SYNOPSIS

The thesis entitled **"Total synthesis of fluvirucinine A_1, formal synthesis of amphidinin B and first stereoselective total synthesis of gallicynoic acids G and H"** is divided into three chapters.

Chapter I: Total synthesis of Fluvirucinine A_1

This chapter dealt with the total synthesis of fluvirucinine A_1 by a combination of chiron approach and asymmetric synthesis.

Fluvirucins A_1, A_2, B_1, B_2, B_3, B_4 and B_5 were isolated by Naruse *et al.*[1] in 1991 from the fermentation broth of actinomycete strains. These are 14-membered macrolactam antibiotics and potent inhibitors of influenza A virus type A strain in Madin Darby Canine Kidney (MDCL) cells.[1]

In addition to strong activity against influenza A virus these antibiotics have inhibitory activity against certain gram positive bacteria, anaerobic bacteria and fungi.[1] Later the structure and stereochemistry of fluvirucins was established by Naruse *et al.*[2,3] in 1991 based on spectroscopic analysis and chemical transformations.

Fluvirucinine A_1 **1** is aglycone of fluvirucin A_1. The absolute stereochemistry of 14-membered macrolactam fluvirucinine A_1 **1** was established[3] as 2*R*, 3*S*, 6*R*, 10*S*. It has potent inhibitory activity against influenza A virus.[2]

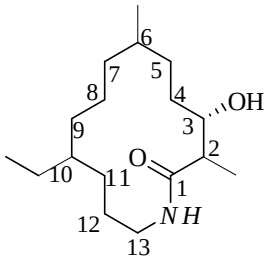
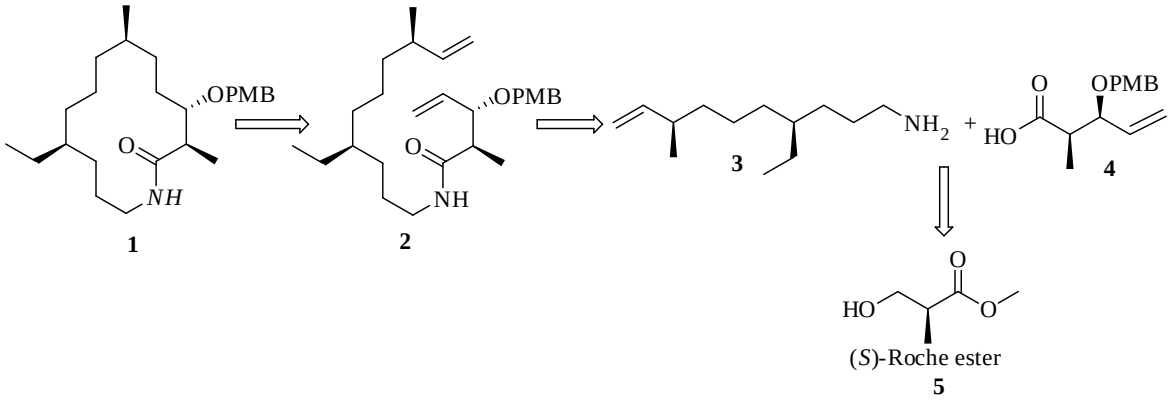


Figure 1: Fluvirucinine A_1 **1**

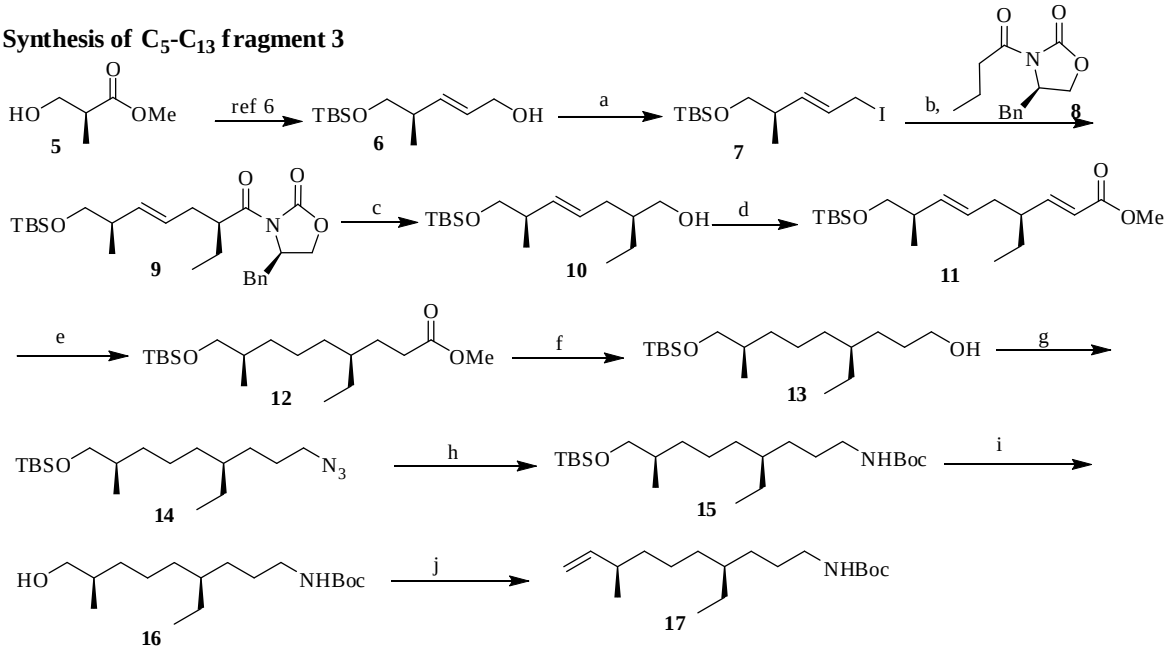
The retrosynthetic strategy envisioned for **1** is delineated in Scheme 1. Fluvirucinine A_1 **1** could be realized by ring-closing metathesis[4,5] of *bis*-olefin **2** followed by hydrogenation, which inturn could be envisaged from fragments **3** and **4**. Both fragments **3** and **4** inturn could be readily accessed from the commercially available (*S*)-Roche ester **5**.



Scheme 1: Retrosynthetic analysis of fluvirucinine A_1 **1**

The synthesis of **3** commenced with known allylic alcohol **6**[6] that was easily accessed in four steps from **5** (Scheme 2). Treatment of **6** with imidazole, triphenyl phospine and iodine in THF produced allyl iodide **7** in 76% yield and set the stage for highly diastereoselective Evans asymmetric alkylation[7] to install the C_{10} ethyl group with the desired stereochemistry.

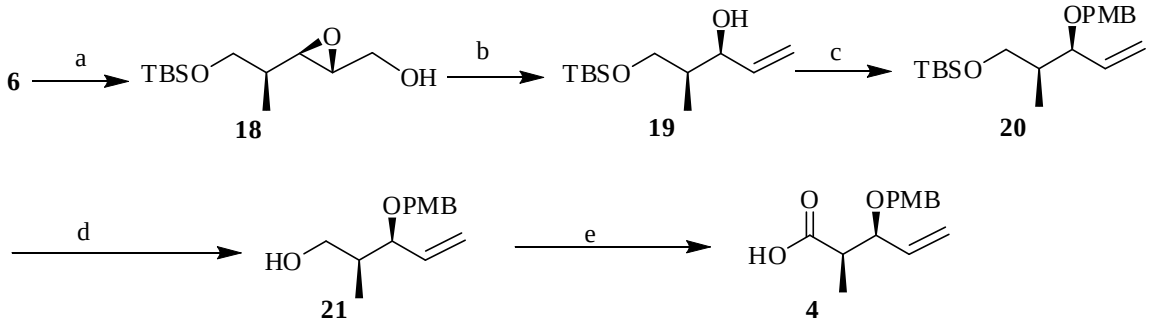
Synthesis of C_5-C_{13} fragment 3



Scheme 2: *Reagents and conditions*: (a) PPh_3, I_2, imidazole, THF, 0.5h, 76%; (b) **8**, LiHMDS, -78 °C, 1h, **7** after 6h, -20 °C, 14h; (c) $NaBH_4$, MeOH, 0 °C to r.t., 1h, 81%; (d) (i) IBX, CH_2Cl_2, DMSO, 0 °C to r.t., 4h; (ii) Ph_3P=CHCOOMe, C_6H_6, reflux, 4h, 85% (over two steps) (e) H_2, Pd/C, EtOAc, 4h, 92%; (f) DIBAL-H, CH_2Cl_2, -40 °C, 1h, 84%; (g) (i) TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 3h; (ii) NaN_3, DMF, 80 °C, 4h, 85% (over two steps); (h) (i) H_2, Pd/C, EtOAc, 9h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 1h, 83% (over two steps); (i) TBAF, THF, 3h, 78%; (j) (i) $(COCl)_2$, DMSO, Et_3N, -78 °C, 1h (ii) Ph_3PMeI, KO^tBu, THF, -10 °C to r.t, 4h, 65% (over two steps).

Accordingly, *N*-butyryl oxazolidinone **8** was alkylated with allylic iodide **7** to afford the corresponding ethylated product **9** in 86% yield and in high diastreoselectivity. An excess of enolate (1.6 eq) was essential to achieve completion of the reaction. The diastereoselectivity was assigned by ^{1}H and ^{13}C NMR of crude reaction mixture. Next, reductive cleavage ($NaBH_4$/MeOH/0 ^{o}C to r.t./1h) of the chiral auxiliary in **9** afforded **10** (81%). Alcohol **10** on oxidation with IBX furnished the corresponding aldehyde, which was exposed to Wittig olefination to afford **11** (85% yield over two steps). Compound **11** was subjected to catalytic hydrogenation (Pd/C in EtOAc) under hydrogen atmosphere to gave the corresponding saturated ester **12** (92%), which upon treatment with DIBAL-H in CH_2Cl_2 gave alcohol **13** (84%). Alcohol **13** was converted to its corresponding tosylate ($TsCl/Et_3N/CH_2Cl_2$/0 ^{o}C to r.t./3h), which was subsequently transformed into the corresponding azide **14** (85%, over two steps) under conventional conditions (NaN_3/DMF/80 ^{o}C/4h). The resulting azide **14** was converted to *N*-Boc derivative **15** in 83% yield by a two-step process, firstly reduction of the azide to the amine *via* hydrogenation (H_2-Pd/C/EtOAc/r.t./9h) followed by the bocylation reaction {$(Boc)_2O/Et_3N/CH_2Cl_2$/0 ^{o}C to r.t./1h}. Desilylation of **15** with TBAF in THF afforded alcohol **16** (78%). Alcohol **16** on oxidation under Swern conditions followed by one carbon Wittig olefination furnished the olefin **17** in 65% yield over two steps.

Synthesis of C_1-C_4 fragment 4

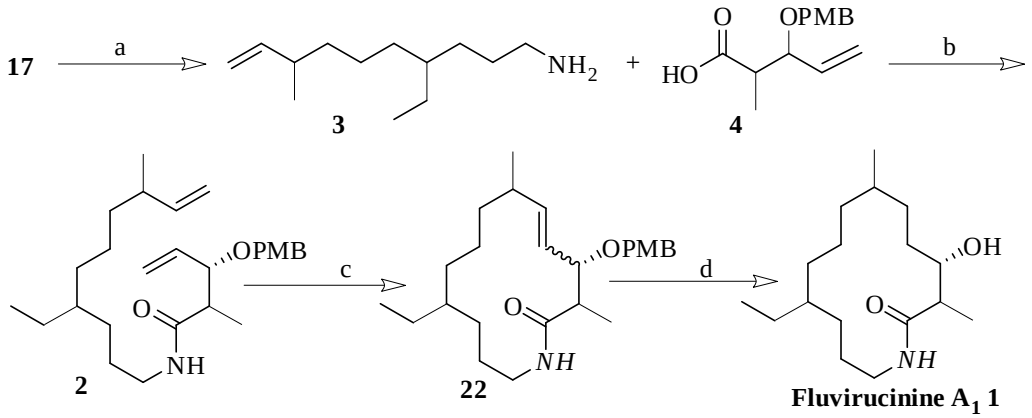


Scheme 3: *Reagents and conditions:* (a) (-)-DIPT, $Ti(O^{i}Pr)_4$, CHP, CH_2Cl_2, -20 ^{o}C, 5h, 86%; (b) (i) PPh_3, I_2, imidazole, THF, 0.5h; (ii) Zn, EtOH, 80 ^{o}C, 3h, 78% (over two steps) (c) NaH, PMBBr, THF, 0 ^{o}C to r.t., 14h, 74%; (d) TBAF, THF, 3h, 79%; (e) (i) $(COCl)_2$, DMSO, Et_3N, -78 ^{o}C, 1h; (ii) $NaClO_2$, NaH_2PO_4. $2H_2O$, 2-Methyl-2-butene, ^{t}BuOH (1:3), 0 ^{o}C to r.t., 12h, 75% (over two steps).

As depicted in Scheme 3, the synthesis of acid **4** began from **6**[6], which on Sharpless asymmetric epoxidation[6] with (-)-DIPT, $Ti(O^iPr)_4$ and CHP in CH_2Cl_2 at -20 °C afforded epoxy alcohol **18**. The alcohol **18** on treatment with imidazole, PPh_3 and I_2 in THF converted into iodo-derivative, which was treated with Zn in ethanol[8] to give allylic alcohol **19** (78% yield over two steps). Later, alcohol **19** was protected as its PMB ether **20** (NaH/PMBBr/THF/ 0 ^oC to rt/14h, 74%). Silyl deprotection of **20** in presence of TBAF in THF afforded primary alcohol **21** (79%). The oxidation of the resultant primary alcohol **21** under Swern conditions furnished the aldehyde, which on subsequent oxidation[9] ($NaClO_2/NaH_2PO_4$/2-methyl-2-butene/12h) afforded acid **4** (75%).

Compound **17** was treated with TFA in CH_2Cl_2 to liberate the free amine **3** which was immediately used for the amidation reaction (Scheme 4). With the requisite fragments **3** and **4** in hand, the coupling reaction was undertaken.

Synthesis of 1



Scheme 4: *Reagents and conditions:* (a) TFA, CH_2Cl_2, DIPEA, 0 ^oC, 15 min; (b) EDCI, HOBT, DIPEA, CH_2Cl_2, 98% (over two steps) (c) Grubbs-II, CH_2Cl_2, 45 ^oC,12h, 79%; (d) Pd/C, EtOAc, 3h, 89%.

Gratifyingly, the reaction proceeded smoothly by treating the acid **4** with EDCI/HOBT/DIPEA followed by addition of amine **3** to afford the desired coupled product **2** in 98% yield. The resulting diene **2** was exposed to the RCM reaction using Grubbs-II catalyst in refluxing dichloromethane to produce macrolactam **22** (79%) as an *E/Z* mixture. Since the isomeric status was irrelevant, no attempts were made to purify compound **22** into separate entities. Finally, fluvirucinine A_1 **1** was obtained by hydrogen-

nation reaction (H_2-Pd/C-/EtOAc/r.t./3h) wherein both the saturation of the C_4-C_5 olefinic bond and PMB deprotection occurred in one-pot. Spectroscopic data (^{1}H and ^{13}C NMR) and specific rotation of the synthetic material **1** was in good agreement with the reported data in the literature.[1-3]

In summary, a stereoselective synthesis of **1** from the common intermediate **6**,[6] using Evans asymmetric alkylation,[7] Sharpless asymmetric epoxidation,[6] amidation and RCM[4,5] as a key steps in an overall yield of 10.5% was described in this chapter.

Chapter II: Formal synthesis of Amphidinin B

This chapter dealt with the formal synthesis of amphidinin B.

Amphidinin B **23**, a linear polyketide was isolated from the dinoflagellate *Amphidinium* sp. (strain number Y-56) by Kobayashi and co-workers (Figure 2).[10] Amphidinin B **23** showed potent activity against MCF-7 (breast cancer cell line) about 100 times better activity[11] than its cyclic analog amphidinolide T_1.[12] The structure of amphidinin B **23** was elucidated[10] based on spectral techniques COSY, HOHAHA, HMBC. The absolute stereochemistry[10] of Amphidinin B **23** was determined to be 2*R*, 6*R*, 11*S*, 16*S*, 17*S*,19*S* based on Mosher's ester method.

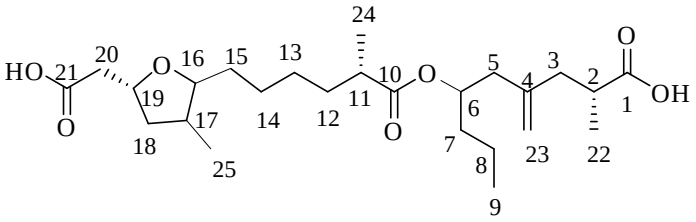
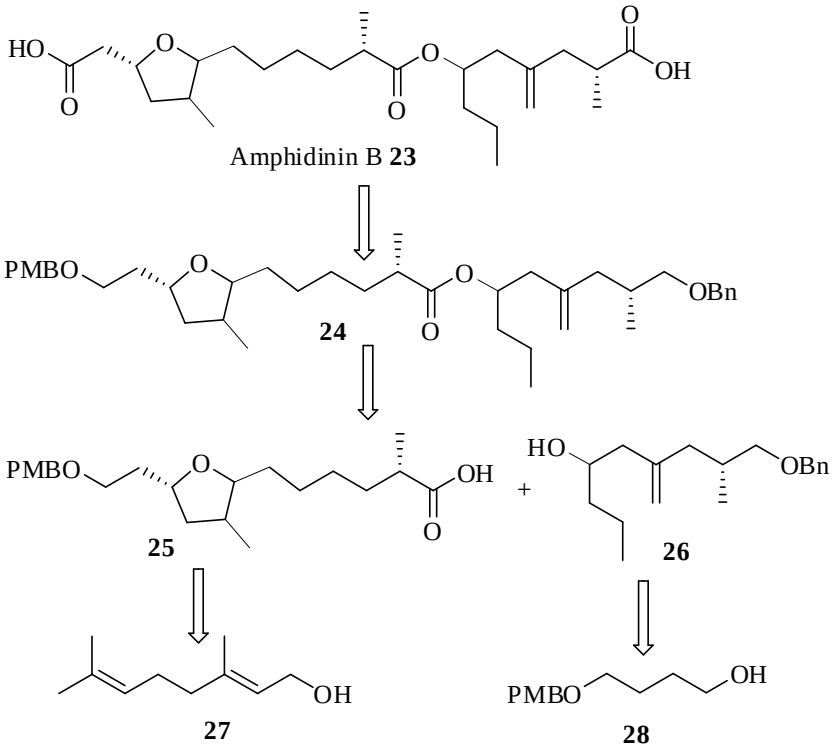


Figure 2: Amphidinin B **23**

Amphidinin B **23** contains a core tri-substituted tetrahydrofuran skeleton with a chiral side-chain at C_{16}. The side chain is embedded with an exo methylene, two branched methyl groups, a propyl and an ester linkage, one carboxyl group while another methyl group adorns at C_{17} on the tetrahydrofuran skeleton. Also, C_{19} is substituted by an ethanoic acid moiety.

As outlined in Scheme 5, the retrosynthetic analysis of **23** reveals that it could be obtained from acid **25** and alcohol **26** by Yamaguchi esterification.[13] Both the fragments

25 and **26** inturn could be accessed from commercially available geraniol **27** and mono-PMB protected 1,4-butane diol **28**[14] respectively by suitable transformations.



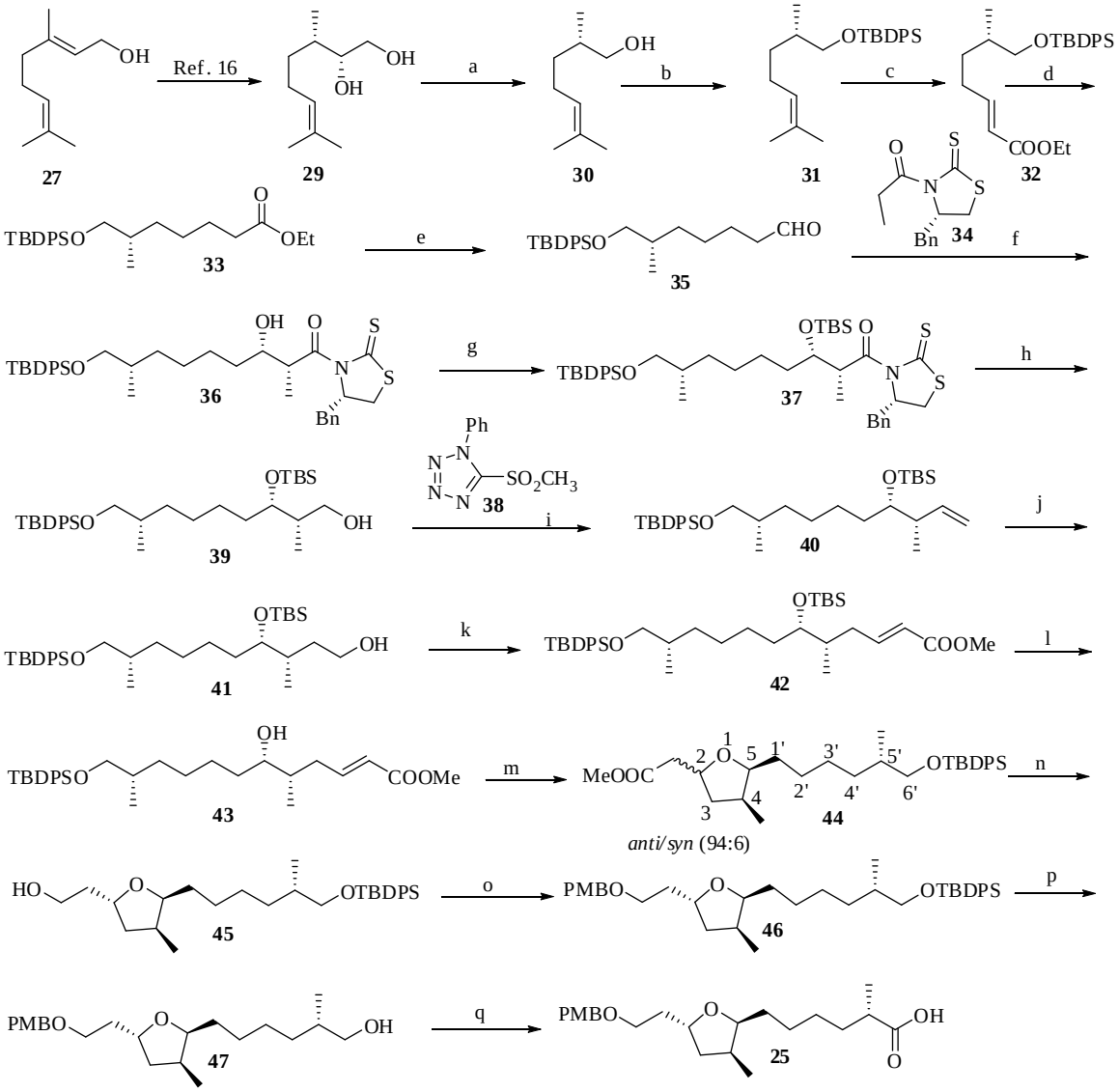
Scheme 5: Retrosynthetic analysis of Amphidinin B **23**

Thus, the synthesis of tetrahydrofuran fragment **25** commenced from known diol **29**[15] which inturn obtained from geraniol **27** (Scheme 6). Oxidative cleavage of **29** with $NaIO_4$ gave the corresponding aldehyde which was reduced ($NaBH_4$/MeOH/0 ^oC) to furnish alcohol **30** (81% yield over two steps). The alcohol **30** was protected as its TBDPS ether by treating with imidazole and TBDPSCl in CH_2Cl_2 to afford **31** in 78% yield.

Ozonolysis of olefin **31** in CH_2Cl_2 followed by Wittig olefination in benzene afforded **32** (74%) as *E*-isomer exclusively. Reduction of the olefin **32** with $NiCl_2.6H_2O/NaBH_4$ furnished the saturated ester **33**[16] (90%). The ester **33** was partially reduced (DIBAL-H/CH_2Cl_2/-78 ^oC/1h) to aldehyde **35** (74%).

Aldehyde **35** was then subjected to non-Evans *syn*-aldol[17] with thiazolidine-2-thione **34**, generating secondary alcohol **36** (75%), whose diastereoselectivity was measured by LCMS (dr, 96.515:3.485) {Column: XDB-C18, acetonitrile:water (70:30), flow rate:1 mL/min, 210 nm, t_r(major) = 1.712 min, t_r(minor) = 3.383 min}. The resulting

Synthesis of C_{10}-C_{21} fragment 25



Scheme 6: *Reagents and conditions*: (a) (i) $NaIO_4$, sat. $NaHCO_3$ soln, acetone:H_2O (5:1), 0 °C, 4h; (ii) $NaBH_4$, MeOH, 0 °C to r.t., 1h, 81% (over two steps); (b) TBDPSCl, imidazole, CH_2Cl_2, r.t., 2h, 78%; (c) (i) O_3, CH_2Cl_2, dimethylsulphide, -78 °C, 15 min; (ii) Ph_3P=CHCOOEt, benzene, reflux, 10 min, 74% (over two steps); (d) $NaBH_4$, $NiCl_2.6H_2O$, MeOH, 0 °C to r.t., 4h, 90%; (e) DIBAL-H, CH_2Cl_2, -78 °C, 1h, 74%; (f) **34**, $TiCl_4$, CH_2Cl_2, 0 °C, 15 min, $^iPr_2EtN$, 20 min, then cooled to -78 °C, **35**, -78 °C to r.t., 2h, 75%; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 82%; (h) $LiBH_4$, MeOH, 0 °C to r.t., 30 min, 74%; (i) (i) $(COCl)_2$, DMSO, Et_3N, -78 °C, 2h, 84%; (ii) **38**, NaHMDS, THF, -78 °C, 30 min., aldehyde, -78 °C to r.t., 4h, 74%; (j) $BH_3.SMe_2$, cyclohexene, THF, 0 °C, 2h, **40**, 0 °C to r.t., 3h, 0 °C, NaOH-H_2O_2, 79%; (k) (i) $(COCl)_2$, DMSO, Et_3N, -78 °C, 2h; (ii) Ph_3P=CHCOOMe, benzene, reflux, 2h, 78% (over two steps); (l) PPTS, MeOH, 0 °C to rt, 12h, 75%; (m) NaOMe, MeOH, -15 °C, 12h, 81%; (n) DIBAL-H, CH_2Cl_2, -40 °C, 1h, 78%; (o) NaH, PMBBr, THF, 0 °C to r.t., 6h, 80%; (p) TBAF, THF, 3h, 0 °C to r.t., 74%; (q) TEMPO, $PhI(OAc)_2$, CH_2Cl_2:H_2O (1:1), 0 °C to r.t., 6h, 84%.

secondary alcohol was protected as silyl ether[18] (TBSOTf/2,6-lutidine/CH_2Cl_2/0 °C) **37** (82%). Reductive cleavage of the auxiliary[19] with $LiBH_4$ afforded alcohol **39** (74%). Alcohol **39** was oxidized under Swern conditions to the corresponding aldehyde, which

was subjected to Julia olefination[20] with 5-(methyl sulfonyl)-1-phenyl-1H-tetrazole **38** using sodium hexamethyldisilazide (NaHMDS) as base in THF at -78 ^{o}C to afford alkene **40**. Alkene **40** underwent hydroboration ($BH_3.SMe_2$/cyclohexene/ H_2O_2/ NaOH) to afford alcohol **41** (79%). The Oxidation of **41** under Swern conditions provided the corresponding aldehyde, which was exposed to Wittig olefination to afford **42** (78% yield over two steps) as the sole product. The coupling constants of the olefin J = 15.4 Hz as a doublet revealed the *E*-isomer. The Oxa-Michael reaction precursor **43** was obtained by selective deprotection of TBS ether[21] with PPTS in MeOH. Oxa-Michael reaction[22] (NaOMe/MeOH/-15 ^{o}C/12h) of **43** afforded **44** (81%) in 94:6 selectivity in favor of *trans*-isomer (major).

The ratio was measured by HPLC. The two diastereoisomers of the compound **44** were separated by preparative HPLC {Column: XDB-C 18, 20% water in acetonitrile**,** flow rate:1 mL/min, 210 nm, t_r(major) = 1.595 min, t_r(minor) = 1.210 min}. The stereochemistry at the newly formed C_2 stereocenter in **44** (major) during Oxa-Michael addition reaction was relatively assigned as '*anti*' to the existing C_5 stereocenter, as evidenced by NOE experiments.

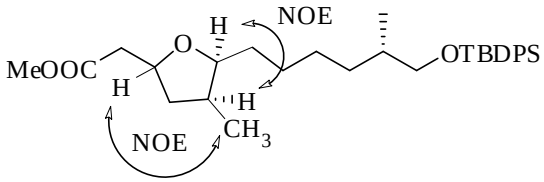


Figure 3: NOE correlations of compound **44**

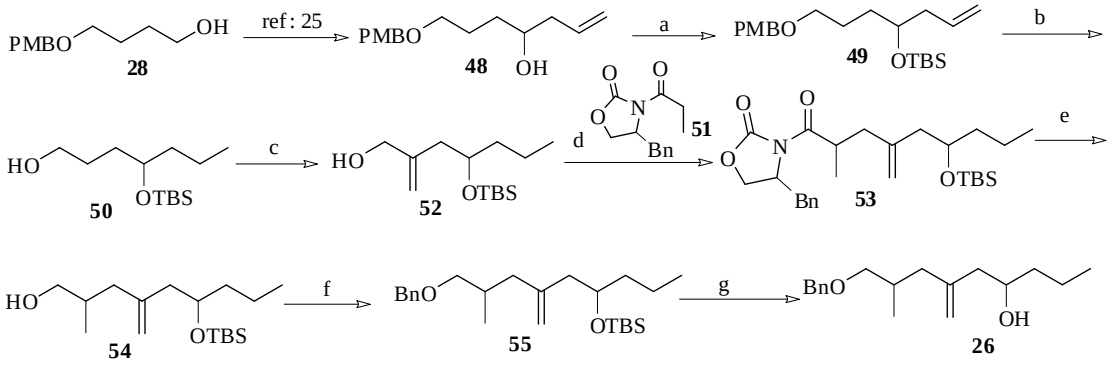
Subsequent transformations on **44** led to **25** which was already reported in the literature;[11] thus, absolute configuration at C_2 was assigned as '*R*'. Accordingly, treatment of ester **44** with DIBAL-H at -40 ^{o}C furnished alcohol **45** (78%), which on reaction with PMBBr (NaH in THF) afforded PMB ether **46** (80%). Desilylation of **46** with TBAF in THF afforded alcohol **47** (74%), which on subsequent oxidation with TEMPO and BAIB[23] furnished acid **25**[11] (84%). The spectroscopic data (^{1}H and ^{13}C NMR) and specific rotation of **25** were in good agreement with the reported data.[11]

The synthesis of fragment **26** commenced with compound **48** which was synthesized as reported in the literature[24] (Scheme 7). Secondary hydroxyl group in **48** was

protected as its *tert*-butyldimethylsilylether **49** (76%). Compound **49** on hydrogenation over Pd/C in EtOAc afforded alcohol **50** (78%). Alcohol **50** underwent Swern oxidation conditions to afford aldehyde, which was subjected to Mannich reaction conditions[25] (CH_2Br_2/Et_2NH/55 ^oC/1.5h/r.t., aldehyde/5 min), followed by DIBAL-H reduction to afford alcohol **52** (66%). Treatment of **52** with imidazole, triphenylphosphine in presence of iodine in THF produced allyl iodide, which on Evans alkylation[7,26] with *N*-propionyl oxazolidinone **51** afforded **53** (75%) as a single isomer as evidenced from ^1H or ^{13}C NMR of crude reaction mixture. Reductive cleavage of the chiral auxiliary using $LiBH_4$ in MeOH furnished alcohol **54** (82%), which was protected (NaH/BnBr/THF/0 ^oC to rt/2h) as its benzyl ether **55** (77%). Deprotection of **55** with TBAF in THF produced **26**[11] (71%).

The spectroscopic data (^1H and ^{13}C NMR) and specific rotation of **26** was in good agreement with the reported data.[11]

Synthesis of C_1-C_9 fragment 26

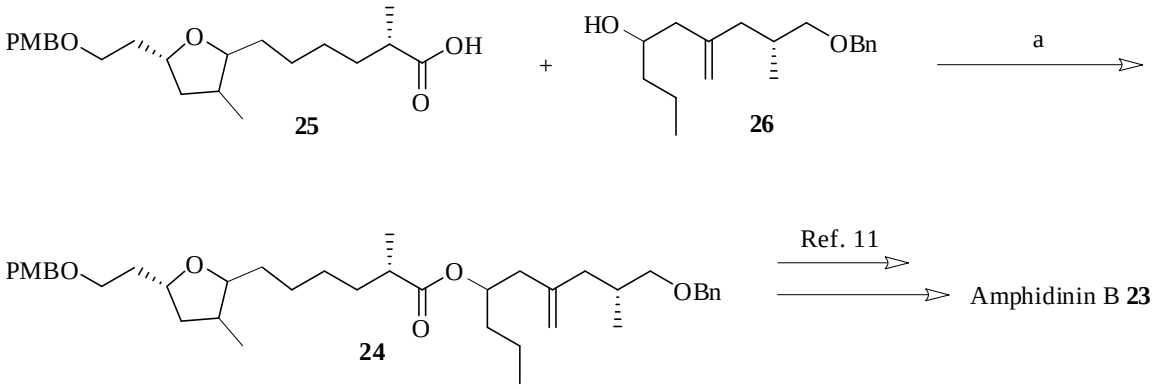


Scheme 7: *Reagents and conditions*: (a) TBSCl, imidazole, CH_2Cl_2, 0 ^oC to r.t., 2h, 76%; (b) H_2, Pd/C, EtOAc, 12h, r.t., 78%; (c) (i) $(COCl)_2$, DMSO, Et_3N, -78 ^oC, 2h, 91%; (ii) Et_2NH, CH_2Br_2, 55 ^oC, 1.5h, r.t., aldehyde, 5 min, 66%; (iii) DIBAL-H, CH_2Cl_2, -40 ^oC, 30 min, 80%; (d) (i) PPh_3, I_2, imidazole, THF, 0 ^oC, 10 min, 73%; (ii) **31**, LiHMDS, -78 ^oC, 1h, allylic iodo compound, -78 to -20 ^oC, 12h, 75% ; (e) $LiBH_4$, MeOH, 0 ^oC to r.t., 30 min, 82%; (f) NaH, BnBr, THF, 0 ^oC to r.t., 2h, 77%; (g) TBAF, THF, 3h, 0 ^oC to r.t., 71%.

With the requisite fragments **25** and **26** in hand**,** coupled the two fragments using an intermolecular Yamaguchi esterification (Scheme 8).[11,13] Esterification of **26** with the mixed anhydride prepared from acid **25** and 2,4,6-trichlorobenzoyl chloride, $^iPr_2NEt$ in THF in the presence of DMAP in toluene afforded **24** (81%). The spectroscopic data (^1H and ^{13}C NMR) and specific rotation of **24** was in good agreement with the reported data.[11]

Thus, synthesis of ester **24** concludes the formal synthesis of **23** since transformation of **24** into **23** was already reported.[11]

Formal synthesis of 23



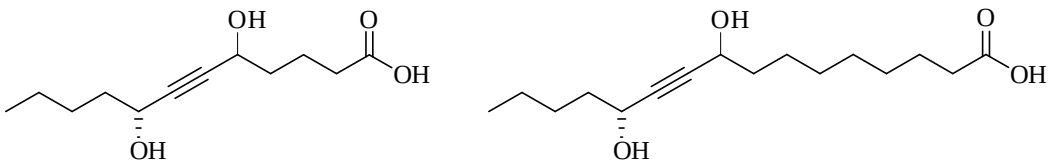
Scheme 8*: Reagents and conditions*: 2,4,6-Cl_3PhCOCl, $^{i}Pr_2$NEt, 10h, DMAP, toluene, 24h, 25 ^{o}C, 81%.

In summary, formal synthesis of **23** from commercially available geraniol **27** and mono-PMB ether of 1,4-butane diol **28**[14] using Sharpless asymmetric epoxidation,[15] non-Evans aldol,[17] Julia olefination,[20] Oxa-Michael,[22] Keck allylation,[24] Mannich reaction,[25] Evans asymmetric alkylation[7,26] and Yamaguchi esterification[11,13] as the key steps was discussed in this chapter.

Chapter III: First stereoselective total synthesis of Gallicynoic acids G and H

This chapter dealt with the total synthesis of gallicynoic acids G and H.

Gallicynoic acids G **56** and H **57** (Figure 4) were isolated from a culture of the basidiomycete *Coriolopsis gallica*[27] along with gallicynoic acids A-F, I, these are acetylenic acids possessing one or more hydroxyl groups and/or olefin moiety. Acetylenic acids dislpay important biological activities such as anticancer, antibacterial, antimicrobial, antitumor, anti HIV and antifungal activities.[28-37]



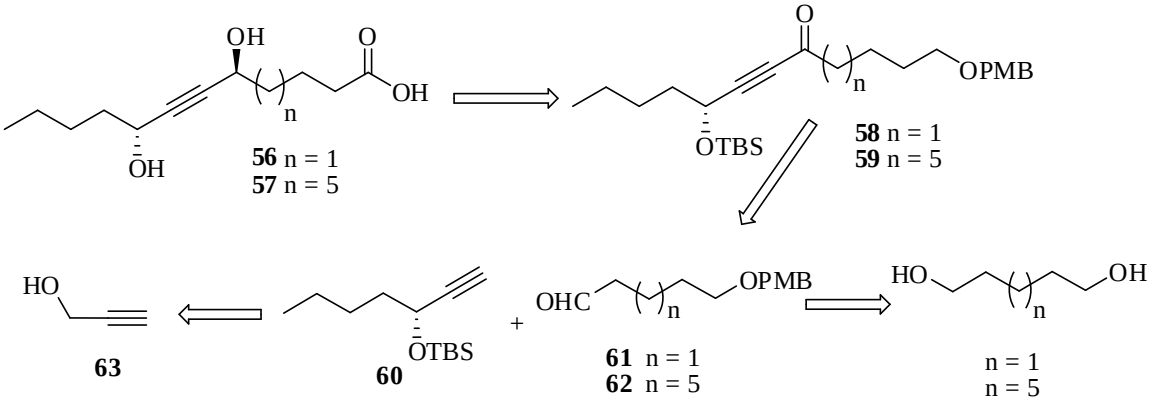
Gallicynoic acid G **56**

Gallicynoic acid H **57**

Figure 4: Gallicynoic acids G **56** and H **57**

The structure and absolute stereochemistry of gallicynoic acids A-I were elucidated based on spectroscopic analysis and chemical transformations.[27]

The retrosynthetic analysis for **56** and **57** is depicted in Scheme 9. It shows that **56** and **57** could be obtained from ynones **58**/**59** by asymmetric reduction. These ynones in turn could be envisaged through a convergent synthesis, from the nucleophilic addition reaction of alkyne **60**[38c, 38d] with aldehydes **61**[39]/**62**[40] and followed by the oxidation of the resultant hydroxy group. The protected hydroxyl alkyne **60** utilized as a common intermediate for the construction of the acetylene part of **56** and **57**.



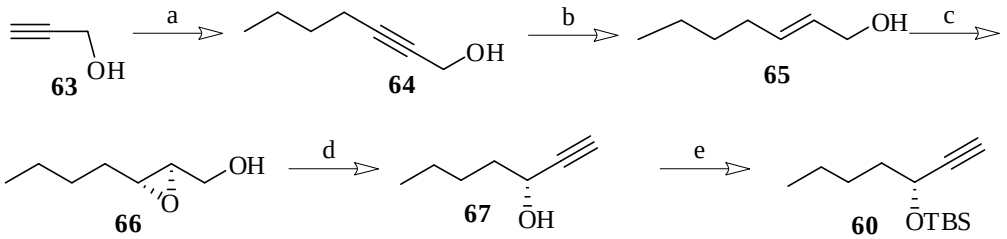
Scheme 9: Retrosynthetic analysis of gallicynoic acids G **56** and H **57**

Accordingly, synthesis of gallicynoic acid G **56** and H **57** commenced with the known protected hydroxyl alkyne **60** (Scheme 10). The enantiopure hydroxy alkyne **60**[39b,39d] was accessed by a modified literature route *via* the Sharpless asymmetric epoxidation protocol and the structure was confirmed by comparing its analytical data with reported values.

To prepare alkyne **60**, propargyl alcohol **63** was subjected to butylation with *n*-butyl bromide in liquid NH_3 and Li at – 33 ^oC to afford **64**[41] and then reduction by $LiAlH_4$ [41b] to give stereochemically pure (*E*)-alkene **65** in 90% yield. Exposure of the ensuing allylic alcohol to Sharples epoxidation [(-)-DIPT/Ti(O^iPr)$_4$/cumene hydroperoxide/CH_2Cl_2/-20 ^oC] furnished epoxy alcohol **66** (90%).[42] Epoxide **66** was chlorinated with Ph_3P in CCl_4 and subjected to base induced double elimination[38b] (LDA/THF) to afford chiral propargylic alcohol **67**[38c,38d] in 65% yield. Further, the free hydroxy group of alkyne **67** was protected as

its *tert*-butyl dimethyl silyl ether **60** (TBSCl/imidazole/CH_2Cl_2/0 ^oC/r.t./2h/78%) (Scheme 10).

Synthesis of fragment 60



Scheme 10: *Reagents and conditions.* (a) Li, liq. NH_3, $Fe(NO_3)_3$, HMPA, THF, C_4H_9Br, -33 ^oC, 6h, 75%; (b) $LiAlH_4$, THF, 0 ^oC- reflux, 5h, 90%; (c) (-)-DIPT, $Ti(^iOPr)_4$, CHP, CH_2Cl_2, -22 ^oC, 5h, 90%; (d) (i) Ph_3P, $NaHCO_3$ (cat), CCl_4, reflux, 2h, 84%, (ii) *n*-BuLi, DIPA, THF, -40 ^oC, 1h, 75%; (e) TBSCl, imidazole, CH_2Cl_2, 0 ^oC - r.t., 2h, 78%.

The construction of the core carbon skeleton of gallicynoic acid G **56** (Scheme 11) was achieved by the alkynylation reaction[43] of the known aldehyde **61** with the silyl protected hydroxy alkyne **60**. The alcohol **68** was obtained as a mixture of diastereoisomers. Asymmetric alkynylation reaction of **60**[43] with **61** under Carreira conditions [44] was not pursued due to poor yield of the product.

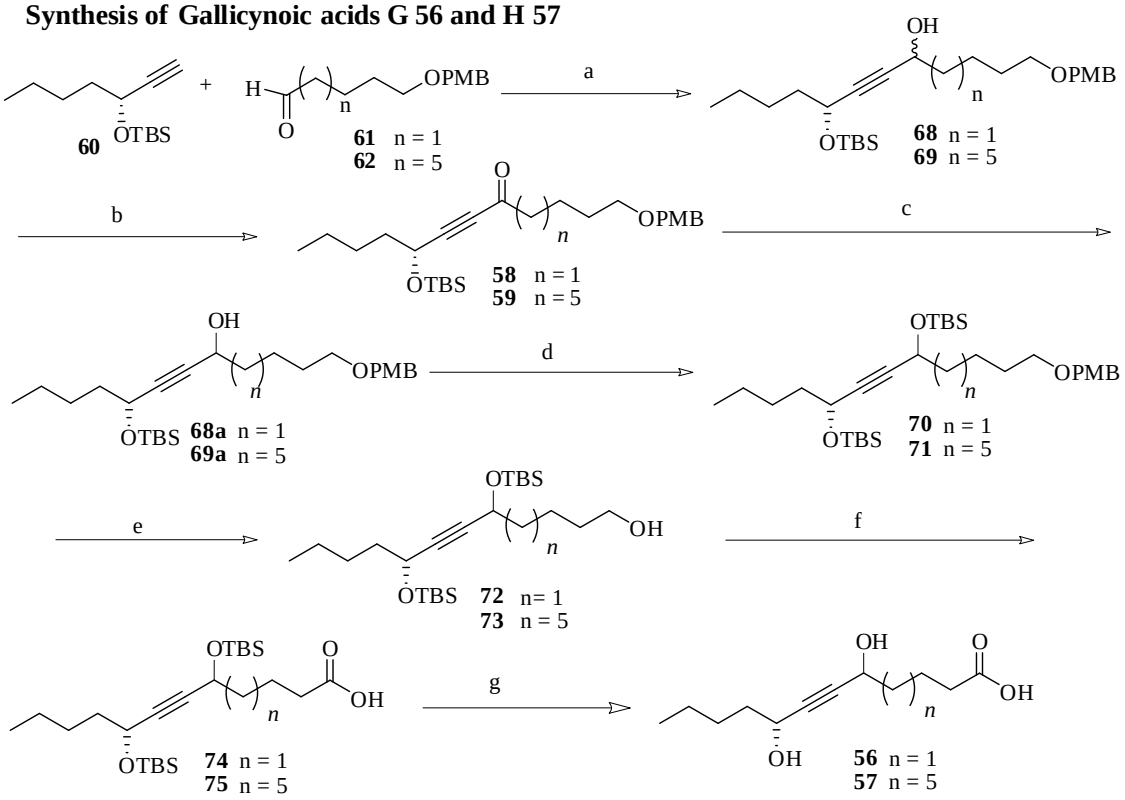
Thus, to achieve the (*S*)-configured hydroxy compound in an optically pure form, hence an oxidation-reduction protocol was resorted. Hence, the hydroxy alkyne **68** was oxidized with IBX to the corresponding ynone **58**. The ^{13}C NMR spectrum of **58** showed signal due to the ketone functionality at 187.4 ppm. At this juncture, the stage was set for crucial asymmetric reduction reaction (Scheme 9). The (*S*)-configured alcohol was obtained *via* asymmetric reduction[45] of **58** using *S*-Corey's catalyst (*S*-CBS catalyst), in 94% yield and in 90% *de* . The diastereoisomeric purity of product **68a** was determined by chiral HPLC analysis {HPLC (Column: Chiral Pak-IC, 3% isopropanol in *n*-hexane, flow rate: 1 mL/min, 210 nm, t_r(major) = 9.922 min, t_r(minor) = 10.809 min}.

The free hydroxy group was protected as its TBS ether (TBSCl/imidazole/CH_2Cl_2/0 ^oC /r.t.) **70**. Oxidative deprotection of PMB group in **70** with DDQ in aq. CH_2Cl_2 produced alcohol **72.** Swern oxidation of alcohol gave the corresponding aldehyde, which on subsequent oxidation with ($NaClO_2$, $NaH_2PO_4.2H_2O$, 2-methyl-2-butene) in *t*-butanol fur-

nished the TBS protected gallicyanoic acid G **74** in 85% yield. The formation of **19** was confirmed by its spectroscopic data. Thus, the ^{1}H NMR spectrum showed a triplet for α-methylene protons at 2.37 ppm and the ^{13}C-NMR spectrum showed a C=O peak at 179.5 ppm.

Finally, the deprotection of the TBS ether with HF (40% aq solution) in MeCN at 0^{o} C for 2h afforded **1** in 61% yield. The $[\alpha]_{D}^{25}$, ^{1}H and ^{13}C NMR data of the synthesized compound **1** matched with the reported data of gallicynoic acid G **56**.[27]

Synthesis of Gallicynoic acids G 56 and H 57



Scheme 11: *Reagents and conditions.* (a) *n*-BuLi, THF, - 78 ºC, 3h, **68** (75%), **69** (70%); (b) IBX, CH_2Cl_2, DMSO, 0 ºC- r.t., 2h, **58** (79%), **59** (77%); (c) 2-methyl (*S*)-CBS oxazaborolidine, $BH_3.SMe_2$, THF, -30 ºC, 1.5h, **68a** (94%), **69a** (91%); (d) TBSCl, imidazole, CH_2Cl_2 , 0 ºC - r.t., 2h, **70** (83%), **71** (81%); (e) DDQ, CH_2Cl_2:H_2O, (19 :1), 0 ºC, 30 min, **72** (76%), **73** (69%); (f) (i) $(COCl)_2$, DMSO, Et_3N, -78 ºC, 1h, 85%; (ii) $NaClO_2$, NaH_2PO_4. $2H_2O$, 2-Methyl-2- butene, ^{t}BuOH (1:3), 0 ºC- r.t., 12h, **74** (85%), **75** (86%); (g) HF (40%), MeCN, 0 ºC, - r.t., 2h, **56** (61%), **57** (58%).

Similarly, **60** and **62** were used as the starting materials and subjected to the same set of transformations (Scheme 11) to give **57** in comparable yields and in 3.7% overall yield. All the products obtained were characterized by Mass, ^{1}H and ^{13}C NMR the spectroscopic data. The data of the synthetic compound **57** were in good agreement with

reported values.[27]

In conclusion, the stereoselective synthesis of gallicynoic acids G **56** and H **57** from a common intermediate, the chiral hydroxy alkyne **60** using asymmetric reduction of ynones **58** and **59** with CBS reagent as the key step was described in this chapter.

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