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Graphical Abstract

Synthesis of the spiroacetal core of the cephalosporolide family of natural products

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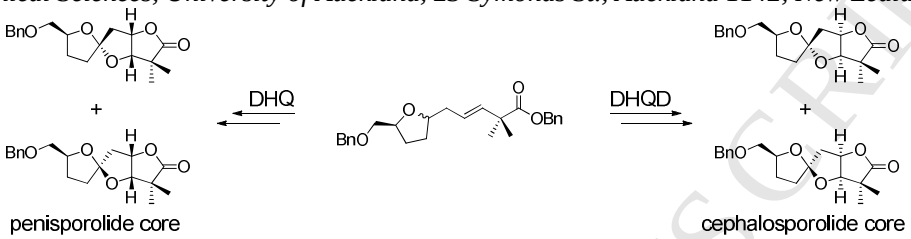

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Synthesis of the spiroacetal core of the cephalosporolide family of natural products

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ABSTRACT

The synthesis of four possible stereoisomers of the spiroacetal core of the natural products cephalosporolides H and I and penisporolides A and B is described. The key steps involve the use of Sharpless asymmetric dihydroxylation to install the desired stereochemistry of the γ-lactone ring and an oxidative radical cyclisation to form the spiroacetal ring system.

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1. Introduction

The 5,5-spiroacetal fused γ-lactone moiety is a structural feature of several biologically relevant natural products, including cephalosporolides E (**1**) and F (**2**),[1-3] cephalosporolides H (**3**) and I (**4**),[4] penisporolides A (**5**) and B (**6**)[5] and ascospiroketal B (**7**)[6] (Figure 1). The simplest members of this family are cephalosporolides E (**1**) and F (**2**), which possess a methyl group at C-9 of the spiroacetal and differ only in the stereochemistry at the C-6 spirocentre. Cephalosporolides H (**3**) and I (**4**) were isolated in 2007 from the marine-derived fungus, *Penicillium* sp.[4] Both cephalosporolides H (**3**) and I (**4**) possess a gem-dimethyl group α to the γ-lactone and differ only in the substituent at C-9. Cephalosporolide H (**3**) has a saturated heptyl side chain whereas cephalosporolide I (**4**) has a four carbon chain bearing a terminal carboxylic acid. Preliminary biological testing on these natural products demonstrated inhibition of the enzymes 3α-hydroxysteroid dehydrogenase and xanthine oxidase, which implicates these natural products as potential anti-inflammatory agents.[7-9]

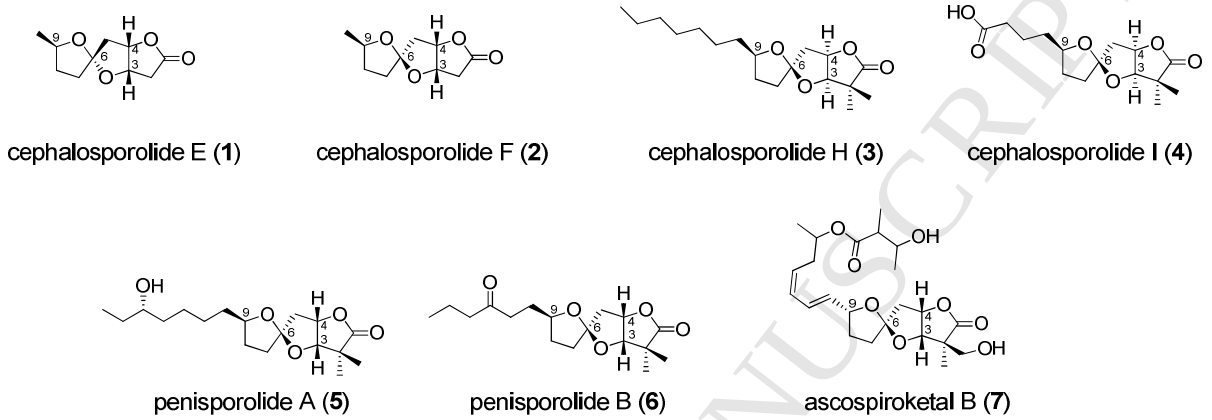


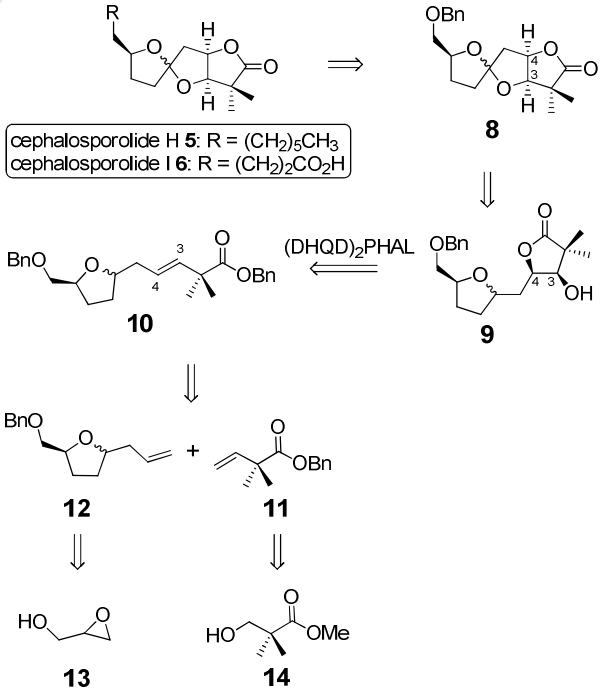
Figure 1: Natural products possessing the 5,5-spiroacetal fused γ-lactone structural moiety.[1, 4-6]

Penisporolides A (**5**) and B (**6**) were isolated from the marine-derived *Penicillium sp.*[5] and possess similar structural features to cephalosporolides H (**3**) and I (**4**). They differ in the C-3 and C-4 stereochemistry of the γ-lactone and the side-chain at C-9. Penisporolide A (**5**) possesses a 5-hydroxyheptyl side chain at C-9 whereas penisporolide B (**6**) bears a 3-oxohexyl substituent. The structures of these natural products as well as cephalosporolides H (**3**) and I (**4**) were tentatively proposed based on comparison of their spectroscopic data and to the spectroscopic data reported for the confirmed structures of cephalosporolides E (**1**) and F (**2**).[10] As a result of our interest in the total synthesis of spiroacetal-containing natural products and our recent synthesis of cephalosporolides E (**1**) and F (**2**),[11] we extended our work to the synthesis of cephalosporolides H (**5**) and I (**6**).

Recent syntheses of cephalosporolide H (**3**) by Dudley *et al.*[12-14] and Fernandes *et al.*[15] have suggested that the proposed stereochemistry of the spiroacetal centre should be revised. With this question in mind, we devised a synthetic strategy to enable the synthesis of each of the four natural products: cephalosporolides H (**3**) and I (**4**) and penisporolides A (**5**) and B (**6**) from a common spiroacetal precursor.

2. Results and discussion

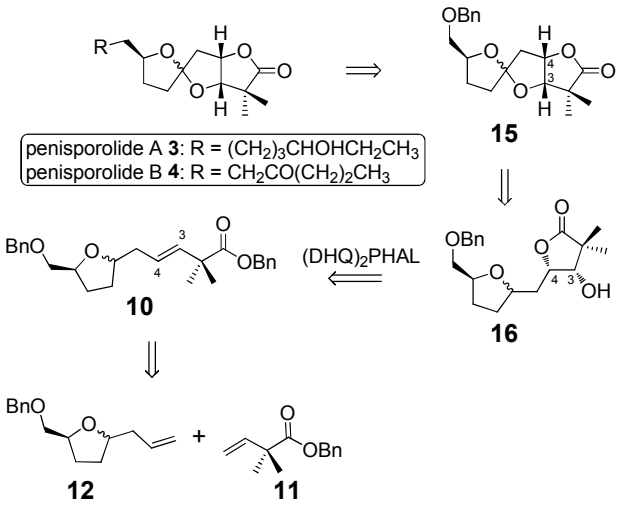
Our retrosynthesis (Scheme 1) allows for the preparation of two diastereomers of the common spiroacetal intermediate **8**, that upon debenzylation and further side-chain extension should afford both natural products cephalosporolides H (**5**) and I (**6**). Oxidative radical cyclisation of hydroxyl-lactone **9** would provide spiroacetal **8**. The lactone is accessible *via* a Sharpless asymmetric dihydroxylation of olefin **10** with concomitant lactonisation. The latter can be assembled *via* a cross metathesis reaction between olefins **11** and **12**, which are obtained from commercially available glycidol **13** and alcohol **14**, respectively.



Scheme 1: Retrosynthesis of cephalosporolide H (**3**) and I (**4**)

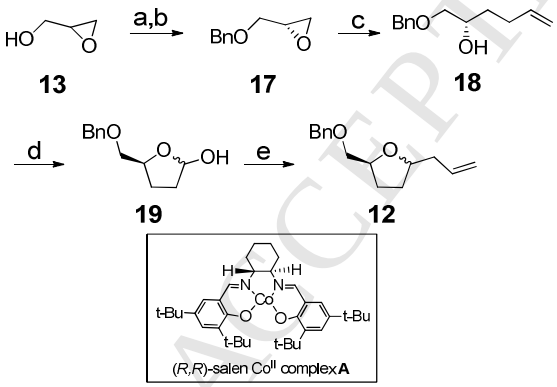
A similar strategy for the synthesis of penisporolides A (**5**) and B (**6**) from spiroacetal precursor **15,** could also be employed simply by changing the Sharpless ligand used for the

asymmetric dihydroxylation of olefin **10** (Scheme 2). Oxidative radical cyclisation of lactone **16** then affords the two diastereomers of the spiroacetal precursor **15.** Sharpless asymmetric dihydroxylation of olefin **10** enables installation of the desired stereochemistry at C-3 and C-4.



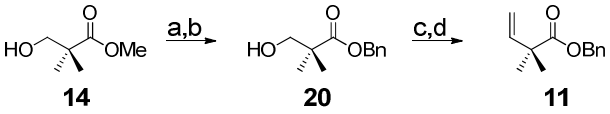
Scheme 2: Retrosynthesis of penisporolides A (**5**) and B (**6**)

Implementation of the synthetic strategy planned for cephalosporolides H (**3**) and I (**4**) summarized in Scheme 1 initially required preparation of olefin **12** in 5 steps from commercially available glycidol **13**. Glycidol **13** was protected as a benzyl ether and treated with (*R,R*)-salen Co^{II} complex **A** affording enantioenriched (*R*)-epoxide **17** which could easily be separated from the (*S*)-diol by column chromatography (Scheme 3).[16] The newly formed epoxide **17** was opened at the terminal position by the addition of an allyl cuprate in THF to afford secondary alcohol **18**.[17] Ozonolysis of alkene **18** furnished lactol **19** as a 1:1 mixture of *cis/trans* isomers. This mixture was then treated with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ to install the desired allyl side-chain, providing **12** as a 1:1 mixture of *cis* and *trans* isomers in 83% yield.[18]



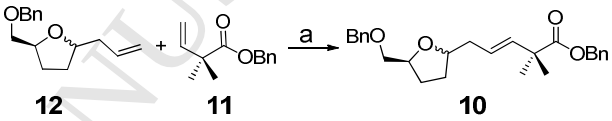
Scheme 3: *Reagents and conditions*: a) BnBr, NaH, DMF, 0 °C to rt, 18 h, 84%; b) AcOH, THF, H_2O, (*R,R*)-salen Co^{II} complex **A**, 0 °C to rt, 16 h, 48%; c) CuI, allylMgBr, THF, -40 °C to rt, 3 h, 70%; d) O_3, CH_2Cl_2, MeOH, PPh_3, -78 °C to rt, 15 h, 71%, 1:1 *cis:trans* mixture; e) allyltrimethylsilane, CH_2Cl_2, $BF_3{\cdot}OEt_2$, rt, 3 h, 83%, 1:1 *cis:trans* mixture.

With olefin **12** in hand, attention turned to the synthesis of olefin **11**, the cross metathesis coupling partner (Scheme 4). Commercially available ester **14** was deprotected to give the carboxylic acid which was converted to benzyl ester **20**. ENREF 15[19] Swern oxidation of alcohol **20** to the corresponding aldehyde[20] followed by Wittig olefination yielded olefin **11**.



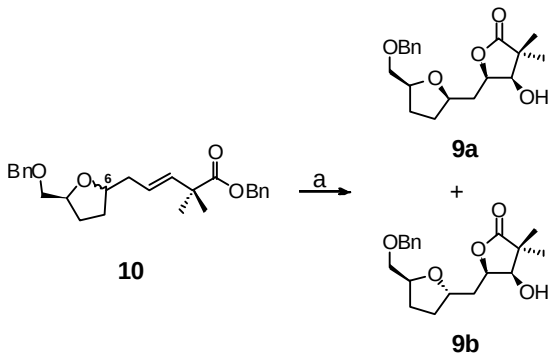
Scheme 4: *Reagents and conditions:* a) LiOH, THF, MeOH, H_2O, 0 °C to rt, 1.5 h, 73%; b) BnBr, DMF, K_2CO_3, rt, 5 h, 86%; c) DMSO, CH_2Cl_2, $(COCl)_2$, NEt_3, -78 °C, 1 h, 82%; d) LiHMDS, $MePh_3P^+Br^-$, THF, 0 °C to rt, 16 h, 46%.

Armed with coupling partners **11** and **12**, attention turned to the cross metathesis reaction (Scheme 5). Grubbs' II catalyst was employed due to its known propensity for *trans* selectivity in cross metathesis reactions involving alkenes with a fully substituted α-quaternary centre.[21] Using a variety of conditions only moderate yields of cross-coupled olefin **10** were obtained. The reaction was carried out in the microwave in the presence of chlorodicyclohexyl borane (catalytic quantity) and 10 mol% Grubbs' II in toluene at 90 °C for 9 h to give the desired (*E*)-olefin **10** in 22% yield.*



Scheme 5: *Reagents and conditions:* a) Grubbs' II, toluene, cy_2BCl, 90 °C, microwave, 9 h, 22%.

Olefin **10** was next subjected to Sharpless asymmetric dihydroxylation using AD-mix β to afford lactones **9a** (α_D +12.1, *c* 1.0 $CHCl_3$) and **9b** (α_D +7.0, *c* 0.3 $CHCl_3$) as a separable 1:1 mixture of diastereomers (Scheme 6). The newly formed lactones exhibit the *cis* stereochemistry between C-3 and C-4 as desired for cephalosporolides H **5** and I **6** and differ only in the stereochemistry at C-6.

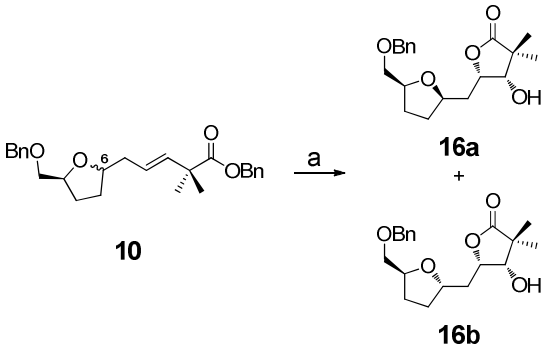


Scheme 6: *Reagents and conditions:* a) $(DHQD)_2PHAL$, methanesulfonamide, K_2CO_3, $K_3Fe(CN)_6$, OsO_4, *t*-BuOH, H_2O, rt, 15 h, 73%, **9a**:**9b** (1:1).

Sharpless asymmetric dihydroxylation of olefin **10** was also carried out using AD-mix α furnishing a 1:1 separable mixture of lactones **16a** (α_D -35.7, *c* 1.0 $CHCl_3$) and **16b** (α_D -18.0, *c* 0.3

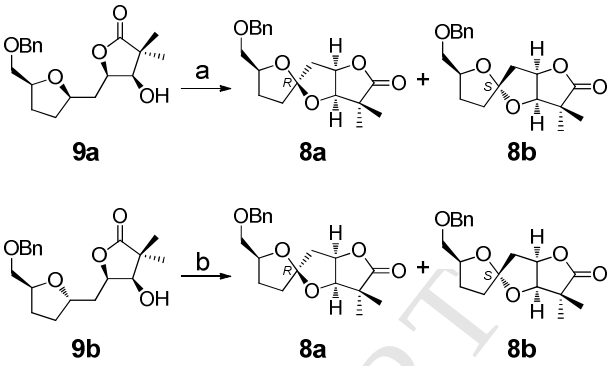
* Recently Fernandes *et al.*[15] reported that a very similar cross metathesis reaction did not proceed, due to steric crowding near the olefin bond caused by geminal methyl substituents. In the absence of these geminal dimethyl groups, the reaction proceeded with high yield and *E* selectivity.

$CHCl_3$) (Scheme 7). The lactones formed in this reaction possess the desired stereochemistry at C-3 and C-4 for penisporolides A (**3**) and B (**4**).



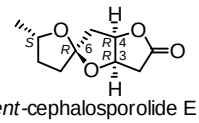
Scheme 7: *Reagents and conditions*: a) $(DHQ)_2PHAL$, methanesulfonamide, K_2CO_3, $K_3Fe(CN)_6$, OsO_4, *t*-BuOH, H_2O, rt, 15 h, 76%, **16a**:**16b** (1:1).

The key oxidative radical cyclisation reaction was separately carried out on lactones **9a** and **9b** (Scheme 8). Treatment of lactone **9a** with iodosobenzene diacetate and iodine afforded a separable 1:1 mixture of spiroacetals **8a** (α_D +42.0, *c* 0.26 $CHCl_3$) and **8b** (α_D -2.9, *c* 1.0 $CHCl_3$). The same 1:1 ratio of spiroacetals **8a** and **8b** was obtained when lactone **9b** was employed in the oxidative cyclisation reaction.



Scheme 8: *Reagents and conditions:* a) $PhI(OAc)_2$, I_2, CH_2Cl_2, hexane, 75 W, 1 h, 51%, **8a:8b** (1:1); b) $PhI(OAc)_2$, I_2, CH_2Cl_2, hexane, 75 W, 1 h, 52%, **8a**:**8b** (1:1).

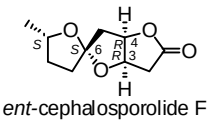
The oxidative cyclisation reaction was also carried out on lactone **16a** affording a 1:1 mixture of spiroacetals **15a** (α_D -41.2, *c* 0.4 $CHCl_3$) and **15b** (α_D -20.4, *c* 0.25 $CHCl_3$). Similarly, a 1:1 mixture of spiroacetals **15a** and **15b** was obtained when the same procedure was carried out on lactone **16b**.



ent-cephalosporolide E **21**

H-4, δ 5.09, t *J* = 5.8 Hz

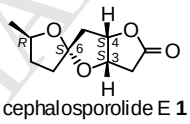
α_D = -48.2 (c 0.5, $CHCl_3$)



ent-cephalosporolide F **22**

H-4, δ 5.02, ddd *J* = 6.6, 4.4, 2.1 Hz

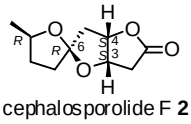
α_D = +95.2 (c 0.9, $CHCl_3$)



cephalosporolide E **1**

H-4, δ 5 .17, t *J* = 5.9 Hz

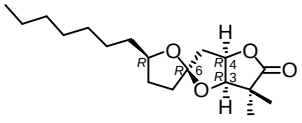
α_D = +27.3 (c 0.41, $CHCl_3$)



cephalosporolide F **2**

H-4, δ 5.08, ddd *J* = 6.6, 4.4, 2.1 Hz

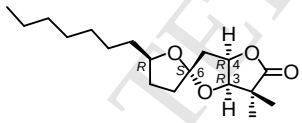
α_D = -33.9 (c 0.79, $CHCl_3$)



isolated cephalosporolide H **3**

H-4, δ 5 .07, t *J* = 4.9 Hz

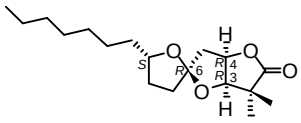
α_D = -5.0 (c 0.7, MeOH)



reassigned cephalosporolide H **3a**

H-4, δ 5.03, ddd *J* = 6.4, 3.8, 1.6 Hz

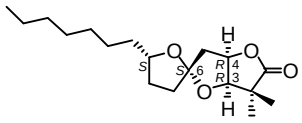
α_D = +65.0 (c 0.7, MeOH)



3b

H-4, δ 5 .10, t *J* = 5.2 Hz

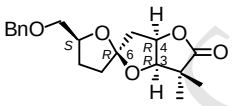
α_D = -7.6 (c 0.7, MeOH)



3c

H-4, δ 5.02, ddd *J* = 6.3, 3.8, 1.6 Hz

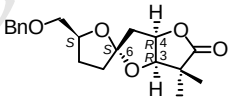
α_D = +41.2 (c 0.7, MeOH)



8a

H-4, δ 5.06, t *J* = 4.8 Hz

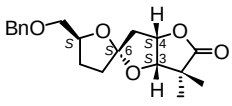
α_D = -2.9 (c 0.17, $CHCl_3$)



8b

H-4, δ 5.02, ddd *J* = 6.4, 3.7, 1.6 Hz

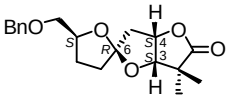
α_D = +42.0 (c 0.26, $CHCl_3$)



15a

H-4, δ 5.10, t *J* = 5.2 Hz

α_D = -20.4 (c 0.25, $CHCl_3$)

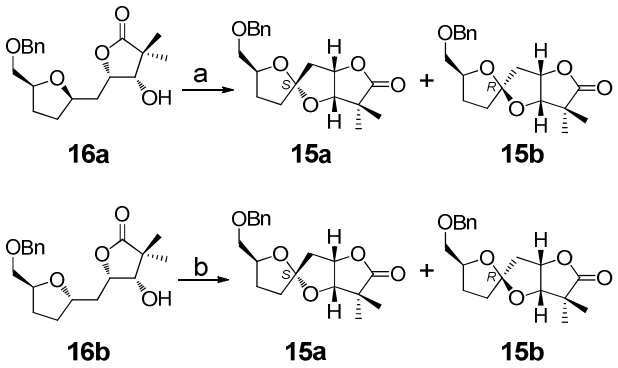


15b

H-4, δ 5.00, ddd *J* = 6.3, 3.9, 1.5 Hz

α_D = -41.2 (c 0.4, $CHCl_3$)

Figure 2: Comparison of H-4 NMR of the known natural products with the four stereoisomers synthesised.[10-12]



Scheme 9: *Reagents and conditions:* a) $PhI(OAc)_2$, I_2, CH_2Cl_2, hexane, 75 W, 1 h, 51%, **15a**:**15b** (1:1); b) $PhI(OAc)_2$, I_2, CH_2Cl_2, hexane, 75 W, 1 h, 51 %, **15a**:**15b** (1:1).

Recently, the stereochemistry of cephalosporolide H **3a** and its C-6 epimer **3** (Figure 2), synthesised by Dudley *et al.*[12-14] and Fernandes *et al*.[15] was determined by comparison of the ^{1}H NMR data reported for cephalosporolides E (**1**) and F (**2**) and their enantiomers **21** and **22** for which X-ray crystallographic data was available (Figure 2).[10-11] The reassignment of the stereochemistry of the isolated cephalosporolide H (**3**) to that of the synthetic **3a** was based primarily on α_D values and comparison of the characteristic coupling pattern for H-4 observed in *ent*-cephalosporolides E (**21**) and F (**22**).

The same approach was used to determine the stereochemistry of the spirocentre in spiroacetals **8a**, **8b**, **15a** and **15b**. Given that the C-4 stereochemistry in these four diastereomeric spiroacetals was installed unequivocally *via* Sharpless asymmetric dihydroxylation, the characteristic H-4 coupling pattern could then be used to determine the stereochemistry of the spirocentre (Figure 2 and 3). In spiroacetal **8a**, H-4 resonated as a triplet at δ 5.06 ppm with a coupling constant, *J* 4.8 Hz, establishing (*R*)-stereochemistry at the spirocentre. Conversely, H-4 in spiroacetal **8b** resonates as a doublet of doublet of doublets at δ 5.02 ppm with coupling constant, *J* 6.6, 3.7, 1.6 Hz establishing (*S*)-stereochemistry at the spirocentre.

Similarly, spiroacetals **15a** and **15b** were assigned as 6*S* and 6*R* based on comparison of the ^{1}H NMR coupling patterns observed for H-4 to the same resonance in cephalosporolides E (**1**) and F (**2**).

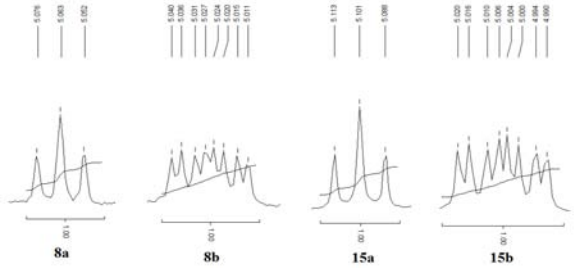
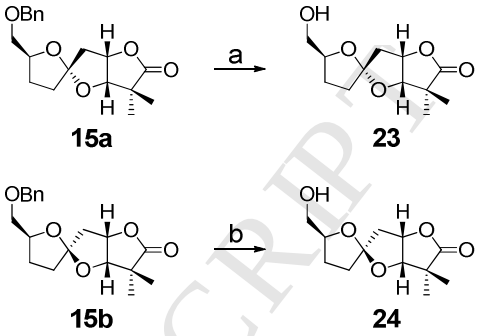


Figure 3: Characteristic H-4 coupling pattern for spiroacetals **8a**, **8b**, **15a** and **15b** ($CDCl_3$, 400 MHz)

The cephalosporolide family poses some interesting questions concerning the stereochemistry of the natural products. Dudley *et al*.[14] has synthesised four possible diastereomers of cephalosporolide H (**3-3c**). Unfortunately without access to an authentic sample of the natural product definitive confirmation of the stereochemistry cannot be substantiated. Therefore uncertainty still exists regarding the configuration of cephalosporolide H and the other members of the cephalosporolide family.

Deprotection of spiroacetals **15a** and **15b** was carried out using 10% Pd/C in EtOAc to give the corresponding primary alcohols **23** (α_D +0.91, *c* 0.22 $CHCl_3$) and **24** (α_D -1.4, *c* 0.13 $CHCl_3$). Further elaboration of **23** and **24** should afford the natural products penisporolides A (**3**) and B (**4**).



Scheme 10: *Reagents and conditions:* a) 10% Pd/C, EtOAc, H_2, 18 h, 87%; b) 10% Pd/C, EtOAc, H_2, 16 h, 68%.

3. Conclusion

The synthetic work described herein provides access to the four stereoisomeric spiroacetals **8a**, **8b**, **15a**, **15b** which comprise the spiroacetal core structures of the natural products cephalosporolides H (**3**) and I (**4**) as well as penisporolides A (**5**) and B (**6**). Use of Sharpless asymmetric dihydroxylation with the appropriate chiral ligand enabled establishment of the desired absolute stereochemistry in the γ-lactone ring. Oxidative radical cyclisation was then used to form the two possible configurations at the spirocentre. The synthetic work undertaken also facilitates biological evaluation of the four individual spiroacetal core structures present in this important family of natural products.

4. Experimental

4.1 General methods

All reactions were carried out in oven-dried glassware which was further dried under high vacuum whilst heating with a heat gun. Reactions were carried out under an atmosphere of argon or nitrogen dried by passing through a cylinder of calcium chloride. Solvents were dried under standard conditions. Analytical thin layer chromatography (TLC) was performed on 0.2 mm aluminium plates of silica gel 60 F_{254} (Merck) and compounds were visualised by ultra-violet fluorescence or by staining with potassium permanganate or vanillin solutions, followed by heating the plate as appropriate. Flash column chromatography was carried out using 40-63 μm, 230-430 mesh silica gel with the solvent indicated. Infrared spectra were obtained using a Perkin Elmer Spectrum One Fourier Transform infrared spectrometer with a universal ATR sampling accessory. Optical rotations were measured at 20 °C using either a Perkin Elmer 341 polarimeter or a Rudolph Research Analytical Autopol IV at λ = 598 nm and are given in units of 10^{-1} deg cm^2 g^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded as indicated on a Bruker AVANCE DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are recorded in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or deuterated chloroform (δ 7.26 ppm or δ 77.0 ppm). Coupling constant *J* values are given in Hertz (Hz). Melting

points were determined on an Electrothermal® melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One Universal ATR Sampling Accessory Fourier Transform IR spectrometer, neat, over a crystal plate or using a Perkin Elmer Spectrum 1000 series Fourier Transform Optical rotations of chiral compounds were obtained using a Perkin Elmer 341 polarimeter in the solvent indicated. High-resolution mass spectra were obtained by electron spray ionisation (ESI) using a microTOF-Q mass spectrometer. Microwave reactions were performed on the Biotage Initiator.

*4.1.8 Benzyl 2,2-dimethylbut-3-enoate **11***

To a solution of methyl triphenylphosphonium bromide (5.2 g, 14.5 mmol) in THF (40 mL) was added LiHMDS (17.1 mL, 0.85 M in THF, 14.5 mmol) at 0 °C. The reaction mixture was stirred for 30 min and a solution of benzyl 2,2-dimethyl-3-oxopropanoate (2 g, 9.71 mmol) in THF (10 ml) was added. The mixture was allowed to warm to rt overnight and quenched by the addition of sat. aq. NH_4Cl (15 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 20:1 hexanes/EtOAc as eluent gave the *title compound* **11** (0.75 g, 38%) as a yellow oil. R_f: 0.77 (90% hexanes/EtOAc); ν_{max} (film)/cm^{-1}: 2977, 1728, 1259, 1132, 695; δ_H (400 MHz, $CDCl_3$): 7.37-7.29 (5H, m, Ph), 6.05 (1H, dd, *J* = 17.4, 10.5 Hz, H-3), 5.11 (3H, s, CH_2Ph, H-4), 5.06 (1H, d, *J* = 10.5 Hz, H-4), 1.33 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 176.1 (C=O, C-1), 142.4 (CH, C-3), 136.3 (C, Ph), 128.5 (2 × CH, Ph), 127.9 (CH, Ph), 127.7 (2 × CH, Ph), 113.0 (CH_2, C-4), 66.3 (CH_2, CH_2Ph), 44.9 (C, C-2), 24.6 (2× CH_3). HRMS (ESI): calcd for $C_{13}H_{16}NaO_2$: 227.1043, found: 227.1040.

*4.1.9 Benzyl 5-((5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-2,2-dimethylpent-3-enoate **10***

A solution of alkene **12** (0.1 g, 0.43 mmol) and alkene **11** (0.35 g, 1.7 mmol) in toluene (3 mL) in a microwave vessel was degassed using the freeze-pump-thaw method. A solution of Grubbs' II catalyst (0.04 g, 0.04 mmol) in toluene (1 mL) under argon was added. Chlorodicyclohexyl borane (0.04 mL, 1 M in hexane, 0.04 mmol) was added and the solution heated in the microwave at 90 °C for 9 h. Purification by column chromatography afforded the *title compound* **10** (0.04 g, 22%) as a 1:1 mixture of diastereomers as a yellow oil. R_f: 0.51 (60% hexanes/EtOAc); ν_{max} (film)/cm^{-1}: 2930, 1726, 1455, 1130, 697; δ_H (400 MHz, $CDCl_3$): 7.36-7.25 (10H, m, PhH), 5.69 (1H, dt, *J* = 15.6, 1.4 Hz, H-3), 5.53-5.45 (1H, m, H-4), 5.09 (2H, s, C*H*$_2$Ph), 4.61-4.52 (2H, m, C*H*$_2$Ph), 4.20-4.14 (0.4 H, m, H-9), 4.10-4.03 (0.6 H, m, H-9), 4.01-3.94 (0.4 H, m, H-6), 3.91-3.84 (0.6 H, m, H-6), 3.48-3.40 (2H, m, H-10), 2.40-2.32 (1H, m, H-5), 2.24-2.13 (1H, m, H-5), 1.98-1.78 (2H, m, H-8), 1.67-1.58 (2H, m, H-7), 1.30 (6 H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 176.3 (C=O, C-1), 138.4 (C, Ph), 136.7 (2 × CH, 2 × C-3), 136.3 (C, Ph), 128.4 (2 × CH, Ph) 128.3 (2 × CH, Ph), 127.9 (CH, Ph),127.7 (2 × CH, Ph), 127.6 (2 × CH, Ph), 127.5 (CH, Ph), 124.9 (2 × CH, 2 × C-4), 79.3 (CH, C-9), 78.8 (CH, C-9), 78.1 (CH, C-6), 77.8 (CH, C-6), 73.3 (CH_2, CH_2Ph), 73.0 (CH_2, C-10), 72.9 (CH_2, C-10), 66.2 (CH_2, CH_2Ph), 44.2 (C, C-2), 38.8 (CH_2, C-5), 38.7 (CH_2, C-5), 30.8 (CH_2, C-7), 29.9 (CH_2, C-7), 28.5 (CH_2, C-8), 28.1 (CH_2, C-8), 25.1 (2 × CH_3). HRMS (ESI): calcd. for $C_{26}H_{32}NaO_4$: 431.2193, found: 431.2194.

*4.1.10 (4R,5R)-5-(((2R,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one **9a** and (4R,5R)-5-(((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one **9b***

A solution of $(DHQD)_2PHAL$ (0.009 g, 0.01 mmol), methanesulfonamide (0.023 g, 0.02 mmol), OsO_4 (0.02 mL, 2.5% solution in *t*-BuOH, 2.4 μmol), $K_3Fe(CN)_6$ (0.23 g, 0.73 mmol) and K_2CO_3 (0.09 g, 0.73 mmol) in *t*-BuOH/H_2O (1:1, 1 mL) was stirred for 30 min. A solution of alkene **10** (0.10 g, 0.24 mmol) in *t*-BuOH/H_2O (1:1, 0.3 mL) was added. The reaction mixture was stirred at rt overnight and Na_2SO_3 (0.02 g) was added. The suspension was stirred for 30 min. The mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with 2 N KOH (0.01 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave a separable 1:1 mixture of **9a:9b** as yellow oils.

Data for **9a**; (0.03g, 36%), R_f: 0.36 (60% hexanes/EtOAc); $[\alpha]_D^{20}$ +12.1 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3438, 2926, 1765, 1456, 1095; δ_H (400 MHz, $CDCl_3$): 7.37-7.27 (5H, m, PhH), 4.55 (2H, s, CH_2Ph), 4.54-4.50 (1H, m, H-4), 4.27-4.21 (1H, m, H-9), 4.07-4.00 (2H, m, H-6, H-3), 3.73 (1H, d, *J* = 2.6 Hz, OH), 3.48 (2H, m, H-10), 2.21-2.13 (2H, m, H-5), 2.08-1.97 (1H, m, H-8), 1.18-1.59 (3H, m, H-8, H-7), 1.26 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 181.0 (C=O, C-1), 138.1 (C, Ph), 128.4 (2 × CH, Ph), 127.6 (CH, Ph), 127.5 (2 × CH, Ph), 80.1 (CH, C-4), 78.6 (CH, C-9), 76.4 (CH, C-6), 75.7 (CH, C-3), 73.2 (CH_2, CH_2Ph), 72.4 (CH, C-10), 45.0 (C, C-2), 34.5 (CH_2, C-5), 32.9 (CH_2, C-7), 28.2 (CH_2, C-8), 23.2 (CH_3), 17.8 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{26}NaO_5$: 357.1672, found: 357.1677.

Data for **9b**; (0.03g, 36%), R_f: 0.25 (60% hexanes/EtOAc); $[\alpha]_D^{20}$ +7.0 (*c* 0.3, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3439, 2920, 1759, 1458, 1088; δ_H (400 MHz, $CDCl_3$): 7.37-7.27 (5H, m, PhH), 4.67-4.62 (1H, m, H-4), 4.54 (2H, s, CH_2Ph), 4.14-4.09 (2H, m, H-9, H-6), 3.95 (1H, d, *J* = 3.4 Hz, H-3), 3.58 (1H, dd, *J* = 10.1, 3.4 Hz, H-10a), 3.51 (1H, m, OH), 3.46 (1H, dd, *J* = 10.2, 4.7 Hz, H-10b), 2.37-2.29 (1H, m, H-5), 2.15-2.09 (1H, m, H-5), 2.03-1.92 (2H, m, H-8), 1.90-1.83 (1H, m, H-7), 1.76-1.65 (1H, m, H-7), 1.21 (3H, s, CH_3), 1.09 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 181.0 (C=O, C-1), 138.1 (C, Ph), 128.4 (2 × CH, Ph), 127.7 (CH, Ph), 127.6 (2 × CH, Ph), 78.1 (CH, C-9), 77.8 (CH, C-4), 76.3 (CH, C-3), 76.1 (CH, C-6), 73.4 (CH_2, CH_2Ph), 72.2 (CH, C-10), 45.0 (C, C-2), 31.3 (CH_2, C-5), 29.1 (CH_2, C-7), 27.7 (CH_2, C-8), 23.2 (CH_3), 17.9 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{26}NaO_5$: 357.1672, found: 357.1682.

*4.1.11 (4S,5S)-5-(((2R,5R)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one **16a** and (4S,5S)-5-(((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one **16b***

A solution of $(DHQ)_2PHAL$ (0.016 g, 0.02 mmol), methanesulfonamide (0.04 g, 0.04 mmol), OsO_4 (0.4 mL, 2.5% solution in *t*-BuOH, 0.04 mmol), $K_3Fe(CN)_6$ (0.4 g, 1.3 mmol) and K_2CO_3 (0.18 g, 1.3 mmol) in *t*-BuOH/H_2O (1:1, 1 mL) was stirred for 30 min. A solution of alkene **10** (0.18 g, 0.43 mmol) in *t*-BuOH/H_2O (1:1, 0.3 mL) was added and the reaction mixture was stirred at rt overnight before Na_2SO_3 (0.02 g) was added. The suspension was stirred for 30 min and the mixture was extracted with EtOAc (3 × 3 mL), the combined organic extracts were washed with 2 N KOH (0.01 mL), dried over

Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave a separable 1:1 mixture of **16a:16b** as colourless solids.

Data for **16a**; (0.05 g, 38%), R_f: 0.36 (60% hexanes/EtOAc); $[\alpha]_D^{20}$ -37.5 (*c* 1.0, $CHCl_3$); mp: 60-64 °C; ν_{max} (film)/cm^{-1}: 3440, 2930, 1762, 1457, 1086; δ_H (400 MHz, $CDCl_3$): 7.36-7.26 (5H, m, PhH), 4.54 (2H, s, CH_2Ph), 4.54-4.50 (1H, m, H-4), 4.18-4.12 (1H, m, H-9), 4.04-4.02 (2H, m, H-6, H-3), 3.99 (1H, d, *J* = 2.9 Hz, OH), 3.52 (1H, dd, *J* = 10.0, 3.6 Hz, H-10), 3.38 (1H, dd, *J* = 10.1, 5.7 Hz, H-10), 2.17-2.04 (3H, m, H-5, H-7), 1.98-1.89 (1H, m, H-8), 1.87-1.78 (1H, m, H-8), 1.74-1.64 (1H, m, H-7), 1.28 (3H, s, CH_3), 1.26 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 181.1 (C=O, C-1), 137.5 (C, Ph), 128.4 (2 × CH, Ph), 128.1 (2 × CH, Ph), 127.8 (CH, Ph), 80.4 (CH, C-4), 78.8 (CH, C-9), 76.5 (CH, C-6), 76.5 (CH, C-3), 73.5 (CH_2, CH_2Ph), 71.8 (CH, C-10), 45.0 (C, C-2), 34.9 (CH_2, C-5), 32.1 (CH_2, C-7), 27.4 (CH_2, C-8), 23.2 (CH_3), 17.9 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{26}KO_5$: 373.1412, found: 373.1407.

Data for **16b**; (0.05 g, 38%), R_f: 0.25 (60% hexanes/EtOAc); $[\alpha]_D^{20}$ -18.0 (c 0.3, $CHCl_3$); mp: 59-65 °C; ν_{max} (film)/cm^{-1}: 3441, 2929, 1763, 1466, 1095; δ_H (400 MHz, $CDCl_3$): 7.36-7.26 (5H, m, PhH), 4.71-4.66 (1H, H-4), 4.55 (2H, s, CH_2Ph), 4.26-4.19 (2H, m, H-6, H-9), 3.92 (1H, t, *J* = 3.6 Hz, H-3), 3.61 (1H, d, *J* = 3.6 Hz, OH), 3.46 (2H, d, *J* = 4.9, H-10), 2.31-2.24 (1H, m, H-5), 2.14-2.02 (3H, m, H-5, H-8), 1.79-1.63 (2H, m, H-7), 1.26 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 180.8 (C=O, C-1), 138.1(C, Ph), 128.4 (2 × CH, Ph), 127.6 (2 × CH, Ph), 127.6 (CH, Ph), 78.3 (CH, C-9), 77.8 (CH, C-4), 76.5 (CH, C-3), 75.4 (CH, C-6), 73.4 (CH_2, CH_2Ph), 72.6 (CH_2, C-10), 45.2 (C, C-2), 31.8 (CH_2, C-5), 30.4 (CH_2, C-7), 28.5 (CH_2, C-8), 23.3 (CH_3), 17.9 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{26}NaO_5$: 357.1672, found: 357.1675.

*4.1.12 2R,3a'R,5S,6a'R)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one **8a** and (2S,3a'R,5S,6a'R)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one **8b***

A solution of lactone **9a** (0.02 g, 0.06 mmol) in CH_2Cl_2 (0.1 mL) was added to a stirring solution of $PhI(OAc)_2$ (0.04 g, 0.12 mmol) and I_2 (0.04 g, 0.14 mmol) in hexane (0.2 mL). N_2 gas was bubbled through the solution for 5 min and the reaction was then irradiated with a 75 W desk lamp for 1 h. The solution was diluted with Et_2O (0.2 mL) and saturated aq. $Na_2S_2O_3$ (0.1 mL) was added, the mixture was extracted with Et_2O (3 × 1 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification on deactivated silica using 9:1 to 3:2 hexanes/EtOAc gave colourless oils.

Data for **8b**; (0.005 g, 25%), R_f: 0.69 (50% hexanes/EtOAc); $[\alpha]_D^{20}$ +42.0 (c 0.26, $CHCl_3$); ν_{max} (film)/cm^{-1}: 2930, 1776, 1050, 754; δ_H (400 MHz, $CDCl_3$): 7.36-7.7 (5H, m, PhH), 5.02 (1H, ddd, *J* = 6.4, 3.7, 1.6 Hz, H-4), 4.56 (2H, dd, *J* = 12.2, 9.0 Hz, CH_2Ph), 4.32 (1H, d, *J* = 3.8 Hz, H-3), 4.30-4.26 (1H, m, H-9), 3.48-3.41 (2H, m, H-10), 2.58 (1H, dd, *J* = 15.0, 6.5 Hz, H-5), 2.36 (1H, dd, *J* = 15.1, 1.5 Hz, H-5), 2.17-1.96 (4H, m, H-7, H-8), 1.74-1.66 (1H, m, H-8), 1.26 (3H, s, CH_3), 1.22 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 175.0 (C=O, C-1), 138.2 (C, Ph), 128.4 (3 × CH, Ph), 127.6 (2 × CH, Ph), 116.0 (C, C-6), 85.3 (CH, C-9), 80.5 (CH, C-4), 77.7 (CH, C-3), 73.4 (CH_2, C-10), 72.4 (CH_2, CH_2Ph), 44.4 (C, C-2), 41.9 (CH_2, C-5), 35.2 (CH_2, C-7), 26.8 (CH_2, C-8), 23.0 (CH_3), 18.0 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{24}NaO_5$: 355.1516, found: 355.1528.

Data for **8a**; (0.005 g, 25%), R_f: 0.56 (50% hexanes: EtOAc); $[\alpha]_D^{20}$ -2.9 (c 0.17 in $CHCl_3$); ν_{max} (film)/cm^{-1}: 2926, 1773, 1214, 746; δ_H (400 MHz, $CDCl_3$): 7.35-7.27 (5H, m, PhH), 5.06 (1H, t, *J* = 4.8 Hz, H-4), 4.53 (2H, dd, *J* = 29.3, 12.1 Hz, CH_2Ph), 4.28 (1H, d, *J* = 4.5 Hz, H-3), 4.25-4.19 (1H, m, H-9), 3.56 (1H, dd, *J* = 9.9, 5.4 Hz, H-10), 3.48 (1H, dd, *J* = 9.8, 5.8 Hz, H-10), 2.51 (1H, d, *J* = 14.2 Hz, H-5), 2.18-1.99 (5H, m, H-5, H-7, H-8), 1.92-1.84 (1H, m, H-7),1.27 (3H, s, CH_3), 1.21 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 178.8 (C=O, C-1), 138.6 (C, Ph), 128.3 (2 × CH, Ph), 127.6 (2 × CH, Ph), 127.4 (CH, Ph), 115.7 (C, C-6), 87.3 (CH, C-9), 85.3 (CH, C-4), 79.7 (CH, C-3), 73.5 (CH_2, C-10), 73.3 (CH_2, CH_2Ph), 44.6 (C, C-2), 41.7 (CH_2, C-5), 36.0 (CH_2, C-7), 27.9 (CH_2, C-8), 24.6 (CH_3), 18.3 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{25}O_5$: 333.1697, found: 333.1694.

*4.1.13 (2S,3a'S,5S,6a'S)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one **15a** and (2R,3a'S,5S,6a'S)-5-((benzyloxy)methyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one **15b***

A solution of lactone **16a** (0.03 g, 0.09 mmol) in CH_2Cl_2 (0.1 mL) was added to a stirring solution of $PhI(OAc)_2$ (0.06 g, 0.18 mmol) and I_2 (0.05 g, 0.21 mmol) in hexane (0.2 mL). N_2 gas was bubbled through the solution for 5 min and the reaction was then irradiated with a 75 W desk lamp for 1 h. The solution was diluted with Et_2O (0.2 mL) and saturated aq. $Na_2S_2O_3$ (0.1 mL) was added, the mixture was extracted with Et_2O (3 × 1 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification on deactivated silica using 9:1 to 3:2 hexanes/EtOAc gave a colourless oil.

Data for **15b**; (0.007 g, 25%), R_f: 0.69 (50% hexanes/EtOAc); $[\alpha]_D^{20}$ -41.5 (c 0.4, $CHCl_3$); ν_{max} (film)/cm^{-1}: 2933, 1776, 1138, 1089,1052; δ_H (400 MHz, $CDCl_3$): 7.36-7.26 (5H, m, PhH), 5.00 (1H, ddd, *J* = 6.3, 3.9, 1.5 Hz, H-4), 4.58 (2H, s, CH_2Ph), 4.34-4.27 (1H, m, H-9), 4.24 (1H, d, *J* = 3.7 Hz, H-3), 3.49 (1H, dd, *J* = 9.9, 7.7 Hz, H-10), 3.42 (1H, dd, *J* = 9.9, 4.0 Hz, H-10), 2.57 (1H, dd, *J* = 15.0, 6.4 Hz, H-5), 2.34 (1H, dd, *J* = 15.0, 1.4 Hz, H-5), 2.10-1.90 (3H, m, H-7, H-8), 1.81-1.70 (1H, m, H-8), 1.19 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 180.8 (C=O, C-1), 138.2 (C, Ph), 128.4 (2 × CH, Ph), 127.8 (2 × CH, Ph), 127.6 (CH, Ph), 115.7 (C, C-6), 85.1 (CH, C-9), 80.3 (CH, C-4), 79.0 (CH, C-3), 74.2 (CH_2, C-10), 73.2 (CH_2, CH_2Ph), 44.3 (C, C-2), 41.5 (CH_2, C-5), 36.1 (CH_2, C-7), 27.3 (CH_2, C-8), 23.0 (CH_3), 17.9 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{24}NaO_5$: 355.1516, found: 355.1516.

Data for **15a**; (0.007 g, 25%), R_f: 0.57 (50% hexanes/EtOAc); $[\alpha]_D^{20}$ -20.4 (c 0.25, $CHCl_3$); ν_{max} (film)/cm^{-1}: 2936, 1774, 1120, 1105; δ_H (400 MHz, $CDCl_3$): 7.36-7.26 (5H, m, PhH), 5.10 (1H, t, *J* = 5.2 Hz, H-4), 4.53 (2H, s, CH_2Ph), 4.35 (1H, d, *J* = 5.0 Hz, H-3), 4.29-4.25 (1H, m, H-9), 3.52-3.42 (2H, m, H-10), 2.47 (1H, d, *J* = 14.1 Hz, H-5), 2.15-2.01 (4H, m, H-5, H-7, H-8), 1.84-1.80 (1H, m, H-8), 1.26 (3H, s, CH_3), 1.22 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 180.8 (C=O, C-1), 138.5 (C, Ph), 128.3 (2 × CH, Ph), 127.6 (2 × CH, Ph), 127.5 (CH, Ph), 115.7 (C, C-6), 86.9 (CH, C-3), 79.9 (CH, C-4), 78.6 (CH, C-9), 73.3 (CH_2, CH_2Ph), 72.1 (CH_2, C-10), 44.3 (C, C-2), 41.4 (CH_2, C-5), 34.2 (CH_2, C-7), 26.7 (CH_2, C-8), 25.2 (CH_3), 18.4 (CH_3). HRMS (ESI): calcd. for $C_{19}H_{24}KO_5$: 371.1255, found: 371.1268.

*4.1.14 (2R,3a'S,5S,6a'S)-5-(hydroxymethyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one **23***

A solution of spiroacetal **15a** (6.0 mg, 0.018 mmol) was stirred in EtOAc (0.5 mL) over 10% Pd/C (0.01 g) under H_2 overnight. The mixture was filtered through a plug of Celite®

and concentrated under reduced pressure to give the *title compound* **23** as a colourless oil (3 mg, 0.012 mmol, 68%). R_f: 0.13 (50% hexanes/EtOAc); $[\alpha]_D$ -1.4 (c 0.13, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3432, 2923, 1772, 1460, 1125, 828; δ_H (400 MHz, $CDCl_3$): 5.14 (1H, t, *J* = 5.1 Hz, H-4), 4.39 (1H, d, *J* = 4.9 Hz, H-3), 4.24-4.18 (1H, m, H-9), 3.68 (1H, dd, *J* = 11.8, 2.9 Hz, H-10), 3.47 (1H, q, *J* = 5.8 Hz, H-10), 2.48 (1H, d, *J* = 14.1 Hz, H-5), 2.17 (1H, dd, *J* = 14.2, 5.5 Hz, H-5), 2.14-2.02 (4H, m, H-5, H-7, H-8), 1.27 (3H, s, CH_3), 1.21 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 180.9 (C=O, C-1), 115.4 (C, C-6), 86.8 (CH, C-3), 79.8 (CH, C-3), 79.8 (CH, C-4), 64.7 (CH_2, C-10), 44.4 (C, C-2), 41.5 (CH_2, C-5), 34.5 (CH_2, C-7), 25.5 (CH_2, C-8), 25.5 (CH_3), 18.2 (CH_3). HRMS (ESI): calcd. for $C_{12}H_{18}KO_5$: 281.0786, found: 281.0790.

*4.1.14 (2S,3a'S,5S,6a'S)-5-(hydroxymethyl)-6',6'-dimethyltetrahydro-3H,3'H-spiro[furan-2,2'-furo[3,2-b]furan]-5'(3a'H)-one **24***

A solution of spiroacetal **15b** (0.011 g, 0.03 mmol) was stirred in EtOAc (1 mL) over 10% Pd/C (0.02 g) under H_2 overnight. The mixture was filtered through a plug of Celite® and concentrated under reduced pressure to give the title *compound* **24** as a colourless oil (7.0 mg, 87%). R_f: 0.13 (50% hexanes/EtOAc); $[\alpha]_D$ +0.91 (c 0.22, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3432, 2923, 1772, 1460, 1125, 828; δ_H (400 MHz, $CDCl_3$): 5.05 (1H, ddd, *J* = 6.0, 3.7, 1.4 Hz, H-4), 4.39-4.31 (2H, m, H-3, H-9), 3.75 (1H, dd, *J* = 9.9 Hz, H-12), 3.51-3.48 (1H, m, H-10), 2.58 (1H, dd, *J* = 15.2, 6.1 Hz, H-5), 2.50 (1H, dd, *J* = 15.2, 0.9 Hz, H-5), 2.20-1.96 (4H, m, H-7, H-8), 1.26 (3H, s, CH_3), 1.23 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 180.4 (C=O, C-1), 115.7 (C, C-6), 85.4 (CH, C-9), 80.9 (CH, C-3), 80.1 (CH, C-4), 64.7 (CH_2, C-10), 44.5 (C, C-2), 41.1 (CH_2, C-5), 37.2 (CH_2, C-7), 24.8 (CH_2, C-8), 22.8 (CH_3), 17.9 (CH_3). HRMS (ESI): calcd. for $C_{12}H_{18}KO_5$: 281.0786, found: 281.0790.

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SUPPORTING INFORMATION

for

Synthesis of the spiroacetal core of the cephalosporolide family of natural products

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2-((Benzyloxy)methyl)oxirane

NaH (60% dispersion in oil, 5.40 g, 135 mmol) was added to a stirred solution of glycidol **13** (10 g, 135 mmol) and BnBr (10.5 mL, 176 mmol) in THF (300 mL) at 0 °C. The reaction mixture was allowed to reach rt and stirred overnight. H_2O (200 mL) was added and the mixture extracted with CH_2Cl_2 (3 ×100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a crude yellow oil. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent afforded the *title compound* (18.8 g, 84%) as a colourless oil. R_f: 0.5 (80% hexanes/EtOAc); δ_H (400 MHz, $CDCl_3$): 7.35-7.25 (5H, m, Ph*H*), 4.61 (1H, d, *J* = 11.9 Hz, C*H*$_2$Ph), 4.55 (1H, d, *J* = 11.9 Hz, C*H*$_2$Ph), 3.76 (1H, dd, *J* = 3.1, 11.4 Hz, H-3), 3.44 (1H, dd, *J* = 5.8, 11.4 Hz, H-3), 3.21-3.16 (1H, m, H-2), 2.81-2.78 (1H, m, H-1´), 2.62-2.60 (1H, m, H-1´); δ_C (100 MHz, $CDCl_3$): 137.8 (C, Ph), 128.4 (2 × CH, Ph), 127.7 (3 × CH, Ph), 73.3 (CH_2, CH_2Ph), 70.8 (CH_2, C-1´), 50.8 (CH, C-2), 44.3 (CH_2, C-3). The spectroscopic data were in agreement with those reported in the literature.[22]

(R)-2-((benzyloxy)methyl)oxirane ***17***

(*R,R*)-*N,N*-Bis-(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanesanediaminocobalt (II) (0.029 g, 0.05 mmol) was added to a mixture of 2-((benzyloxy)methyl)oxirane (1.63 g, 9.91 mmol), AcOH (0.011 mL, 0.198 mmol) and THF (0.15 mL). The mixture was cooled to 0 °C and treated with H_2O (0.098 mL, 5.45 mmol). The reaction was allowed to reach rt overnight. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent gave the *title compound* **17** (0.795g, 4.84 mmol, 48%) as a colourless oil. R_f: 0.5 (80% hexanes/EtOAc); $[\alpha]_D^{20}$ +6.03 (*c* 1.76, CH_2Cl_2) lit. $[\alpha]_D$+5.4 (*c* 1.76 in CH_2Cl_2);[16] δ_H (400 MHz, $CDCl_3$): 7.35-7.25 (5H, m, Ph*H*), 4.61 (1H, d, *J* = 11.9 Hz, C*H*$_2$Ph), 4.55 (1H, d, *J* = 11.9 Hz, C*H*$_2$Ph), 3.76 (1H, dd, *J* = 3.1, 11.4 Hz, H-3), 3.44 (1H, dd, *J* = 5.8, 11.4 Hz, H-3), 3.21-3.16 (1H, m, H-2), 2.81-2.78 (1H, m, H-1´), 2.62-2.60 (1H, m, H-1´); δ_C (100 MHz, $CDCl_3$): 137.8 (C, Ph), 128.4 (2 × CH, Ph), 127.7 (3 × CH, Ph), 73.3 (CH_2, CH_2Ph), 70.8 (CH_2, C-1´), 50.8 (CH, C-2), 44.3 (CH_2, C-3). The spectroscopic data were in agreement with those reported in the literature.[16]

(2S)-1-(benzyloxy)hex-5-en-2-ol ***18***

Allylmagnesium bromide (4.57 mL, 1M in Et_2O) was added to a stirring solution of (*R*)-benzyl glycidyl ether **17** (0.5 g, 3.05 mmol) and CuI (0.058 g, 0.305 mmol) in THF (20 mL) at -40 °C. The black solution was allowed to warm to rt over 3 h and quenched with sat. aq. NH_4Cl (20 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. Purification by flash chromatography using 4:1 hexanes/EtOAc as eluent gave the *title compound* **18** (0.44 g, 2.13 mmol, 70%) as a yellow oil. R_f: 0.38 (80% hexanes/EtOAc); $[\alpha]_D^{20}$ + 7.36 (*c* 1.00, $CHCl_3$); lit. $[\alpha]_D^{20}$-7.28 (c 1.00, $CHCl_3$) (for enantiomer);[23] δ_H (400 MHz, $CDCl_3$): 7.38-7.29 (5H, m, PhH), 5.87-5.77 (1H, m, H-5), 5.06-4.95 (2H, m, H-6), 4.56 (2H, s, CH_2Ph), 3.87-3.80 (1H, m, H-2), 3.50 (1H, dd, *J* = 9.4, 3.3 Hz, H-1), 3.34 (1H, dd, *J* = 7.9, 9.4 Hz, H-1), 2.31 (1H, d, *J* = 3.5 Hz, OH), 2.27-2.08 (2H, m, H-4), 1.62-1.47 (2H, m, H-3); δ_C (100 MHz, $CDCl_3$): 138.4 (CH, C-5), 138.0 (C, Ph), 128.5 (2 × CH, Ph), 127.8 (CH, Ph), 127.7 (2 × CH, Ph), 115.0 (CH_2, C-6), 74.5 (CH_2, CH_2Ph), 73.4 (CH_2, C-1), 70.0 (CH, C-2), 32.3 (CH_2, C-3), 29.8 (CH_2, C-4). The spectroscopic data were in agreement with those reported in the literature.[17]

(2S)-Tetrahydro-5-hydroxy-2-(benzyloxymethyl)furan ***19***

To a solution of alkene **18** (0.2 g, 0.97 mmol) in dioxane/H_2O (3:1, 4 mL) was added 2,6-lutidine (0.11 mL, 0.97 mmol), OsO_4 (0.25 mL, 2.5% solution in *t*-BuOH, 2 µmol) and $NaIO_4$ (0.42 g, 1.94 mmol) respectively. The suspension was stirred for 2 h and sat. aq. $Na_2S_2O_3$ (2 mL) was added. The reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography using 9:1 hexanes/EtOAc as eluent gave the *title compound* **19** (0.14 g, 0.694 mmol, 71%) as a colourless oil (1:1 mixture of diastereomers). R_f: 0.23 (90% hexanes/EtOAc); δ_H (400 MHz, $CDCl_3$): 7.37-7.27 (10H, m, PhH), 5.60-5.58 (1H, m, H-4), 5.45-5.42 (1H, m, H-4´), 4.60-4.56 (4H, m, CH_2Ph), 4.47-4.40 (1H, m, H-1), 4.33-4.27 (1H, m, H-1´), 3.70-3.56 (2H, m, H-5), 3.51-3.42 (2H, m, H-5´), 2.66-1.66 (8H, m, H-2, H-2´, H-3, H-3´), 1.95 (2H, br s, 2 × OH); δ_C (100 MHz, $CDCl_3$): 138.2 (C, Ph), 137.6 (C´, Ph), 128.5 (2 × CH, Ph), 128.3 (CH, Ph), 127.9 (2 × CH, Ph), 127.8 (2 × CH, Ph), 127.7 (CH, Ph), 127.6 (CH, Ph), 127.6 (CH, Ph), 98.9 (CH, C-4), 98.8 (CH, C-4´), 78.9 (CH, C-1), 78.7 (CH, C-1´), 73.5 (CH_2, CH_2Ph), 72.5 (CH_2, CH_2Ph), 34.6 (CH_2, C-3), 32.7 (CH_2, C-3´), 25.8 (CH_2, C-2), 24.5 (CH_2, C-2´). The spectroscopic data were in agreement with those reported in the literature.[24]

(2S)-Benzyloxymethyl-5-allyltetrahydrofuran ***12***

To a solution of alcohol **19** (5.34 g, 25.9 mmol) in CH_2Cl_2 (125 mL) at -78 °C was added allyltrimethylsilane (12.4 mL, 77.7 mmol) followed by dropwise addition of $BF_3{\cdot}OEt_2$ (3.49 mL, 28.5 mmol). The reaction mixture was stirred for 3 h, sat. aq. NH_4Cl (20 mL) added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave a 1:1 mixture of *cis/trans* isomers of the *title compound* **12** (5.0 g, 21.5 mmol, 83%) as a yellow oil. R_f: 0.38 (90% hexanes/EtOAc); δ_H (400 MHz, $CDCl_3$): 7.36-7.25 (5H, m, PhH), 5.81 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, H-8), 5.10-5.02 (2H, m, H-9), 4.57 (2H, dd, *J* = 5.6, 12.3 Hz, CH_2Ph), 4.23-4.17 (0.3H, m, H-2), 4.11-4.00 (1H, m, H-2´, H-5´), 3.97-3.90 (0.7H, m, H-5), 3.51-3.42 (2H, m, H-6), 2.42-2.35 (1H, m, H-7), 2.27-2.19 (1H, m, H-7´), 2.03-1.87 (2H, m, H-4, H-3), 1.71-1.64 (1H, m, H-3´), 1.59-1.51 (1H, m, H-4´); δ_C (100 MHz, $CDCl_3$): 138.4 (C, Ph), 135.0 (2 × CH, C-7, C-7´), 128.3 (2 × CH, Ph), 127.6 (2 × CH, Ph), 127.5 (CH, Ph), 116.8 (CH_2, C-8), 116.8 (CH_2, C-8´), 79.2 (CH, C-4), 78.7 (CH, C-4´), 78.1 (CH, C-1), 77.7 (CH, C-1´), 73.3 (CH_2, CH_2Ph), 73.0 (CH_2, C-5), 72.9 (CH_2, C-5´), 40.2 (CH_2, C-6), 40.1 (CH_2, C-6´), 31.1 (CH_2, C-2), 30.2 (CH_2, C-2´), 28.5 (CH_2, C-3), 28.1 (CH_2, C-3´). The spectroscopic data were in agreement with those reported in the literature.[18]

*Benzyl 3-hydroxy-2,2-dimethylpropanoate **20***

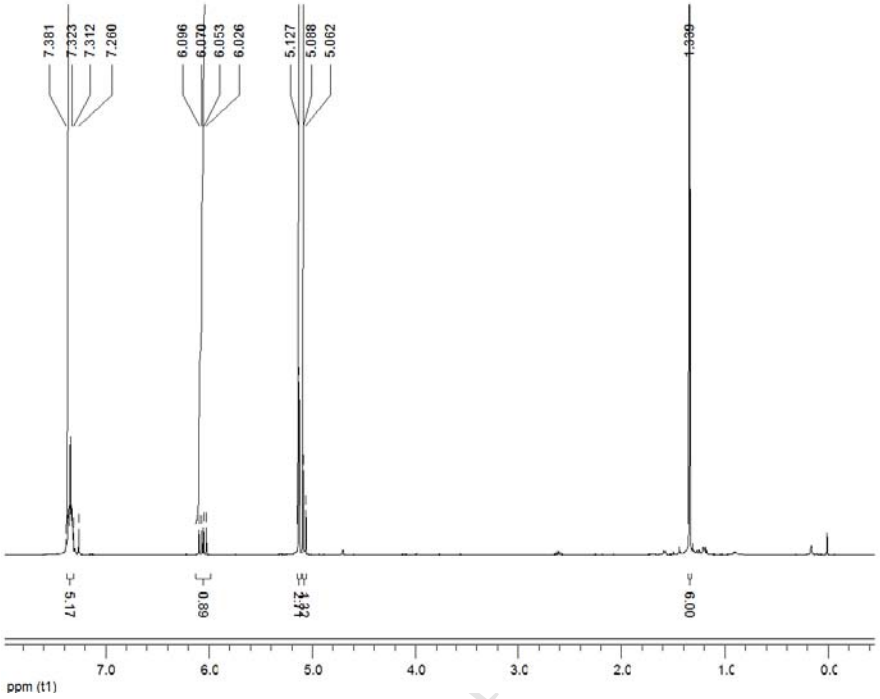
LiOH (15.9 g, 37.9 mmol) in THF/MeOH/H_2O (1:1:0.5, 62.5 mL) was added to a solution of 3-hydroxy-2,2-dimethylpropionate **14** (5 g, 37.9 mmol) in THF/MeOH (1:1, 25 mL) at 0 °C. The solution was warmed to rt and stirred for 1.5 h, the reaction mixture was adjusted to pH 2 by addition of H_2SO_4. The solution was concentrated under reduced pressure to remove THF and the residue washed with H_2O (10 mL), extracted with EtOAc (3 × 12 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the acid (3.3 g, 27.9 mmol, 73%) as a white solid. Benzyl bromide (1.9 mL, 16.1 mmol) was added to a solution of crude acid (2.0 g, 16.9 mmol) and K_2CO_3 (2.57 g, 18.6 mmol) in DMF (20 mL). The reaction mixture was stirred for 5 h then quenched by the addition of H_2O (5 mL). The reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 9:1 to 3:2 hexanes/EtOAc as eluent gave the *title compound* **20** (3.04 g, 86%) as a yellow oil. R_f: 0.48 (60% hexanes/EtOAc); δ_H (400 MHz, $CDCl_3$): 7.39-7.29 (5H, m, Ph), 5.14 (2H, s, CH_2Ph), 3.57 (2H, d, *J* = 6.4 Hz, H-3), 2.54 (1H, br s, OH), 1.21 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 176.9 (C=O, C-1), 135.8 (C, Ph), 128.3 (2 × CH, Ph), 127.9 (CH, Ph), 127.5 (2 × CH, Ph), 69.3 (CH_2, C-3), 66.1 (CH_2, CH_2Ph), 44.2 (C, C-2), 21.8 (2 × CH_3). The spectroscopic data were in agreement with those reported in the literature. [19]

Benzyl 2,2-dimethyl-3-oxopropanoate

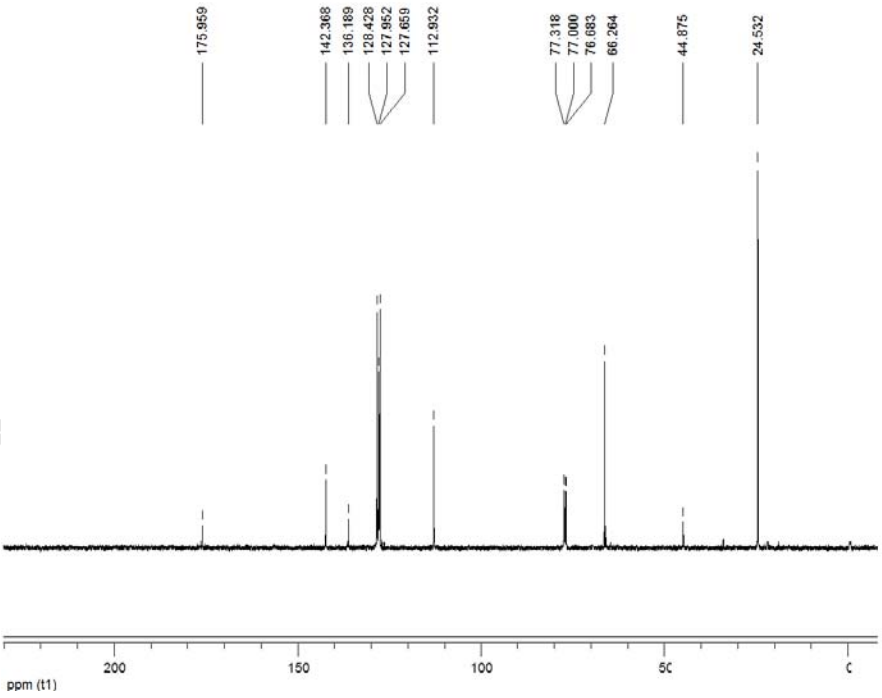
Oxalyl chloride (2.5 mL, 29.2 mmol) was added dropwise to a solution of DMSO (4.14 mL, 58.4 mmol) in CH_2Cl_2 (100 mL) at -78 °C. The reaction mixture was stirred for 10 min and a solution of alcohol **20** (5.0 g, 24.3 mmol) in CH_2Cl_2 (20 mL) was added. The solution was stirred for 1 h, NEt_3 (13.5 mL, 97.3 mmol) added and the solution allowed to warm to rt. H_2O (25 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 9:1 hexanes/EtOAc as eluent gave the *title compound* (4.13 g, 82%) as a yellow oil. R_f: 0.58 (80% hexanes/EtOAc); δ_H (400 MHz, $CDCl_3$): 9.68 (1H, s, H-3), 7.39-7.31 (5H, m, Ph), 5.19 (2H, s, CH_2Ph), 1.37 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$): 198.9 (C=O, C-3), 172.5 (C=O, C-1), 135.3 (C, Ph), 128.6 (2 × CH, Ph) 128.3 (CH, Ph), 127.9 (2 × CH, Ph), 67.1 (CH_2, CH_2Ph), 45.9 (C, C-2), 19.6 (2 × CH_3). The spectroscopic data were in agreement with those reported in the literature._ENREF_20[20]

11 ^{1}H NMR (400 MHz, $CHCl_3$):

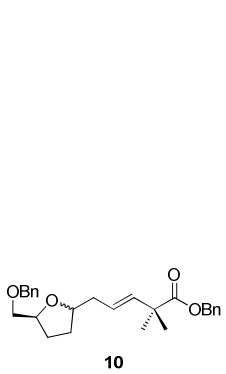
11



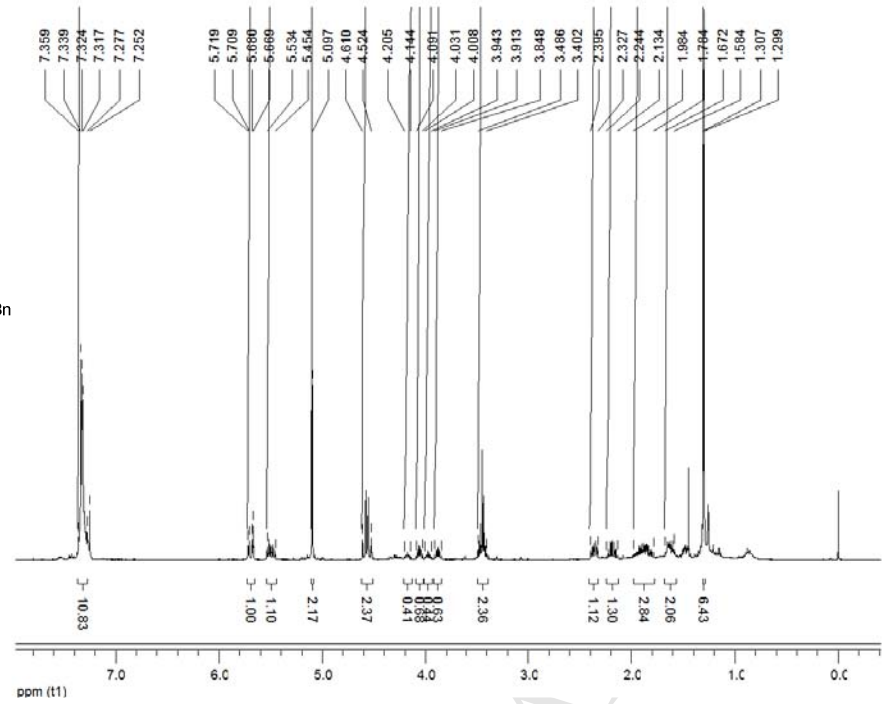
^{13}C NMR (100 MHz, $CHCl_3$):



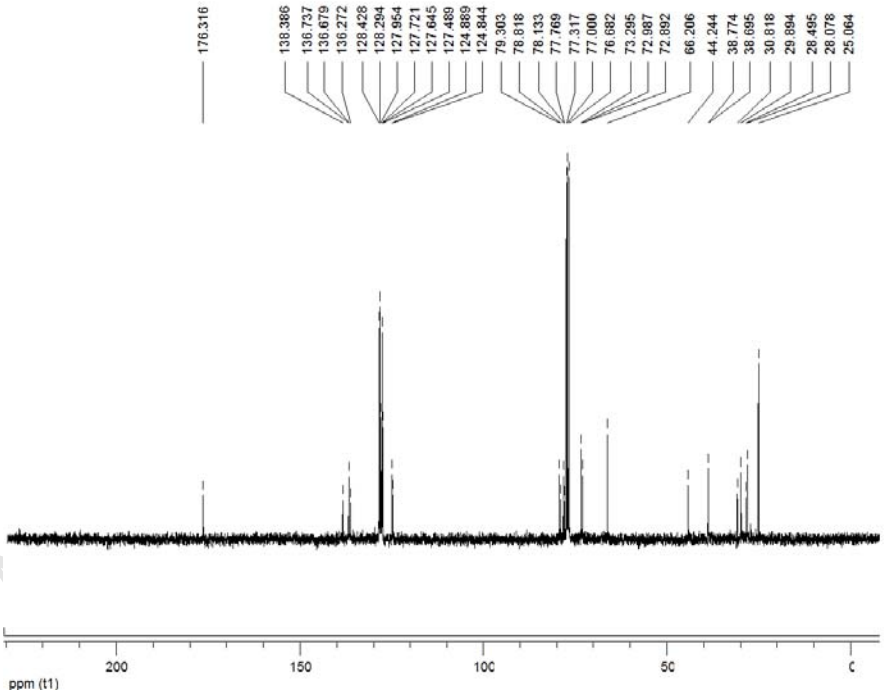
10 ^{1}H NMR (400 MHz, $CHCl_3$):



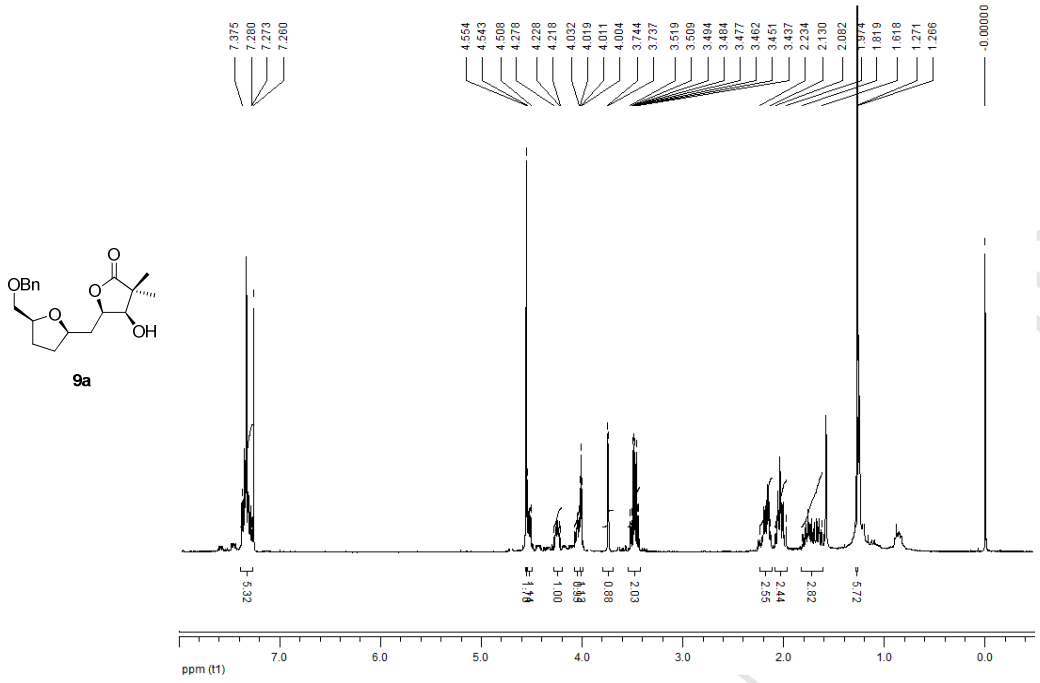
10



^{13}C NMR (100 MHz, $CHCl_3$):

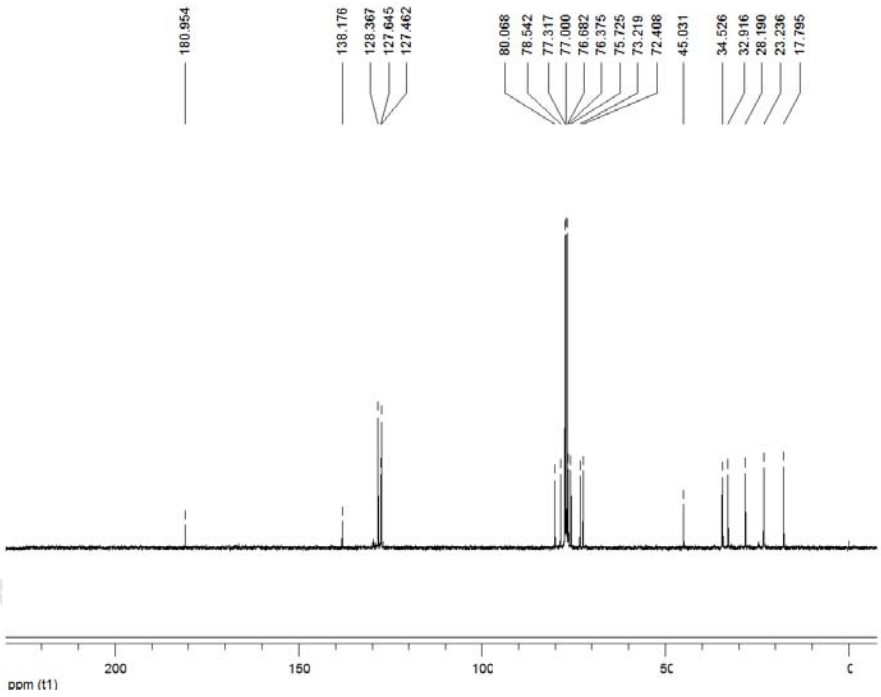


9a ^{1}H NMR (400 MHz, $CHCl_3$):

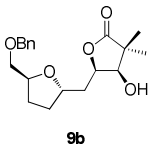


9a

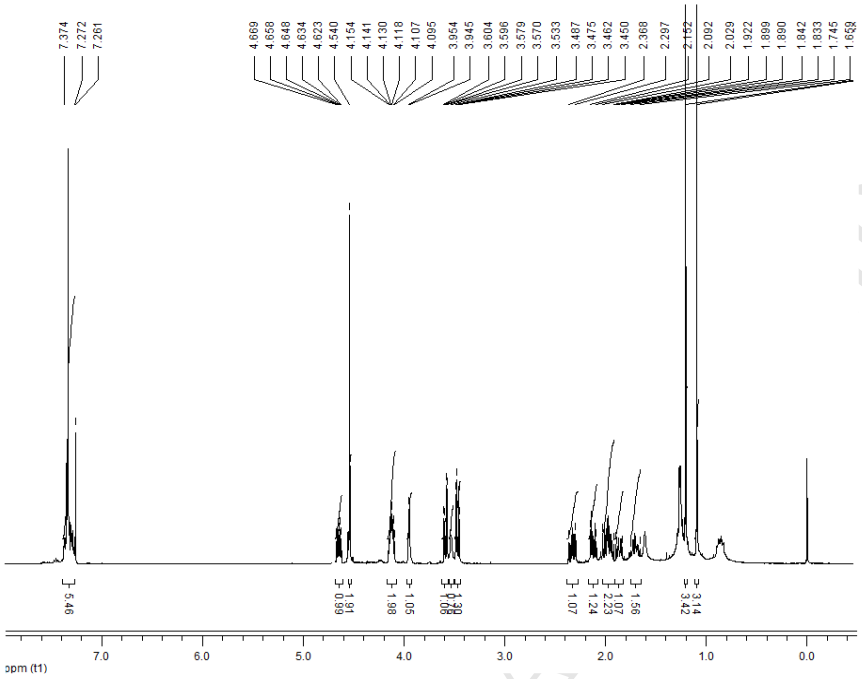
^{13}C NMR (100 MHz, $CHCl_3$):



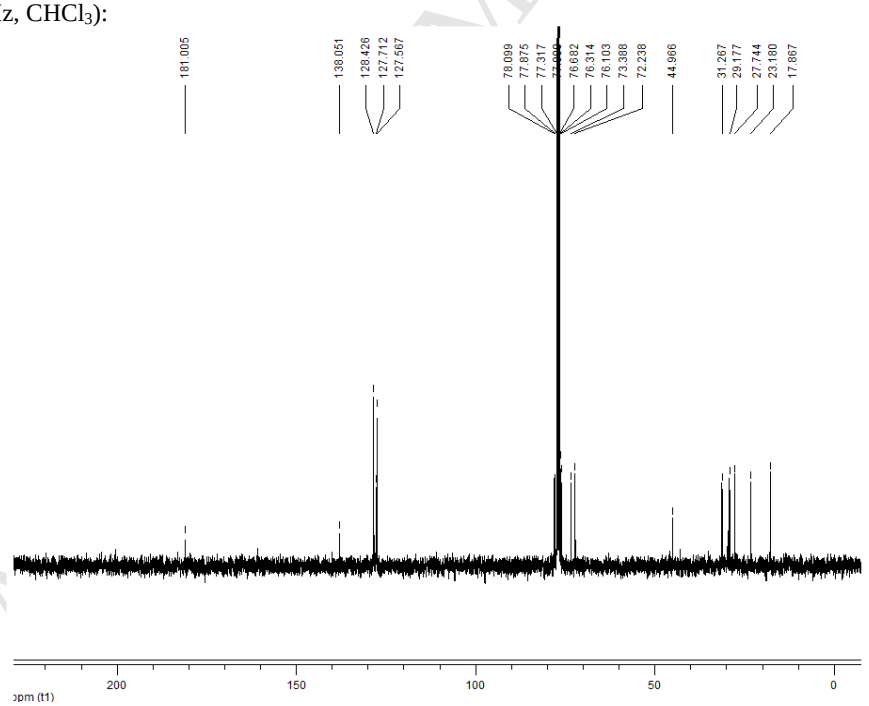
9b ^{1}H NMR (400 MHz, $CHCl_3$):



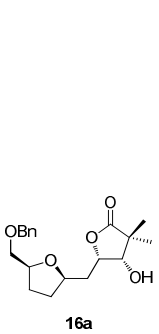
9b



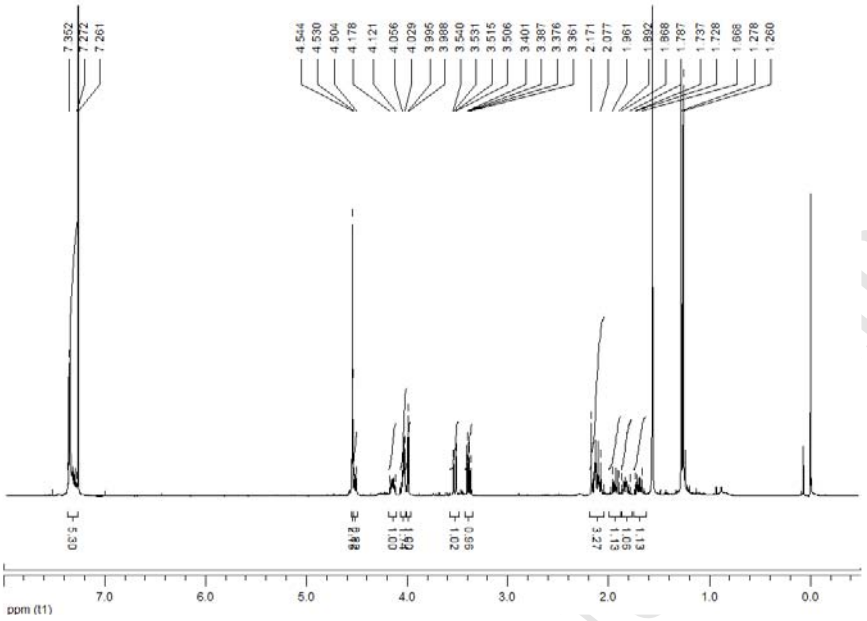
^{13}C NMR (100 MHz, $CHCl_3$):



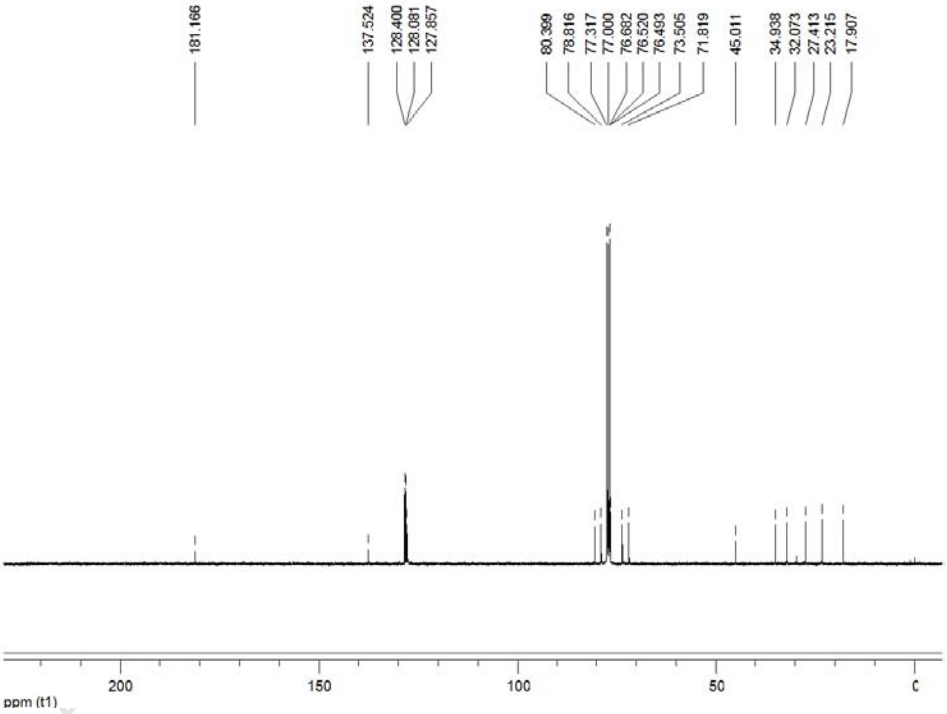
16a ^{1}H NMR (400 MHz, $CHCl_3$):



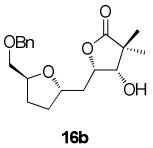
16a



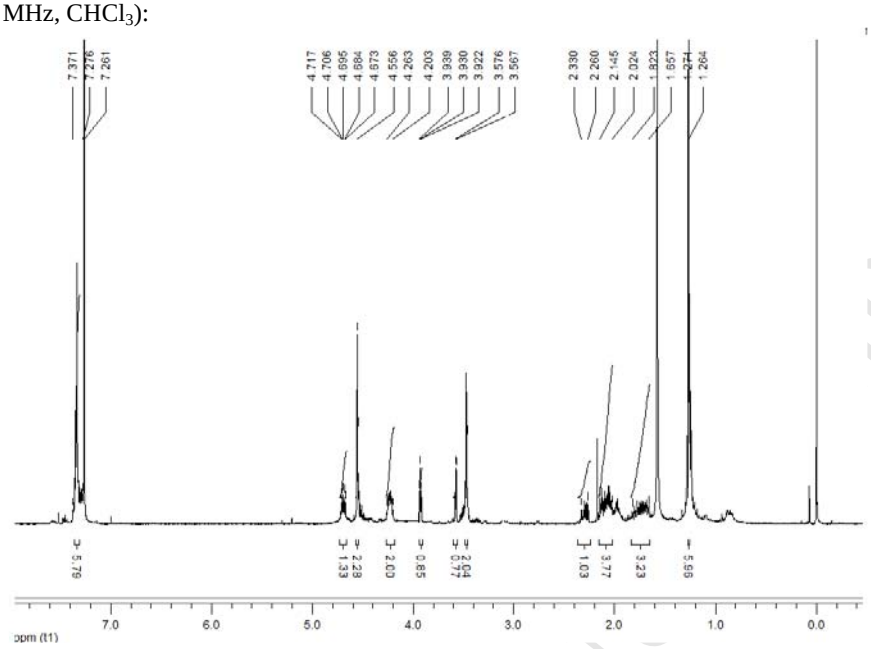
^{13}C NMR (100 MHz, $CHCl_3$):



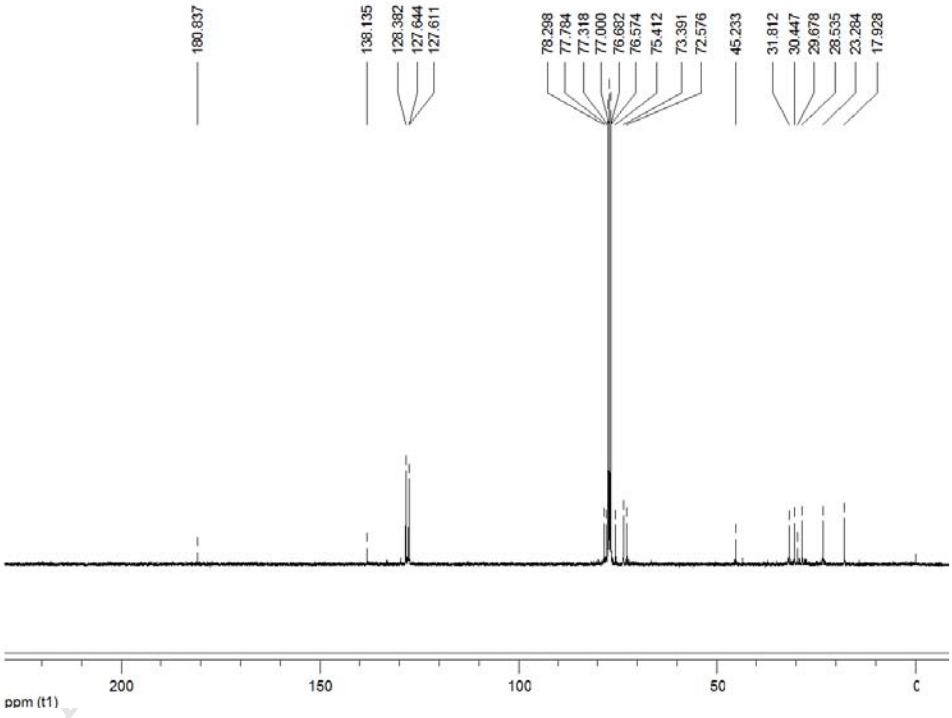
16b ^{1}H NMR (400 MHz, $CHCl_3$):



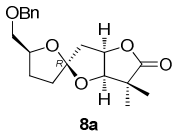
16b

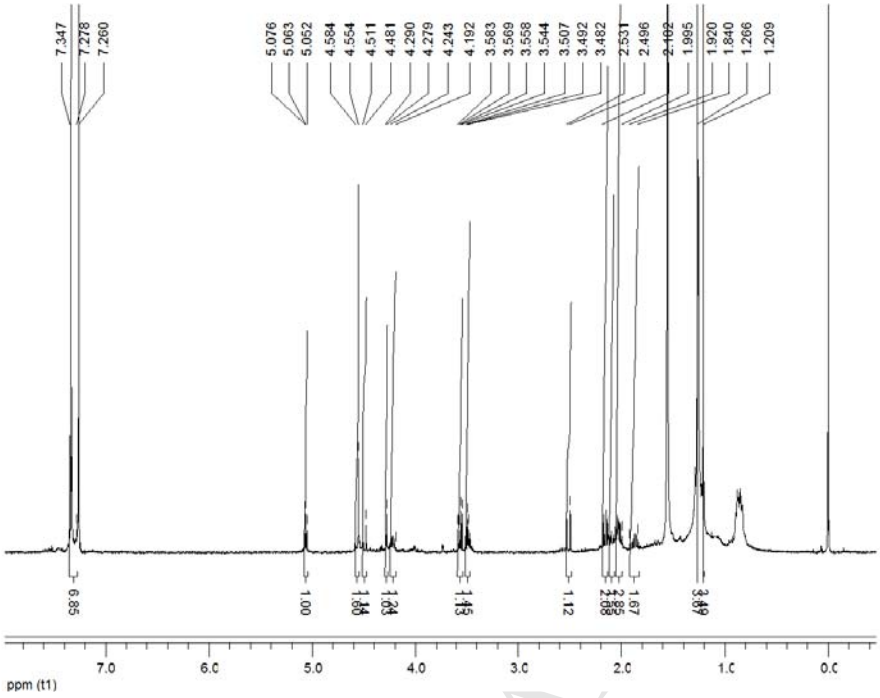


^{13}C NMR (100 MHz, $CHCl_3$):

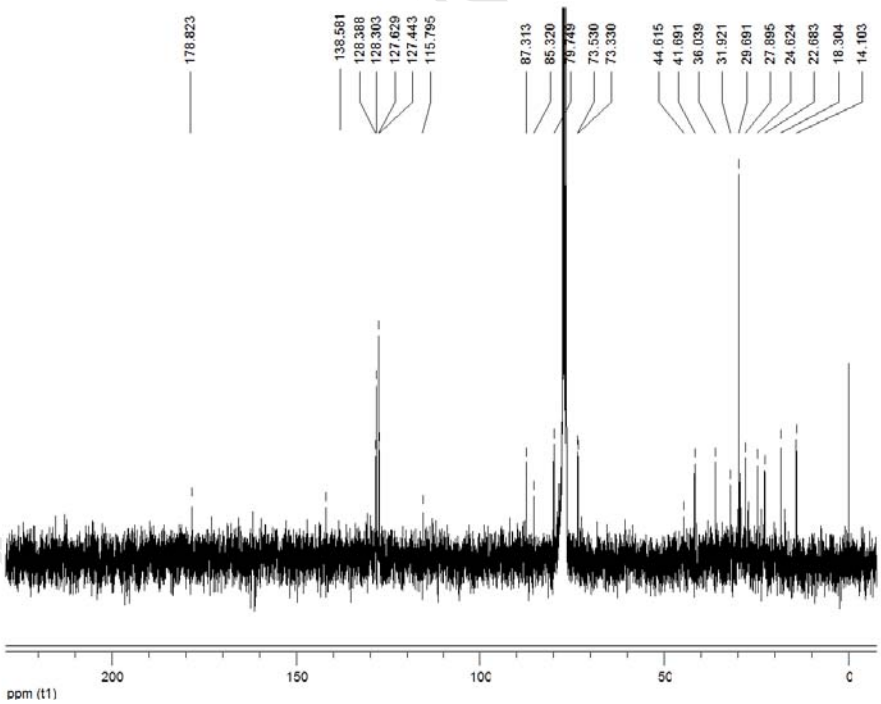


8a ^{1}H NMR (400 MHz, $CHCl_3$):

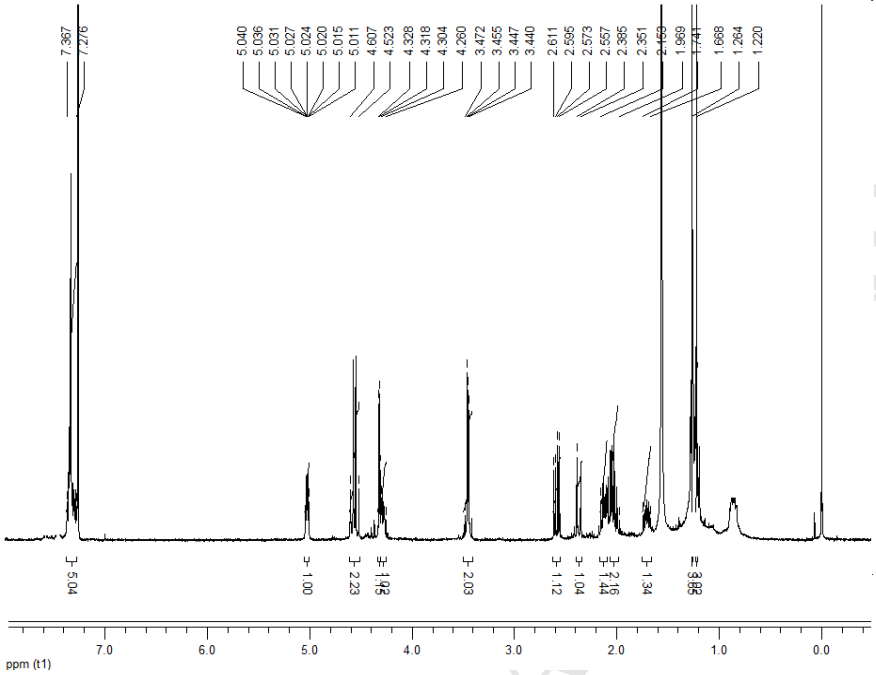




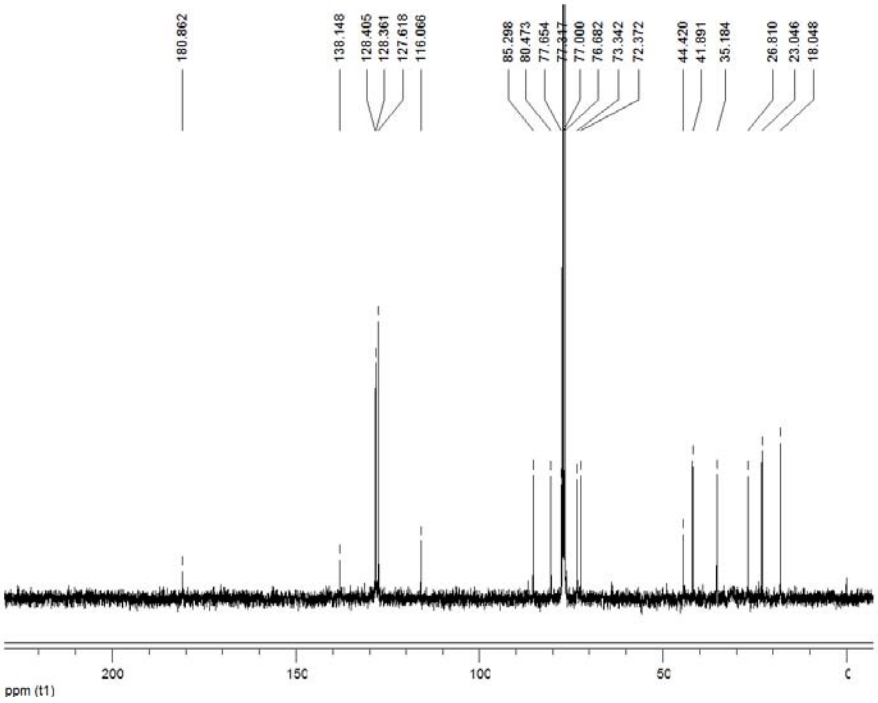
^{13}C NMR (100 MHz, $CHCl_3$):



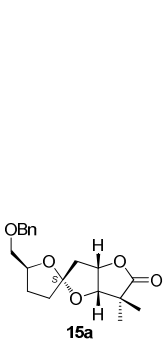
8b ^{1}H NMR (400 MHz, $CHCl_3$):

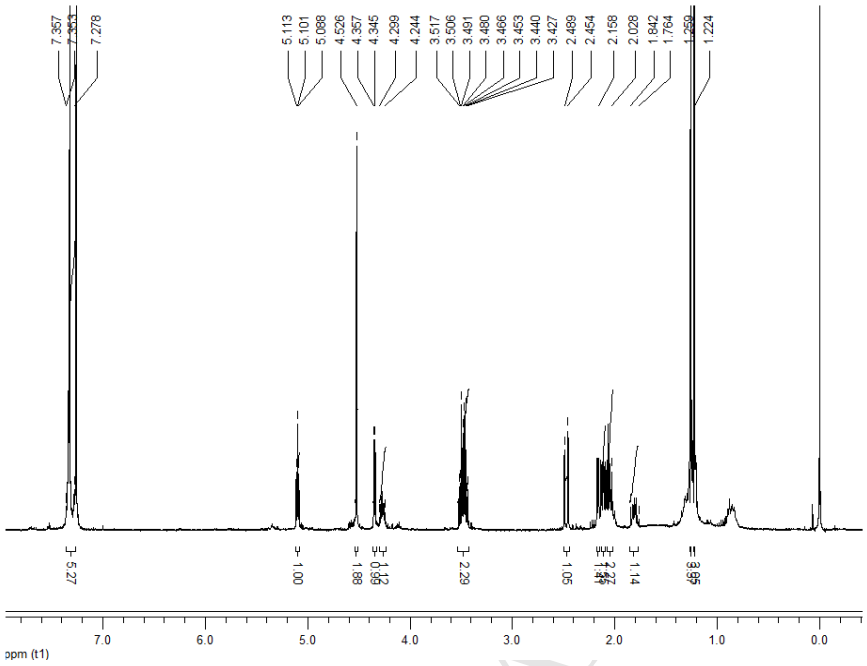


^{13}C NMR (100 MHz, $CHCl_3$):

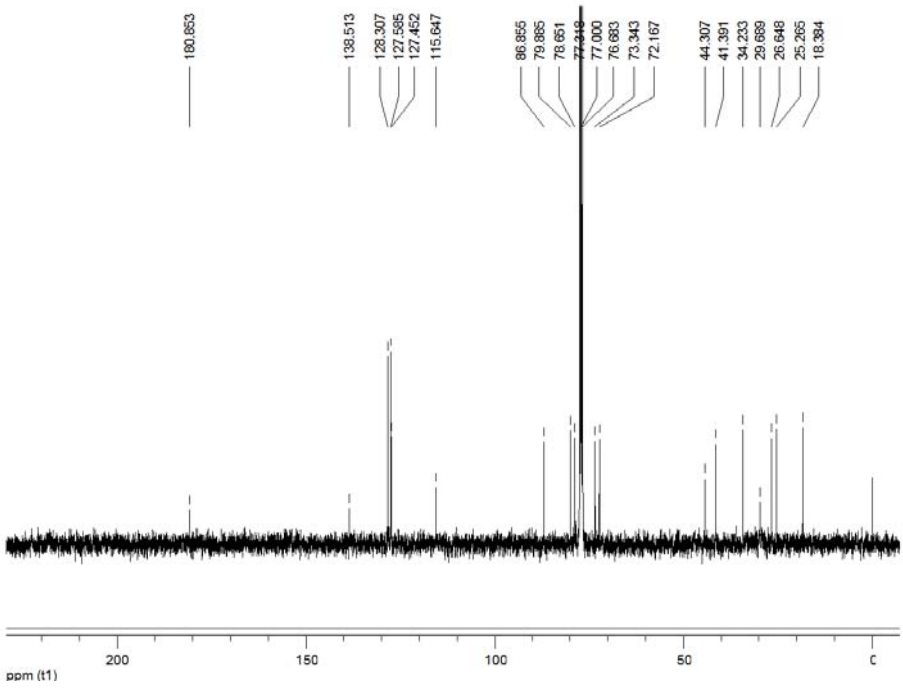


15a ^{1}H NMR (400 MHz, $CHCl_3$):

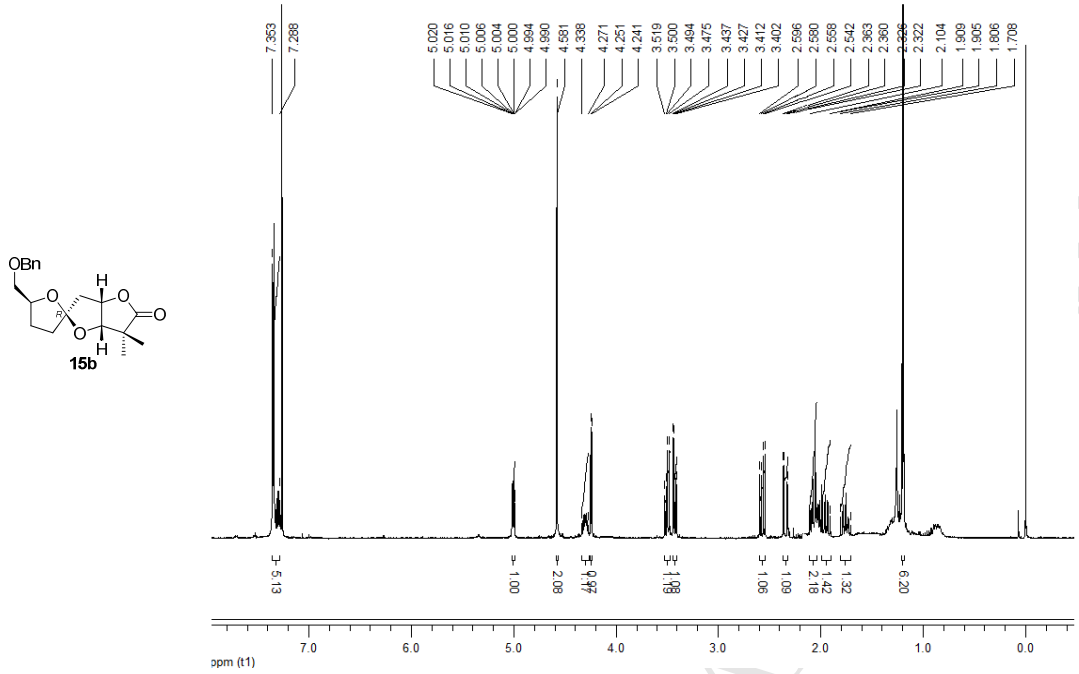




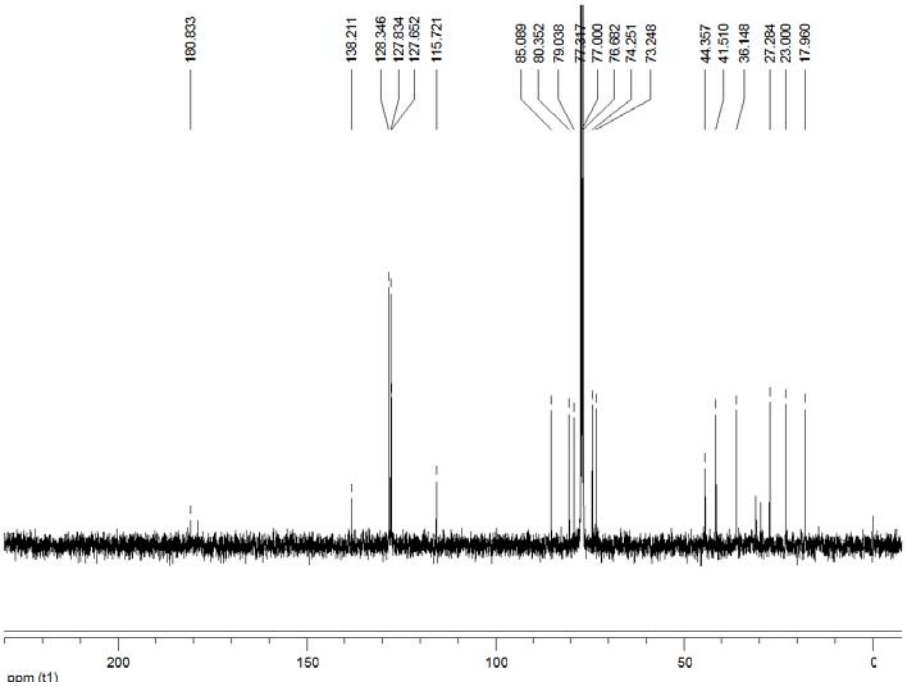
^{13}C NMR (100 MHz, $CHCl_3$):



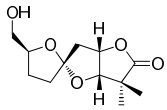
15b ^{1}H NMR (400 MHz, $CHCl_3$):



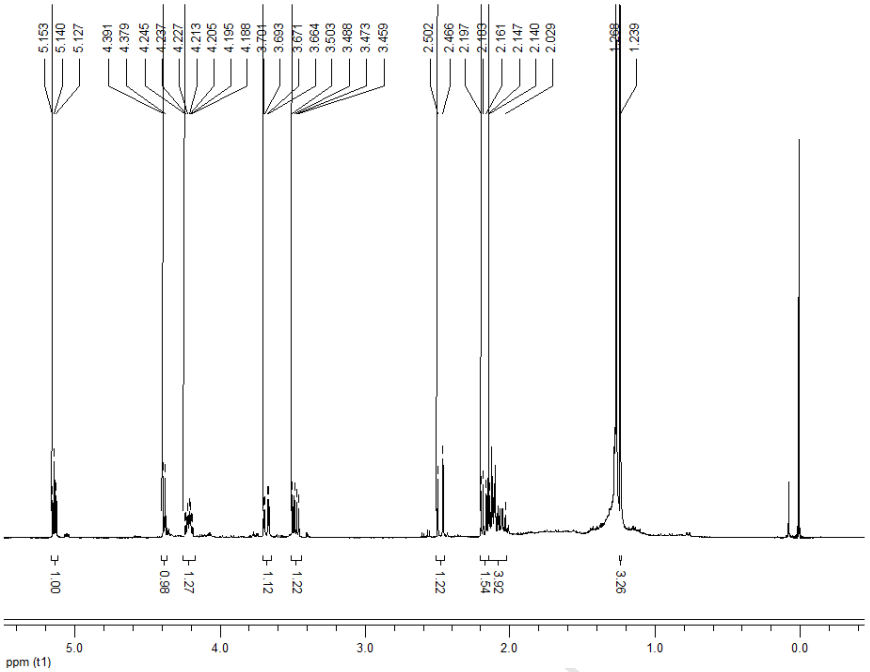
^{13}C NMR (100 MHz, $CHCl_3$):



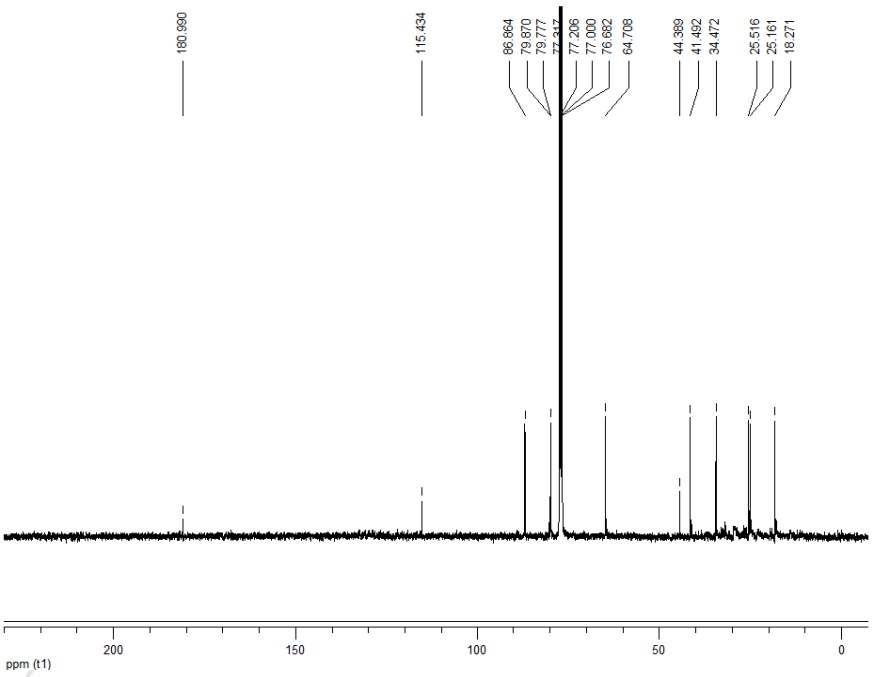
23 ^{1}H NMR (400 MHz, $CHCl_3$):



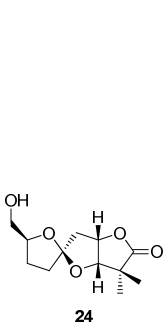
23



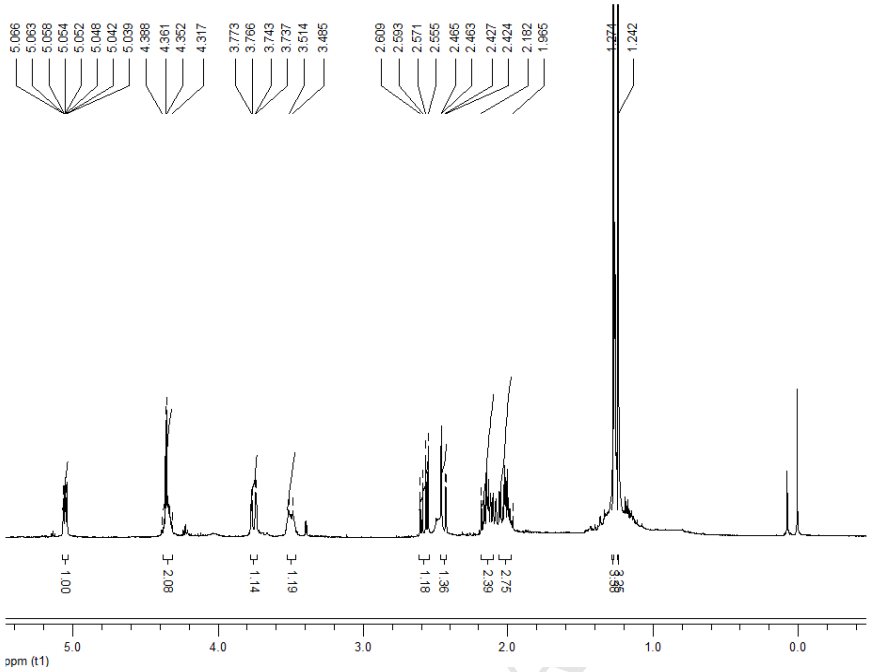
^{13}C NMR (100 MHz, $CHCl_3$):



24 ^{1}H NMR (400 MHz, $CHCl_3$):



24



^{13}C NMR (100 MHz, $CHCl_3$):