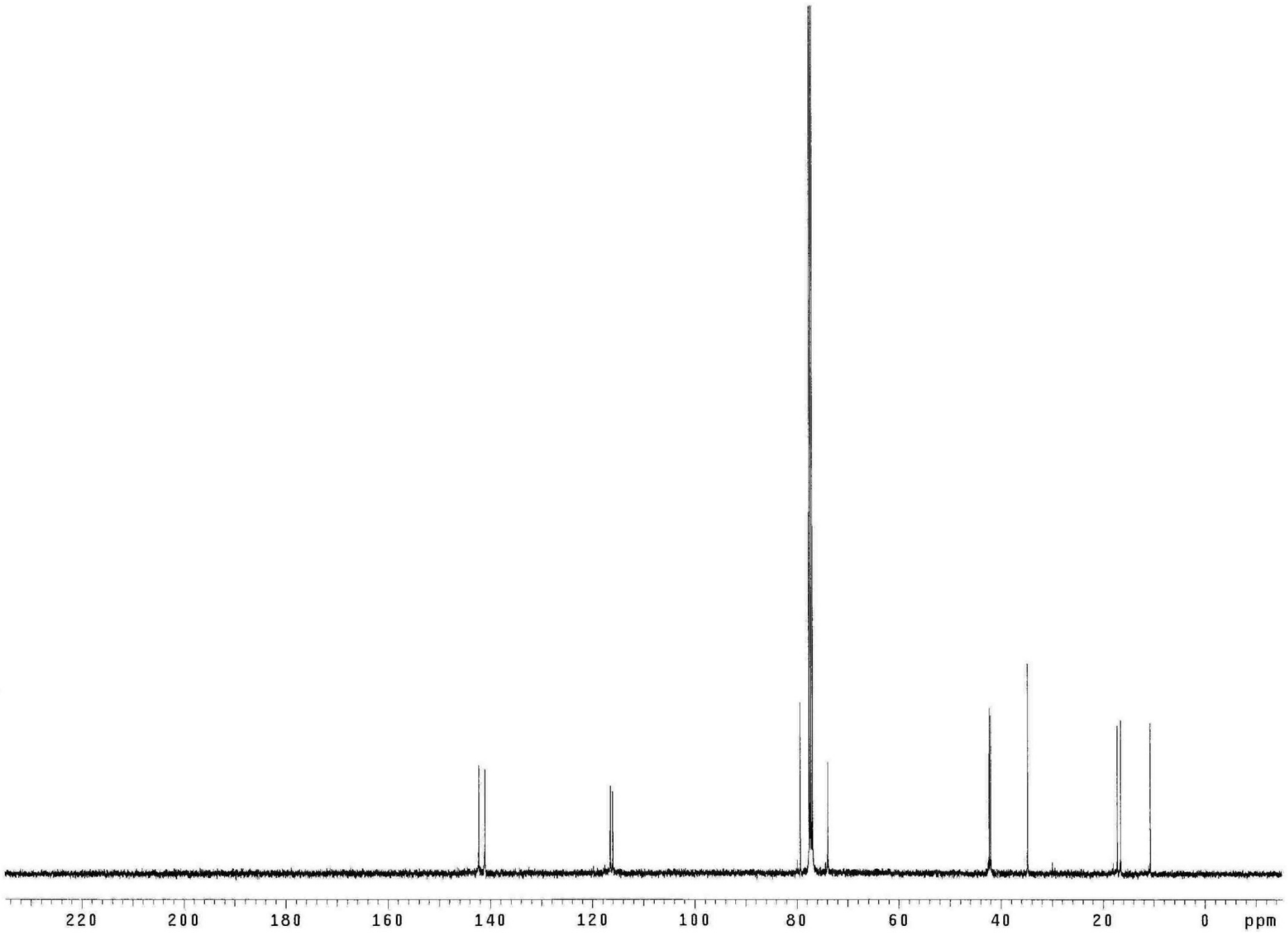
9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20
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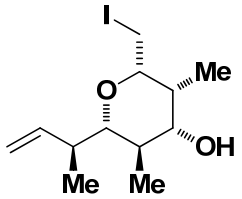
ppm

(*2S,3R,4R,5R,6S*)-2-((*S*)-but-3-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol



7a

A solution of (*3S,4S,6S,7S*)-3,5,7-trimethylnona-1,8-diene-4,6-diol (535 mg, 2.70 mmol, 100 mol%) and $NaHCO_3$ (566.6 mg, 6.74 mmol, 250 mol%) in acetonitrile (54.0 mL, 0.05 M) was cooled to -20 °C. To this solution was added iodine (2.054 g, 8.09 mmol, 300 mol%) in one portion. The reaction was stirred at -20 °C for 1 hr. The reaction mixture was warmed to 0 °C and was allowed to stir at this temperature for 6 hr. Saturated aqueous $Na_2S_2O_3$ was added and the reaction mixture was allowed to stir until the solution became colorless. The reaction mixture was transferred to a separatory funnel and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) to give the title compound (656.5 mg, 2.025 mmol) as a colorless oil in 75% yield, ≥ 99% ee as a single diastereomer.

TLC (SiO_2): R_f = 0.52 (ethyl acetate:hexanes, 1:3).

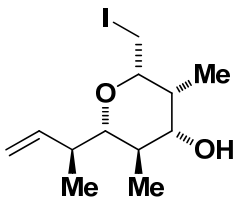
^{1}H NMR(400 MHz, $CDCl_3$): δ 5.87-5.78 (m, 1H), 5.02-4.97 (m, 2H), 3.54-3.50 (m, 1H), 3.40 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.25 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.08 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.88 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.44-2.37 (m, 1H), 2.19-2.13 (m, 1H), 1.56-1.49 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 139.2, 115.2, 85.1, 78.7, 76.4, 39.9, 38.2, 34.6, 18.8, 12.2, 6.2, 4.6.

$[\alpha]_D^{25}$ = +37.2 (c = 0.46, $CHCl_3$).

FTIR (neat): υ3350, 3075, 2963, 2925, 2853, 2362, 1640, 1458, 1416, 1372, 1336, 1300, 1271, 1242, 1175, 1091, 1070, 1043, 997, 972, 915, 876, 808, 773, 692, 668.

HRMS: (CI) Calcd. for $C_{12}H_{22}O_2I$ $[M+H]^+$: 325.0665, Found: 325.0667.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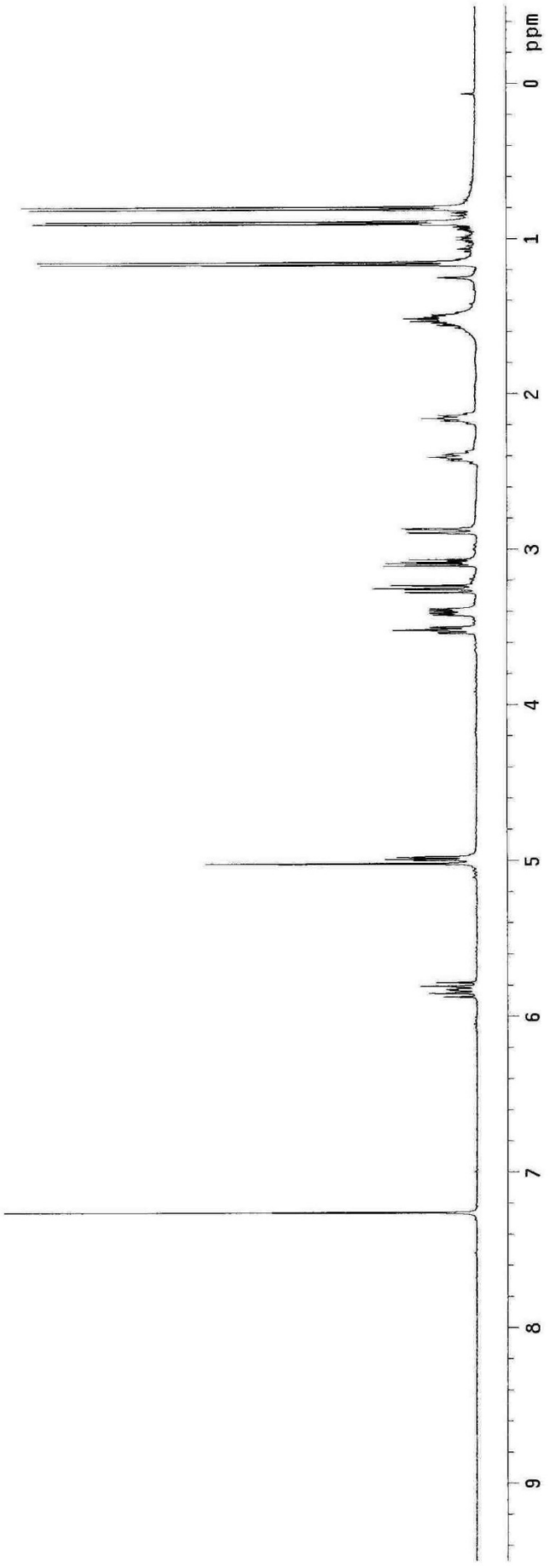
OH
Me
Me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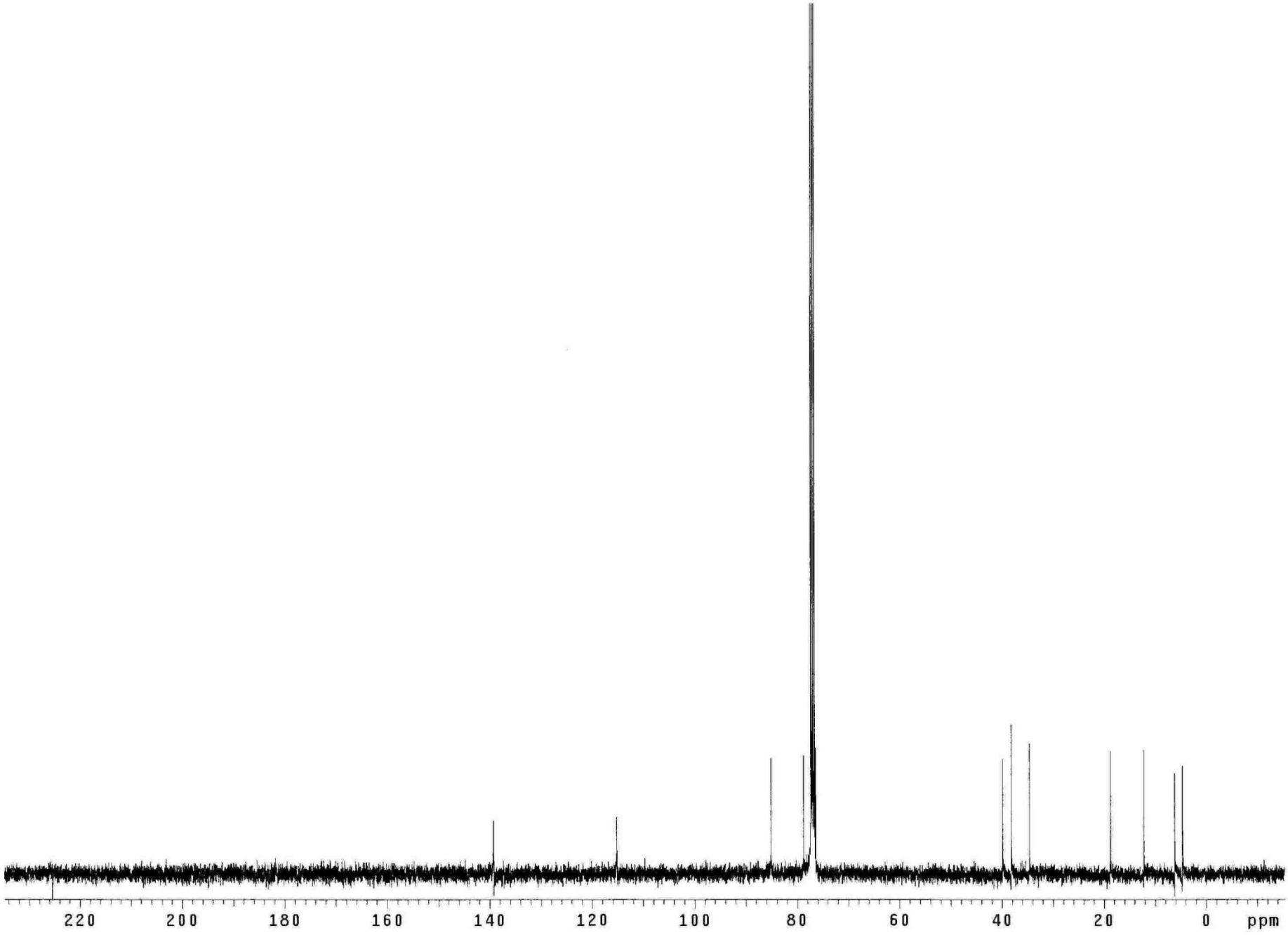
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60
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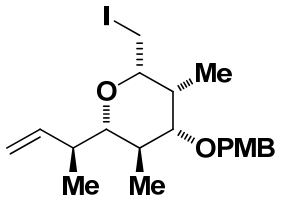
20
0
ppm

(*2S,3R,4R,5R,6S*)-2-((*S*)-but-3-en-2-yl)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran



8

A solution of (*2S,3R,4R,5R,6S*)-2-((*S*)-but-3-en-2-yl)-6-(iodomethyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-ol (628 mg, 2.00 mmol, 100 mol%) and PMB-imidate (2825.5 mg, 10.00 mmol, 500 mol%) in diethyl ether (6.7 mL, 0.30 M) was heated to 30 °C. To this solution was added camphorsulfonic acid (46.5 mg, 0.2 mmol, 10 mol%) in one portion. The reaction was stirred at 30 °C overnight. Saturated aqueous $NaHCO_3$ was added and the reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with DCM (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) to give the title compound (702.1 mg, 1.58 mmol) as a colorless oil in 79% yield.

TLC (SiO_2): R_f = 0.72 (ethyl acetate:hexanes, 1:3).

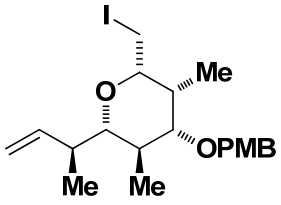
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 2H), 6.89-6.86 (m, 2H), 5.81 (dt, *J* = 18.0, 9.2 Hz, 1H), 4.99-4.95 (m, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.47 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H), 3.27 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.11 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.87 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.43-2.32 (m, 2H), 1.70-1.60 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 159.2, 139.2, 130.5, 129.4, 115.2, 113.8, 85.4, 82.9, 78.6, 69.7, 55.3, 39.9, 33.8, 32.2, 18.7, 12.6, 6.6, 4.9.

$[\alpha]_D^{25}$ = +51.2 (c = 0.58, $CHCl_3$).

FTIR (neat): υ3100, 2977, 2952, 2332, 1638, 1458, 1455, 1350, 1324, 1212, 1155, 1082, 967, 958, 773, 699, 650.

HRMS: (CI) Calcd. for $C_{20}H_{30}O_3I$ $[M+H]^+$: 445.1240, Found: 445.1247.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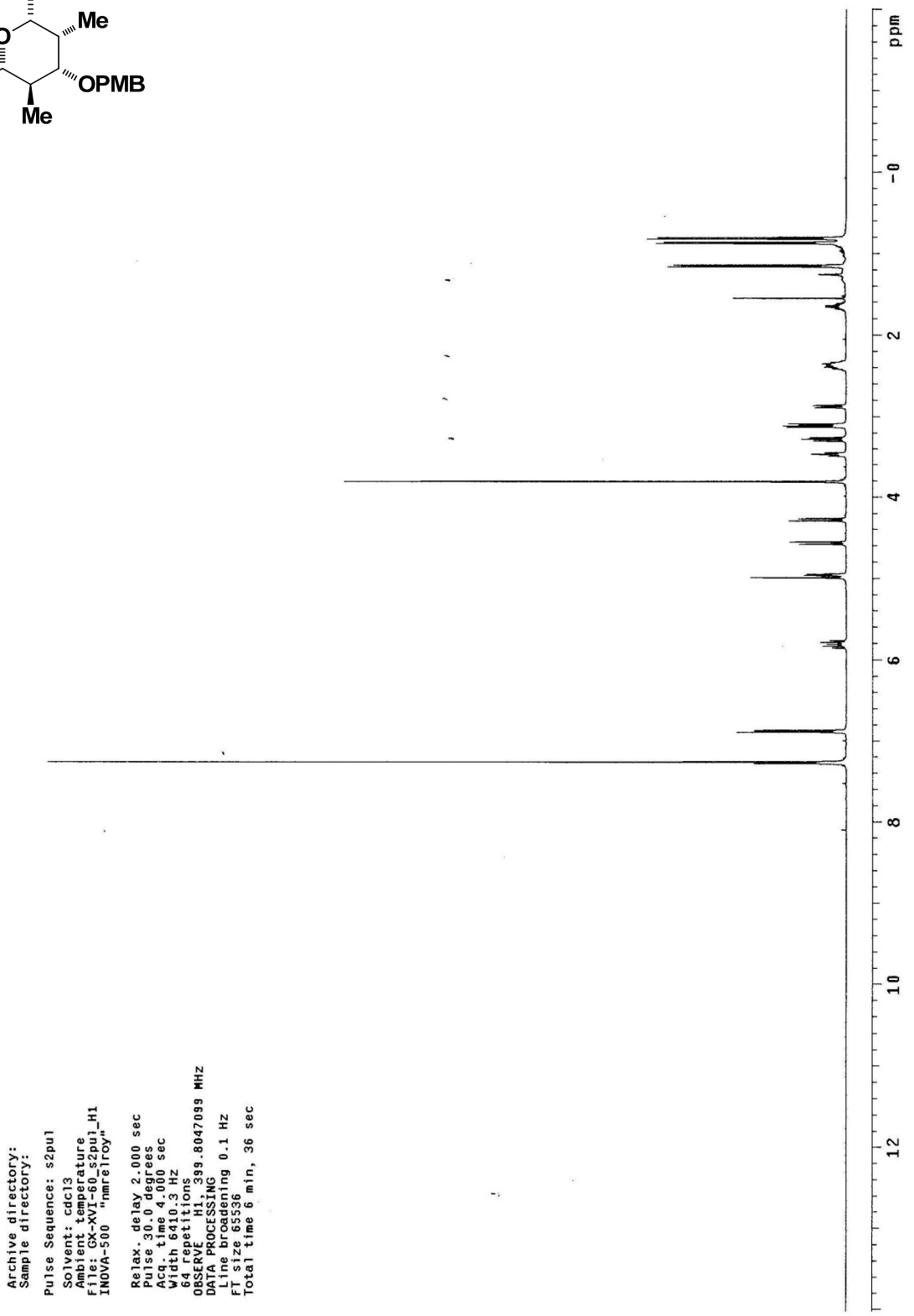
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File: GX-XVI-60_s2pul_H1
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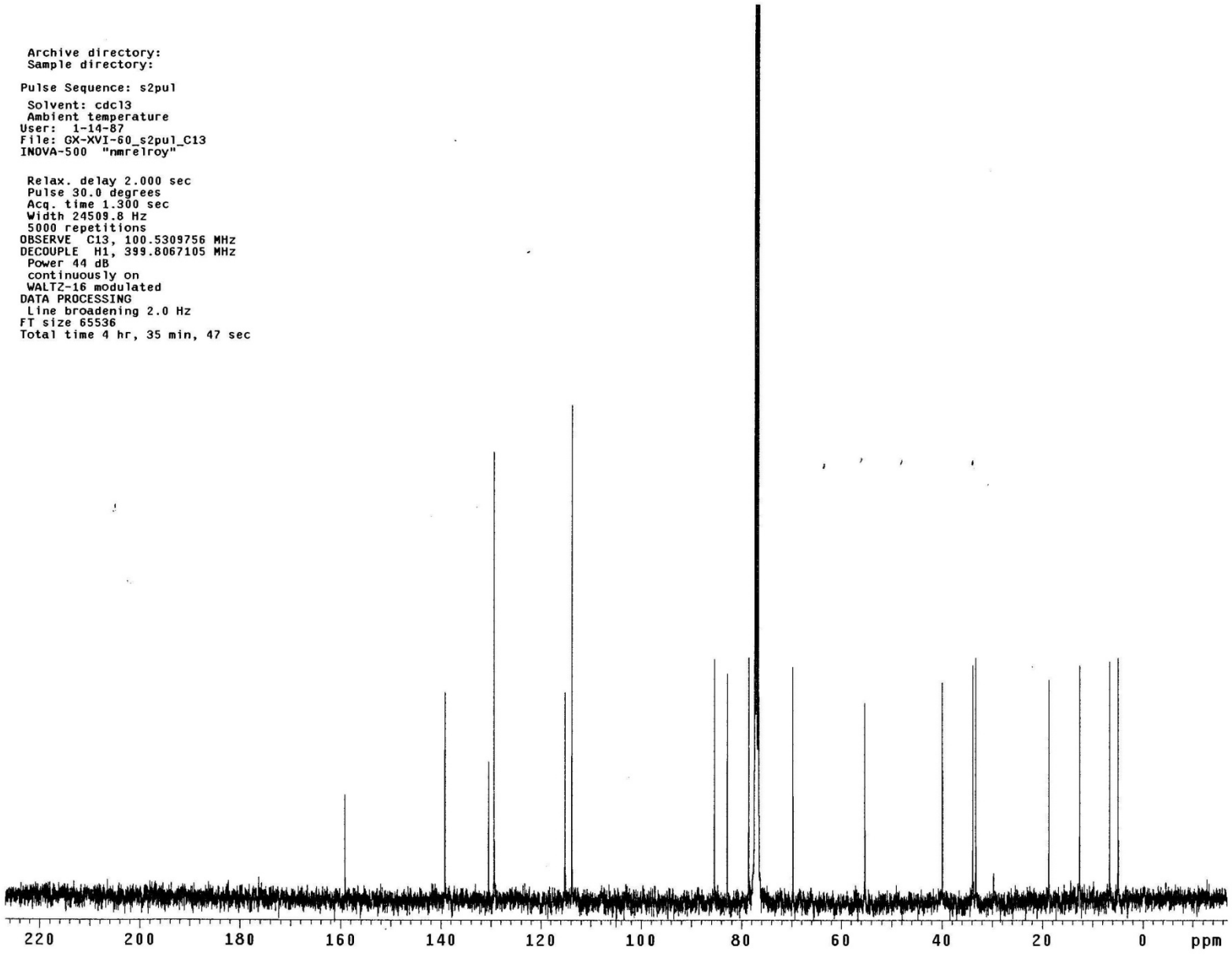
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047099 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm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Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
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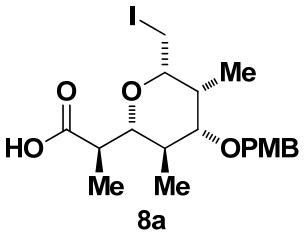
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*R*)-2-((*2R,3R,4R,5R,6S*)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propanoic acid



8a

A solution of (*2S,3R,4R,5R,6S*)-2-((*S*)-but-3-en-2-yl)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran (300 mg, 0.675 mmol, 100 mol%) and $NaHCO_3$ (84.9 mg, 1.01 mmol, 150 mol%) in DMF (15.0 mL, 0.05 M) was added stock solution of OsO_4 in *t*-butanol (128.7 mg, 4% in H_2O, 0.02 mmol, 3 mol%). After 5 min stirring under room temperature, solid Oxone (1.660 g, 2.7 mmol, 400 mol%) was added to this solution in one portion. The reaction was stirred at room temperature for 6 hr. The reaction mixture was warmed to 0 °C and was allowed to stir at this temperature for 6 hr. Saturated aqueous $Na_2S_2O_3$ was added and the reaction mixture was stirred vigorously for 15 min. The reaction mixture was acidified with pH = 4.00 buffer solution and transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:10) to give the title compound (274.6 mg, 0.594 mmol) as a colorless oil in 88% yield.

TLC (SiO_2): R_f = 0.39 (ethyl acetate:hexanes, 1:2).

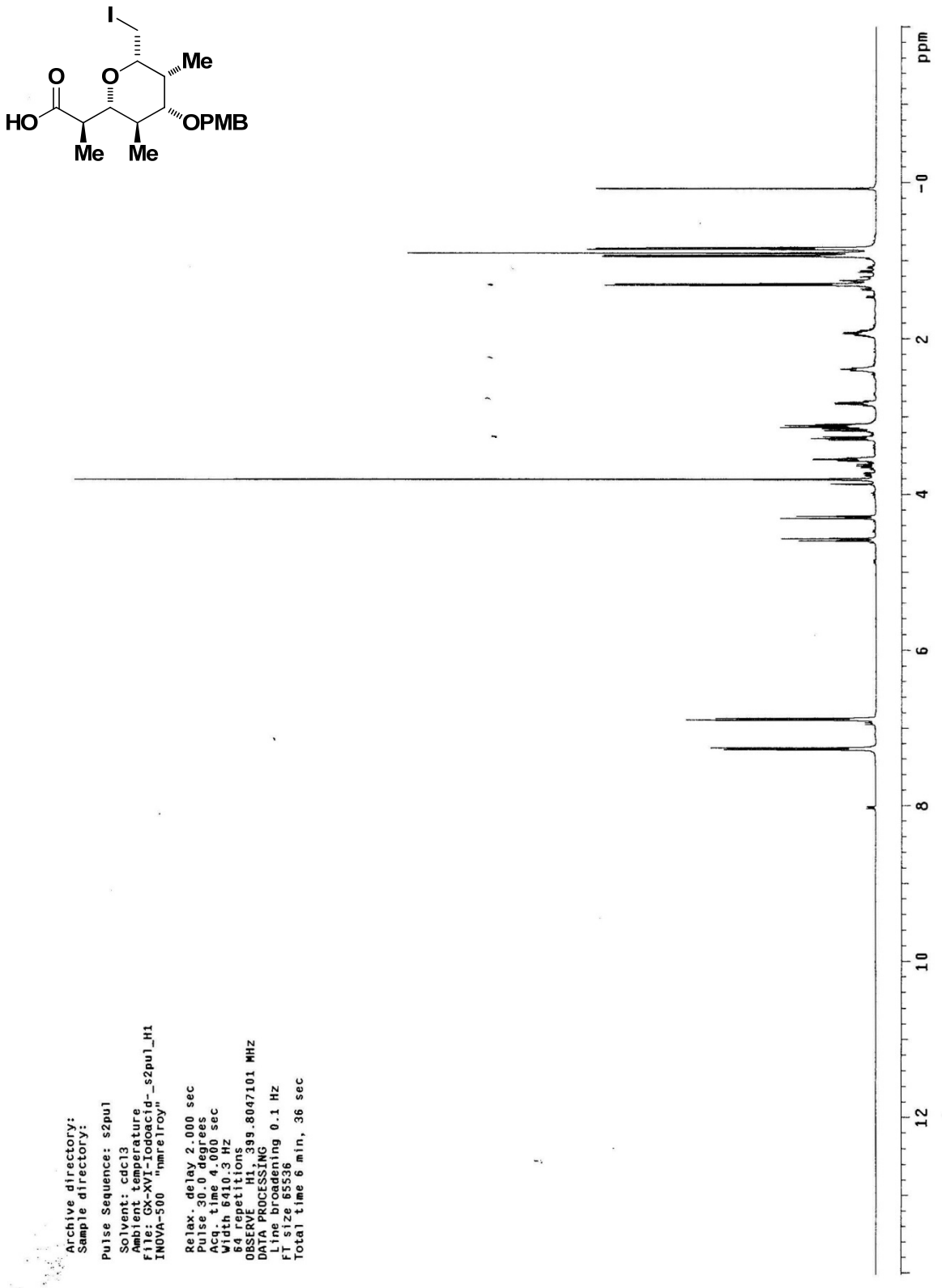
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.28-7.26 (m, 2H), 6.89-6.87 (m, 2H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.29 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.57-3.53 (m, 1H), 3.27 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.16 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.13-3.09 (m, 2H), 2.82 (td, *J* = 7.2, 2.4 Hz, 1H), 2.41-2.36 (m, 1H), 1.98-1.88 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 177.7, 159.2, 130.1, 129.4, 113.8, 83.7, 82.3, 79.3, 69.8, 55.3, 41.5, 33.7, 33.4, 13.9, 12.8, 5.4, 4.9.

$[\alpha]_D^{25}$ = +45.9 (c = 0.55, $CHCl_3$).

FTIR (neat): υ 3500, 3348, 3150, 3000, 2976, 2951, 1705, 1620, 1543, 1243, 1175, 1067, 922, 878, 842, 773, 692, 668.

HRMS: (CI) Calcd. for $C_{19}H_{28}O_5I$ $[M+H]^+$: 463.0982, Found: 463.0981.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HO
OPMB
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Sample directory:
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Solvent: cdcl3
Ambient temperature
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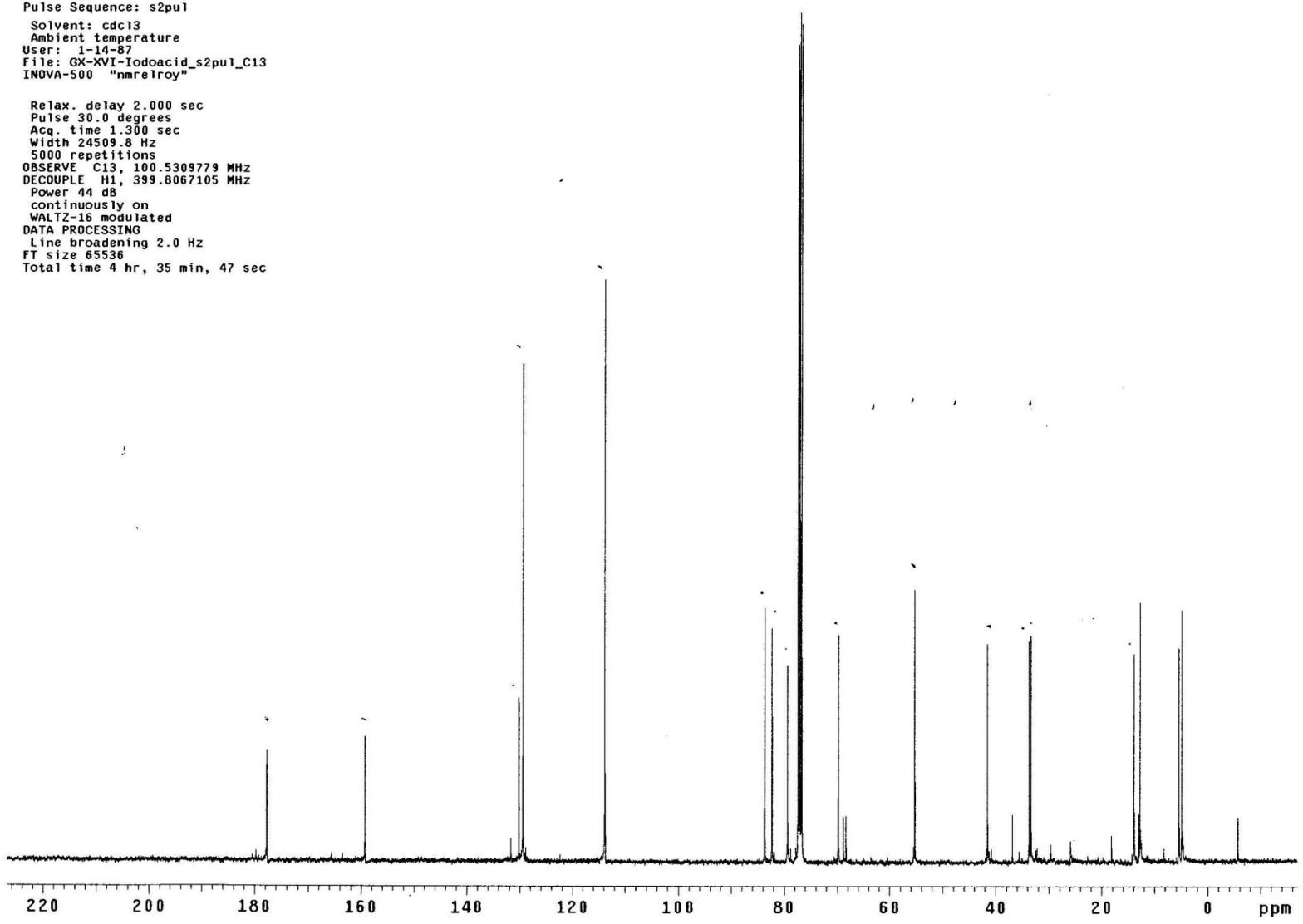
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047101 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
ppm
12
10
8
6
4
2
-0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Solvent: cdcl3
Ambient temperature
User: 1-14-87
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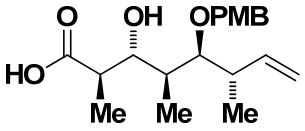
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309779 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*2R,3R,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid



9

A solution of (*R*)-2-((*2R,3R,4R,5R,6S*)-6-(iodomethyl)-4-((4-methoxybenzyl)oxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)propanoic acid (137.1 mg, 0.297 mmol, 100 mol%) in EtOH (3 mL, 0.1 M) was added activated Zn (289.6 mg, 4.455 mmol, 1500 mol%) and NH_4Cl (158.9 mg, 2.97 mmol, 1000 mol%). The reaction mixture was heated under refluxing for 1 hr. The crude reaction mixture was diluted with ethyl acetate (15 mL) and HCl in THF (1 mL, 1.0M) and filtered through a silica plug. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) gave the title compound (91.9 mg, 0.273 mmol) as a colorless oil in 92% yield.

TLC (SiO_2): R_f = 0.45 (methanol:DCM, 1:9).

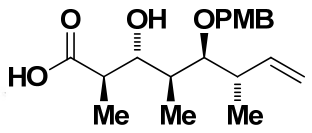
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.89-6.87 (m, 2H), 5.97 (ddd, *J* = 17.2, 10.0, 8.0 Hz, 1H), 5.14 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.58 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.67-2.53 (m, 2H), 2.08-1.99 (m, 1H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 177.4, 159.5, 141.0, 129.8, 129.6, 115.2, 114.0, 84.0, 76.3, 73.1, 55.3, 42.4, 40.1, 37.1, 18.3, 14.8, 12.2.

$[\alpha]_D^{25}$ = -21.7 (c = 0.58, $CHCl_3$).

FTIR (neat): υ3500, 3428, 3050, 3044, 2984, 2941, 1705, 1616, 1533, 1249, 1170, 1060, 922, 878, 842.

HRMS: (CI) Calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2015, Found: 337.2020.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OPMB
HO
Me
Me
Me

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Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047103 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
ppm
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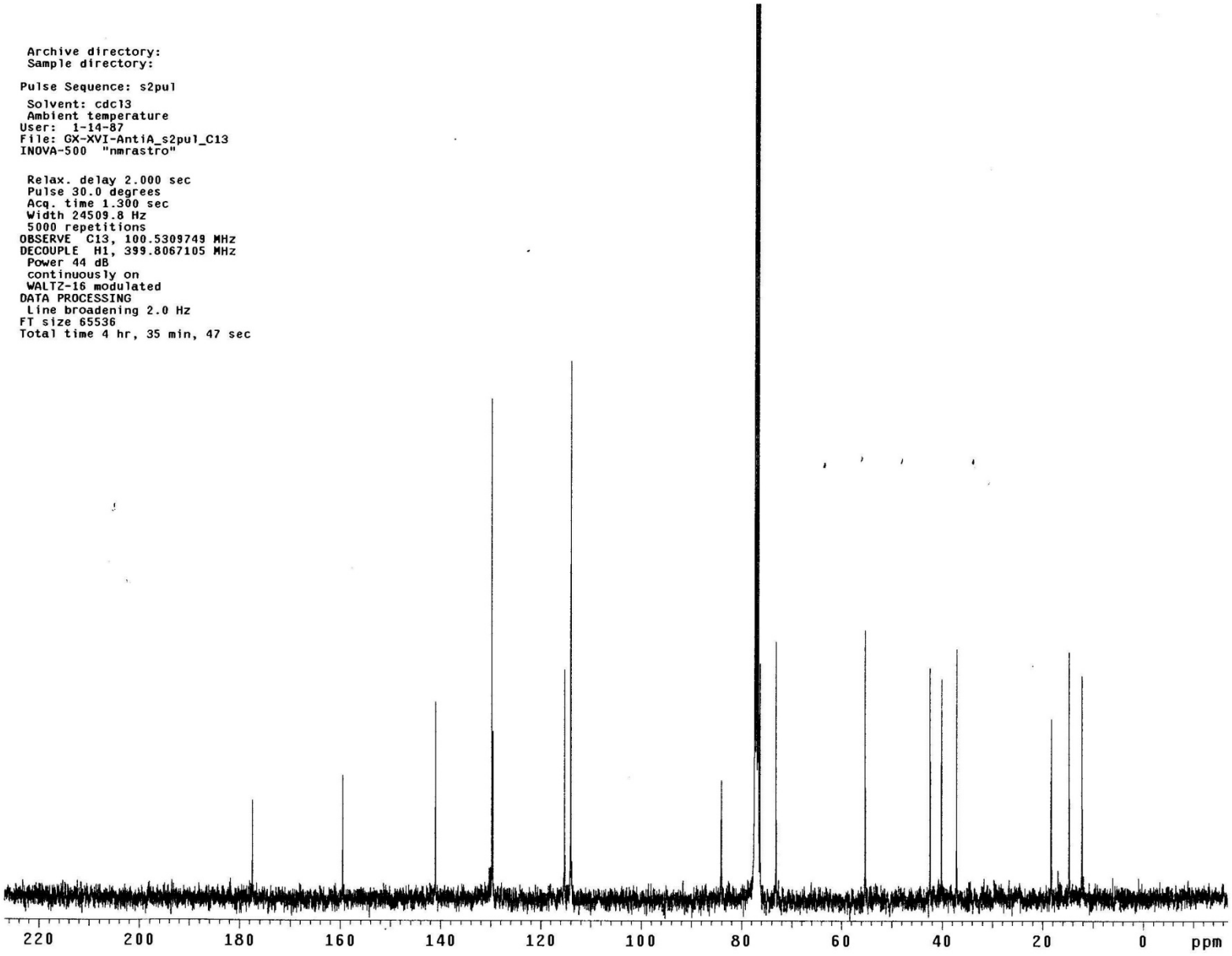
8
6
4
2
-0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Solvent: cdcl3
Ambient temperature
User: 1-14-87
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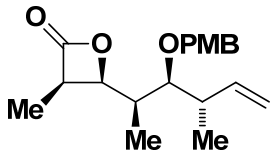
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*3R,4S*)-4-((*2R,3S,4S*)-3-((4-methoxybenzyl)oxy)-4-methylhex-5-en-2-yl)-3-methyloxetan-2-one



10

A solution of (*2R,3R,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid (34 mg, 0.1 mmol, 100 mol%) in THF:HMPA (0.5, 1:1, 0.20 M) was cooled to -78 °C. To this solution was added *s*-butyl lithium (0.26 mL, 1.4 M, 0.35 mmol, 350 mol%) dropwise. The reaction was warmed to -20 °C and stirred for 2 hr. Chloromethanesulfonyl chloride (52.2 mg, 0.35 mmol, 350 mol%) in THF (0.1 mL) was added to the reaction mixture and stirring was continued for another 2 hr. Pyridine:H_2O (15 mL, 40:1) was added and the reaction mixture was allowed to stir under 35 °C overnight. The reaction mixture was diluted with ethyl acetate (100 mL) and transferred to a separatory funnel. The organic phase was washed with $CuSO_4$ (30 mL), water (30 mL) and brine (30 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) to give the title compound (22.9 mg, 0.072 mmol) as a colorless oil in 72% yield.

TLC (SiO_2): R_f = 0.73 (ethyl acetate:hexanes, 1:2).

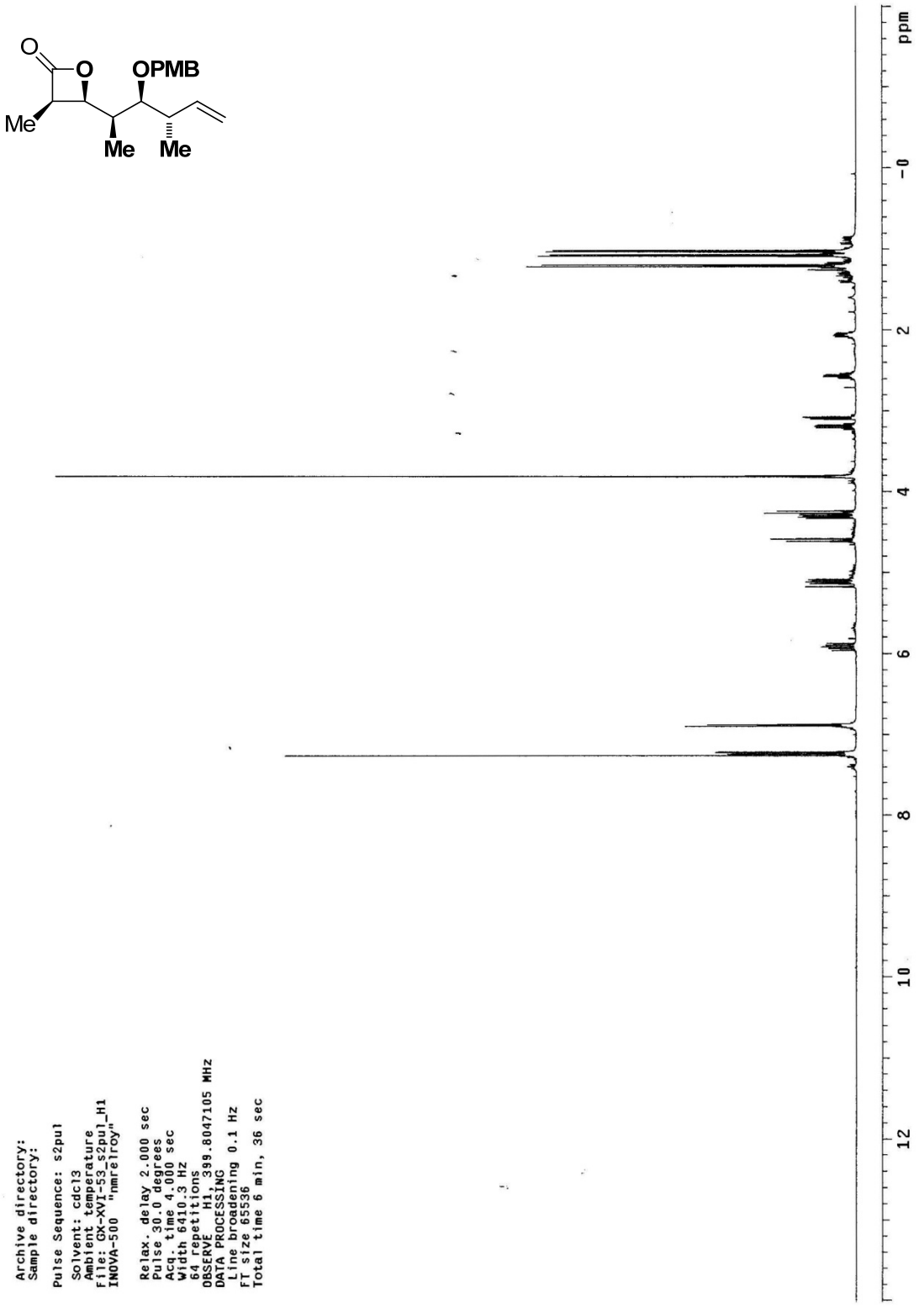
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.24-7.22 (m, 2H), 6.89-6.87 (m, 2H), 5.91 (ddd, *J* = 18.0, 10.4, 8.0 Hz, 1H), 5.15 (dd, *J* = 18.0, 1.2 Hz, 1H), 5.09 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.30 (dd, *J* = 10.8, 6.4 Hz, 1H), 4.25 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 3.19 (qd, *J* = 8.0, 6.0 Hz, 1H), 3.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 2.56 (qd, *J* = 14.8, 6.8 Hz, 1H), 2.06 (dqd, *J* = 13.6, 6.8, 1.6 Hz, 1H), 1.20 (d, *J* = 8.0 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 172.7, 159.4, 141.2, 130.1, 129.9, 115.2, 113.8, 80.4, 77.6, 73.3, 55.3, 46.4, 41.0, 35.6, 16.7, 9.4, 9.0.

$[\alpha]_D^{25}$ = -20.1 (c = 0.34, $CHCl_3$).

FTIR (neat): υ3300, 3080, 2963, 2925, 1821, 1466, 1377, 1128, 1043, 1000, 970, 923, 888, 842, 761, 731.

HRMS: (CI) Calcd. for $C_{19}H_{26}O_4$ $[M]^+$: 316.1675, Found: 316.1673.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Ambient temperature
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Pulse 30.0 degrees
Acq. time 4.000 sec
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64 repetitions
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DATA PROCESSING
Line broadening 0.1 Hz
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Total time 6 min, 36 sec
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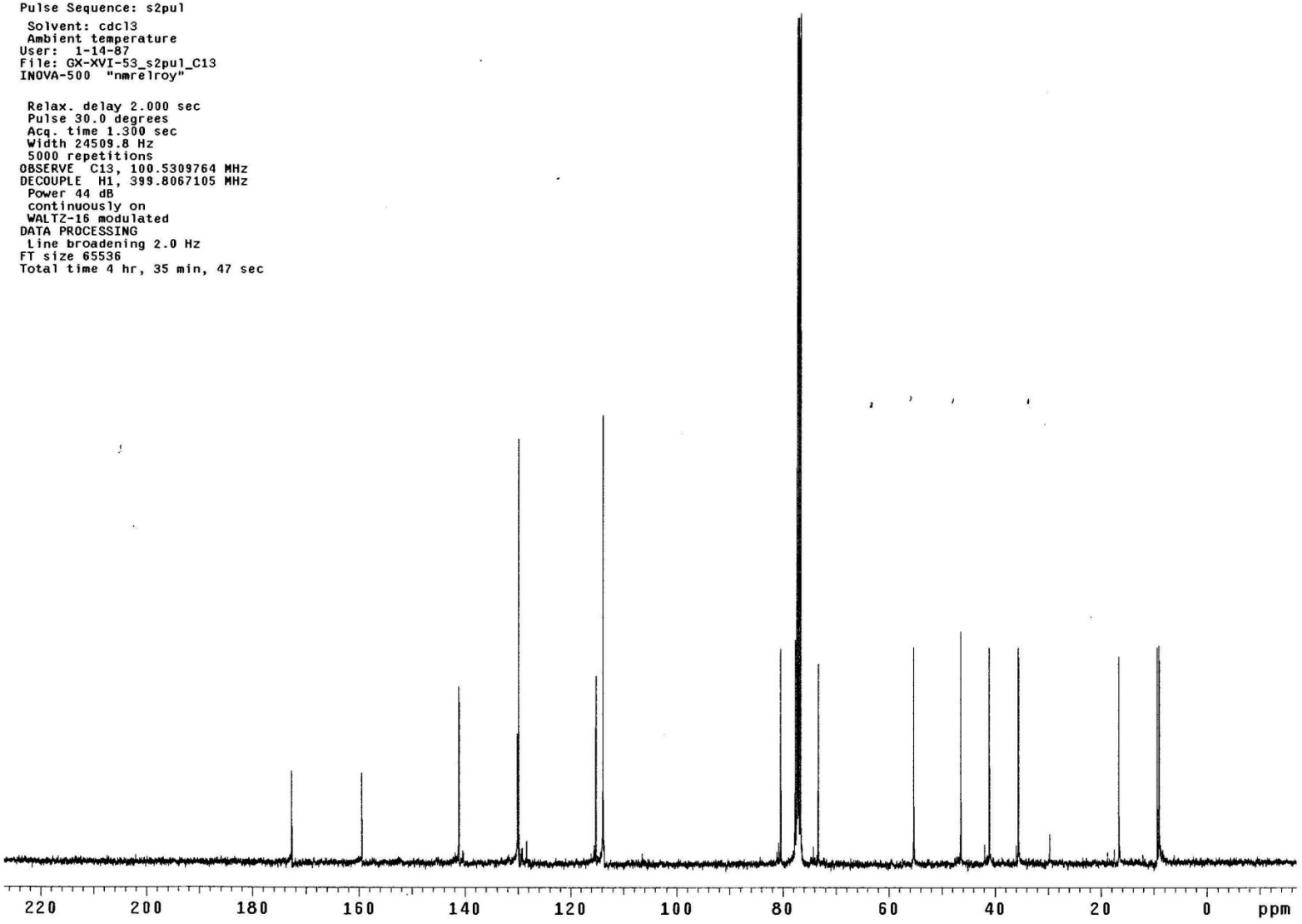
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Solvent: cdcl3
Ambient temperature
User: 1-14-87
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Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309764 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
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120
100
80
60
40
20
0
ppm

GX-XVI-53

exp4 Noesy

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np	2048	dfrq	150.821		
sw	6613.8	dn	C13		
fb	4000	dpwr	31		
bs	32	dof	0		
ss	4	dm	n		
tpwr	61	dmm	c		
pw	11.6	dmf	29412		
compH	1.0639	dseq			
d1	2.000	dres	9.0		
mix	0.800	homo	n		
tof	54.5	temp	27.0		
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gain	30	dn2			
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hsgt	0.0020	dmm2	c		
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zqflg	y	dfrq3	0		
alt_grd	n	dn3			
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il	n	dof3	0		
in	n	dm3	n		
dp	y	dmm3	c		
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DISPLAY		gfs	not used		
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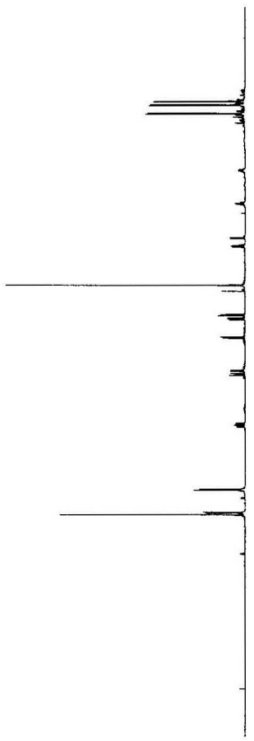
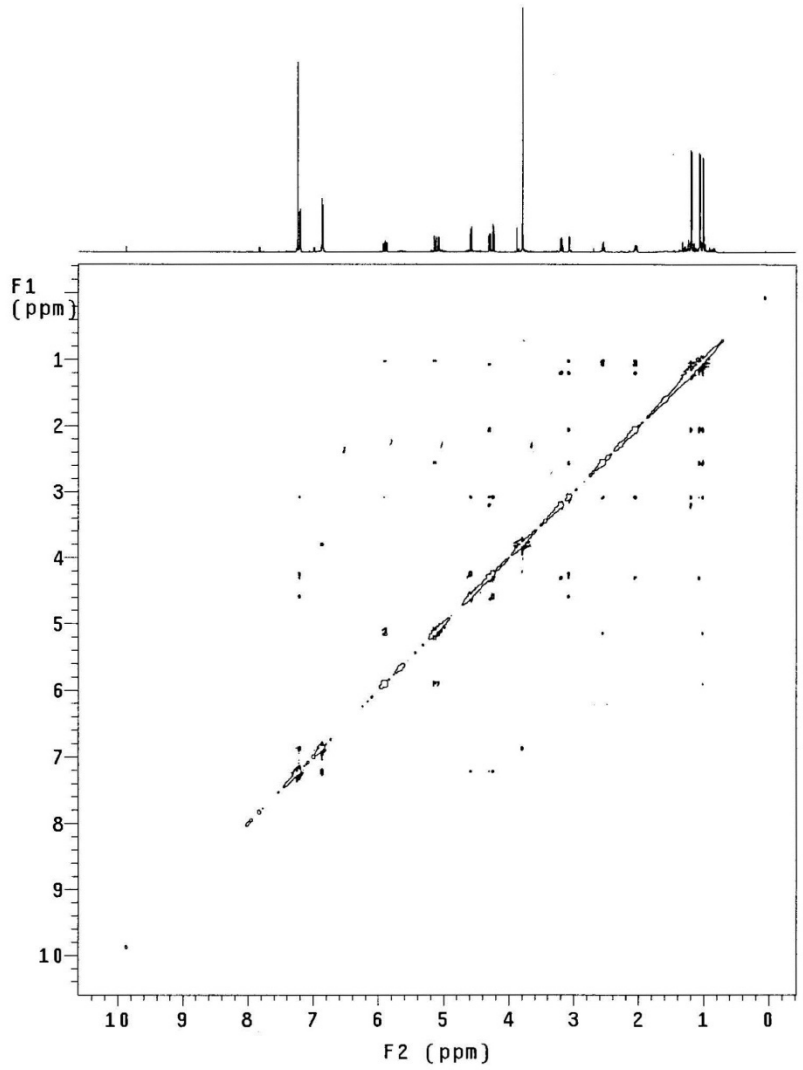
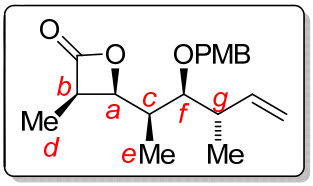
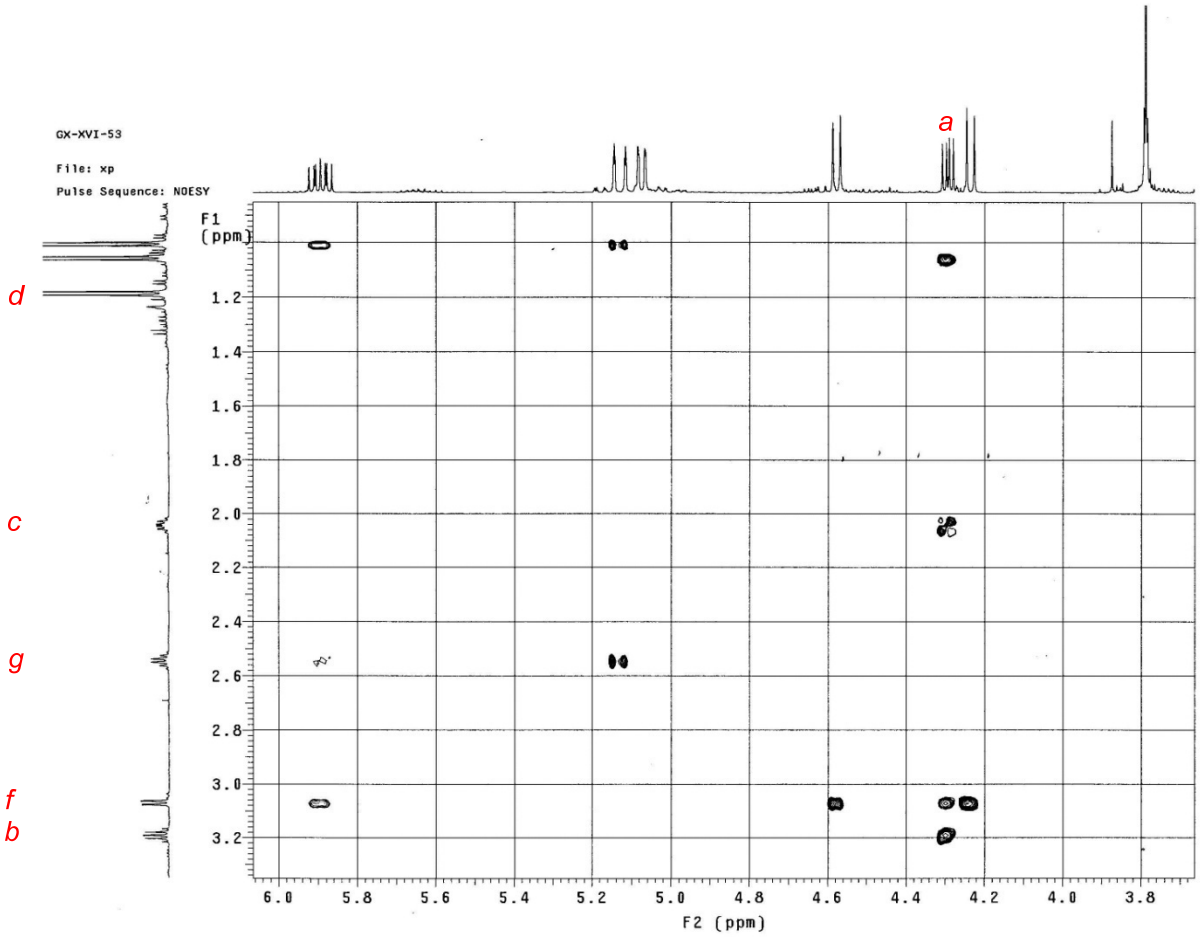


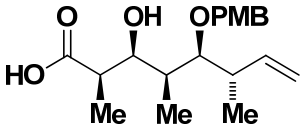






The NOE experiment shows clearly the NOE interaction between ^{a}H and ^{b}H, while ^{a}H and ^{d}H shows no NOE interaction towards each other. This data suggest a *syn* relationship of stereochemistry across the lactone ring.

(*2R,3S,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid



10a

A solution of (*3R,4S*)-4-((*2R,3S,4S*)-3-((4-methoxybenzyl)oxy)-4-methylhex-5-en-2-yl)-3-methyloxetan-2-one (200 mg, 0.63 mmol, 100 mol%) in dioxane:H_2O (12.6 mL, 1:1, 0.05 M) was added LiOH monohydrate (52.9 mg, 1.26 mmol, 200 mol%) in one portion. The reaction was stirred overnight. pH = 4 buffer solution (15 mL) was added and the reaction mixture was transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:3) to give the title compound (148.4 mg, 0.441 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.32 (ethyl acetate:hexanes, 1:1).

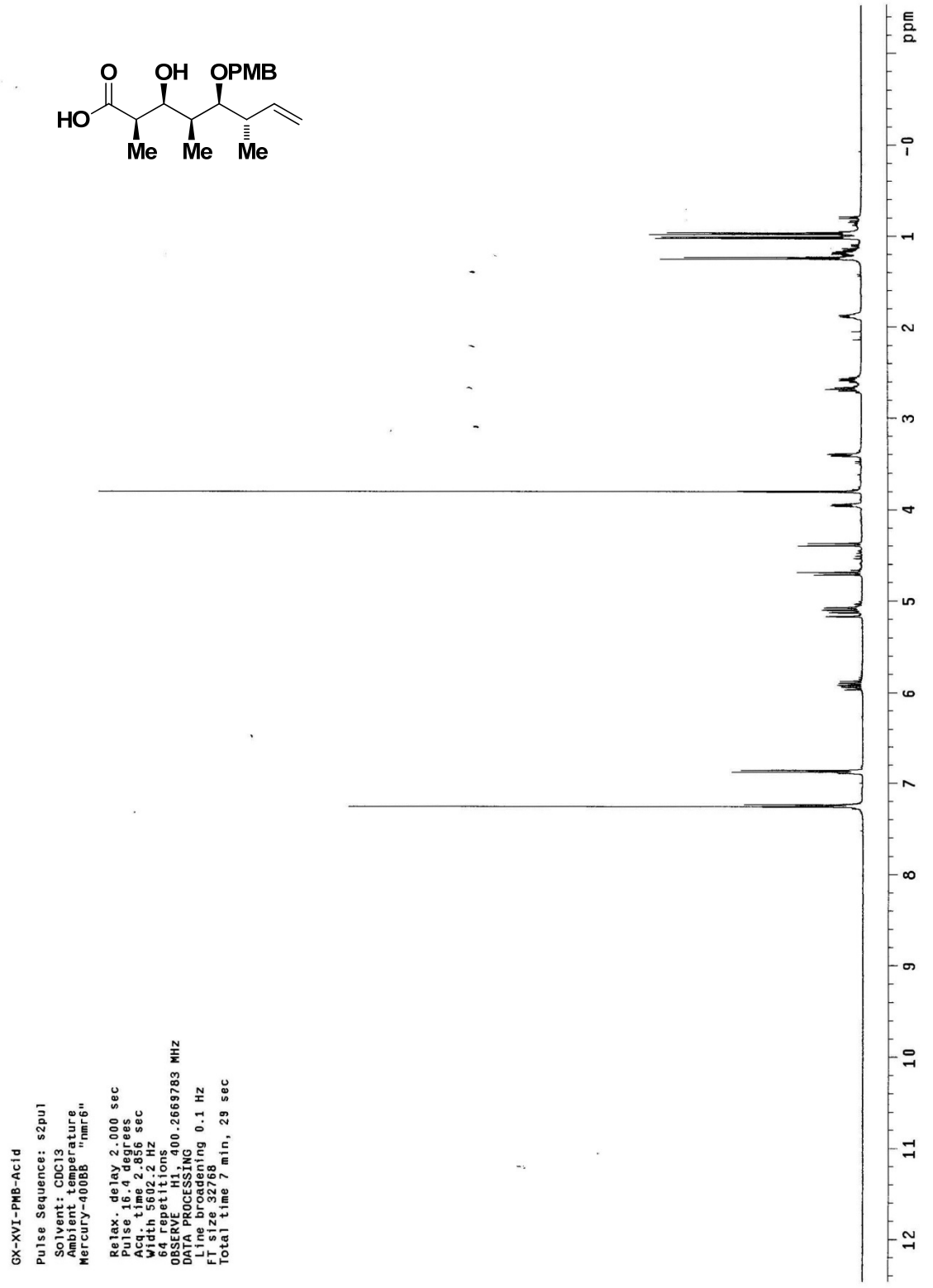
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.89-6.86 (m, 2H), 5.92 (ddd, *J* = 17.6, 10.4, 8.4 Hz, 1H), 5.15 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.08 (ddd, *J* = 10.4, 2.0, 0.8 Hz, 1H), 4.70 (d, *J* = 10.4 Hz, 1H), 4.38 (d, *J* = 10.4 Hz, 1H), 3.95 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.80 (s, 3H), 3.40 (dd, *J* = 7.6, 3.2 Hz, 1H), 2.72-2.65 (m, 1H), 2.62-2.53 (m, 1H), 1.88 (qdd, *J* = 8.4, 7.2, 4.0 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.6, 159.4, 141.3, 129.8, 129.6, 115.2, 113.9, 87.5, 76.0, 73.6, 55.3, 42.6, 41.1, 36.6, 16.9, 13.2, 6.9.

$[\alpha]_D^{25}$ = -47.2 (c = 0.83, $CHCl_3$).

FTIR (neat): υ3478, 3409, 3081, 3068, 2974, 2938, 1707, 1613, 1514, 1459, 1249, 1175, 1035, 916, 820.

HRMS: (CI) Calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2015, Found: 337.2018.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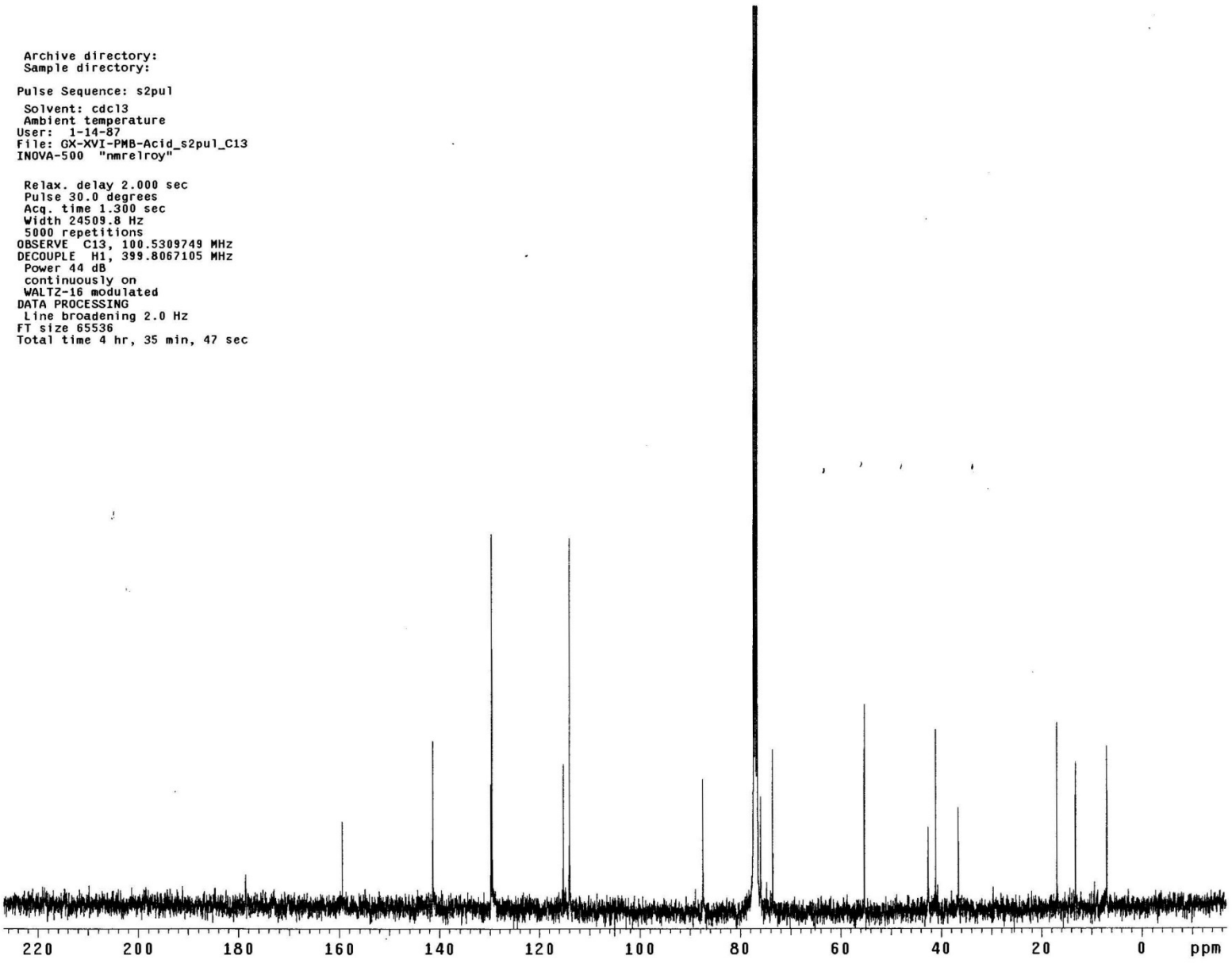
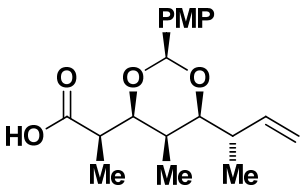
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
64 repetitions
OBSERVE H1, 400.2669783 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 7 min, 29 sec
O
OH
OPMB
HO
Me
Me
Me
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-PMB-Acid_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*R*)-2-((*2S,4S,5R,6S*)-6-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanoic acid



Fragment B

A solution of (*2R,3S,4S,5S,6S*)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethyloct-7-enoic acid (148.4 mg, 0.441 mmol, 100 mol%) and 4Å molecular sieves (480.5 mg) in DCM (8.82 mL, 0.05 M) was cooled to 0 °C. To this solution was added DDQ (120.1 mg, 0.529 mmol, 120 mol%) in three portions. The reaction was stirred at 0 °C for 1 hr. The reaction mixture was loaded on to the column directly. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:3) gave the title compound (118.0 mg, 0.353 mmol) as a colorless oil in 80% yield.

TLC (SiO_2): R_f = 0.69 (ethyl acetate:hexanes, 1:1).

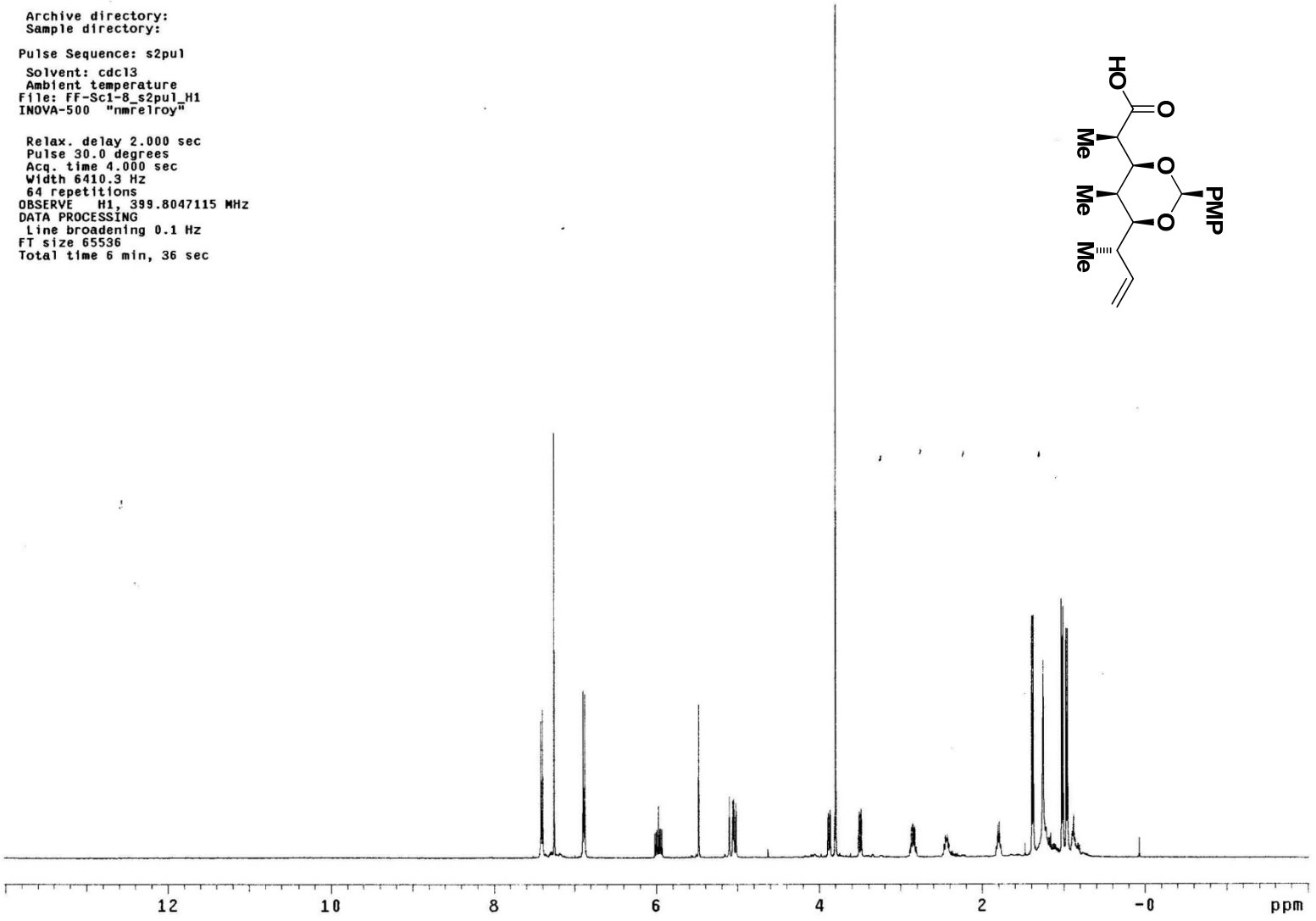
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 6.90-6.88 (m, 2H), 5.97 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.48 (s, 1H), 5.08 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.03 (dt, *J* = 10.4, 1.6 Hz, 1H), 3.88 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.85 (qdd, *J* = 6.8, 6.4, 2.0 Hz, 1H), 2.44 (qd, *J* = 6.8, 3.2 Hz, 1H), 1.80 (qd, *J* = 6.8, 2.0 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 178.7, 159.9, 141.6, 131.1, 127.2, 114.0, 113.5, 101.3, 84.5, 81.8, 55.3, 41.7, 38.3, 29.7, 14.9, 14.3, 6.0.

$[\alpha]_D^{25}$ = -90.2 (c = 0.36, CH_2Cl_2).

FTIR (neat): υ3334, 3255, 2970, 2922, 2852, 1737, 1645, 1557, 1517, 1375, 1302, 1170, 1132, 1104, 1033, 1011, 976, 914, 828, 668.

HRMS: (CI) Calcd. for $C_{19}H_{27}O_5$ $[M+H]^+$: 335.1859, Found: 335.1855.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Sample directory:
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Solvent: cdcl3
Ambient temperature
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INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047115 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
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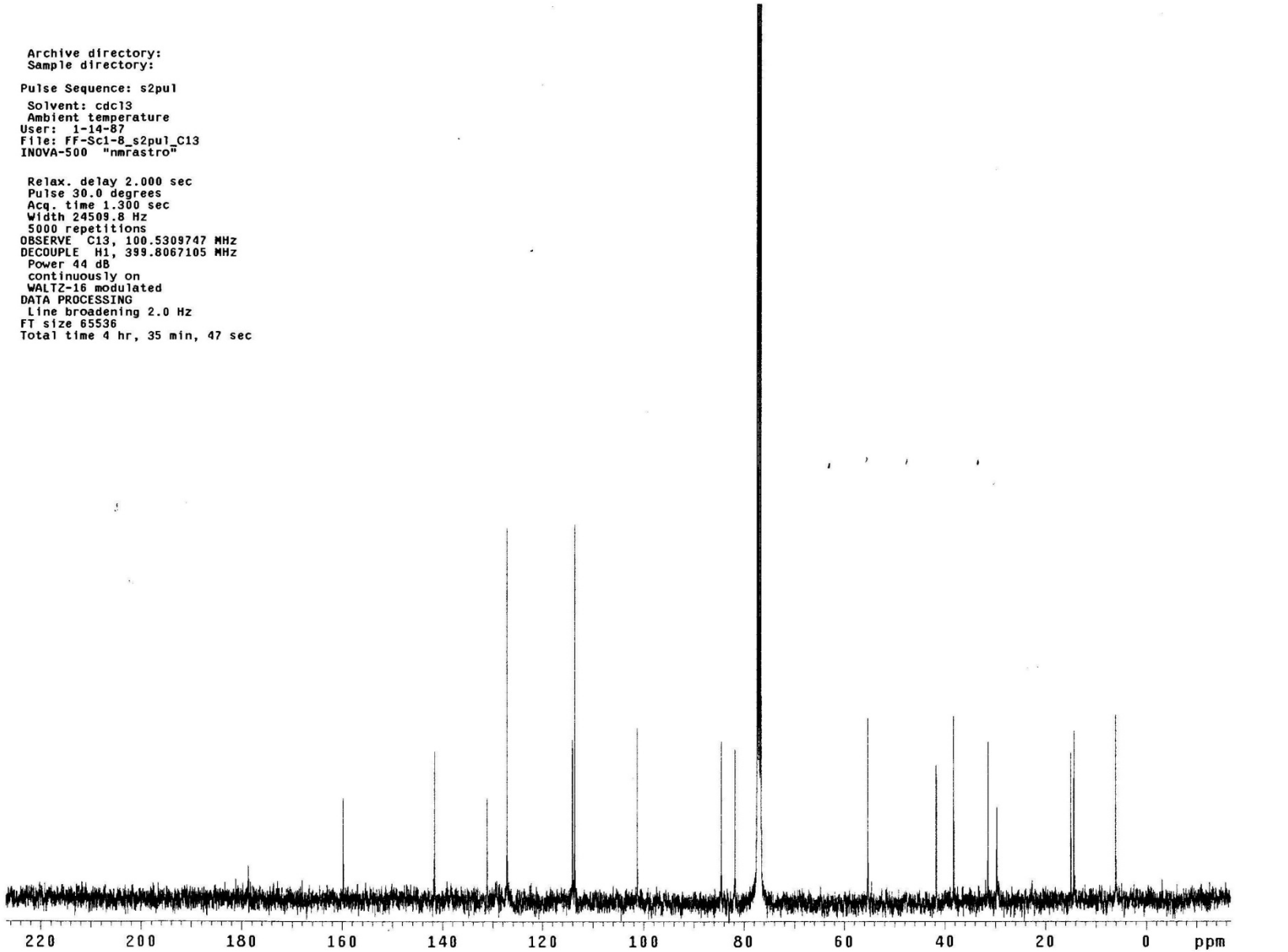
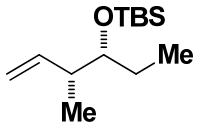
O
Me
Me
Me
O
O
PMP
12
10
8
6
4
2
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: FF-Sc1-8_s2pul_C13
INOVA-500 "nmrastro"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309747 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Procedure and Spectral Data for Alcohol Fragment Synthesis (Fragment A)

***tert*-Butyldimethyl(((*3R,4R*)-4-methylhex-5-en-3-yl)oxy)silane**[1]



2

To a resealable pressure tube equipped with a magnetic stir bar was added $RuH_2(CO)(PPh_3)_3$ (321.5 mg, 0.35 mmol, 7 mol%), (*S*)-SEGPHOS (213.5 mg, 0.35 mmol, 7 mol%), TADDOL-phosphoric acid (488 mg, 0.7 mmol, 14 mol%). The tube was sealed with a rubber septum and purged with argon. Propanol (382.5 μL, 5. 0 mmol, 100 mol%) and acetone (5. 0 mL, 1.0 M concentration with respect to alcohol) were added and the solution was cooled to -78 °C. Butadiene (1.69 mL, 20.0 mmol, 400 mol%) was quickly added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 95 °C (oil bath temperature) for 3 days, at which point the reaction mixture was allowed to cool to ambient temperature. TBSCl (1.507 g, 10.0 mmol, 200 mol%) and imidazole (0.851 g, 12.5 mmol, 250 mol%) were added and the reaction mixture was diluted with DMF (25 mL) and stirred under 70 °C for another 15 hours. Aqueous $CuSO_4$ solution was added and the reaction mixture was extract with ether (20 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes) to furnish the title compound (673.9 mg, 2.95 mmol, *syn*:*anti* = 4.7:1, 98% ee) as a colorless oil in 59% yield.

TLC (SiO_2): R_f = 0.64 (hexanes).

^{1}H NMR(400 MHz, $CDCl_3$): δ5.83 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.02-4.96 (m, 2H), 3.51-3.44 (m, 1H), 2.35-2.26 (m, 1H), 1.46-1.37 (m, 2H), 0.96 (d, *J* = 7.2 Hz, 1H), 0.90 (s, 9H), 0.86 (t, *J* = 7.2 Hz, 1H), 0.04 (s, 6H).

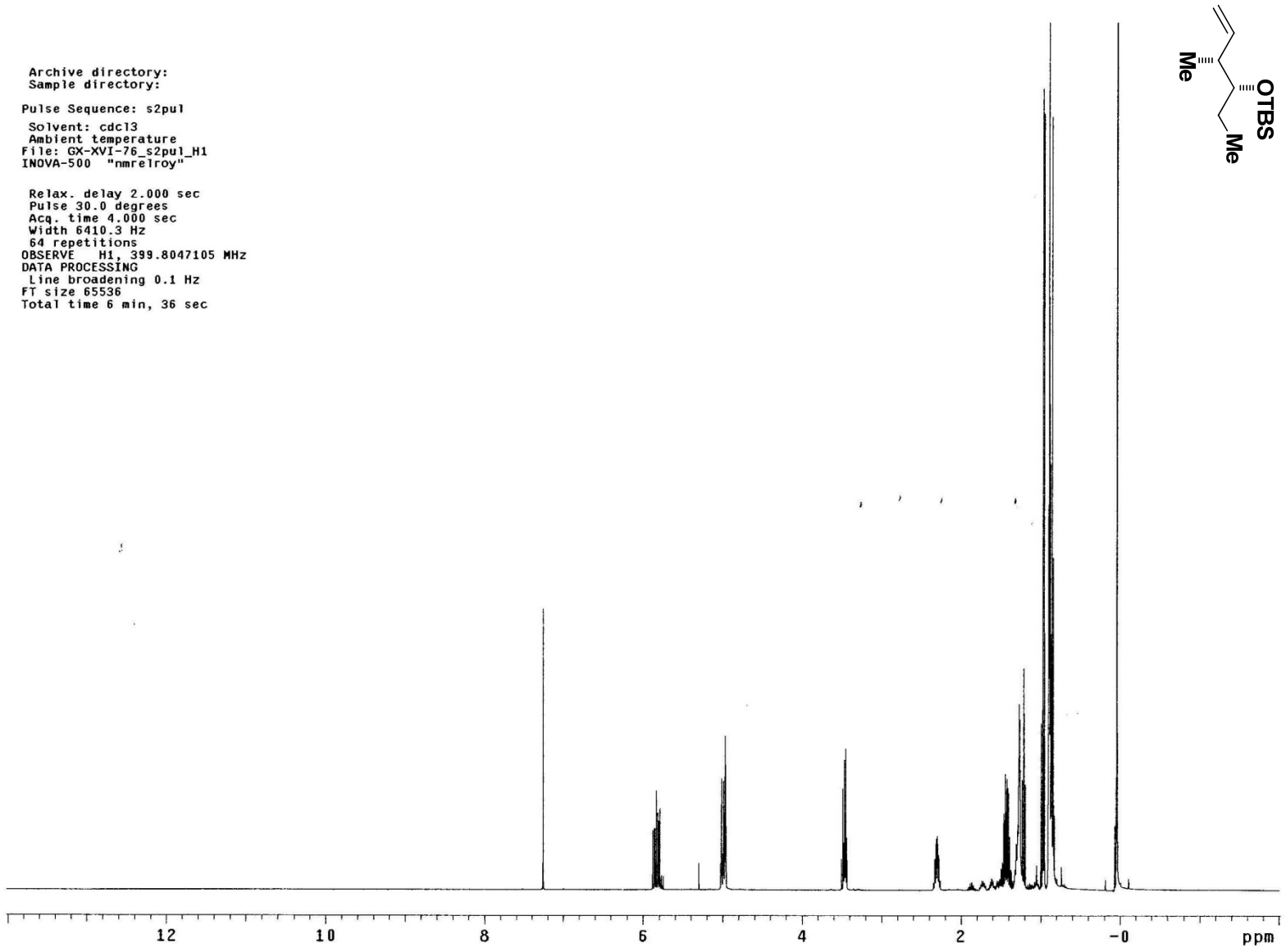
^{13}C NMR (100 MHz, $CDCl_3$): δ141.8, 113.6, 76.7, 42.3, 26.5, 25.9, 15.0, 9.5, -4.3, -4.4.

FTIR (neat): υ2956, 2927, 1462, 1251, 771.

$[\alpha]_D^{25}$ = +20.8 (c = 1.1, CH_2Cl_2).

[1] Narasimhulu, C. P.; Das, P. *Synthesis*, **2009**, 474.

HPLC Enantiomeric excess was determined by HPLC analysis of the 4-nitrobenzoate derivative of the product (Chiralcel AD-H column, hexanes:*i*-PrOH = 99:1, 0.5 mL/min, 254 nm), t_{major} = 55.3 min, t_{minor} = 66.0 min; ee = 98%.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Sample directory:
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Ambient temperature
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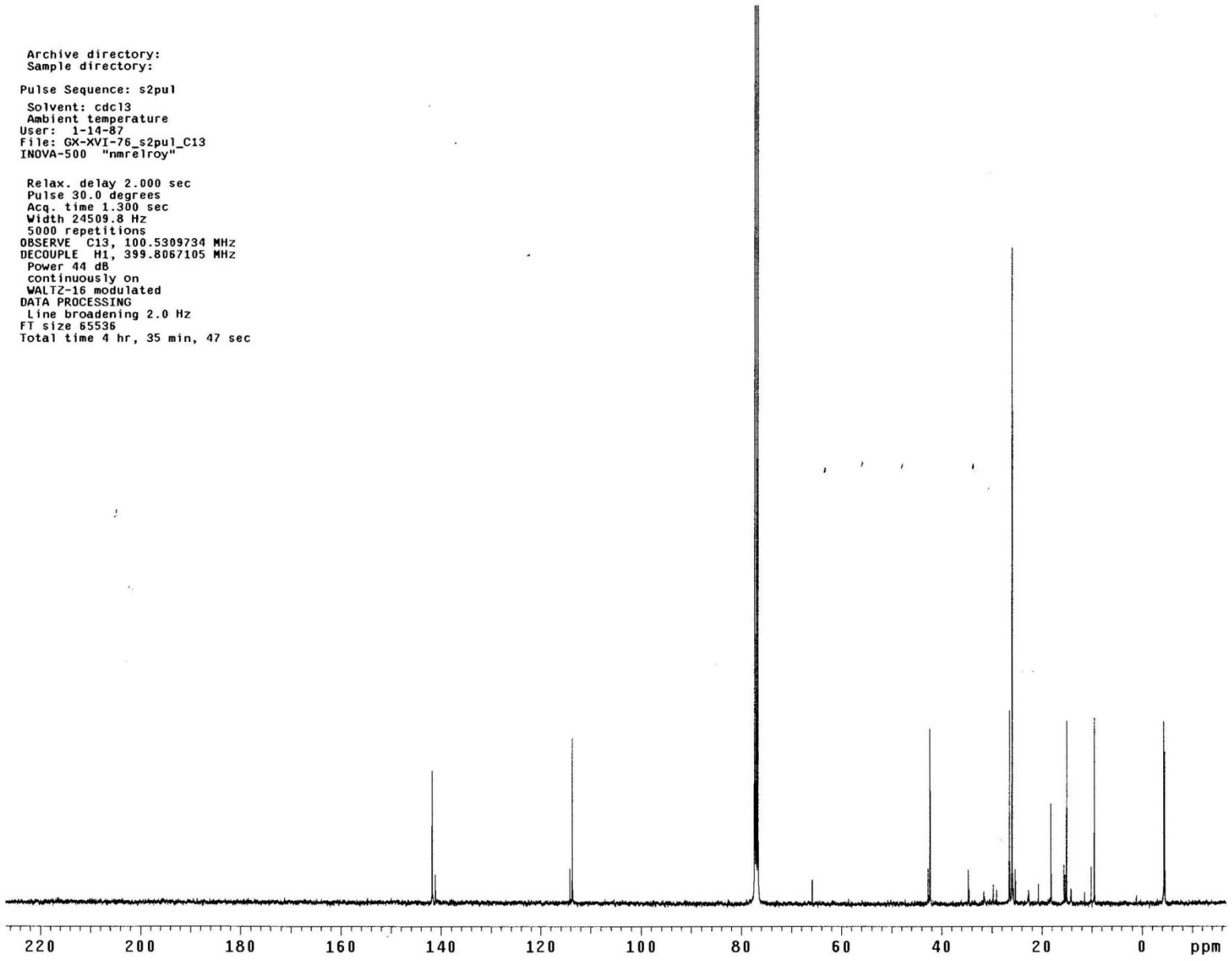
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047105 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
Me
OTBS
Me
12
10
8
6
4
2
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-76_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309734 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
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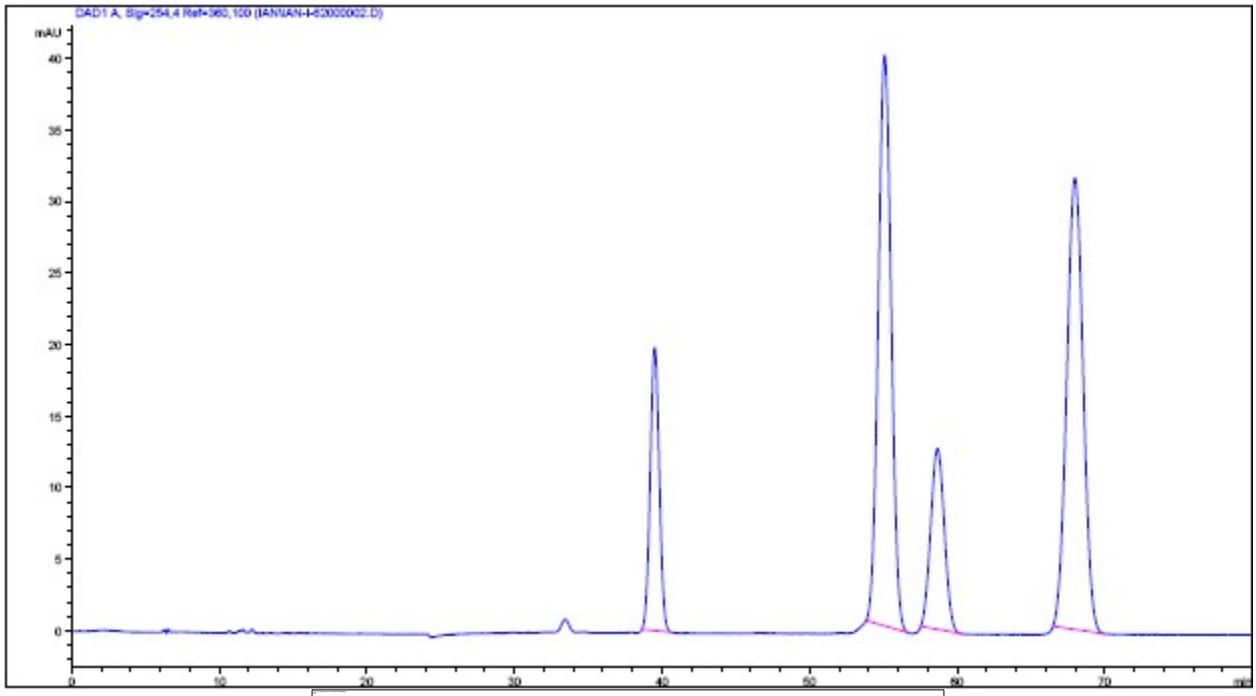
200
180
160
140
120
100
80
60
40
20
0
ppm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30
25
20
15
10
5
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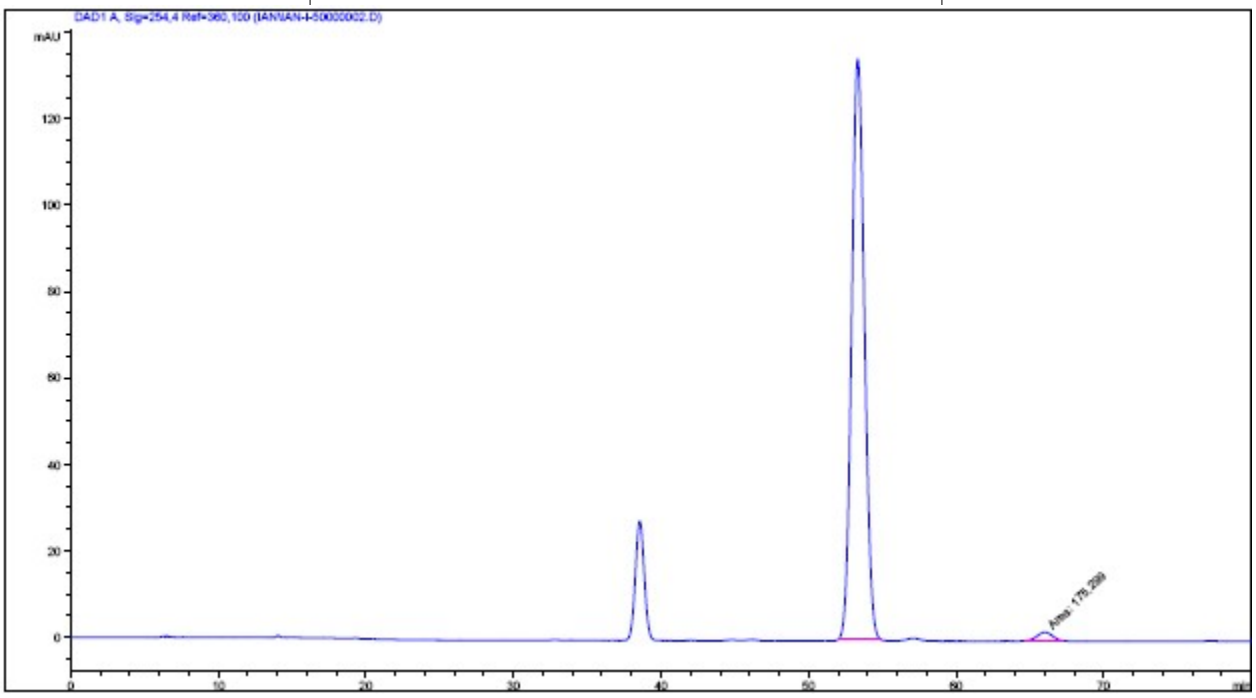
0
10
20
30
40
50
60
70
min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100
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60
40
20
0
Area: 179.299
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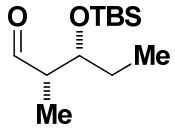
30
40
50
60
70
min

(*2S,3R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal



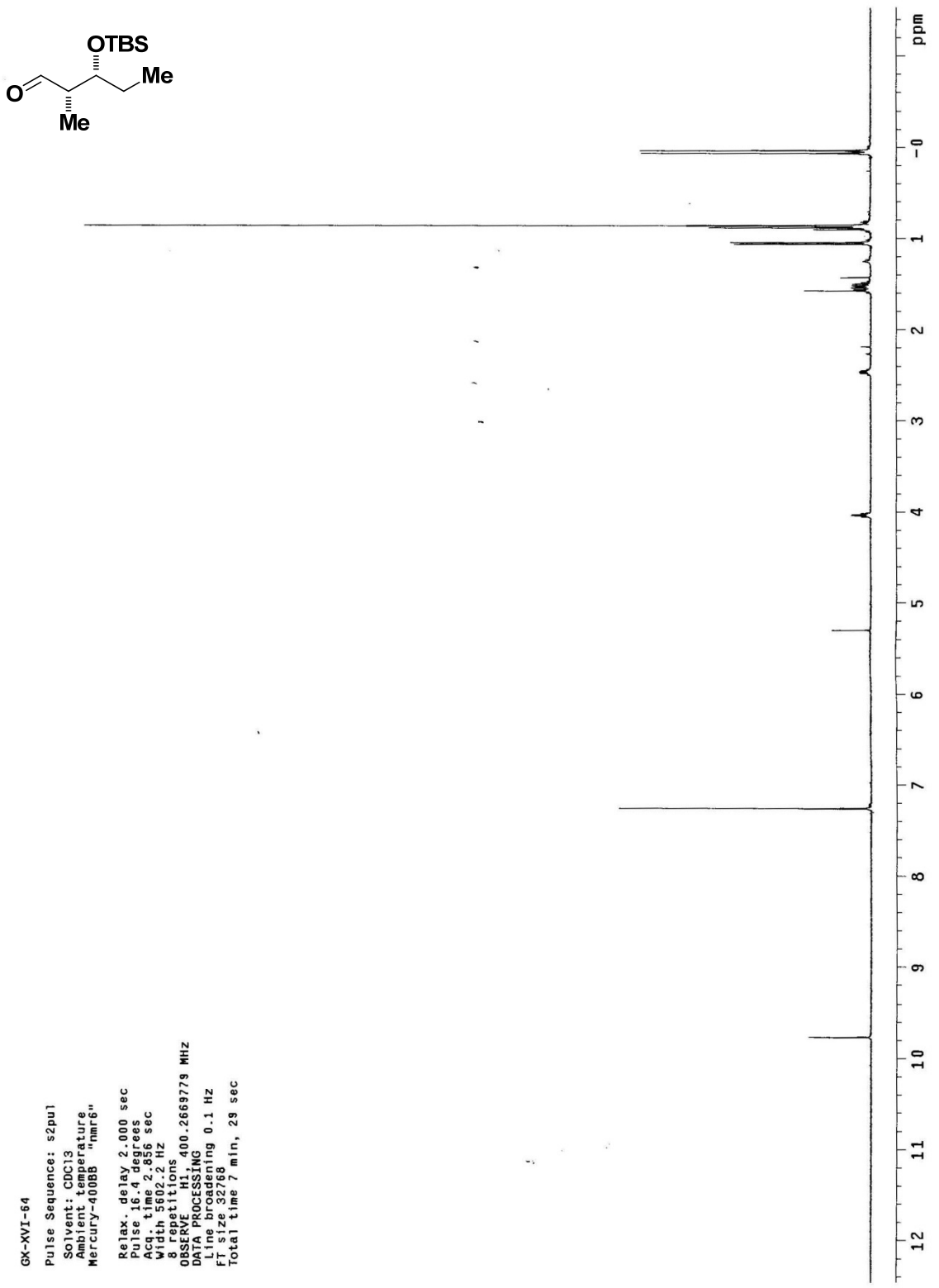
2a

An oven-dried round bottom flask under an atmosphere of N_2 was charged with *tert*-Butyldimethyl(((*3R,4R*)-4-methylhex-5-en-3-yl)oxy)silane (290 mg, 1.27 mmol, 100 mol%), 2,6-lutidine (271.9 mg, 2.54 mmol, 200 mol%), and THF:H_2O (12.7 mL, 3:1, 0.1 M). OsO_4 in *t*-butanol (0.76 mL, 0.05M, 0.038 mmol, 3 mol%) was added under 0 ^oC. After being stirring for 5 min, solid $NaIO_4$ (542.9 mg, 2.54 mmol, 200 mol%) was added in one portion. Stirring was continued for another 12 hr fallowed by saturated aqueous $Na_2S_2O_3$ (20 mL) was added. The reaction mixture was stirred vigorously for 15 min and then transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was run through a silica plug to give the title compound (262 mg, 0.977 mmol) as a colorless oil in 77% yield and used in the next step without further purification.

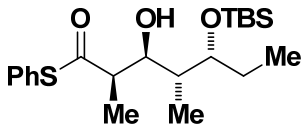
TLC (SiO_2): R_f = 0.63 (hexanes:ethyl acetate, 10:1).

^{1}H NMR(400 MHz, $CDCl_3$): δ 9.77 (d, *J* = 0.8 Hz, 1H), 4.03 (ddd, *J* = 10.4, 7.2, 3.6 Hz, 1H), 2.47 (qdd, *J* = 7.2, 3.6, 0.8 Hz, 1H), 1.60-1.47 (m, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

FTIR (neat): υ2980, 2977, 2962, 1710, 1458, 1231, 998, 960, 822, 771, 654.


OTBS
Me
O
Me
GX-XVI-64
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
8 repetitions
OBSERVE H1, 400.2669779 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 7 min, 29 sec
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0

(*2R,3S,4R,5R*)-*S*-phenyl 5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanethioate



3

An oven-dried round bottom flask under an atmosphere of N_2 was charged with *S*-phenyl propanethioate (170 mg, 1.0 mmol, 150 mol%) and ether (0.5 mL). 9-BBNOTf solution (2.0 mL, 0.5 M, 150 mol%) was added under 0 ^oC followed by triethylamine (0.186 mL, 1.2 mmol, 180 mol%). The bright yellow reaction mixture was stirred under room temperature for 30 min, and then cooled to -78 ^oC. (*2S,3R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal (154 mg, 0.67 mmol, 100 mol%) in ether (0.5 mL, 0.7 M) was added to the reaction mixture. Stirring was continued for 1 hr then pH = 7 buffer (2 mL) was added. The layer was separated and the aqueous layer was extract with DCM (10 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes:ether = 11:1-8:1) to furnish the title compound (207.3 mg, 0.52 mmol) as a colorless oil in 78% yield.

TLC (SiO_2): R_f = 0.42 (ethyl acetate:hexanes, 1:9).

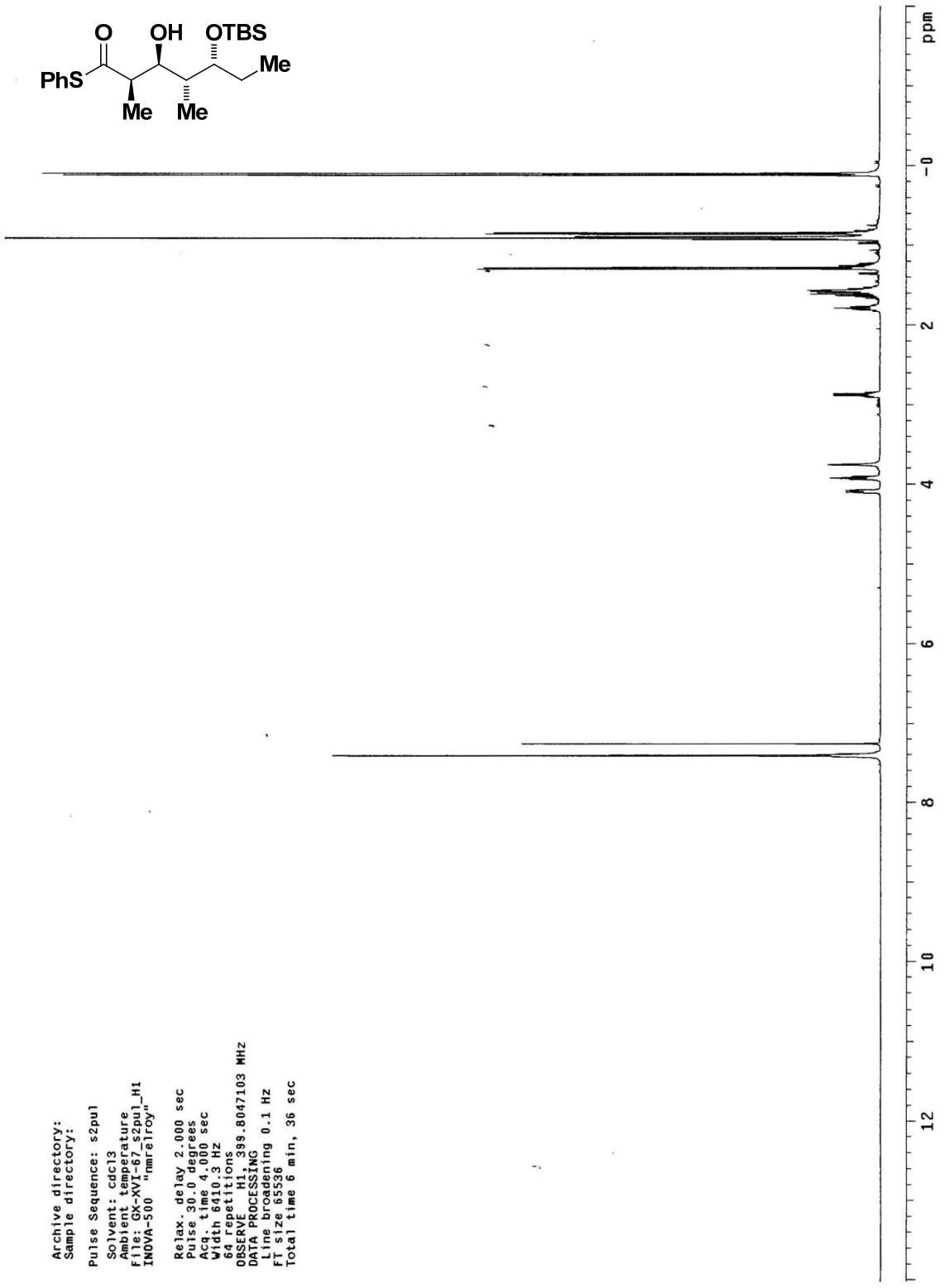
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.43-7.39 (m, 5H), 4.10-4.08 (m, 1H), 3.94-3.90 (m, 1H), 3.76 (br, 1H), 2.87 (qd, *J* = 7.8, 3.2 Hz, 1H), 1.83-1.75 (m. 1H), 1.66-1.51 (m, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 201.2, 134.6, 129.3, 129.1, 127.6, 76.5, 74.2, 51.1, 38.7, 25.9, 25.8, 18.0, 11.5, 10.9, 10.2, -4.2, -4.5.

$[\alpha]_D^{25}$ = -28.8 (c = 0.55, CH_2Cl_2).

FTIR (neat): υ2928, 2858, 1714, 1457, 1252, 1217, 1003, 954, 834, 774, 744, 688, 668.

HRMS: (CI) Calcd. for $C_{21}H_{37}O_3SSi$ $[M+H]^+$: 397.3320, Found: 397.3318.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OH
OTBS
PhS
Me
Me
Me
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Sample directory:
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Solvent: cdcl3
Ambient temperature
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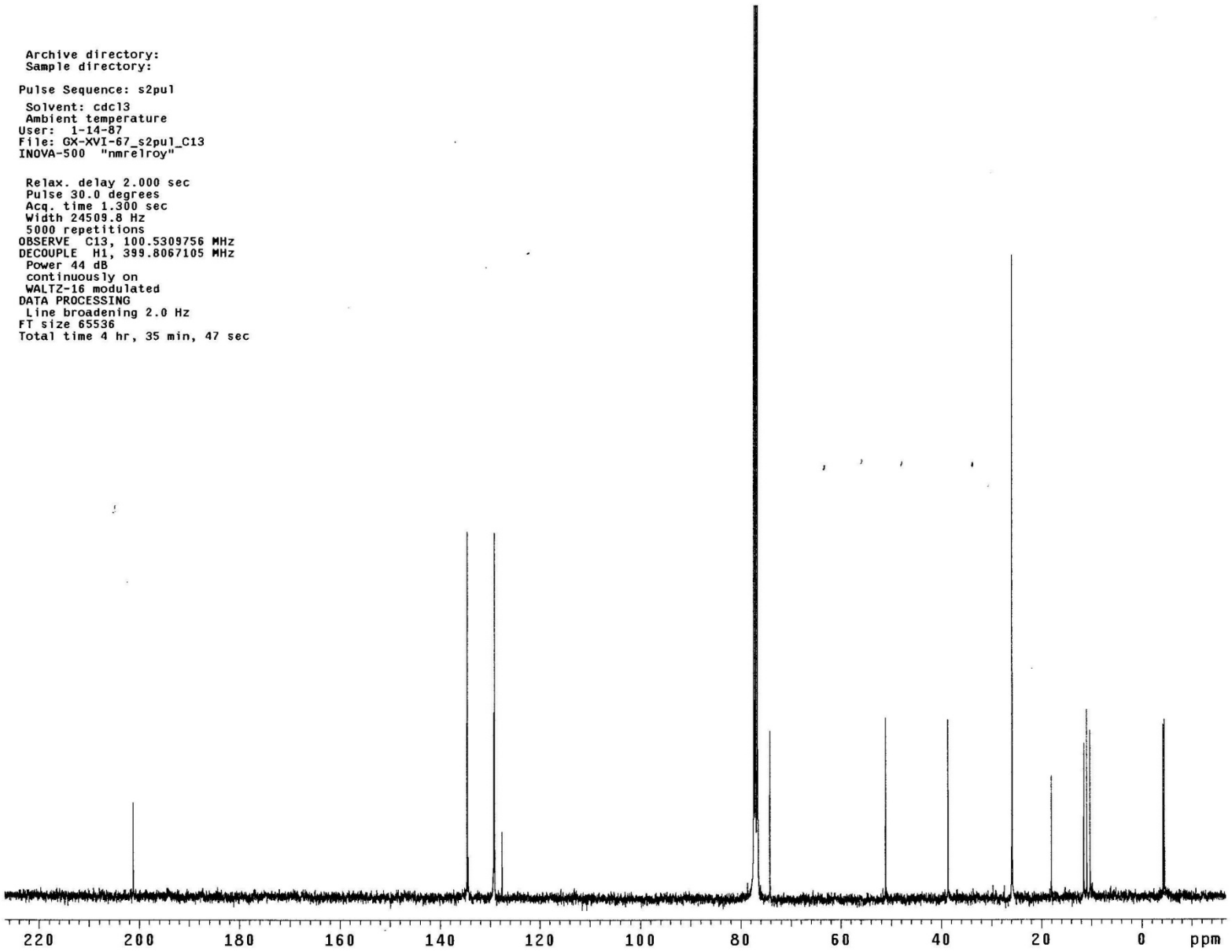
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047103 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
ppm
12
10
8
6
4
2
-0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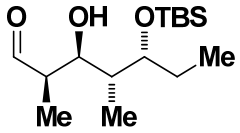
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-67_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*2R,3S,4R,5R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanal



3a

An oven-dried round bottom flask under an atmosphere of N_2 was charged with **(***2R,3S,4R,5R*)-*S*-phenyl 5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanethioate (230 mg, 0.58 mmol, 100 mol%), 10% Pd/C (31 mg, 0.029 mmol, 5 mol%), and acetone (11.6 mL, 0.05M). Triethylsilane (0.930 mL, 5.8 mmol, 1000 mol%) was added in ten portions and the mixture was allowed to stir at room temperature until all starting material was consumed. The reaction mixture was run through a silica plug and concentrated *in vacuo* to give the title compound (142.2 mg, 0.49 mmol) as a colorless oil in 85% yield and used in the next step without further purification.

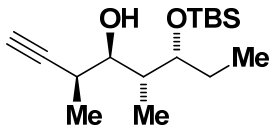
TLC (SiO_2): R_f = 0.42 (ethyl acetate:hexanes, 1:9).

^{1}H NMR(400 MHz, $CDCl_3$): δ9.77 (d, *J* = 0.4 Hz, 1H), 4.31 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.27 (s, 1H), 3.72 (dt, *J* = 8.8, 3.2 Hz, 1H), 3.34 (qd, *J* = 6.8, 2.0 Hz, 1H), 1.91 (dqd, *J* = 8.8, 7.2, 2.8 Hz, 1H), 1.68-1.52 (m, 2H), 1.12 (d, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.79 (d, *J* = 7.2 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 3H).

FTIR (neat): υ3349, 2963, 2928, 2856, 1713, 1459, 1384, 1249, 1148, 957, 931, 833, 772, 666.

O
OH
OTBS
Me
Me
Me
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: GX-XVI-71_s2pul_H1
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047103 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
ppm
12
10
8
6
4
2
-0

(*3S,4R,5R,6R*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethyloct-1-yn-4-ol



4

An oven-dried round bottom flask under an atmosphere of N_2 was charged with Ohira-Bestmann reagent (119.9 mg, 0.62 mmol, 300 mol%) and methanol (6 mL, 0.1 M). Solid K_2CO_3 (86.2 mg, 0.62 mmol, 300 mol%) was added in one portion and the mixture was allowed to stir at room temperature for 30 min. The clear solution was transferred via syringe to another reaction flask with (*2R,3S,4R,5R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylheptanal (60 mg, 0.21 mmol, 100 mol%) in THF (4.2 mL, 0.05 M) under 0 ^oC. The reaction was stirred for 1 hr and pH = 7 buffer (20 mL) was added. The layer was separated and the aqueous layer was extract with DCM (20 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes:ether = 9:1) to furnish the title compound (52.7 mg, 0.19 mmol) as a colorless oil in 89% yield.

TLC (SiO_2): R_f = 0.62 (ethyl acetate:hexanes, 1:9).

^{1}H NMR(400 MHz, $CDCl_3$): δ 3.90 (d, *J* = 4.0 Hz, 1H), 3.86 (td, *J* = 7.2, 2.0 Hz, 1H), 3.65 (p, *J* = 4.0 Hz, 1H), 2.58 (qdd, *J* = 7.2, 5.2, 2.4 Hz, 1H), 2.09 (d, *J* = 2.4 Hz, 1H), 1.93 (pd, *J* = 10.8, 2.4 Hz, 1H), 1.63-1.48 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 87.3, 77.3, 76.6, 69.2, 37.7, 29.9, 25.8, 25.6, 17.9, 14.4, 11.8, 10.8, -4.1, -4.6.

$[\alpha]_D^{25}$ = -6.1 (c = 0.33, CH_2Cl_2).

FTIR (neat): υ 2928, 2858, 1714, 1457, 1252, 1217, 1003, 954, 834, 774, 744, 688, 668.

HRMS: (CI) Calcd. for $C_{16}H_{32}O_2Si$ $[M]^+$: 284.3258, Found: 284.3253.

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Archive directory:
Sample directory:

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Ambient temperature
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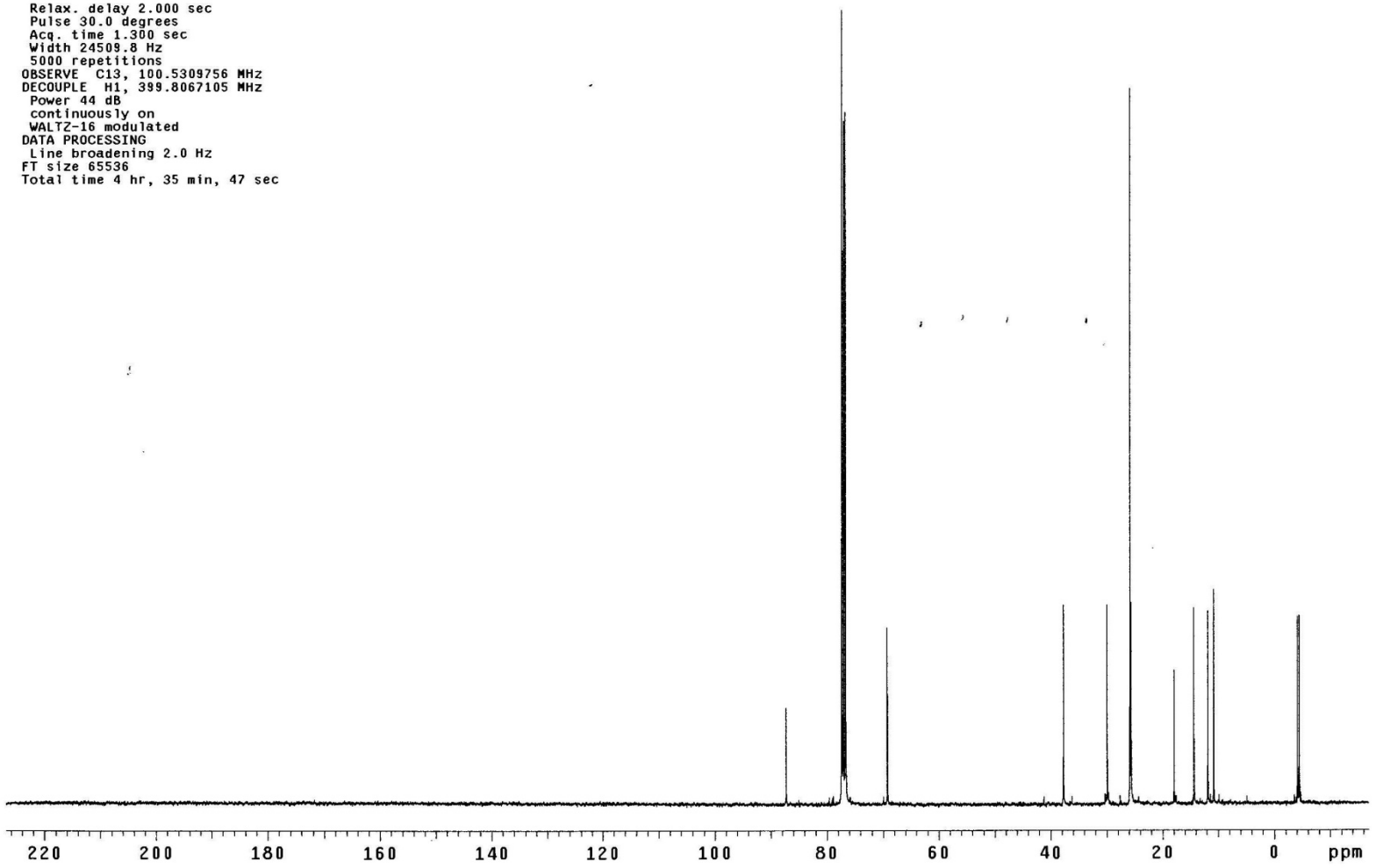
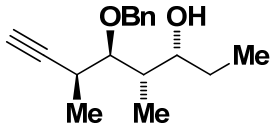


(*3R,4S,5R,6S*)-5-(benzyloxy)-4,6-dimethyloct-7-yn-3-ol



Fragment A

An oven-dried sealed tube under an atmosphere of N_2 was charged with (*3S,4R,5R,6R*)-6-((*tert*-butyldimethylsilyl)oxy)-3,5-dimethyloct-1-yn-4-ol (350 mg, 1.23 mmol, 100 mol%), Ag_2O (855 mg, 3.69 mmol, 300 mol%) and benzyl bromide (2.104 g, 12.3 mmol, 1000 mol%). The mixture was allowed to stir at 50 ^oC for 24 hr. Methanol (5 mL) was added to the reaction mixture and the reaction was acidified by conc. HCl (~0.5 mL). After stirring for 30 min under room temperature, pH = 7 buffer (10 mL) was added and the mixture was transferred to a separatory funnel. The aqueous layer was extract with DCM (20 mL × 3). Combined organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2; hexanes:ether = 9:1) to furnish the title compound (230.6 mg, 0.886 mmol) as a colorless oil in 72% yield.

TLC (SiO_2): R_f = 0.48 (ethyl acetate:hexanes, 1:9).

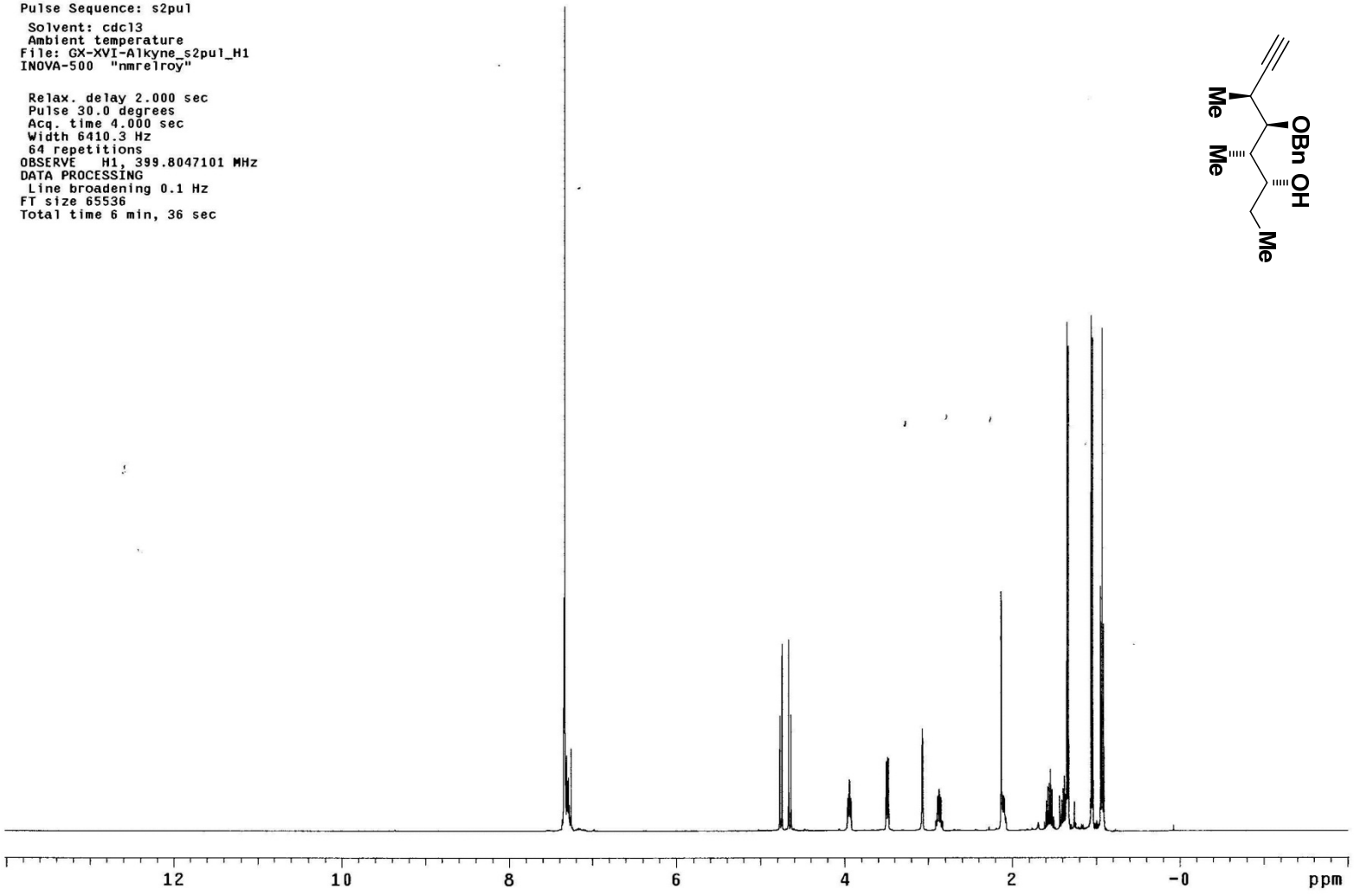
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 5H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 10.8 Hz, 1H), 3.96-3.93 (m, 1H), 3.49 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.07 (d, *J* = 1.6 Hz, 1H), 2.87 (dqd, *J* = 10.0, 6.8, 2.8 Hz, 1H), 2.13 (d, *J* = 2.8 Hz, 1H), 2.11 (qdd, *J* = 6.8, 4.0, 1.6 Hz, 1H), 1.62-1.51 (m, 1H), 1.43-1.32 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 137.6, 128.5, 128.0, 127.9, 88.2, 86.3, 76.0, 72.1, 70.5, 38.2, 29.4, 27.3, 17.3, 11.4, 10.6.

$[\alpha]_D^{25}$ = -9.3 (c = 0.22, CH_2Cl_2).

FTIR (neat): υ 3484, 3302, 2968, 2935, 2876, 1454, 1378, 1347, 1117, 1052, 953, 735, 699.

HRMS: (CI) Calcd. for $C_{17}H_{25}O_2$ $[M+H]^+$: 261.1855, Found: 261.1860.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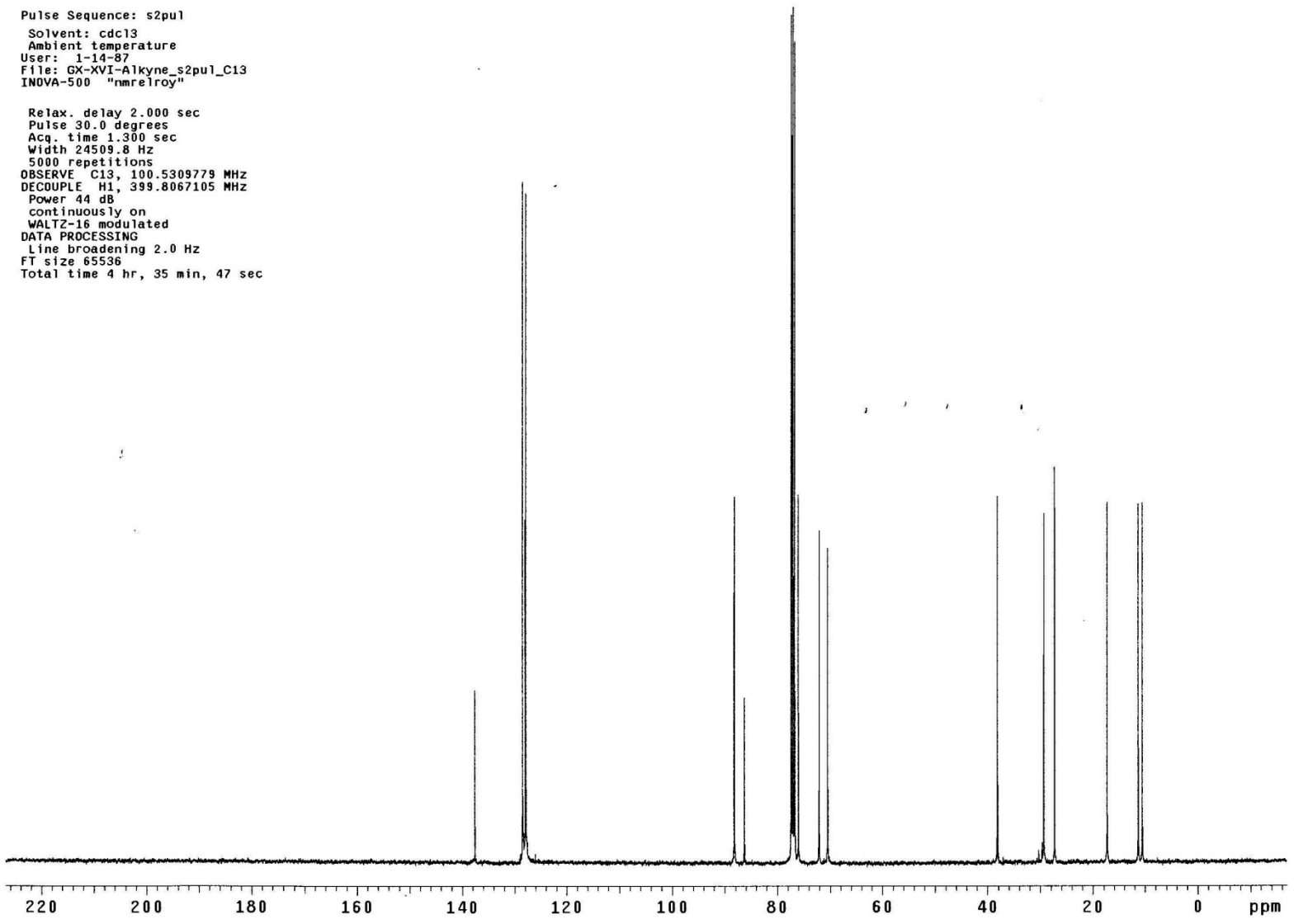
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Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309779 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
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200
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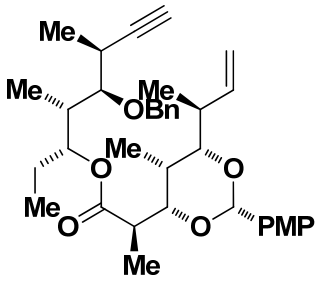
80
60
40
20
0
ppm

Procedure and Spectral Data for 6-Deoxyerythronolide B Synthesis

(*R*)-(*3R,4S,5R,6S*)-5-(benzyloxy)-4,6-dimethyloct-7-yn-3-yl 2-((*2S,4S,5R,6S*)-6-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanoate



11

An oven-dried round bottom flask under an atmosphere of N_2 was charged with acid fragment (77.1 mg, 0.23 mmol, 100 mol%), triethylamine (64.3 μL, 0.46 mmol, 200 mol%) and THF (2.3 mL, 0.1 M). 2,4,6-Trichlorobenzoyl chloride (72 μL, 0.46 mmol, 200 mol%) was added and the mixture was allowed to stir at room temperature for 3 hr. The reaction mixture was filtered through a Celite plug and concentrated *in vacuo*. The residue was dissolved in toluene (1.5 mL) and added to a mixture of alcohol fragment (60.0 mg, 0.23 mmol, 100 mol%), DMAP (112.6 mg, 0.92 mmol, 400 mol%) and toluene (2.3 mL, 0.1 M). The reaction mixture was stirred at room temperature overnight, and loaded on to column directly. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) provides the title compound (90.6 g, 0.16 mmol) as a colorless oil in 70% yield.

TLC (SiO_2): R_f = 0.59 (ethyl acetate:hexanes, 1:9).

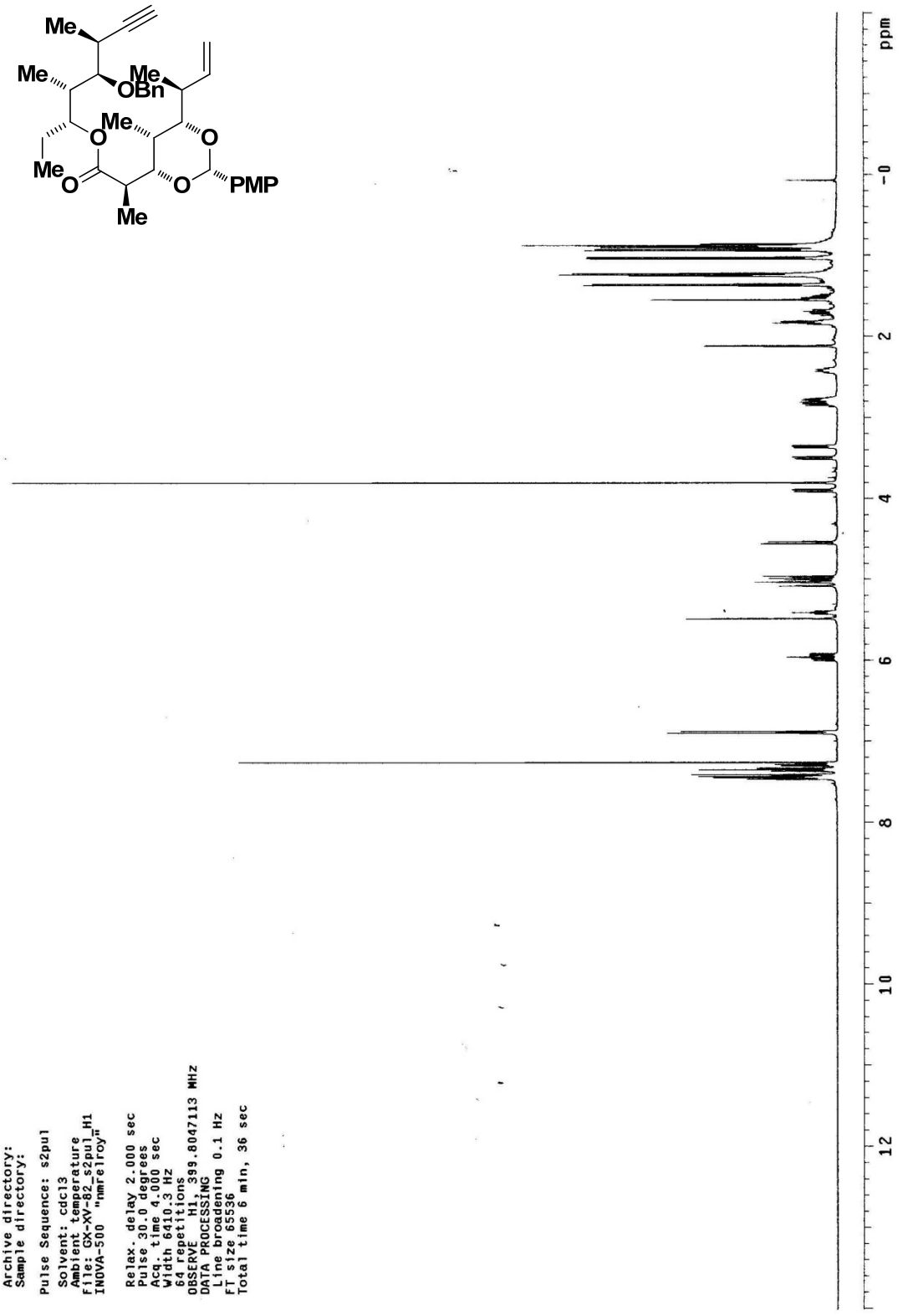
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.47-7.28 (m, 7H), 6.90-6.88 (m, 2H), 5.96 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.48 (s, 1H), 5.41 (td, *J* = 8.4, 2.4 Hz, 1H), 5.08-5.00 (m, 2H), 4.97 (d, *J* = 10.0, 1H), 4.54 (d, *J* = 10.0, 1H), 3.90 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.80 (s, 3H), 3.50 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.36 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.87-2.75 (m, 2H), 2.41 (qd, *J* = 6.8, 1.6 Hz, 1H), 2.11 (d, *J* = 2.4 Hz, 1H), 1.86-1.80 (m, 2H), 1.74-1.67 (m, 1H), 1.55-1.49 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 159.7, 141.6, 138.4, 131.3, 128.3, 128.3, 127.7, 127.1, 113.9, 113.5, 101.2, 87.8, 84.5, 82.2, 82.1, 74.8, 74.5, 69.8, 55.3, 42.6, 38.9, 38.1, 31.4, 27.6, 25.7, 15.7, 14.4, 14.3, 10.2, 10.2, 6.2.

$[\alpha]_D^{27}$ = -14.4 (c = 0.44, CH_2Cl_2).

FTIR (neat): υ 3090, 2970, 2972, 2940, 2924, 1740, 1454, 1377, 1350, 1121, 1052, 765, 730, 668.

HRMS: (CI) Calcd. for $C_{36}H_{47}O_6$ $[M-H]^+$: 575.3374, Found: 575.3377.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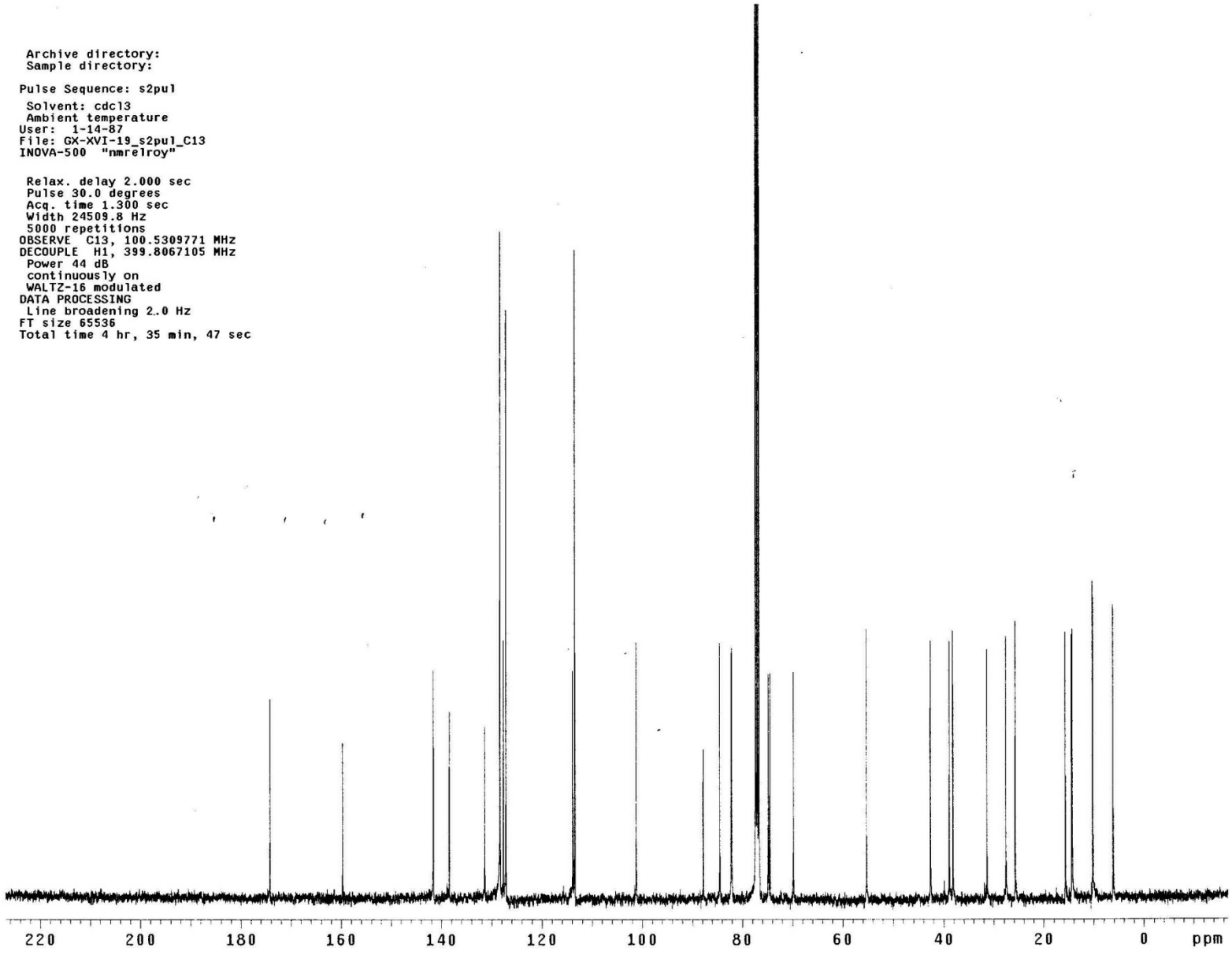
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DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
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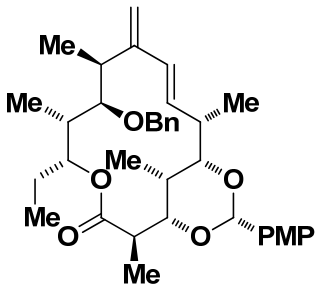
ppm

(*1S,2R,5R,6S,7R,8S,12S,13S,15S,17R,E*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-9-methylene-4,14,16-trioxabicyclo[11.3.1]heptadec-10-en-3-one



12

An oven-dried round bottom flask under an atmosphere of ethylene (balloon pressure) was charged with (*R*)-(*3R,4S,5R,6S*)-5-(benzyloxy)-4,6-dimethyloct-7-yn-3-yl-2-((*2S,4S,5R,6S*)-6-((*S*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanoate (105.2 mg, 0.18 mmol, 100 mol%), Hoveyda-Grubbs 2nd generation catalyst (34.3 mg, 0.60 mmol, 30 mol%) and toluene (182.4 mL, 0.001 M). The mixture was allowed to stir at 80 ^{o}C overnight. Blowing nitrogen through the reaction system to remove the ethylene and the reaction mixture was allowed to stir at 110 ^{o}C for another 24 hr followed by loading on to column directly. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) provides the title compound (93.6 mg, 0.16 mmol) as a colorless viscous oil in 89% yield.

TLC (SiO_2): R_f = 0.62 (ethyl acetate:hexanes, 1:9).

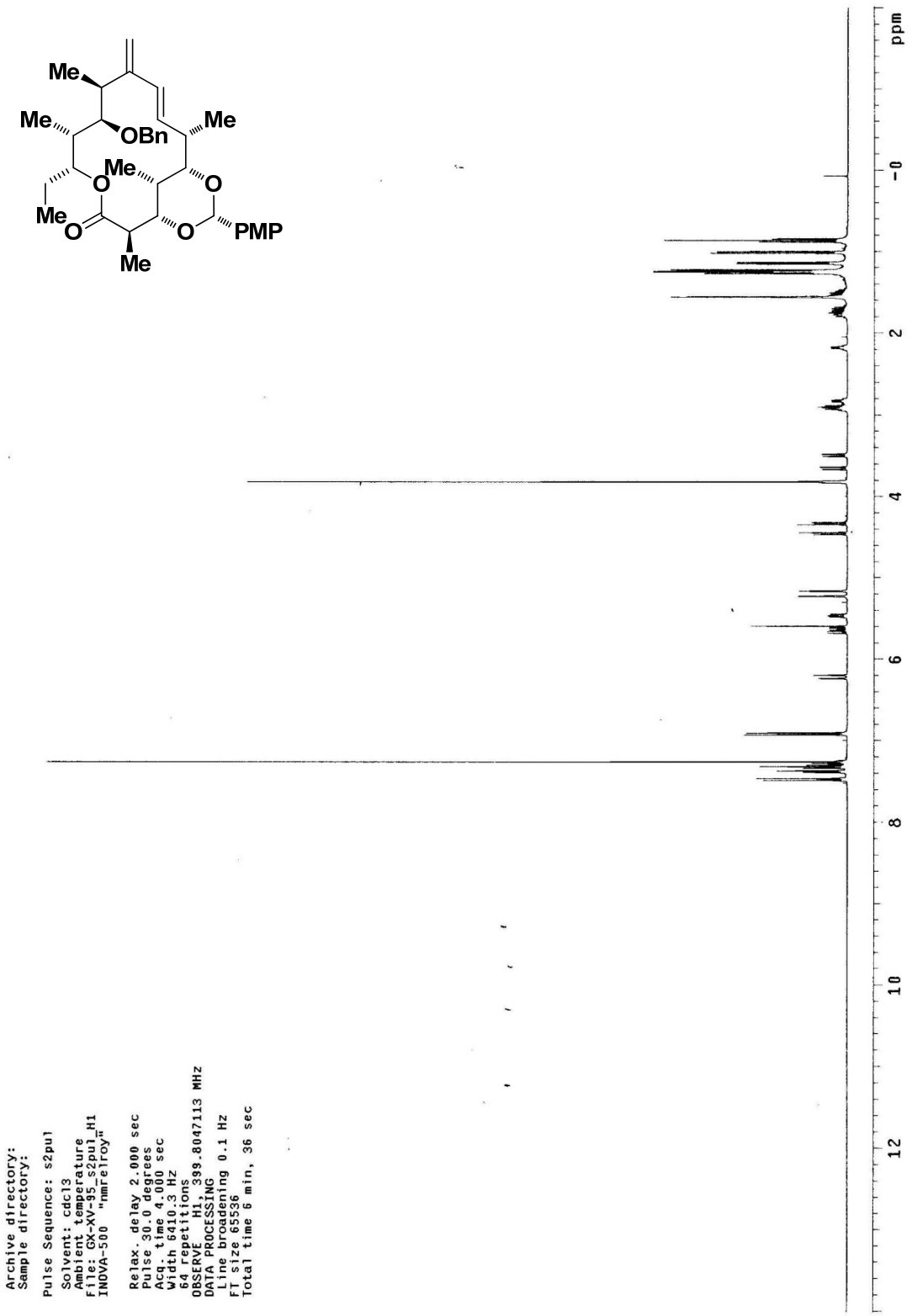
^{1}H NMR(400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.39-7.27 (m, 5H), 6.94-6.90 (m, 2H), 6.22 (d, *J* = 16.0 Hz, 1H), 5.65 (dd, *J* = 16.0, 9.6 Hz, 1H), 5.60 (s, 1H), 5.47 (dd, *J* = 8.4, 5.6 Hz, 1H), 5.23 (s, 1H), 5.16 (s, 1H), 4.46 (d, *J* = 9.2 Hz, 1H), 4.33 (d, *J* = 9.2 Hz, 1H), 3.83-3.80 (m, 1H), 3.82 (s, 3H), 3.65 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 2.96-2.80 (m, 3H), 2.17 (q, *J* = 6.8 Hz, 1H), 1.81-1.66 (m, 1H), 1.54-1.45 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 160.0, 148.7, 138.7, 132.8, 132.7, 131.2, 128.4, 128.3, 127.6, 127.5, 115.7, 113.6, 102.6, 84.5, 83.7, 80.0, 76.0, 75.1, 55.3, 41.6, 40.2, 40.1, 35.5, 33.4, 26.5, 14.1, 13.0, 10.6, 9.9, 9.9, 9.4.

$[\alpha]_D^{27}$ = -19.9 (c = 0.58, CH_2Cl_2).

FTIR (neat): υ 2972, 2936, 2880, 1723, 1616, 1518, 1458, 1385, 1302, 1249, 1174, 1153, 1096, 1071, 1030, 1005, 891, 829, 755, 733, 699.

HRMS: (CI) Calcd. for $C_{36}H_{48}O_6$ $[M]^+$: 576.3452, Found: 576.3442.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Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047113 MHz
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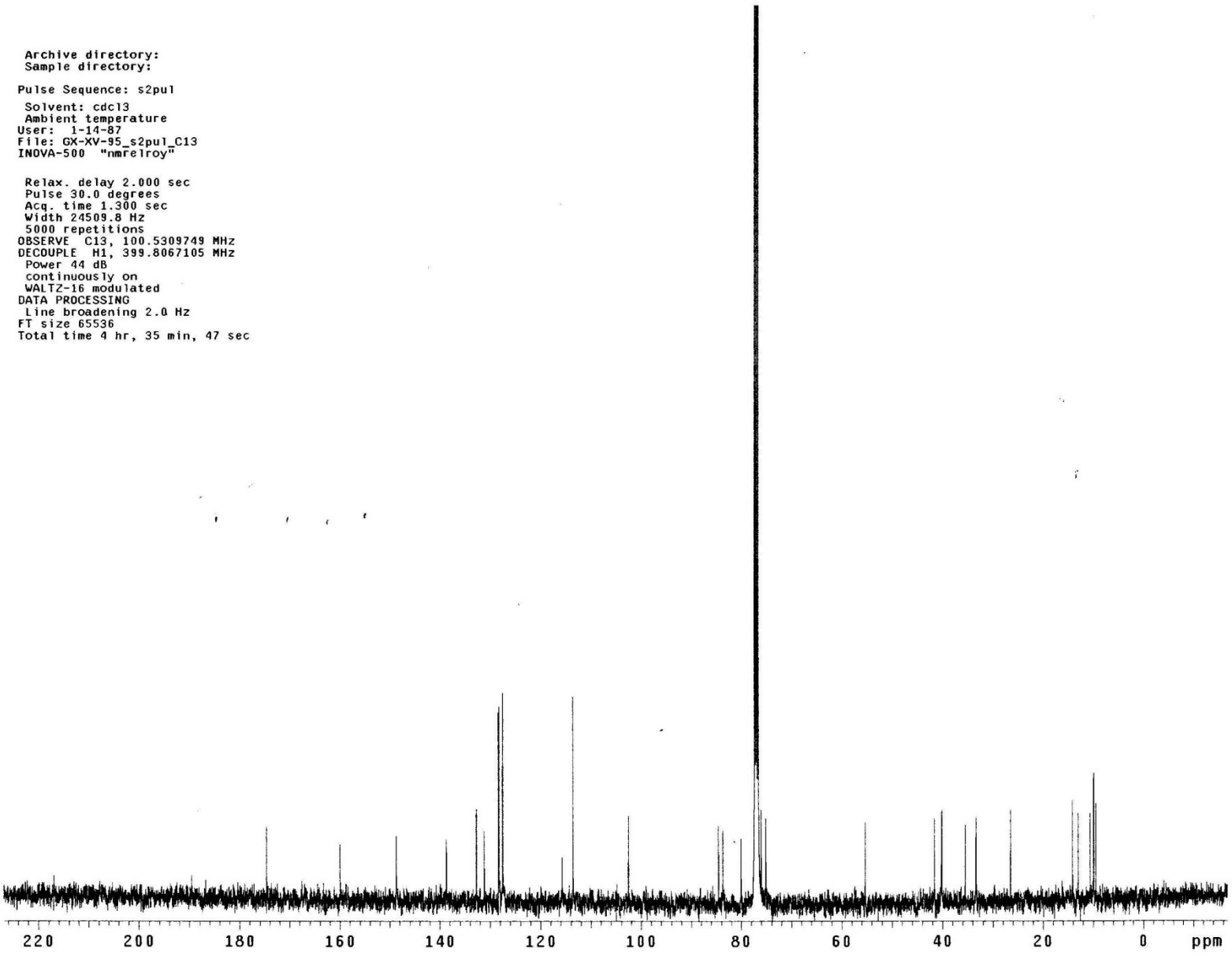
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Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8067105 MHz
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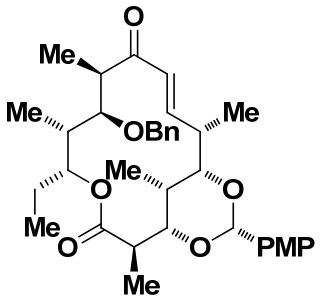


13

An oven-dried round bottom flask under an atmosphere of N_2 was charged with (*1S,2R,5R,6S,7R,8S,12S,13S,15S,17R,E*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-9-methylene-4,14,16-trioxabicyclo[11.3.1]heptadec-10-en-3-one (33.0 mg, 0.0607 mmol, 100 mol%) and THF:H_2O (3.0 mL, 1:1, 0.02 M). OsO_4 in *t*-butanol (0.303 mL, 0.02M, 0.00607 mmol, 10 mol%) was added under 0 ^oC and NMO (27.1 g, 0.200 mmol, 300 mol%) was added in one portion. The reaction mixture was stirred overnight, and solid $NaIO_4$ (66.5 mg, 0.243 mmol, 400 mol%) was added in one portion. Stirring was continued for another 12 hr fallowed by saturated aqueous $Na_2S_2O_3$ (8 mL) was added. The reaction mixture was stirred vigorously for 15 min and then transferred to a separatory funnel. The aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:20) to give the title compound (19.3 mg, 0.0334 mmol) as a colorless oil in 55% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes, 1:9).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2H), 7.41-7.28 (m, 5H), 6.93-6.91 (m, 2H), 6.59 (dd, *J* = 16.4, 9.6 Hz, 1H), 6.10 (dd, *J* = 16.4 Hz, 1H), 5.61 (s, 1H), 5.51 (dd, *J* = 8.8, 5.6 Hz, 1H), 4.26-4.20 (m, 2H), 3.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.82 (s, 3H), 3.75 (d, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 10.0 Hz, 1H), 3.27 (q, *J* = 6.4 Hz, 1H), 3.08-2.99 (m, 1H), 2.95-2.87 (m, 1H), 2.07-2.02 (m, 1H), 1.85-1.68 (m, 2H), 1.63-1.45 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.6 Hz, 3H).

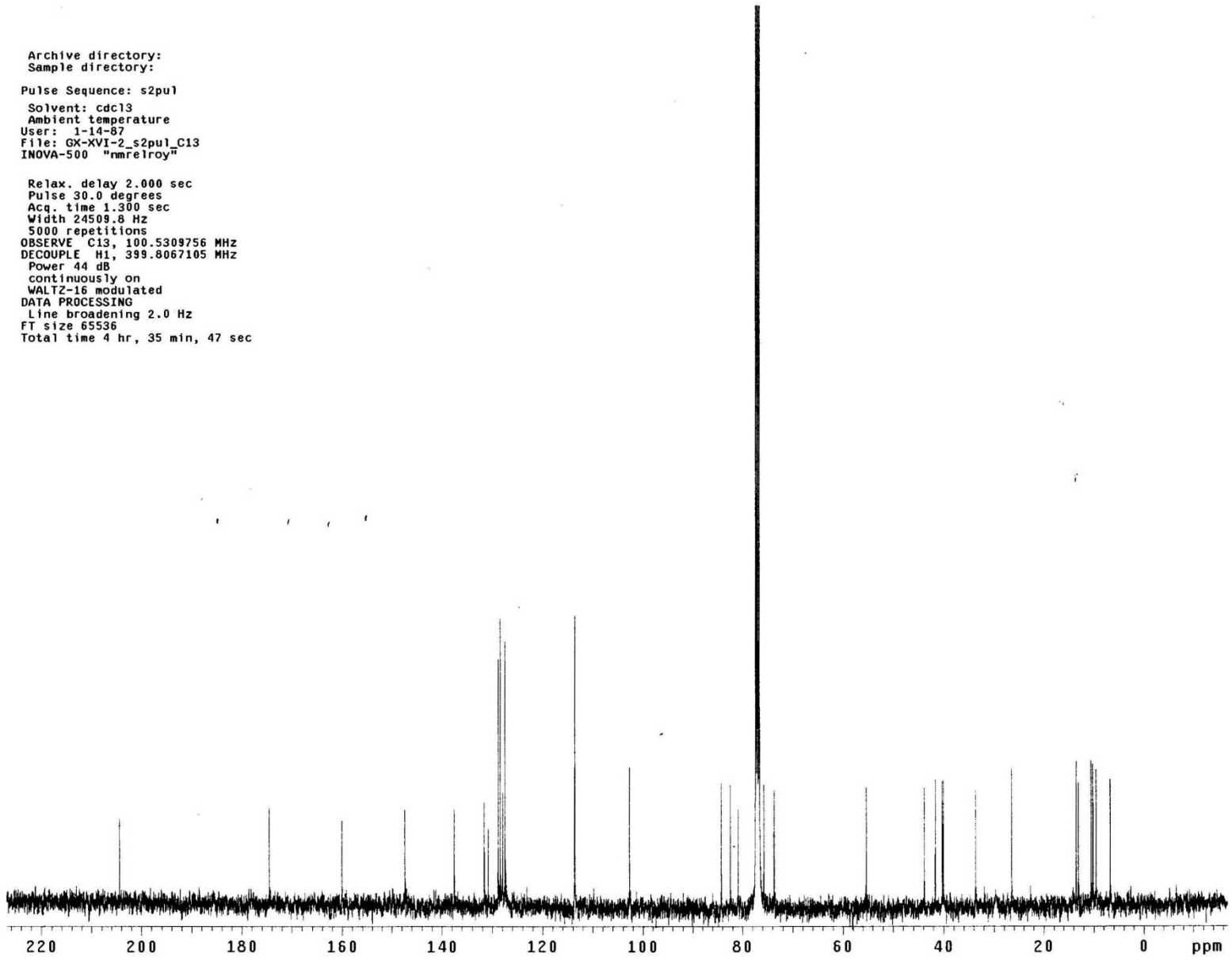
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 174.5, 160.0, 147.4, 137.5, 131.6, 130.8, 128.8, 128.4, 127.9, 127.5, 113.6, 102.7, 84.2, 82.4, 80.9, 75.7, 73.7, 55.3, 43.8, 41.6, 40.2, 40.0, 33.6, 26.4, 13.5, 13.1, 10.5, 10.1, 9.5, 6.7.

$[\alpha]_D^{27}$ = -33.7 (c = 0.21, CH_2Cl_2).

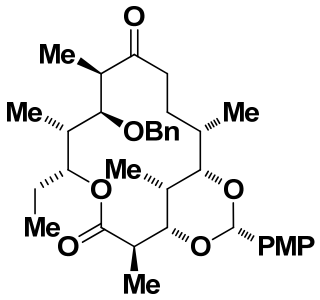
FTIR (neat): υ 3477, 2930, 1734, 1628, 1455, 1377, 1247, 1188, 1099, 1022, 808, 630.

HRMS: (CI) Calcd. for $C_{35}H_{47}O_7$ $[M+H]^+$: 579.3323, Found: 579.3330.

O
Me
Me
OBn
Me
Me
O
Me
O
O
O
PMP
Me
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: GX-XVI-2-s2pul_H1
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047111 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-2_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*1S,2R,5R,6S,7S,8R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione



13a

A solution of (*1S,2R,5R,6S,7S,8R,12S,13S,15S,17R,E*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-4,14,16-trioxabicyclo[11.3.1]heptadec-10-ene-3,9-dione (12.3 mg, 0.0213 mmol, 100 mol%) in THF:MeOH (0.9 mL, 1:1, 0.025 M) was cooled to 0 °C. To this solution was added $NiCl_2$ hexahydrate (2.5 mg, 0.0106 mmol, 50 mol%) in one portion. The reaction was stirred at 0 °C for 10 min, and $NaBH_4$ (1.6 mg, 0.0425 mmol, 200 mol%) was added in three portions. The reaction mixture was stirred for another 1 hr. Purification by column chromatography (SiO_2; ethyl acetate: hexanes, 1:20) gave the title compound (11.1 mg, 0.0191 mmol) as a colorless oil in 90% yield, > 10:1 regioselectivity.

TLC (SiO_2): R_f = 0.31 (ethyl acetate:hexanes, 1:9).

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 7.41-7.28 (m, 5H), 6.93-6.90 (m, 2H), 5.64-5.61 (m, 2H), 4.34 (d, *J* = 9.2 Hz, 1H), 4.23 (d, *J* = 9.2 Hz, 1H), 3.97 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 3.81-3.78 (m, 2H), 3.00-2.92 (m, 1H), 2.90-2.80 (m, 2H), 2.41-2.33 (m, 1H), 2.26-2.19 (m, 1H), 2.01 (q, *J* = 6.8 Hz, 1H), 1.87-1.69 (m, 2H), 1.56-1.46 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.4, 175.2, 160.0, 137.5, 131.0, 128.6, 128.4, 127.9, 127.5, 113.6, 102.7, 84.3, 80.9, 80.2, 75.9, 72.8, 55.3, 44.9, 41.6, 40.8, 39.5, 35.0, 32.5, 30.3, 26.2, 15.8, 13.4, 10.5, 10.1, 9.2, 6.5.

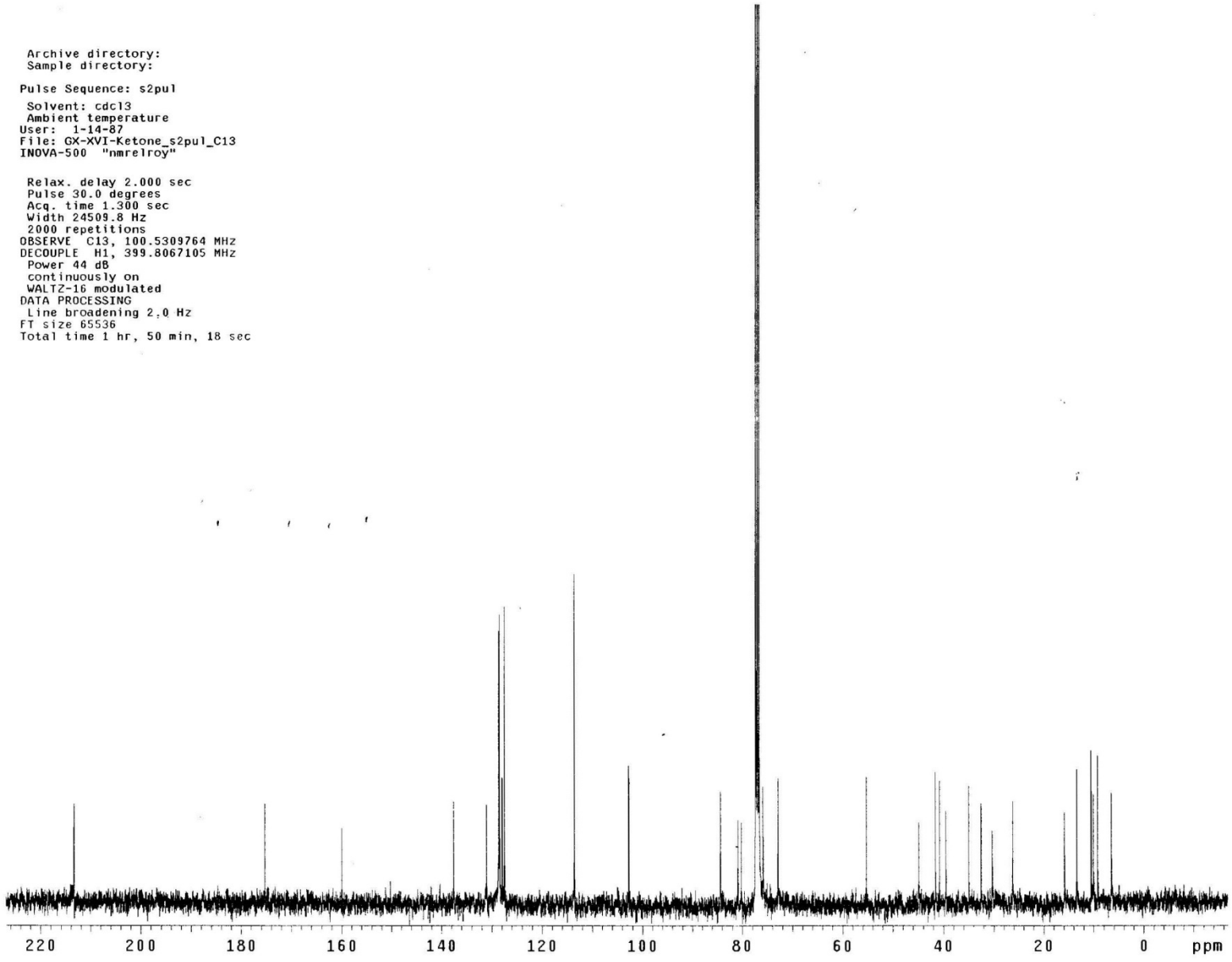
$[\alpha]_D^{27}$ = -39.0 (c = 0.16, CH_2Cl_2).

FTIR (neat): υ 2972, 2940, 2923, 1730, 1717, 1366, 1214, 1099, 765, 729, 663.

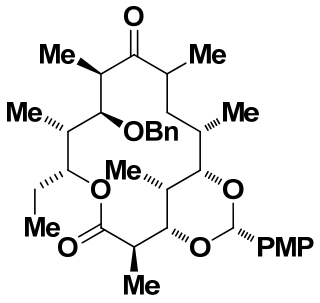
HRMS: (CI) Calcd. for $C_{35}H_{48}O_7$ $[M]^+$: 580.3401, Found: 580.3400.

O
Me
Me
OBn
Me
Me
Me
O
O
Me
O
O
PMP
Me

Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: GX-XVI-Ketone_s2pul_H1
INOVA-500 "rmarelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047111 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-Ketone_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
2000 repetitions
OBSERVE C13, 100.5309764 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 1 hr, 50 min, 18 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*1S,2R,5R,6S,7S,8R,10R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,10,12,17-hexamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione



14

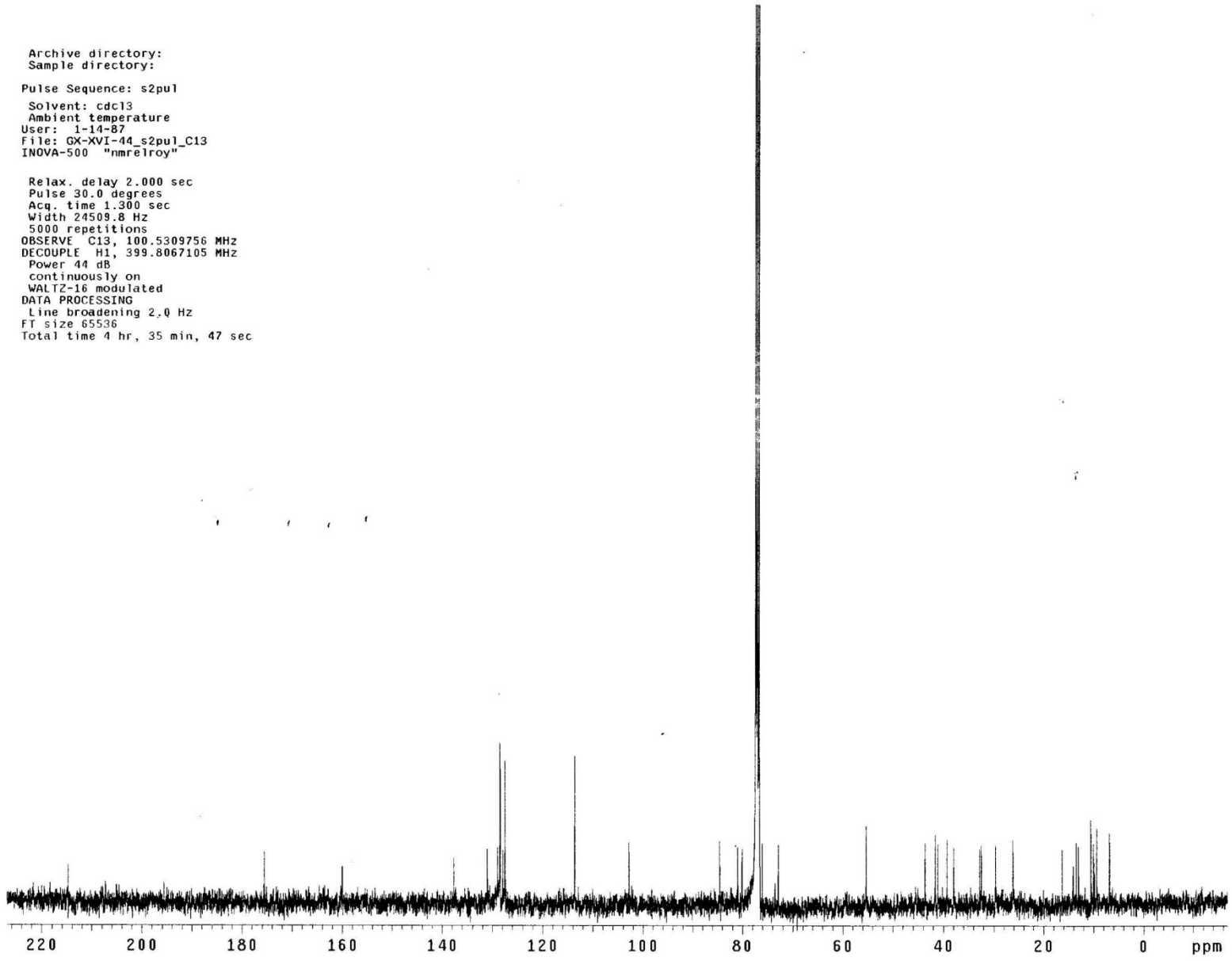
A solution of (*1S,2R,5R,6S,7S,8R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,12,17-pentamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione (16.5 mg, 0.0284 mmol, 100 mol%) in THF (0.8 mL, 0.05 M) was cooled to -78 °C. To this solution was added LHMDS (0.071 mL, 1.0 M, 0.071 mmol, 250 mol%) dropwise. The reaction was stirred at -40 °C for 30 min, and recooled to -78 °C. Freshly distilled MeI (20.2 mg, 0.142 mmol, 500 mol%) was added to the reaction and the mixture was warmed to room temperature slowly. pH = 7 buffer solution was added and the mixture was extracted with ethyl ether (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2: ethyl acetate:hexanes, 1:15) to give the title compound (14.4 mg, 0.024 mmol) as a colorless oil in 85% yield, mixture of diastereomers.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:9).

FTIR (neat): υ 2971, 2934, 2034, 1701, 1618, 1518, 1454, 1305, 1248, 1173, 983, 891, 830, 809, 726, 719, 667.

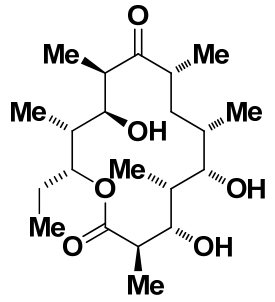
HRMS: (CI) Calcd. for $C_{36}H_{51}O_7$ $[M+H]^+$: 595.3636, Found: 595.3636.

O
Me
Me
Me
OBn
Me
Me
O
Me
O
O
O
PMP
Me
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: GX-XVI-44_s2pul_H1
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
64 repetitions
OBSERVE H1, 399.8047113 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 6 min, 36 sec
12
10
8
6
4
2
-0
ppm


Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: GX-XVI-44_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
5000 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 4 hr, 35 min, 47 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

6-Deoxyerythronolide B:

(*3R,4S,5R,6S,7S,9R,11R,12S,13R,14R*)-14-ethyl-4,6,12-trihydroxy-3,5,7,9,11,13-hexamethyloxacyclotetradecane-2,10-dione



6-Deoxyerythronolide B

An oven-dried sealed tube under an atmosphere of H_2 was charged with (*1S,2R,5R,6S,7S,8R,10R,12S,13S,15S,17R*)-7-(benzyloxy)-5-ethyl-15-(4-methoxyphenyl)-2,6,8,10,12,17-hexamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione (15 mg, 0.025 mmol, 100 mol%), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 40 mol%) and *i*-propanol (0.5 mL, 0.05 M). The mixture was allowed to stir at room temperature under balloon pressure of H_2 overnight. Hexane was added when reaction was finished. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:5) provides the title compound (9.0 mg, 0.0233 mmol) as a colorless viscous oil which solidified on standing in 93% yield.

TLC (SiO_2): R_f = 0.34 (ethyl acetate:hexanes, 1:3).

^{1}H NMR(500 MHz, $CDCl_3$): δ 5.15 (ddd, J = 9.5, 4.0, 1.5 Hz, 1H), 4.02-4.00 (m, 1H), 3.93 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.86 (dd, *J* = 4.5, 1.0 Hz, 1H), 3.68 (ddd, *J* = 10.5, 5.0, 2.5 Hz, 1H), 2.84 (d, *J* = 3.0 Hz, 1H), 2.82-2.74 (m, 1H), 2.66-2.50 (m, 1H), 2.08-2.00 (m, 1H), 2.01 (d, *J* = 3.5 Hz, 1H), 1.86 (qd, *J* = 6.5, 1.5 Hz, 1H), 1.84-1.79 (m, 1H), 1.74-1.72 (m, 1H), 1.70-1.65 (m, 1H), 1.55-1.50 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.28-1.21 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.4, 178.4, 79.5, 76.5, 76.3, 70.9, 44.0, 43.4, 40.6, 39.3, 37.7, 37.5, 35.6, 25.4, 16.6, 14.8, 13.3, 10.6, 9.2, 6.9, 6.2.

$[\alpha]_D^{22}$ = -34.1 (c = 0.41, CH_2Cl_2).

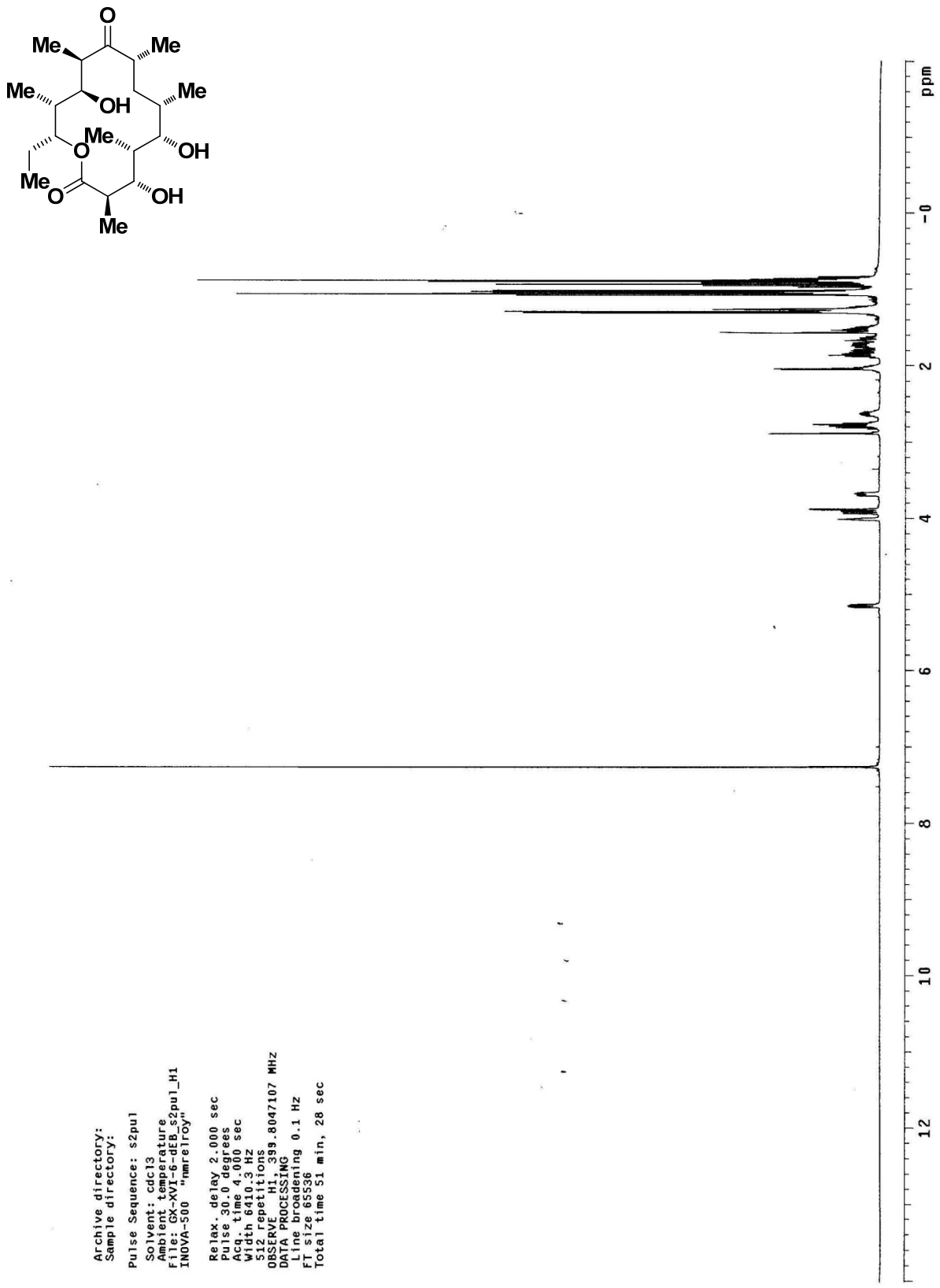
.

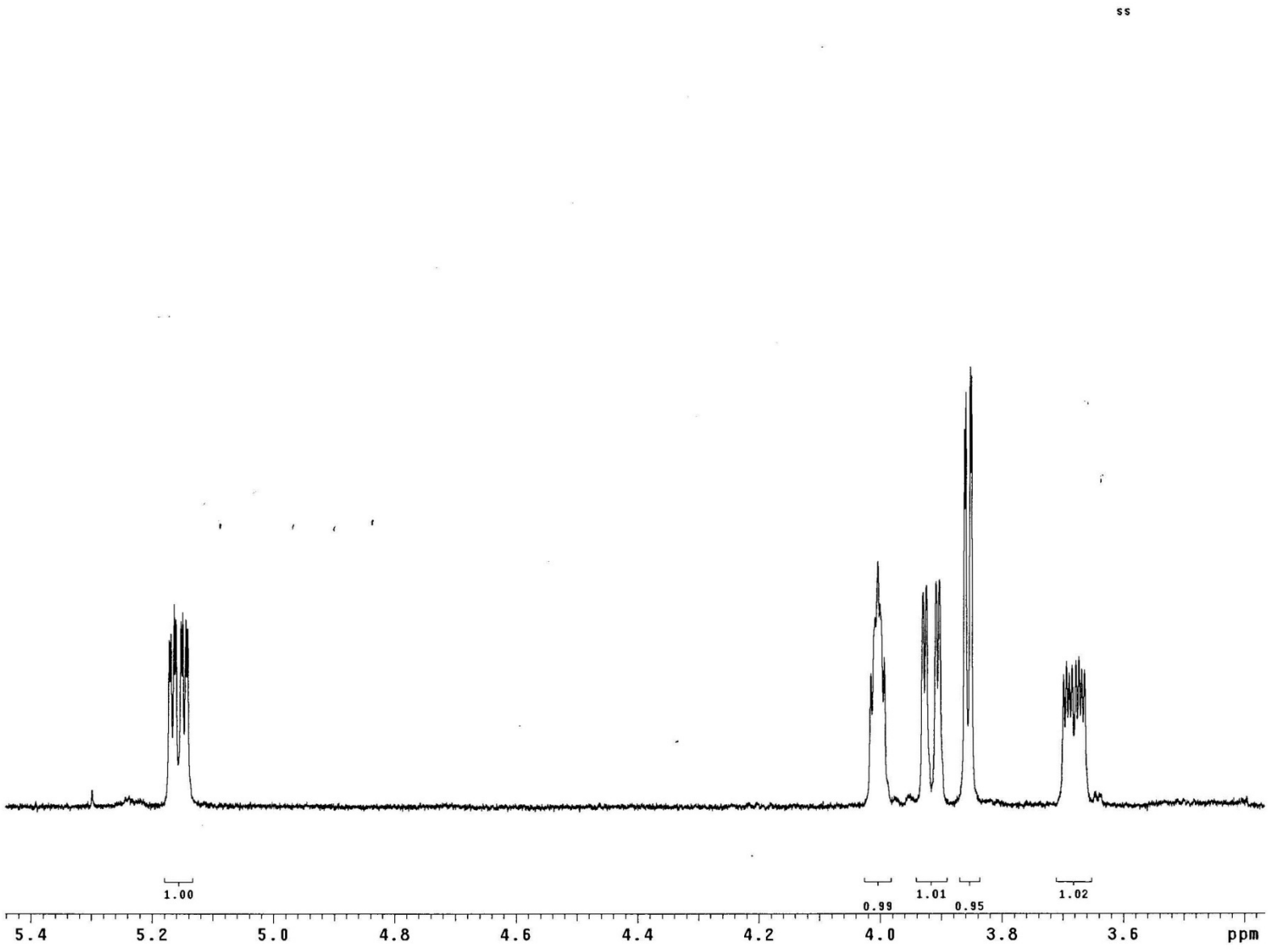
FTIR (neat): υ3363, 2973, 1700, 1640, 1458, 1373, 1185, 1097, 940, 905, 727, 580.

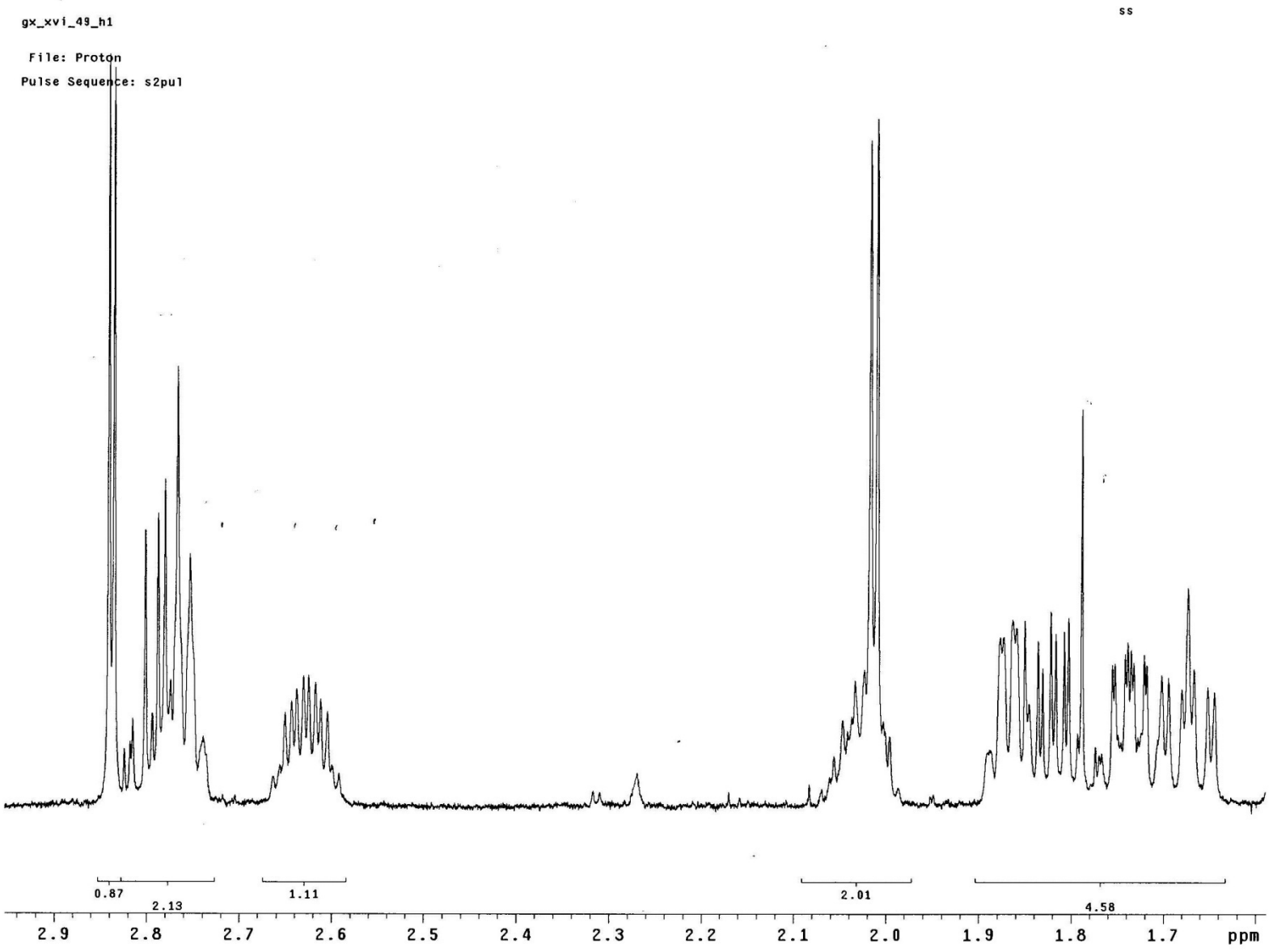
HRMS: (CI) Calcd. for $C_{21}H_{38}O_6Na$ $[M+Na]^+$: 409.25606, Found: 409.25614.

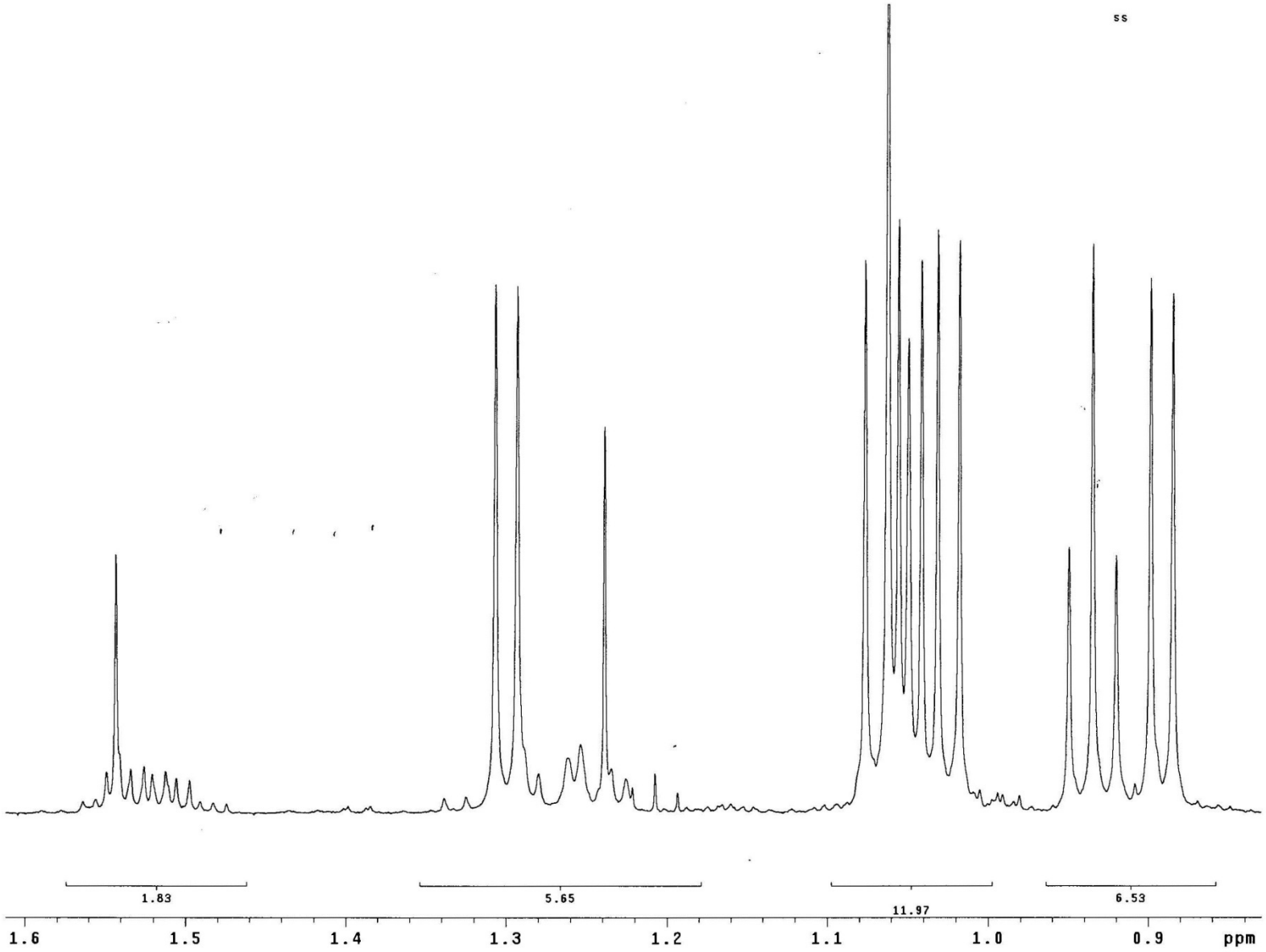
The spectroscopic properties of this compound were consistent with the data available in the literature.[2]

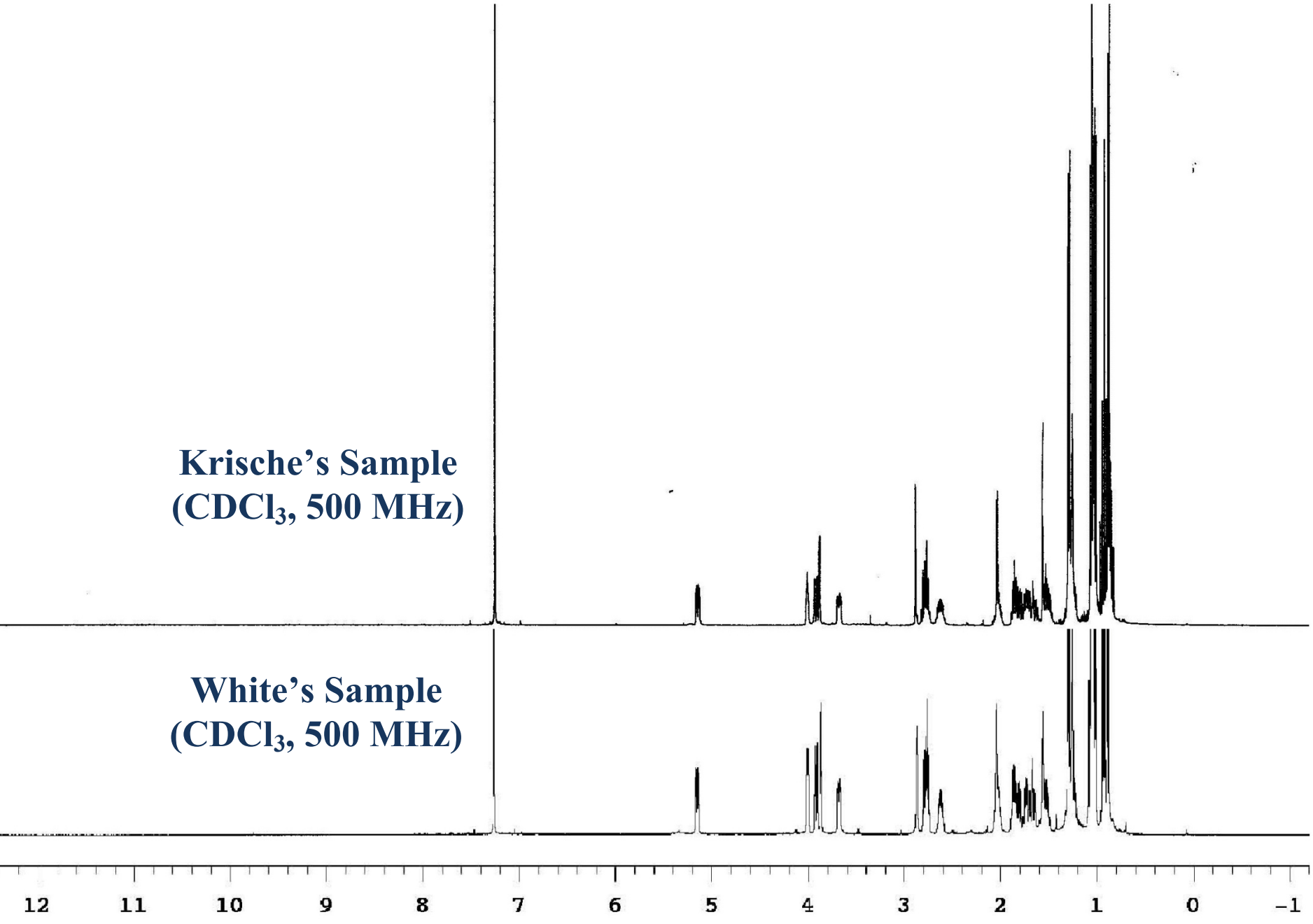
[2] (a) Evans, D. A.; Kim, A. S. *Tetrahedron Lett.* **1997**, *38*, 53. (b) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921. (c) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547.

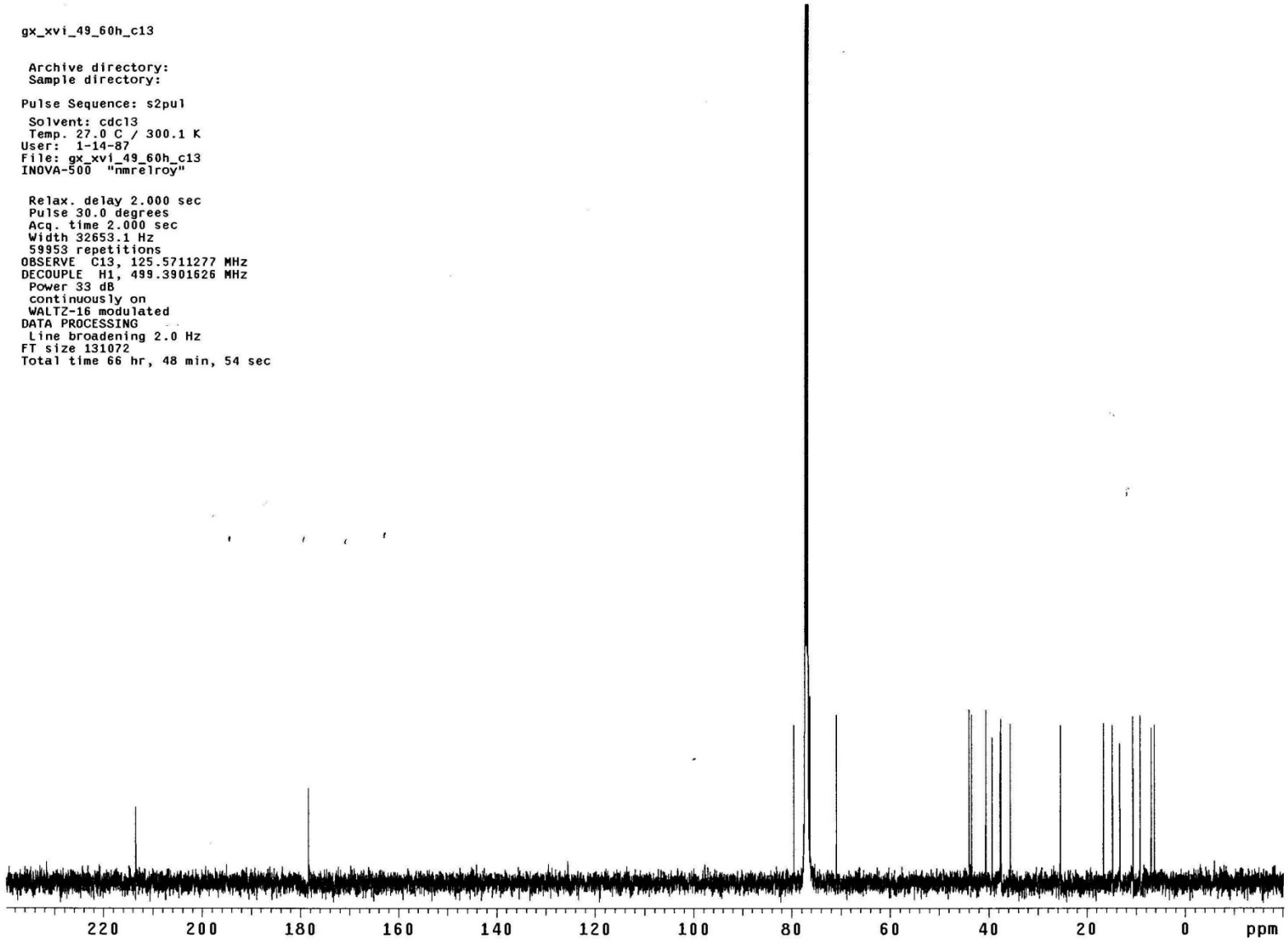

Me
Me
Me
OH
Me
Me
O
OH
Me
O
OH
Me
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
File: GX-XVI-6-dEB_S2pul_H1
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 4.000 sec
Width 6410.3 Hz
512 repetitions
OBSERVE H1, 399.8047107 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 51 min, 28 sec
12
10
8
6
4
2
-0
ppm


ss
1.00
0.99
1.01
0.95
1.02
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
ppm


gx_xvi_49_h1
File: Proton
Pulse Sequence: s2pul
ss
0.87
2.13
1.11
2.01
4.58
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
ppm


ss
1.83
5.65
11.97
6.53
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
ppm

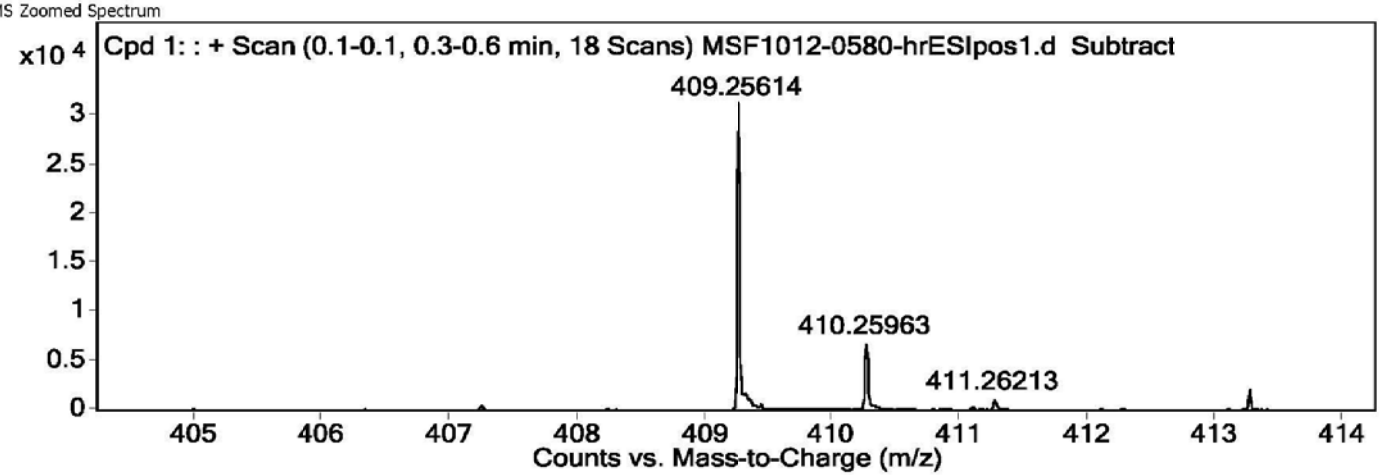

Krische's Sample
(CDCl3, 500 MHz)
White's Sample
(CDCl3, 500 MHz)
12
11
10
9
8
7
6
5
4
3
2
1
0
−1


gx_xvi_49_60h_c13
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 27.0 C / 300.1 K
User: 1-14-87
File: gx_xvi_49_60h_c13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 2.000 sec
Width 32653.1 Hz
59953 repetitions
OBSERVE C13, 125.5711277 MHz
DECOUPLE H1, 499.3901626 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 66 hr, 48 min, 54 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Target Compound Screening Report

Data File	MSF1012-0580-hrESIpos1.d	**Sample Name**	MSF1012-0580	**Comment**	GX-6-dEB
Position	P1-B9	**Instrument Name**	US10252005	**User Name**	
Acq Method	DualESIposMeOH_gt250_vcap3000.m	**Acquired Time**	11/2/2012 2:55:31 PM	**DA Method**	FindByFormula_22Nov2011.m

MS Zoomed Spectrum



MS Spectrum Peak List

Obs. m/z	Calc. m/z	Charge	Abund	Formula	Ion/Isotope	Tgt Mass Error (ppm)
409.25614	409.25606	1	32141.7	C21H38NaO6	(M+Na)+	0.19
410.25963	410.25948	1	6974.8	C21H38NaO6	(M+Na)+	0.37
411.26213	411.26207	1	1103.3	C21H38NaO6	(M+Na)+	0.16
412.26739	412.26474	1	172.8	C21H38NaO6	(M+Na)+	6.41

--- End Of Report ---

Comparison of ^{1}H NMR for Synthetic 6-Deoxyerythronolide B

Proton#	Evans (CDCl3, 400 MHz)	White (CDCl3, 500 MHz)	Krische (CDCl3, 500 MHz)
1	5.14 (ddd, 9.6, 4.0, 1.1)	5.15 (ddd, 9.6, 4.0, 1.0)	5.15 (ddd, 9.5, 4.0, 1.5)
2	3.99 (ddd, 4.8, 3.4, 1.7)	4.00 (m)	4.02-4.00 (m)
3	3.91 (ddd,10.3, 2.8, <1.0)	3.92 (d, 10.5)	3.93 (dd, 10.5, 3.0)
4	3.87 (d, 4.4)	3.87 (d, 4.0)	3.86 (dd, 4.5, 1.0)
5	3.67 (ddd, 10.2, 4.4, 2.0)	3.68 (ddd, 10.0, 4.5, 2.0)	3.68 (ddd, 10.5, 5.0, 2.5)
6	3.02 (d, 2.8)	2.87 (d, 1.5)	2.84 (d, 3.0)
7	2.78 (m)	2.78 (m)	2.82-2.74 (m)
8	2.62 (m)	2.63 (m)	2.66-2.50 (m)
9	2.25 (d, 3.4)	2.05-2.00 (m)	2.08-2.00 (m)
10	2.02 (m)		2.01 (d, 3.5)
11	1.86 (qd, 6.2, 1.7)	1.89-1.79 (m)	1.86 (qd, 6.5, 1.5)
12	1.82 (m)		1.84-1.79 (m)
13	1.73 (m)	1.75-1.64 (m)	1.74-1.72 (m)
14	1.67 (m)		1.70-1.65 (m)
15	1.51 (m)	1.53 (m)	1.55-1.50 (m)
16	1.29 (d, 6.7)	1.30 (d, 7.0)	1.30 (d, 7.0)
17	1.25 (m)	1.25 (m)	1.28-1.21 (m)
18	1.06 (d, 7.0)	1.07 (d, 7.0)	1.07 (d, 7.0)
19	1.04 (d, 6.4)	1.06 (d, 7.0)	1.06 (d, 6.5)
20	1.04 (d, 7.2)	1.05 (d, 7.0)	1.05 (d, 7.0)
21	1.01 (d, 6.8)	1.02 (d, 6.5)	1.02 (d, 6.5)
22	0.93 (t, 7.3)	0.93 (t, 7.5)	0.94 (t, 7.5)
21	0.88 (d, 7.0)	0.89 (d, 7.0)	0.89 (d, 7.0)

Comparison of ^{13}C NMR for Synthetic 6-Deoxyerythronolide B

Carbon#	White ($CDCl_3$, 125 MHz)	Krische ($CDCl_3$, 125 MHz)
1	213.5	213.4
2	178.4	178.4
3	79.5	79.5
4	76.5	76.5
5	76.3	76.3
6	70.9	70.9
7	43.9	44.0
8	43.4	43.4
9	40.6	40.6
10	39.2	39.3
11	37.7	37.7
12	37.5	37.5
13	35.6	35.6
14	25.4	25.4
15	16.6	16.6
16	14.8	14.8
17	13.2	13.3
18	10.6	10.6
19	9.2	9.2
20	6.9	6.9
21	6.2	6.2