Accepted Manuscript

Synthesis of Highly Substituted Pyranonaphthalene Spiroketals Related to the Griseusins using a Hauser-Kraus Annulation Strategy

Briar Naysmith, Daniel Furkert, Margaret Brimble

PII: S0040-4020(13)01934-0

DOI: 10.1016/j.tet.2013.12.066

Reference: TET 25150

To appear in: *Tetrahedron*

Received Date: 31 October 2013

Revised Date: 18 December 2013

Accepted Date: 24 December 2013

Please cite this article as: Naysmith B, Furkert D, Brimble M, Synthesis of Highly Substituted Pyranonaphthalene Spiroketals Related to the Griseusins using a Hauser-Kraus Annulation Strategy, *Tetrahedron* (2014), doi: 10.1016/j.tet.2013.12.066.

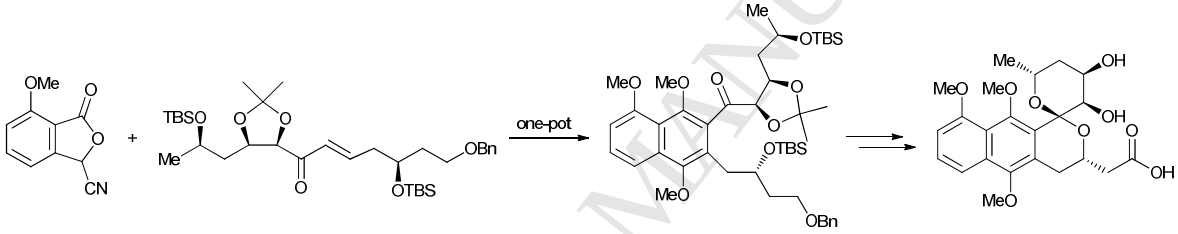
Synthesis of Highly Substituted Pyranonaphthalene Spiroketals Related to the Griseusins using a Hauser-Kraus Annulation Strategy

Briar Naysmith, Daniel Furkert and Margaret Brimble*

School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland, New Zealand

Abstract

The synthesis of an advanced pyranonaphthalene spiroketal as an intermediate for the total synthesis of griseusin B is described. A one-pot Hauser-Kraus annulation-methylation via reaction of a highly-substituted enone with a cyanophthalide was employed to construct the naphthalene framework. Other key steps include Sharpless asymmetric dihydroxylation of a (*Z*)-alkene and an HF-pyridine mediated double TBS deprotection-spirocyclisation.



1. Introduction

The pyranonaphthoquinones are a large family of over one hundred natural products, mostly isolated from bacteria and fungi. Many pyranonaphthoquinones have been found to exhibit a variety of antibacterial, antifungal and anticancer properties.[1,2] The griseusins (Figure 1) are a subgroup of the pyranonaphthoquinone family that contain a 6,6-spiroketal ring fused to a juglone moiety. The first griseusins were isolated from the fermentation broth of a *Streptomyces griseus* K-63 bacterium found in a soil sample from Peru.[3] Griseusin A **1** contains a C9-C10 fused γ-lactone ring whereas in griseusin B **2** the lactone is ring-opened to the carboxylic acid. Since the discovery of griseusin A **1** and B **2** in 1976, fifteen more griseusin natural products have been isolated (**3**-**17**, Figure 1),[4-11] some as recently as 2012. Some of these compounds occur naturally as both enantiomers and differ in oxidation state, acetylation and stereochemistry around the spiroketal ring. The griseusins display variable substitution at C9 of the dihydropyran ring or the C2a-C8a quinone double bond. 3′-*O*-α-D-forosaminyl-(+)-griseusin A **8** contains a sugar moiety at C-3′[4] while yoropyrazone **14** possesses an amide side chain and an additional 2-pyridazone ring.[10]

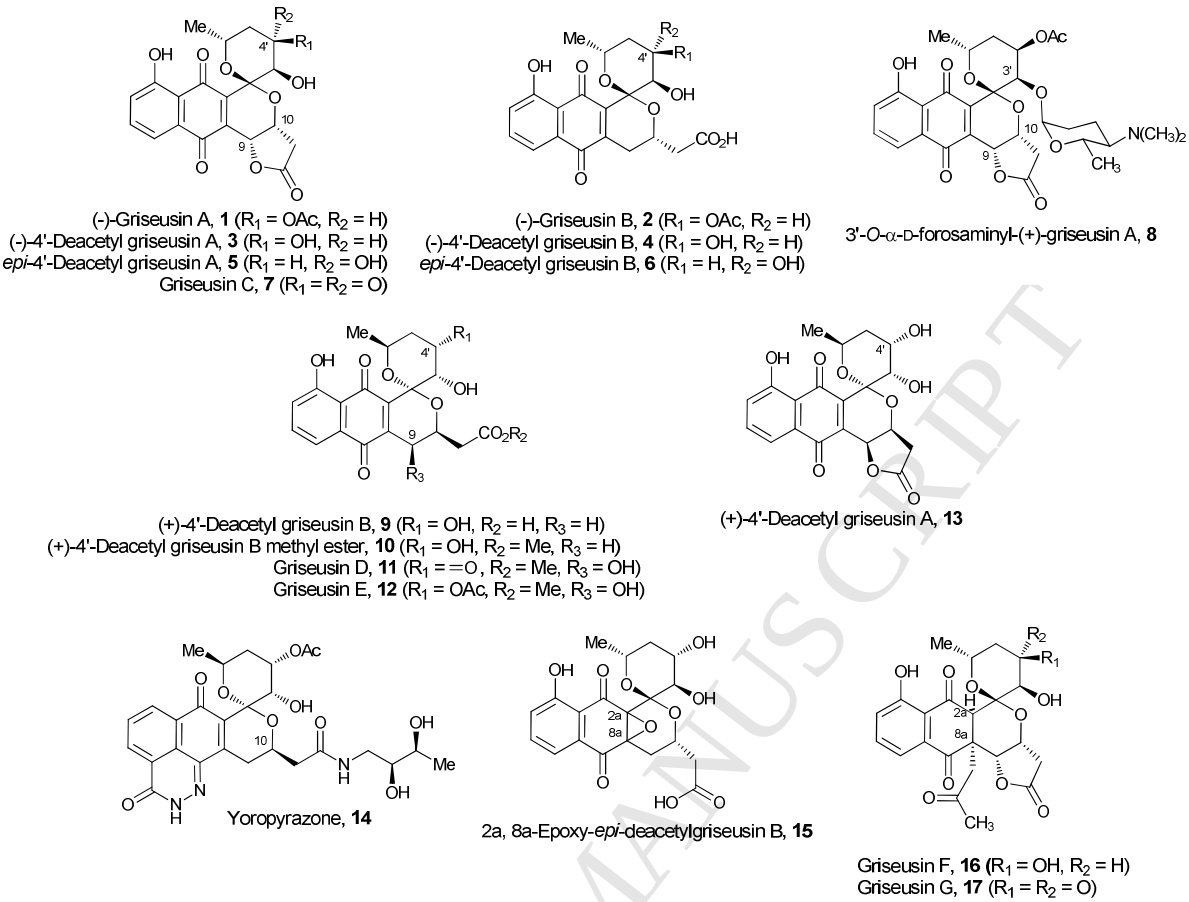
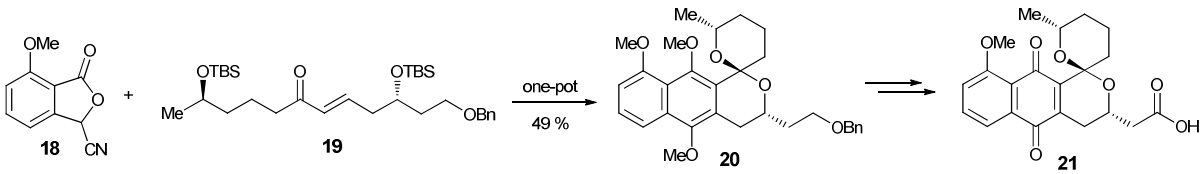


Figure 1. Griseusin natural products.

The griseusins demonstrate interesting biological activity including antibacterial and anticancer properties.[3,4] Pyranonaphthoquinones in general have long been proposed to act as bioreductive alkylating agents[12] and have recently been shown to exhibit selective inhibitory activity against serine/threonine AKT,[13] both of which may contribute to their activity against cancer cells. Due to their biological activity and interesting structures, the griseusins constitute attractive synthetic targets. Despite this, there is only one total synthesis of (+)-griseusin A and B to date, achieved by Yoshii *et al.* in 1983.[14]

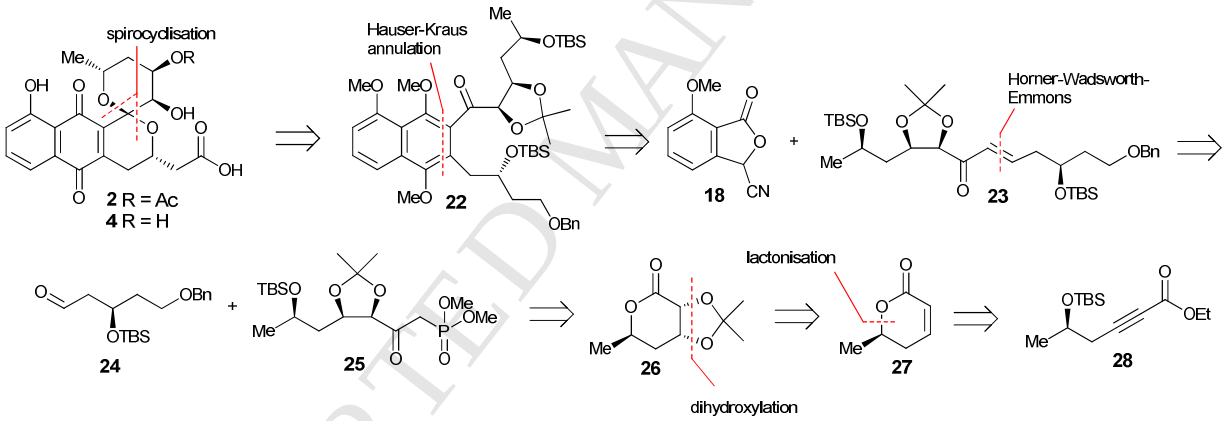
We have recently reported the enantioselective synthesis of a griseusin B model spiroketal **21** using a Hauser-Kraus (HK) annulation strategy to construct the tetracyclic griseusin B framework **20** (Scheme 1).[15] Remarkably, enone **19** underwent a one-pot annulation-methylation-double deprotection-spirocyclisation sequence with cyanophthalide **18** to give a single isomer of the spiroketal framework of griseusin B **20**. Spiroketal **20** was elaborated to model griseusin B **21** by side-chain manipulation and AgO facilitated oxidative demethylation.[15]



Scheme 1. Synthesis of model griseusin B **21**.[15]

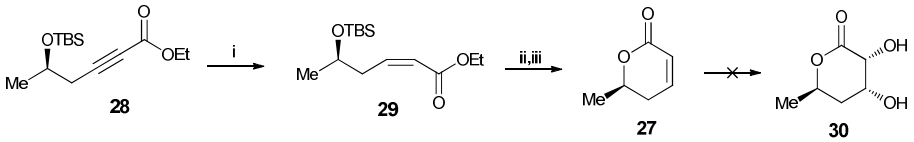
2. Results and Discussion

It was envisioned that the griseusin B model strategy could be extended to the synthesis of the natural products 4′-deacetyl griseusin B **4** and griseusin B **2** from naphthalene **22** that is assembled via an HK annulation between phthalide **18** and highly substituted enone **23** (Scheme 2). Horner-Wadsworth-Emmons (HWE) reaction of highly oxygenated phosphonate **25** with aldehyde **24**, which was used our previous griseusin B model synthesis,[15] would furnish enone **23**. Phosphonate **25** should be accessible by opening of lactone **26** with the anion derived from dimethyl methylphosphonate.[16] Lactone **26** would be obtained by dihydroxylation of unsaturated lactone **27** that in turn is formed via partial reduction, deprotection and lactonisation of previously synthesised alkyne **28**.[15]



Scheme 2. Retrosynthetic analysis of griseusin B **2** and 4′-deacetyl griseusin B **4**.

Our synthetic endeavours began with efforts towards diol **30** (Scheme 3) that is required for the preparation of phosphonate **25**. Alkyne **28**, synthesised according to the previous model synthesis,[15] was partially hydrogenated over Lindlar catalyst in EtOAc. Initial efforts gave a complex mixture of the (*Z*)- and (*E*)-alkenes as well as the fully saturated product, however the addition of quinoline afforded a 93% yield of the desired (*Z*)-alkene **29** after 1.5 hours. Deprotection of the silyl ether using TBAF followed by CSA-mediated lactonisation furnished unsaturated lactone **27**. Dihydroxylation of lactone **27** using NMO and osmium tetroxide resulted in complete consumption of the starting material, however the desired lactone diol **30** could not be isolated.

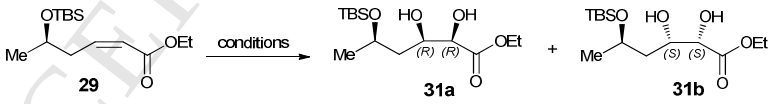


Reagents and conditions: (i) Lindlar catalyst (20 wt%), quinoline (1 v/v%), H_2, EtOAc, 93%; (ii) TBAF (1 M), THF; (iii) CSA, CH_2Cl_2, 39% (2 steps).

Scheme 3. Initial route to lactone diol **30**.

In order to address this problem, Sharpless asymmetric dihydroxylation of (*Z*)-alkene **29**, the precursor to lactone **27**, was investigated. Dihydroxylation of alkene **29** with NMO and osmium tetroxide gave a 1.2:1 ratio of the undesired (*S*,*S*)-diol **31b** to the desired (*R*,*R*)-diol **31a**, revealing a slight bias of this system towards the (*S*,*S*)-diol **31b** (Table 1, entry 1). Sharpless asymmetric dihydroxylation using the $(DHQ)_2PHAL$ ligand with standard Sharpless conditions[17] was not complete after 7 days and proceeded with no selectivity (entry 2). Increasing the reaction temperature and the concentration of ligand and osmium tetroxide gave an 84% yield of a 2.5:1 ratio of inseparable diols **31a**:**31b** in favour of the (*R*,*R*)-diol **31a** after 3 days (entry 3). Decreasing the temperature did not increase the diastereoselectivity, only yielding a 2.3:1 diastereomeric ratio of **31a**:**31b** (entry 4). Dihydroxylation of (*Z*)-alkenes is known to be unreliable among the various alkene types subjected to Sharpless asymmetric dihydroxylation, becoming increasingly difficult when the two substituents are close in size.[17] Our approach was additionally disadvantaged by attempting to override the natural bias of the system. Bearing these factors in mind, we chose to proceed with the 2.5:1 ratio of diols **31a**:**31b** obtained.

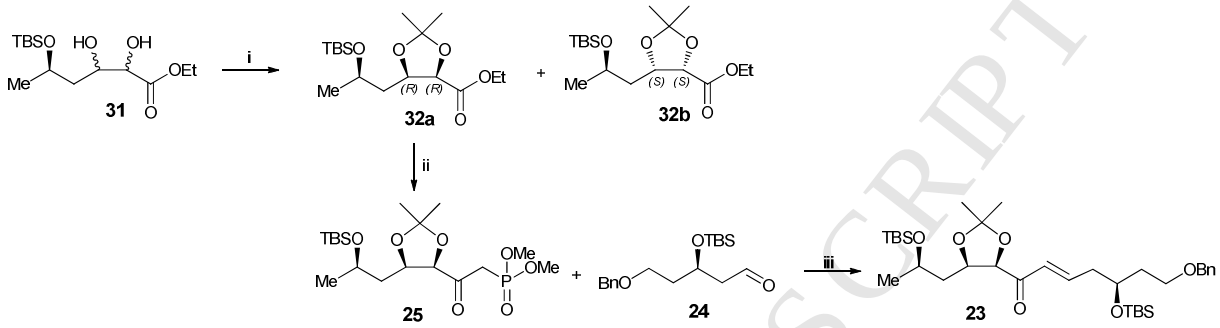
Table 1. Sharpless *cis*-dihydroxylation of alkene **29**



Entry	Ligand	Ligand (mol%)	OsO_4 (mol%)	Temp	Time (days)	Yield	dr (31a:31b)
1[a]	NMO	n/a	0.4	rt	3	70%	1:1.2
2[b]	$(DHQ)_2PHAL$	1	0.4	0 °C	7	16%[c]	1:1
3[b]	$(DHQ)_2PHAL$	5	1	rt	3	84%	2.5:1
4[b]	$(DHQ)_2PHAL$	5	1	4 °C	4	69%	2.3:1

[a] Reaction carried out in $H_2O/(CH_3)_2CO$
[b] Reaction carried out in 1:1 *t*-BuOH/H_2O with $K_3Fe(CN)_6$, K_2CO_3 and $MeSO_2NH_2$
[c] 43% starting material recovered

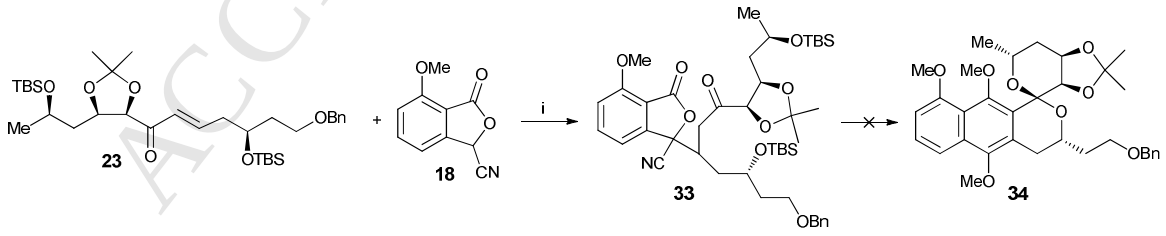
The mixture of diols **31a** and **31b** was protected using 2-methoxypropene, affording acetonides **32a** and **32b**, which were separable by careful flash chromatography (Scheme 4). The (*R*,*R*)-diastereomer **32a** was then converted to phosphonate **25** in 86% yield by treatment with lithiated dimethyl methylphosphonate.[15] HWE reaction of chiral phosphonate **25** with aldehyde **24**[15] under mild aqueous conditions[18] gave the desired (*E*)-enone **23** in 81% yield.



Reagents and conditions: (i) 2-methoxypropene, PPTS, CH_2Cl_2, **32a** 42%, **32b** 16%; (ii) $MeP(O)(OMe)_2$, *n*-BuLi, THF, -78 °C then **32a**, THF, -78 °C, 86%; (iii) K_2CO_3, H_2O/Et_2O, 81%.

Scheme 4. Preparation of enone **23**.

With enantiopure enone **23** in hand, attention turned to the key HK annulation to form the pyranonaphthoquinone framework. The reaction was first attempted using the one pot annulation-methylation conditions previously established in our lab for the synthesis of the model griseusin B framework. This procedure enabled trapping of the unstable dihydroxynaphthalene annulation product as a dimethyl ether.[15] Annulation was effected using *t*-BuOK followed by biphasic methylation with sodium hydroxide and dimethyl sulfate. However, in the present case, the product isolated was not the desired spiroketal product **34** but the intermediate Michael addition product **33** (Scheme 5).

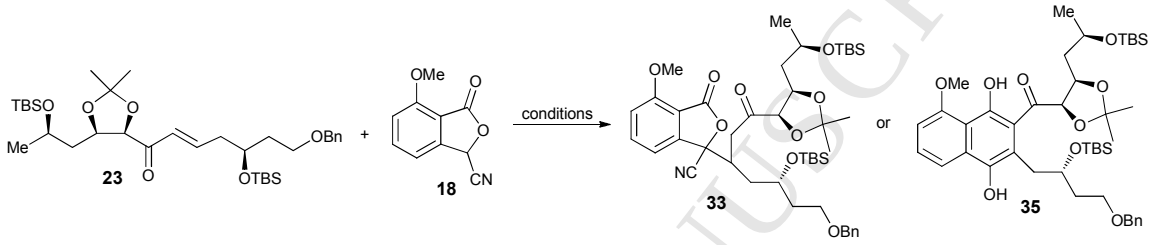


Reagents and conditions: (i) a. *t*-BuOK, THF, b. aq NaOH, Me_2SO_4, H_2, 42%.

Scheme 5. Formation of Michael addition product **33**.

The mechanism of HK annulation involves Michael addition followed by Dieckmann-like condensation to form the bicyclic system.[19] A range of alternative bases and reaction conditions were screened to effect complete HK annulation to afford the desired hydroquinone product **35** (Table 2). Use of *t*-BuOK in THF only afforded the previously isolated Michael addition product **33** (Table 2, entries 1-2). Attempts to cyclise the isolated Michael addition product **33** using *t*-BuOK, LDA or sodium hydride resulted in no reaction or degradation. Use of DME as solvent or LDA as base were also both unsuccessful (entries 3-4). Finally, use of *t*-BuOLi in THF afforded the desired hydroquinone **35**, albeit in modest yield (entry 5).

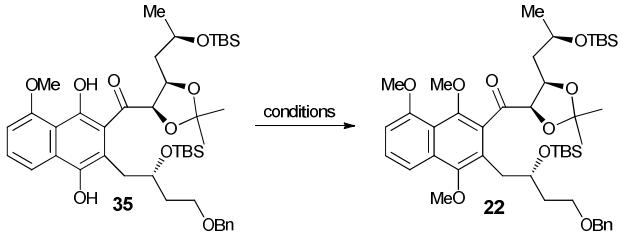
Table 2. HK annulation of enone **23** with phthalide **18**.



Entry	Base	Solvent	Temperature	Result
1	*t*-BuOK	THF	rt	**33** (33%)
2	*t*-BuOK	THF	rt → 55 °C	**33** (42%)
3	*t*-BuOK	DME	100 °C	decomposition
4	LDA	THF	-78 °C	decomposition
5	*t*-BuOLi	THF	rt	**35** (49%)

Conditions for the methylation of **35** to afford the more stable trimethoxynaphthalene **22** were next investigated (Table 3). Attempted methylation of isolated hydroquinone **35** using methyl iodide with either cesium carbonate or sodium hydride was unsuccessful (Table 3, entries 1-2). Reaction of **35** with potassium carbonate and dimethyl sulfate in refluxing acetone produced the trimethoxynaphthalene **22** in 24% yield over two steps (entry 3). Use of cesium carbonate resulted in only a 5% yield of trimethoxynaphthalene **22** (entry 4). Pleasingly, an acceptable yield of trimethoxynaphthalene **22** was obtained employing an adaptation of the one-pot annulation-methylation from the model synthesis using *t*-BuOLi for the annulation in place of *t*-BuOK, followed by the biphasic methylation. These conditions afforded a 41% yield of trimethoxynaphthalene **22** from enone **23** and phthalide **18** in one pot (entry 5).

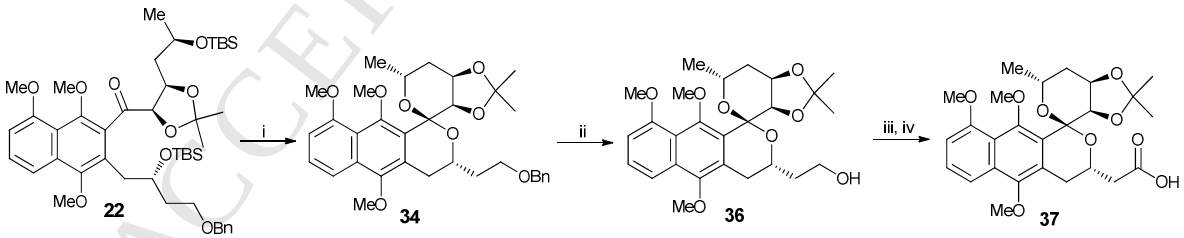
Table 3. Methylation of annulation product **35**.



Entry	Base	Methylating agent	Solvent	Yield
*methylation of isolated hydroquinone **35***				
1	Cs_2CO_3	MeI	THF[a]	decomposition
2	NaH	MeI	THF[a]	decomposition
3	K_2CO_3	Me_2SO_4	acetone[b]	24%
4	Cs_2CO_3	Me_2SO_4	acetone[b]	5%
*one-pot annulation/methylation of enone **23** and phthalide **18***[c]				
5	aq NaOH	Me_2SO_4	THF[a]	41%

[a] room temperature
[b] reflux
[c] using *t*-BuOLi in THF for annulation step and TBAB in the methylation step

Trimethoxynaphthalene **22** could be deprotected and cyclised using HF·pyridine to afford a single spiroketal **34** in 73% yield (Scheme 6). Subsequent progress toward the natural product proceeded in excellent yields according to conditions established in the model synthesis.[15] The benzyl ether was deprotected by exposure to hydrogen at high pressure in the presence of $Pd(OH)_2/C$ to give alcohol **36**. Two-step oxidation with IBX followed by Pinnick oxidation cleanly afforded carboxylic acid **37** (Scheme 6).



Reagents and conditions: (i) HF·pyr, THF, 73%; (ii) $Pd(OH)_2/C$, H_2 (30 psi), THF, 100%; (iii) IBX, DMSO, 30 °C; (iv) 2-methyl-2-butene, $NaClO_2$, KH_2PO_4, *t*-BuOH, H_2O, 90% (2 steps).

Scheme 6. Preparation of advanced carboxylic acid spiroketal **37**.

In the previous model synthesis, an X-ray structure was obtained showing that the spirocyclisation gave solely the thermodynamic isomer with the C2-O1′ bond pseudoaxial, stabilised in part by the

anomeric effect.[15] Based on this precedent, spiroketal **34** is expected to have the anomeric configuration shown (Figure 2). Additionally, nOe correlations from 3′-H, 4′-H and 7′-Me to the 3-OMe group of the pyranonaphthoquinone ring were observed, that are only possible in the configuration shown.

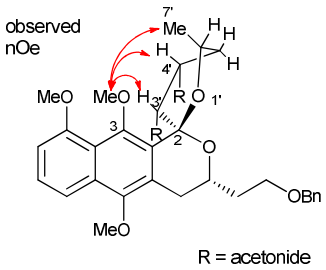
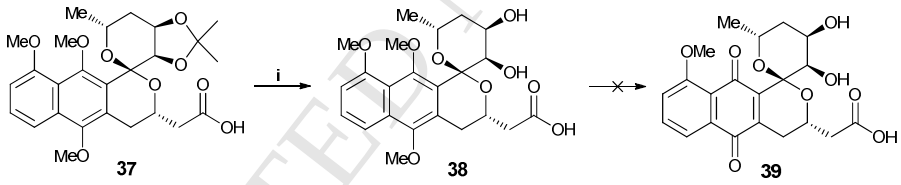


Figure 2. Observed nOe correlations in spiroketal **34**.

Disappointingly, initial efforts to elaborate advanced intermediate **37** to griseusin B **2** via oxidative demethylation followed by global deprotection proved unsuccessful. The acetonide was cleaved using aqueous HCl in THF affording diol acid **38** in 90% yield (Scheme 7). Frustratingly, all efforts to effect oxidative demethylation of trimethoxynaphthalene **38** to form quinone **39** using a variety of reagents (AgO, CAN, PIFA) were unsuccessful.[20]



Reagents and conditions: (i) 1M HCl, THF, 90%.

Scheme 7. Synthesis of advanced spiroketal diol **38**.

3. Conclusion

In summary, the synthesis of advanced spiroketal **38** required to execute the total synthesis of griseusin B **2** has been achieved. Key steps include Sharpless asymmetric dihydroxylation of (*Z*)-alkene **29**, HWE reaction of phosphonate **25** with aldehyde **24** and a one-pot Hauser-Kraus annulation-methylation reaction to afford complex trimethoxynaphthalene intermediate **22**. This synthetic route is potentially adaptable to other griseusin natural products by varying the substitution of the enone in the HK annulation step. Difficulties in achieving oxidative demethylation of advanced trimethoxynaphthalene intermediate **38** prevented the total synthesis of griseusin B **2** and 4′-deacetylgriseusin B **4**. Notwithstanding this, the work reported herein demonstrates the application of the HK annulation using a highly functionalised enone partner. The work also constitutes the

synthesis of advanced trimethoxynaphthalene spiroketals **34**, **36**, **37** and **38** providing valuable materials for biological evaluation.

4. Experimental Section

4.1 General Methods.

THF and Et_2O were freshly distilled over sodium/benzophenone ketyl. CH_2Cl_2 was freshly distilled from CaH_2 and acetone was freshly distilled from $CaCl_2$. Reactions were monitored by thin-layer chromatography (TLC) using Kieselgel F254 0.2 mm (Merck) silica plates with visualisation by ultraviolet irradiation (254 nm) followed by staining with vanillin or potassium permanganate. Optical rotations were measured at wavelength 589 nm, with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded on a film ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded operating at 300MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei or 400MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei, as stated. Chemical shifts were referenced to δ 7.26 and 77.0 ppm from tetramethylsilane for chloroform for ^1H and ^{13}C, respectively. All coupling constants *J* are reported in hertz. All ^{13}C NMR spectra were acquired using broadband decoupled mode, and assignments were determined using DEPT135, DEPT90, COSY, HSQC and NOESY experiments where required. High resolution mass spectra were obtained by electrospray ionisation in positive ion mode at a nominal accelerating voltage of 70 eV.

Compounds **18**, **24** and **28** were synthesised as described previously.[15]

4.2 Ethyl (*R,Z*)-5-(*tert*-butyldimethylsilyloxy)hex-2-enoate (29)

Alkyne **28** (1.59 g, 5.88 mmol) was dissolved in EtOAc (60 mL) and quinoline (60 µL). Lindlar catalyst (314 mg, 20 wt%) was added and the reaction stirred under a H_2 atmosphere for 1.5 h until TLC showed complete consumption of **28**. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude oil was purified by flash chromatography (hexanes/EtOAc 19:1) to give the title compound **29** (1.50 g, 93%) as a colourless oil; R_f (hexanes/EtOAc 19:1): 0.58; ν_{max}(neat)/cm^{-1} 2957, 2930, 2858, 1720; $[\alpha]_D^{20}$ -9.25 (*c* 1.02 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9 H), 1.16 (d, *J* = 5.9, 3H), 1.28 (t, *J* = 7.1, 3H), 2.79 (m, 2H), 3.96 (m, 1H), 4.15 (q, *J* = 7.1, 2H), 5.83 (ddd, *J* = 1.9, 1.9, 11.3, 1H), 6.35 (ddd, *J* = 7.3, 7.3, 11.7, 1H); δ_C (400 MHz; $CDCl_3$) -4.8, -4.5, 14.3, 18.0, 23.7, 25.8, 38.6, 59.8, 67.9, 120.8, 146.9, 166.4; m/z (ESI+) $[M^+ + Na^+]$ 295.1700 calcd for $C_{14}H_{28}NaO_3Si^+$ 295.1700.

4.3 (*R*)-6-Methyl-5,6-dihydro-2*H*-pyran-2-one (27)

Alkene **29** (560 mg, 2.06 mmol) was dissolved in distilled THF (12 mL) and TBAF (1 M in THF, 4.1 mL, 4.1 mmol) was added. The reaction mixture was stirred for 24 h then diluted with EtOAc (6 mL), quenched with sat. aq $NaHCO_3$ (10 mL), extracted with EtOAc (3 × 5 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was then dissolved in distilled CH_2Cl_2 (8 mL) and a spatula tip of (+)-camphorsulfonic acid was added. The reaction mixture was stirred for 21 h then quenched by the addition of solid $NaHCO_3$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc 1:1) to give recovered alkyne **29** (92 mg) and the title compound **27** (90 mg, 39%, 2 steps) as colourless oils; δ_H (400 MHz; $CDCl_3$) 1.41 (d, *J* = 6.3, 3H), 2.31 (m, 2H), 4.55 (m, 1H), 5.98 (m, 1H), 6.85 (m, 1H); δ_C (400 MHz; $CDCl_3$) 20.6, 30.9, 74.3, 121.2, 144.9, 164.4. NMR data closely matched those previously reported.[21]

4.4 Ethyl (5*R*)-5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyhexanoate (31)

$(DHQ)_2PHAL$ (313 mg, 0.40 mmol), $K_3Fe(CN)_6$ (7.94 g, 24.12 mmol), K_2CO_3 (3.33 mg, 24.09 mmol) and OsO_4 (2.5 wt% in *t*-BuOH, 820 µL, 0.08 mmol) were added with stirring to H_2O (40 mL) and *t*-BuOH (40 mL). $MeSO_2NH_2$ (766 mg, 8.05 mmol) was added. The mixture was stirred until clear then cooled to 0 °C and alkene **29** (2.19 g, 8.04 mmol) was added. The reaction was warmed to rt and stirred for 3 days until TLC showed complete consumption of the starting material. The reaction was quenched with sat. aq $Na_2S_2O_3$ (40 mL) and stirred a further 30 min. The aqueous layer was extracted with EtOAc (3 × 30 mL), the combined organic layers were washed with 2 M KOH (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc 1:1) to give the title compound **31** (2.34 g, 95%, 2.5:1 mixture of isomers) as a colourless oil; R_f (hexanes/EtOAc 1:1): 0.60; ν_{max}(neat)/cm^{-1} 3452, 2956, 2930, 2894, 1733; δ_H (400 MHz; $CDCl_3$) 0.09 (2 × s, 2.4H*), 0.11 (2 × s, 6H), 0.89 (s, 9H), 1.20 (m, 3H), 1.31 (m, 3H), 1.56 (m, 1H), 1.76 (m, 1H), 4.03 (m, 1H), 4.10 (m, 1H), 4.17 (m, 1H), 4.28 (q, *J* = 7.5, 2H); δ_C (400 MHz; $CDCl_3$) -5.1*, -4.8, -4.5*, -4.0, 14.2, 17.9, 23.1*, 24.2, 25.7, 39.4*, 40.6, 61.7, 66.4*, 69.1, 70.1*, 72.7, 74.2, 172.4; m/z (ESI+) $[M^+ + Na^+]$ 329.1756 calcd for $C_{14}H_{30}NaO_5Si^+$ 329.1755. * = denotes minor isomer.

4.5 Ethyl (4*R*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (32)

Mixed diol **31** (400 mg, 1.30 mmol) was dissolved in distilled CH_2Cl_2 (6 mL) and 2-methoxypropene (300 µL, 2.61 mmol) was added followed by pyridinium *p*-toluenesulfonic acid (26 mg, 0.10 mmol). The reaction was stirred for 1.25 h then quenched with sat. aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL), the combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product

was purified by flash chromatography (hexanes/EtOAc 19:1) to give the major diastereomer **32a** (190 mg, 42%) and the minor diastereomer **32b** (74 mg, 16%) as colourless oils. **Major isomer, 32a.** R_f (hexanes/EtOAc 19:1): 0.50; ν_{max}(neat)/cm^{-1} 2955, 2931, 2858, 1759; $[\alpha]_D^{20}$ -13.67 (*c* 1.18 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.17 (d, *J* = 6.2, 3H), 1.29 (t, *J* = 7.0, 3H), 1.36 (s, 3H), 1.58 (m, 4H), 1.73 (m, 1H), 4.00 (m, 1H), 4.20 (m, 2H), 4.43 (m, 1H), 4.53 (d, *J* = 6.5, 1H); δ_C (400 MHz; $CDCl_3$) -4.8, -4.4, 14.2, 18.0, 23.4, 25.6, 25.8, 27.0, 39.7, 61.0, 65.8, 74.5, 77.2, 110.3, 170.3; m/z (ESI+) [M^+ + Na^+] 369.2077 calcd for $C_{17}H_{34}NaO_5Si$+ 369.2068. **Minor isomer, 32b.** R_f (hexanes/EtOAc 19:1): 0.42; ν_{max}(neat)/cm^{-1} 2950, 2929, 2858, 1758; $[\alpha]_D^{20}$ -9.96 (*c* 0.42 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.13 (d, *J* = 6.3, 3H), 1.28 (t, *J* = 7.0, 3H), 1.35 (m, 4H), 1.59 (s, 3H), 1.64 (m, 1H), 4.00 (m, 1H), 4.19 (q, *J* =7.0, 2H), 4.51 (m, 2H); δ_C (400 MHz; $CDCl_3$) -4.9, -4.3, 14.2, 18.0, 24.7, 25.7, 25.8, 27.0, 39.9, 60.8, 65.2, 74.2, 77.2, 110.5, 170.6; m/z (ESI+) [M^+ + Na^+] 369.2072 calcd for $C_{17}H_{34}NaO_5Si$+ 369.2068.

4.6 Dimethyl (2-((4*R*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)phosphonate (25)

Dimethylmethylphosphonate (752 µL, 6.94 mmol) was dissolved in distilled THF (35 mL) under a N_2 atmosphere and cooled to -78 °C. *n*-BuLi (3.5 mL, 2.0 M in cyclohexane, 7.00 mmol) was added and the reaction stirred for 30 min. Diastereomerically pure ester **32a** (801 mg, 2.31 mmol) in distilled THF (10 mL) was added and stirred for a further 2.5 h at -78 °C. The reaction was quenched with sat. aq NH_4Cl (20 mL), extracted with EtOAc (3 × 20 mL) then washed with brine (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc neat) to give the title compound **25** (844 mg, 86%) as a colourless oil; R_f (EtOAc neat): 0.49; ν_{max}(neat)/cm^{-1} 2988, 2953, 2893, 2856, 1741; $[\alpha]_D^{20}$ +26.34 (*c* 1.51 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.15 (d, *J* = 5.8, 3H), 1.37 (s, 3H), 1.58 (m, 5H), 3.03 (dd, *J* = 15.5, $^2J_{HP}$ = 20.9, 1H), 3.48 (dd, *J* = 15.3, $^2J_{HP}$ = 20.9, 1H), 3.78 (d, $^3J_{HP}$ = 4.8, 3H), 3.81 (d, $^3J_{HP}$ = 4.9, 3H), 3.96 (m, 1H), 4.47 (m, 2H); δ_C (400 MHz; $CDCl_3$) -4.9, -4.5, 18.0, 23.3, 24.7, 25.8, 27.0, 37.9 (d, J_{CP} = 135.4), 39.5, 52.8 (d, $^2J_{CP}$ = 6.5), 53.0 (d, $^2J_{CP}$ = 6.5), 65.7, 75.2, 82.5 (d, $^3J_{CP}$ = 3.7), 110.1, 202.9 (d, $^2J_{CP}$ = 7.4); m/z (ESI+) [M^+ + Na^+] 447.1942 calcd for $C_{18}H_{37}NaO_7PSi$+ 447.1938.

4.7 Enone (23)

Phosphonate **25** (430 mg, 1.01 mmol) was stirred in a solution of K_2CO_3 (2 g, 14.5 mmol) in H_2O (2 mL) for 30 min at 0 °C. Aldehyde **24** (272 mg, 0.84 mmol) in distilled Et_2O (2.0 mL) was added, the mixture warmed to rt and stirred for 18 h. The reaction mixture was diluted with Et_2O (3 mL) and H_2O (2 mL) then extracted with Et_2O (3 × 2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1) to give the title compound **23** (426 mg, 81%) as a colourless

oil; R_f (hexanes/EtOAc 9:1): 0.58; ν_{max}(neat)/cm^{-1} 2953, 2929, 2856, 1692, 1623; $[\alpha]_D^{20}$ +28.63 (*c* 1.20 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 0.03 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.88 (s, 9H), 1.13 (d, *J* = 6.1, 3H), 1.37 (s, 3H), 1.46 (m, 1H), 1.59 (m, 4H), 1.74 (m, 2H), 2.41 (m, 2H), 3.52 (m, 2H), 3.95 (m, 1H), 4.02 (m, 1H), 4.47 (m, 3H), 4.55 (m, 1H), 6.52 (d, *J* = 15.8, 1H), 6.97 (ddd, *J* = 7.3, 7.3, 15.8, 1H), 7.32 (m, 5H); δ_C (400 MHz; $CDCl_3$) -4.8, -4.8, -4.5, -4.5, 18.0, 23.2, 25.0, 25.8, 27.2, 37.2, 40.0, 41.0, 65.9, 66.6, 68.3, 73.0, 75.3, 82.0, 109.8, 127.5, 127.6, 127.6, 127.9, 128.3, 128.3, 129.5, 138.4, 145.4, 197.3; m/z (ESI+) [M^+ + Na^+] 643.3798 calcd for $C_{34}H_{60}NaO_6Si_2$+ 643.3821.

4.8 Michael addition product (33)

Phthalide **18** (18 mg, 0.10 mmol) was dissolved in distilled THF (1 mL). *t*-BuOK (16 mg, 0.14 mmol) was added and the bright yellow mixture stirred for 20 min. Enone **23** (30 mg, 0.05 mmol) in distilled THF (0.5 mL) was added and the solution stirred for 5 h at 55 °C until TLC showed disappearance of the enone **23**. The reaction was quenched with sat. aq NH_4Cl (3 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc 2:1) to give the title compound **33** (16 mg, 42%) as a yellow oil; R_f (hexanes/EtOAc 2:1): 0.53; δ_H (400 MHz; $CDCl_3$) 0.05 (m, 12H), 0.83 (s, 9H), 0.88 (s, 9H), 1.07 (m, 1H), 1.15 (d, *J* = 6.3, 3H), 1.26 (m, 1H), 1.36 (s, 3H), 1.59 (s, 3H), 1.65 (m, 4H), 2.96 (m, 1H), 3.22 (m, 2H), 3.34 (m, 2H), 3.47 (m, 1H), 4.00 (m, 4H), 4.37 (m, 3H), 4.51 (m, 1H), 6.98 (d, *J* = 8.6, 1H), 7.13 (d, *J* = 7.3, 1H), 7.30 (m, 5H), 7.56 (t, *J* = 7.7, 1H); δ_C (400 MHz; $CDCl_3$) -4.6, -4.6, -4.5, -4.5, 17.9, 18.0, 23.3, 24.8, 25.8, 27.1, 36.1, 36.5, 36.8, 39.4, 42.4, 56.2, 65.8, 66.4, 67.1, 73.0, 75.2, 80.7, 82.7, 108.5, 109.8, 113.0, 114.2, 116.3, 125.2, 127.6, 127.6, 127.7, 127.7, 128.4, 137.9, 147.6, 158.9, 165.3, 208.4; m/z (ESI+) [M^+ + Na^+] 832.4251 calcd for $C_{44}H_{67}NNaO_9Si_2$+ 832.4247.

4.9 Trimethoxynaphthalene (22)

One-pot procedure. Phthalide **18** (115 mg, 0.61 mmol) was dissolved in distilled THF (6 mL). *t*-BuOLi (48 mg, 0.61 mmol) was added and the bright yellow mixture stirred for 20 min. Enone **23** (188 mg, 0.30 mmol) in distilled THF (3 mL) was added and the solution turned green. The solution turned brown as it was stirred for 30 min until TLC showed disappearance of the enone **23**. TBAB (15 mg, 0.05 mmol) and NaOH (242 mg, 6.05 mmol) in H_2O (3.6 mL) were added followed by Me_2SO_4 (600 µL, 6.33 mmol) and the reaction was stirred for 16.5 h. The reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3 × 4 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1) to give the title compound **22** (101 mg, 41%) as a yellow oil; R_f (hexanes/EtOAc 9:1): 0.46; ν_{max}(neat)/cm^{-1} 2938, 2856, 1703; $[\alpha]_D^{20}$ -4.82 (*c* 1.10 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) -0.07 (s, 3H), 0.00 (s, 3H), 0.04 (s, 6H), 0.78 (s, 9H), 0.88 (s, 9H),

1.14 (m, 6H), 1.28 (s, 3H), 1.77 (m, 3H), 1.97 (m, 1H), 2.66 (dd, *J* = 6.5, 13.5, 1H), 3.06 (dd, *J* = 7.8, 13.5, 1H), 3.53 (m, 2H), 3.76 (s, 3H), 3.83 (s, 3H), 3.98 (s, 3H), 4.01 (m, 1H), 4.24 (m, 1H), 4.43 (m, 3H), 4.92 (d, *J* = 7.0, 1H), 6.86 (d, *J* = 7.2, 1H), 7.28 (m, 5H), 7.44 (t, *J* = 7.8, 1H), 7.65 (dd, *J* = 0.7, 8.3, 1H); δ_C (400 MHz; $CDCl_3$) -5.0, -4.8, -4.4, 17.9, 23.5, 25.6, 25.9, 26.7, 36.4, 37.3, 39.0, 56.1, 61.6, 64.2, 66.2, 67.4, 70.1, 72.8, 76.3, 82.9, 106.1, 109.2, 115.1, 119.5, 126.4, 127.3, 127.6, 127.6, 128.2, 128.2, 129.6, 131.8, 132.8, 138.7, 150.5, 151.1, 156.6, 206.3; m/z (ESI+) $[M^+ + Na^+]$ 833.4430 calcd for $C_{45}H_{70}NaO_9Si_2$+ 833.4551.

Two-step procedure. Annulation. Phthalide **18** (49 mg, 0.26 mmol) was dissolved in distilled THF (2.6 mL). *t*-BuOLi (23 mg, 0.29 mmol) was added and the bright yellow mixture stirred for 20 min. Enone **23** (80 mg, 0.13 mmol) in distilled THF (1.2 mL) was added and the solution turned green. The solution turned brown as it was stirred for 20 min until TLC showed disappearance of the enone **23**. The reaction was quenched with sat. aq NH_4Cl (3 mL) and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude annulation products which were immediately subjected to methylation conditions.

Methylation. (i) Using K_2CO_3/Me_2SO_4. Crude annulation products were dissolved in distilled acetone (1 mL). K_2CO_3 (18 mg, 0.13 mmol) and Me_2SO_4 (30 µL, 0.32 mmol) were added and the mixture refluxed for 6.25 h. The reaction was quenched with sat. aq NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude annulation products. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1) to give the title compound **22** (12 mg, 24% over 2 steps) as a yellow oil. ***(ii)Using Cs_2CO_3/Me_2SO_4.*** Crude annulation products (max. 0.14 mmol) were dissolved in distilled acetone (3 mL). Cs_2CO_3 (220 mg, 0.68 mmol) and Me_2SO_4 (130 µL, 1.37 mmol) were added and the mixture refluxed for 21 h. The reaction was quenched with sat. aq NH_4Cl (2 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude annulation products. The crude product was purified by flash chromatography (hexanes/EtOAc 9:1) to give the title compound **22** (5 mg, 5% over 2 steps) as a yellow oil.

4.10 Spiroketal (34)

Trimethoxynaphthalene **22** (30 mg, 0.037 mmol) was dissolved in distilled THF (2 mL) in a plastic vial and cooled to 0 °C. HF.pyridine (70%, 50 µL, 1.53 mol) was added and the reaction stirred at rt. After 40 min further HF.pyridine (70%, 50 µL, 1.53 mol) was added and the reaction stirred for another 90 min. The reaction was quenched with dropwise addition of sat. aq $NaHCO_3$ (2 mL) at 0 °C and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (hexanes/EtOAc 4:1) to give the title compound **34** (16 mg,

73%) as a pale yellow oil; R_f (hexanes/EtOAc 4:1): 0.35; ν_{max}(neat)/cm^{-1} 2932, 2855, 1571; $[\alpha]_D^{20}$ +3.15 (*c* 2.86 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.19 (d, *J* = 6.3, 3H), 1.30 (s, 3H), 1.60 (s, 3H), 1.90 (m, 1H), 2.09 (m, 2H), 2.16 (ddd, *J* = 2.0, 2.0, 14.6, 1H), 2.65 (dd, *J* = 11.9, 16.4, 1H), 3.06 (dd, *J* = 2.5, 16.4, 1H), 3.77 (m, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.01 (s, 3H), 4.27 (m, 1H), 4.34 (m, 1H), 4.55 (m, 3H), 5.21 (d, *J* = 5.8, 1H), 6.82 (d, *J* = 7.7, 1H), 7.32 (m, 6H), 7.65 (dd, *J* = 0.8, 8.1, 1H); δ_C (400 MHz; $CDCl_3$) 21.2, 25.8, 26.2, 29.5, 34.4, 36.0, 56.2, 59.7, 60.8, 63.9, 64.3, 67.0, 72.8, 73.0, 74.7, 98.2, 105.5, 109.4, 114.6, 120.0, 126.2, 126.4, 127.4, 127.5, 127.5, 128.2, 128.3, 128.3, 131.1, 138.5, 148.3, 151.3, 156.4; m/z (ESI+) $[M^+ + Na^+]$ 587.2613 calcd for $C_{33}H_{40}NaO_8$ 587.2615.

4.11 Spiroketal alcohol (36)

Benzyl ether **34** (24 mg, 0.043 mmol) was dissolved in distilled THF (30 mL) and $Pd(OH)_2/C$ (spatula tip) was added. The mixture was shaken under H_2 (30 psi) using a Parr hydrogenator for 3 h then filtered through celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexanes/EtOAc 1:1) to give the title compound **36** (20 mg, 100%) as a colourless oil; R_f (hexanes/EtOAc 1:1): 0.31; ν_{max}(neat)/cm^{-1} 3471, 2936, 2859, 1571; $[\alpha]_D^{20}$ -9.09 (*c* 0.25 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.29 (m, 6H), 1.62 (s, 3H), 1.92 (m, 1H), 2.01 (m, 1H), 2.10 (m, 1H), 2.23 (ddd, *J* = 2.0, 2.0, 14.9, 1H), 2.70 (dd, *J* = 11.6, 15.8, 1H), 2.79 (m, 1H), 3.06 (dd, *J* = 2.1, 16.4, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.94 (m, 2H), 4.01 (s, 3H), 4.22 (m, 1H), 4.32 (m, 1H), 4.54 (m, 1H), 5.22 (d, *J* = 5.9, 1H), 6.83 (d, *J* = 7.5, 1H), 7.38 (t, *J* = 7.9, 1H), 7.64 (dd, *J* = 0.8, 8.2, 1H); δ_C (400 MHz; $CDCl_3$) 21.5, 25.8, 25.9, 29.5, 34.1, 37.9, 56.2, 60.2, 60.8, 61.6, 63.9, 67.7, 72.6, 74.2, 98.3, 105.6, 109.3, 114.6, 120.0, 125.7, 126.6, 127.3, 131.1, 148.3, 151.5, 156.4; m/z (ESI+) $[M^+ + H^+]$ 475.2317 calcd for $C_{26}H_{35}O_8$+ 475.2326.

4.12 Spiroketal acid (37)

Solid IBX (13 mg, 0.046 mmol) was added to alcohol **36** (13 mg, 0.028 mmol) with stirring followed by DMSO (1.0 mL, stored over molecular sieves) and warmed to 50 °C for 4 h. The reaction was quenched with sat. aq $Na_2S_2O_3$ (2 mL) and diluted with Et_2O (2 mL). The aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with sat. aq $Na_2S_2O_3$ (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow oil. The crude aldehyde was immediately dissolved in *t*-BuOH (1.5 mL) and 2-methyl-2-butene (150 µL, 1.42 mmol). A mixture of $NaClO_2$ (22 mg, 0.24 mmol) and KH_2PO_4 (30 mg, 0.22 mmol) in H_2O (220 µL) was added dropwise. The reaction was warmed to 30 °C and stirred for 75 min. The reaction was diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (4 × 1 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc neat) to give the title compound **37** (12 mg, 90%, 2 steps) as a pale yellow oil; R_f (EtOAc neat): 0.50; ν_{max}(neat)/cm^{-1} 3017, 2930, 2859, 1715, 1571, 1215; $[\alpha]_D^{20}$ +7.00 (*c* 0.30 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1.25 (d, *J* = 6.5, 3H), 1.30 (s, 3H), 1.61 (s, 3H), 1.90 (ddd, *J* =

4.5, 11.7, 15.2, 1H), 2.16 (ddd, *J* = 1.9, 1.9, 14.7, 1H), 2.70 (dd, *J* = 11.9, 16.1, 1H), 2.80 (dd, *J* = 4.6, 15.8, 1H), 2.89 (dd, *J* = 8.4, 15.8, 1H), 3.14 (dd, *J* = 2.5, 16.1, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.02 (s, 3H), 4.36 (m, 1H), 4.59 (m, 2H), 5.16 (d, *J* = 6.2, 1H), 6.83 (d, *J* = 7.1, 1H), 7.39 (t, *J* = 8.2, 1H), 7.64 (dd, *J* = 0.7, 8.6, 1H); δ_C (400 MHz; $CDCl_3$) 21.0, 25.8, 26.1, 28.8, 34.1, 40.3, 56.2, 60.1, 60.9, 63.9, 64.2, 72.8, 74.8, 98.4, 105.7, 109.3, 114.6, 120.1, 125.2, 126.6, 127.8, 131.1, 148.3, 151.4, 156.4, 174.7; m/z (ESI+) [$M^+ + Na^+$] 511.1939 calcd for $C_{26}H_{32}NaO_9$+ 511.1939.

4.13 Spiroketal diol (38)

Acid **37** (8 mg, 0.016 mol) was stirred in distilled THF (800 µL) and aq HCl (1 M, 800 µL) for 19.5 h. The reaction was diluted with H_2O (1 mL) and extracted with EtOAc (4 × 1 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound **38** (6.5 mg, 90%) as a pale yellow oil; R_f (CH_2Cl_2/CH_3OH/AcOH 9:1:0.1): 0.37; ν_{max}(neat)/cm^{-1} 3384, 2924, 2854, 1721, 1570, 1372; $[\alpha]_D^{20}$ -6.50 (*c* 0.20 in CH_3OH); δ_H (400 MHz; $CDCl_3$) 1.28 (d, *J* = 6.1, 3H), 1.84 (m, 1H), 2.12 (m, 1H), 2.76 (m, 3H), 3.16 (dd, *J* = 2.1, 15.8, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 4.01 (s, 3H), 4.16 (d, *J* = 4.1, 1H), 4.36 (m, 1H), 4.57 (m, 1H), 4.97 (d, *J* = 4.1, 1H), 6.85 (d, *J* = 7.3, 1H), 7.41 (t, *J* = 8.0, 1H), 7.64 (dd, *J* = 8.1, 1H); δ_C (400 MHz; $CDCl_3$) 21.2, 28.9, 39.8, 40.4, 56.2, 60.9, 61.2, 63.8, 64.9, 68.4, 69.7, 102.0, 106.0, 114.5, 120.2, 124.7, 124.9, 126.9, 131.2, 148.4, 151.6, 156.6, 173.2; m/z (ESI+) [$M^+ + Na^+$] 471.1626 calcd for $C_{23}H_{28}NaO_9$+ 471.1626.

Acknowledgment

The authors thank The University of Auckland for financial support (BJN).

Supporting Information Available

Supplementary data for this article can be found at xxxxxxxxxxx. These include ^{1}H NMR and ^{13}C NMR spectra for all novel compounds.

References

(1) Brimble, M. A.; Nairn, M. R.; Duncalf, L. J. *Nat. Prod. Rep.* **1999**, *16*, 267.
(2) Sperry, J.; Bachu, P.; Brimble, M. A. *Nat. Prod. Rep.* **2008**, *25*, 376.
(3) Tsuji, N.; Kobayashi, M.; Wakisaka, Y.; Kawamura, Y.; Mayama, M.; Matsumoto, K. *J. Antibiot.* **1976**, *29*, 7.
(4) Maruyama, M.; Nishida, C.; Takahashi, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 952.
(5) Igarashi, M.; Chien, W.; Tsuchida, T.; Umekita, M.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1502.
(6) Li, X.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharmacal Res.* **2006**, *29*, 942.
(7) Li, Y.-Q.; Li, M.-G.; Li, W.; Zhao, J.-Y.; Ding, Z.-G.; Cui, X.-L.; Wen, M.-L. *J. Antibiot.* **2007**, *60*, 757.
(8) He, J.; Roemer, E.; Lange, C.; Huang, X.; Maier, A.; Kelter, G.; Jiang, Y.; Xu, L.-H.; Menzel, K.-D.; Grabley, S.; Fiebig, H.-H.; Jiang, C.-L.; Sattler, I. *J. Med. Chem.* **2007**, *50*, 5168.

(9) Abdelfattah, M. S.; Kazufumi, T.; Ishibashi, M. *J. Antibiot.* **2011**, *64*, 729.

(10) Abdelfattah, M. S.; Toume, K.; Ishibashi, M. *J. Antibiot.* **2012**, *65*, 245.

(11) Ding, Z.-G.; Zhao, J.-Y.; Li, M.-G.; Huang, R.; Li, Q.-M.; Cui, X.-L.; Zhu, H.-J.; Wen, M.-L. *J. Nat. Prod.* **2012**, *75*, 1994.

(12) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(13) Salaski, E. J.; Krishnamurthy, G.; Ding, W.-D.; Yu, K.; Insaf, S. S.; Eid, C.; Shim, J.; Levin, J. I.; Tabei, K.; Toral-Barza, L.; Zhang, W.-G.; McDonald, L. A.; Honores, E.; Hanna, C.; Yamashita, A.; Johnson, B.; Li, Z.; Laakso, L.; Powell, D.; Mansour, T. S. *J. Med. Chem.* **2009**, *52*, 2181.

(14) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 2311.

(15) Naysmith, B. J.; Brimble, M. A. *Org. Lett.* **2013**, *15*, 2006.

(16) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325.

(17) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(18) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, *1986*, 403.

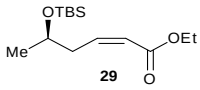
(19) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892.

(20) The complex mixture possibly resulted from different oxidation patterns at the quinone ring (C3, C4) and spiroketal diol (C3′, C4′). Mass spectra suggested oxidation of one of the spiroketal hydroxy groups, however no products could be isolated or identified.

(21) Park, Y. S.; Grove, C. I.; Gonzalez-Lopez, M.; Urgaonkar, S.; Fettinger, J. C.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 3730.

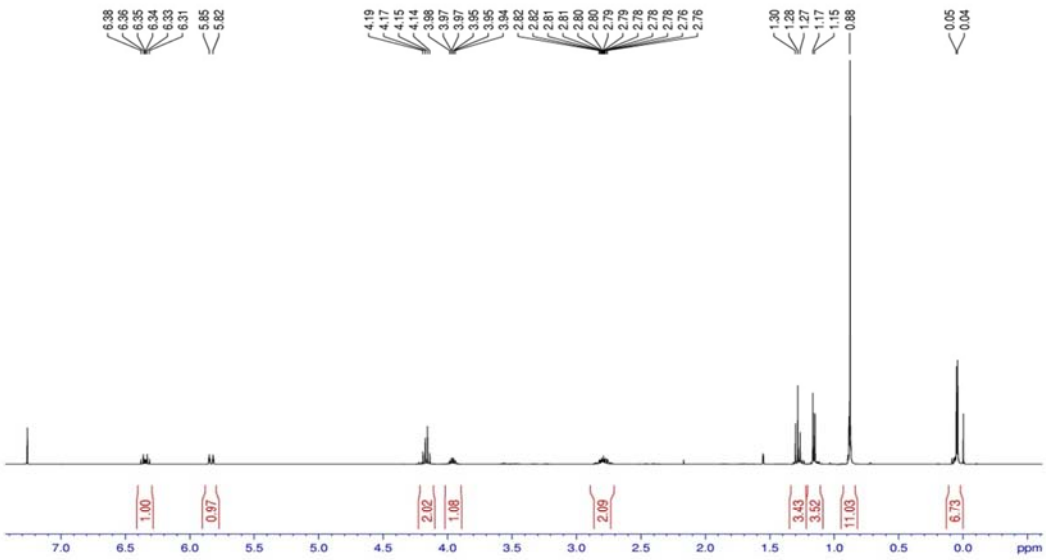
Supporting Information – NMR spectra of novel compounds

Ethyl (*R,Z*)-5-(*tert*-butyldimethylsilyloxy)hex-2-enoate, 29

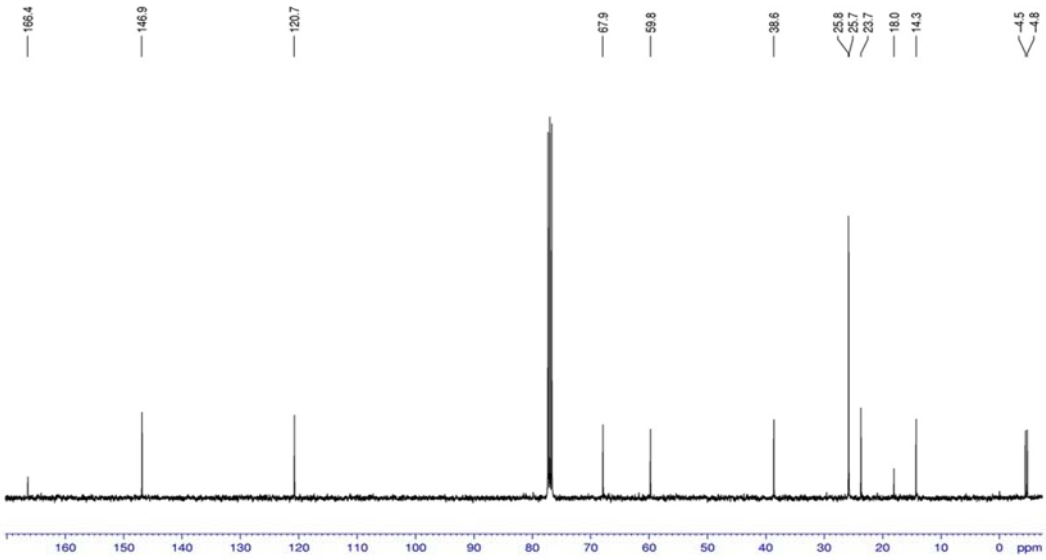


29

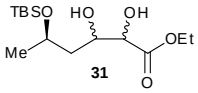
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)

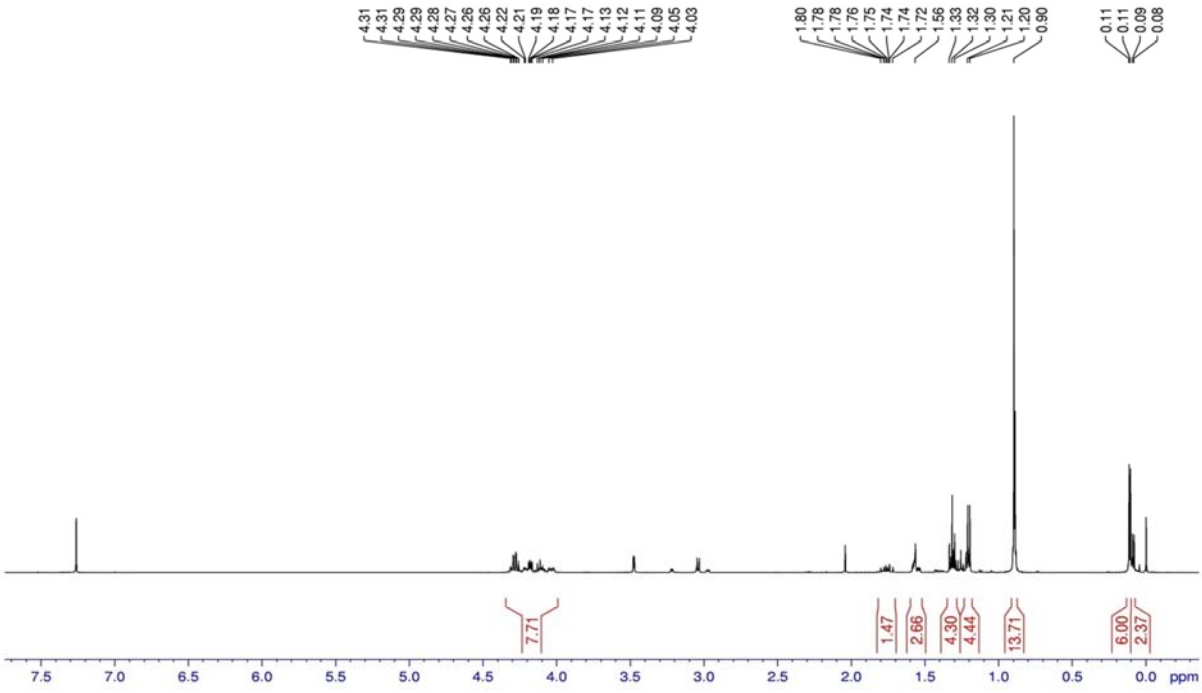


Ethyl (5*R*)-5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyhexanoate, 31

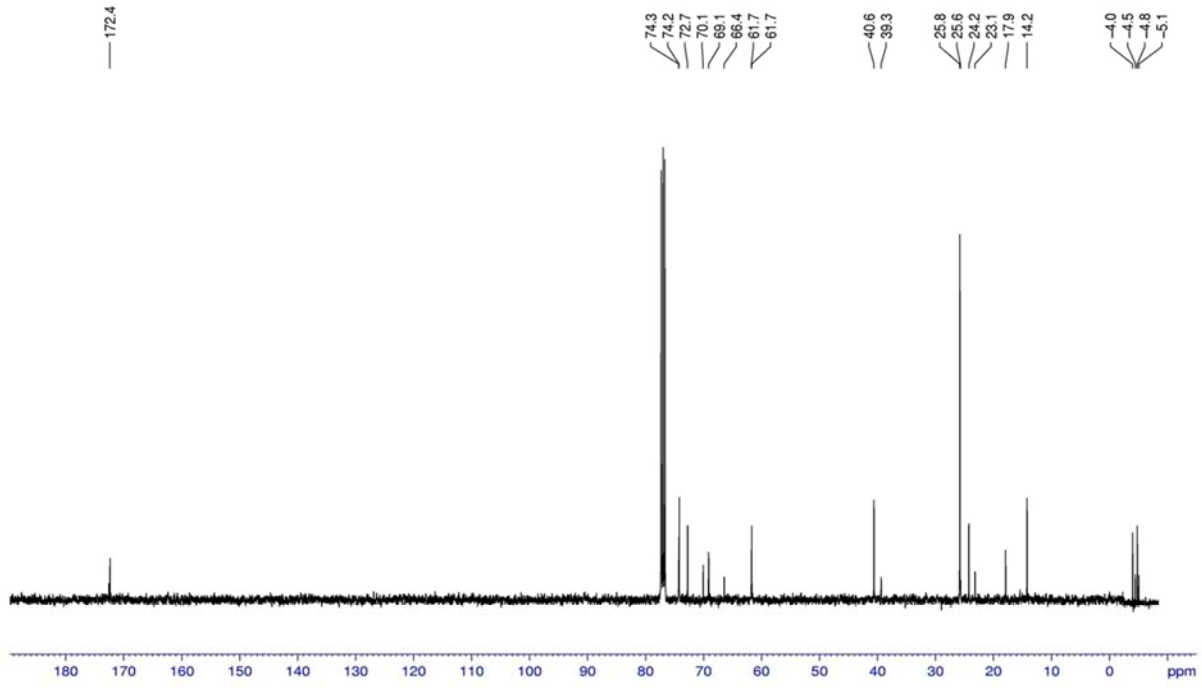


31

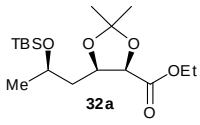
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)

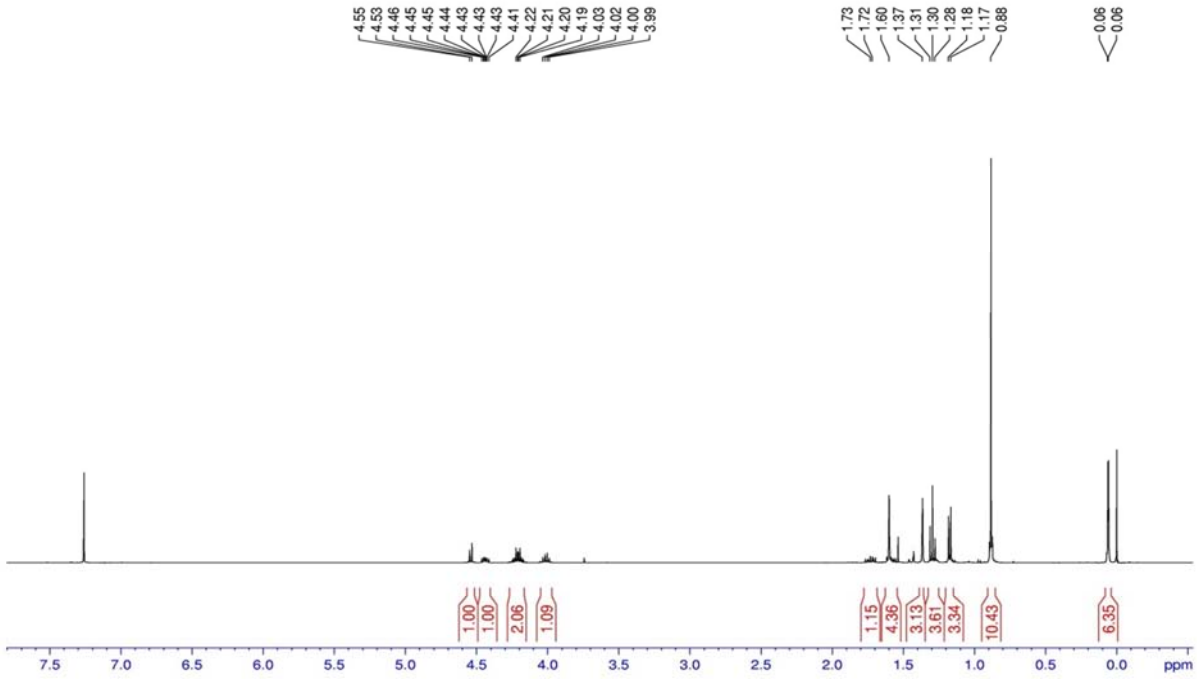


(4*R*,5*R*)-Ethyl 5-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate, 32a

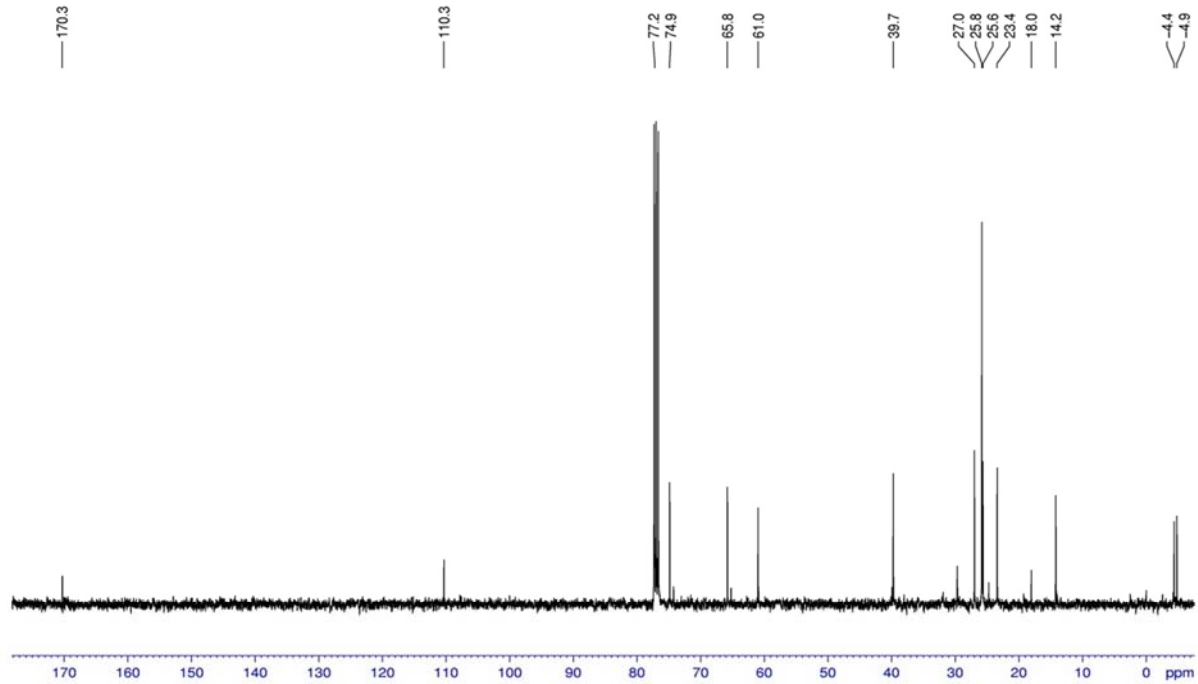


32a

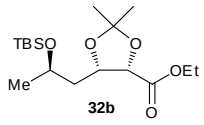
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)

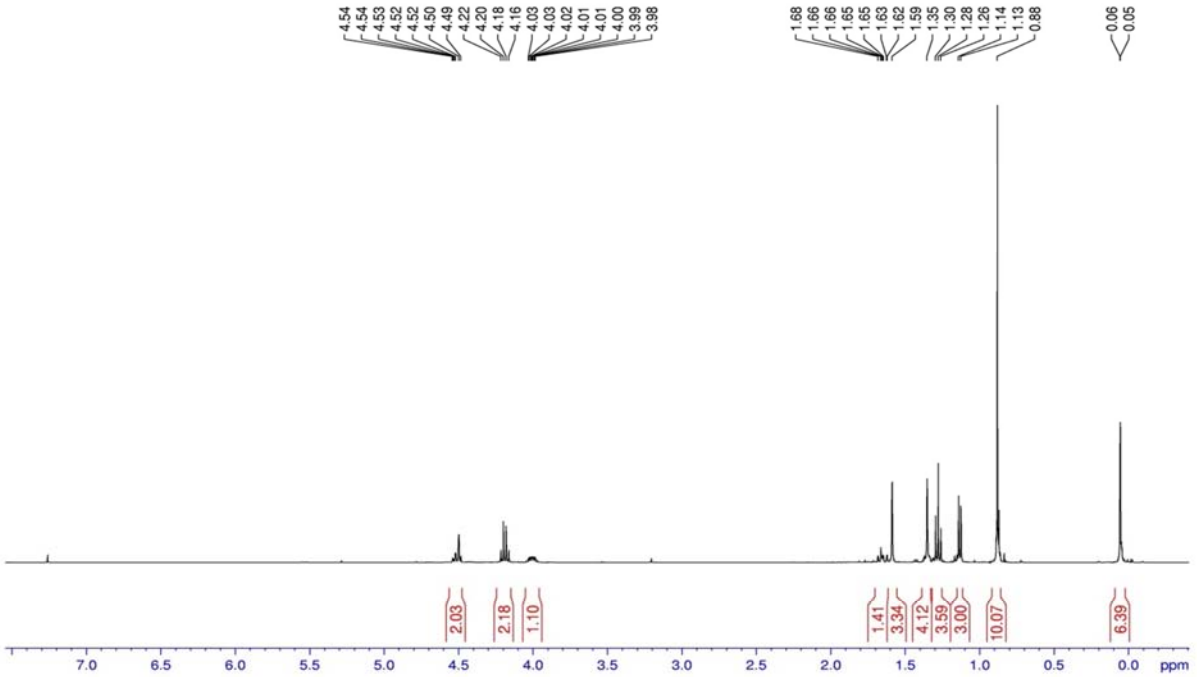


(4*S*,5*S*)-Ethyl 5-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate, 32b

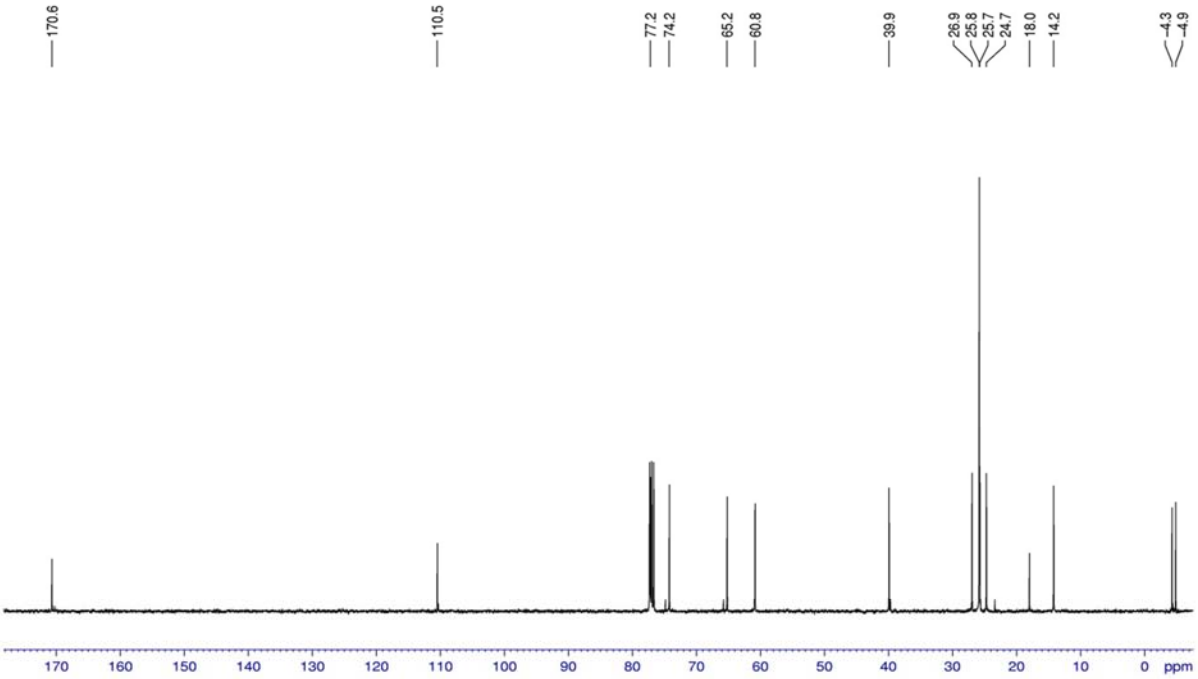


32b

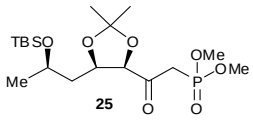
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)

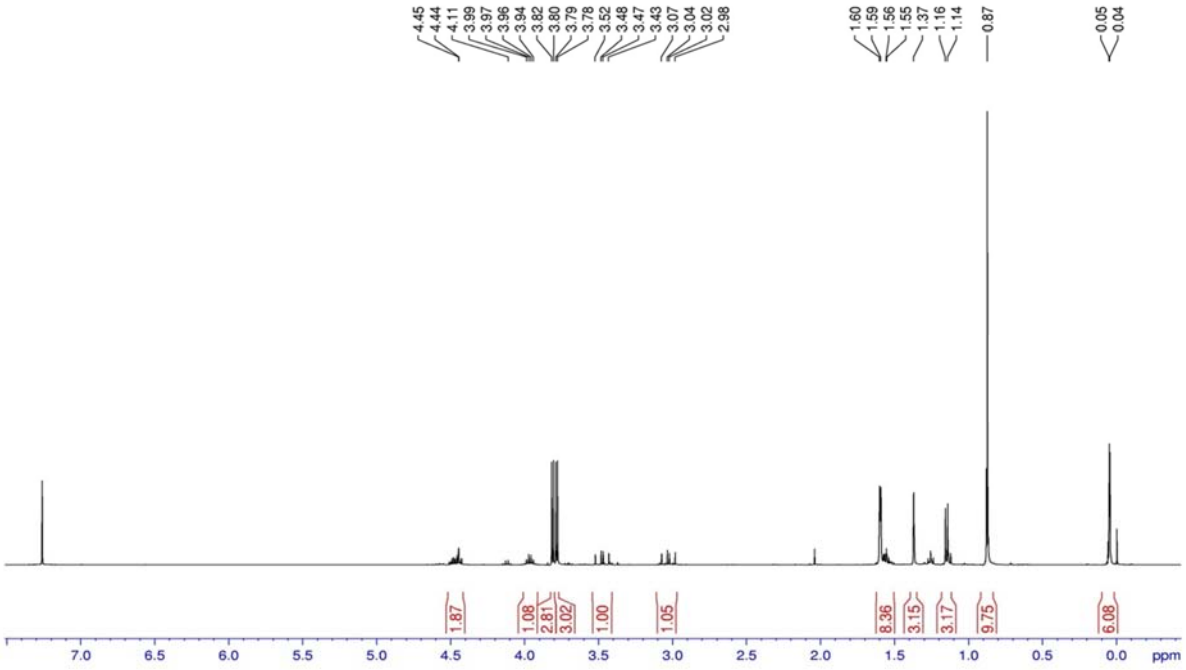


Dimethyl (2-((4*R*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl)phosphonate, 25

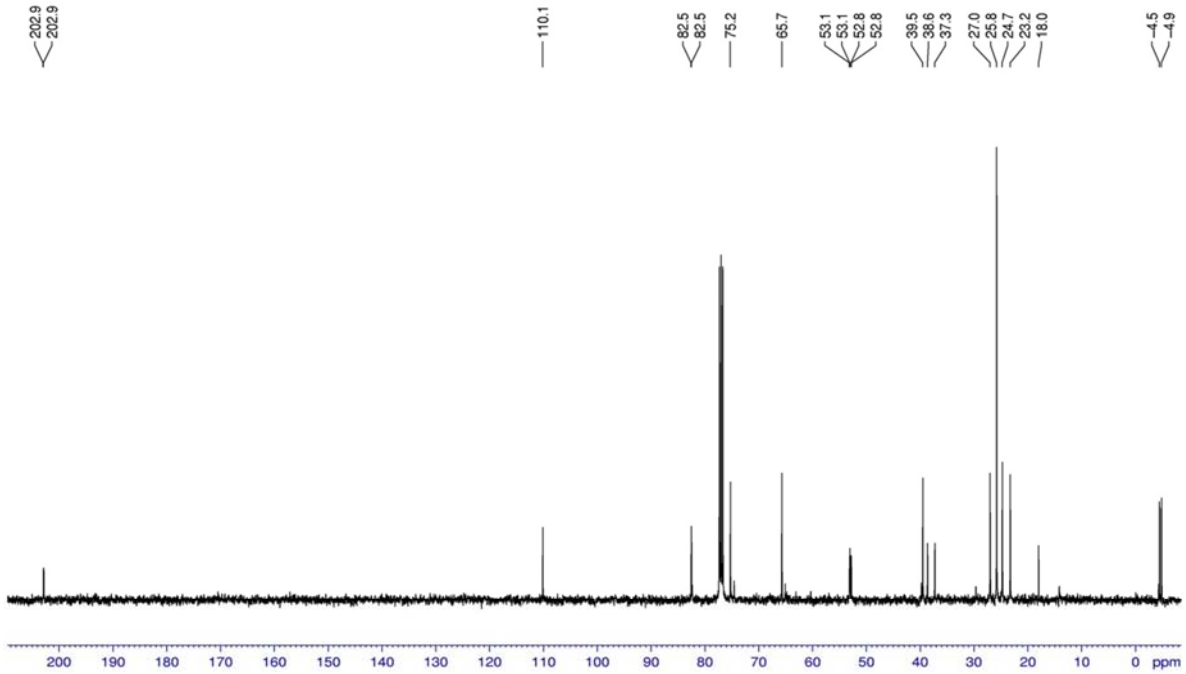


25

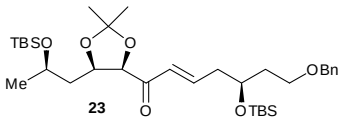
^{1}H NMR (400 MHz, $CDCl_3$)



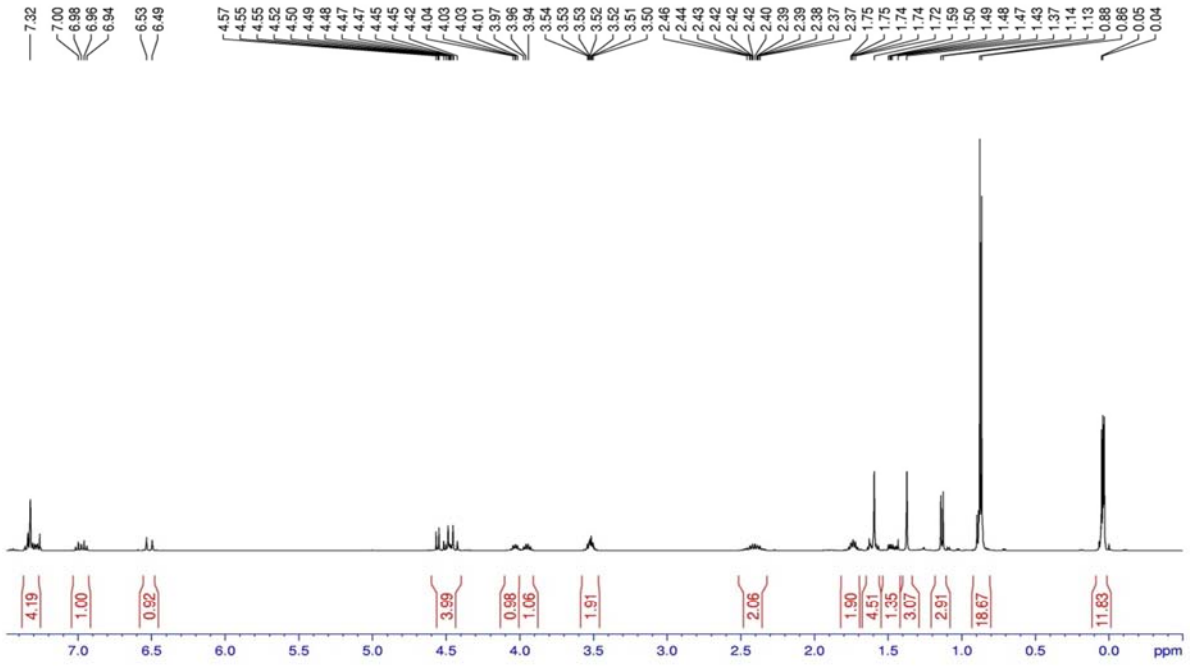
^{13}C NMR (400 MHz, $CDCl_3$)



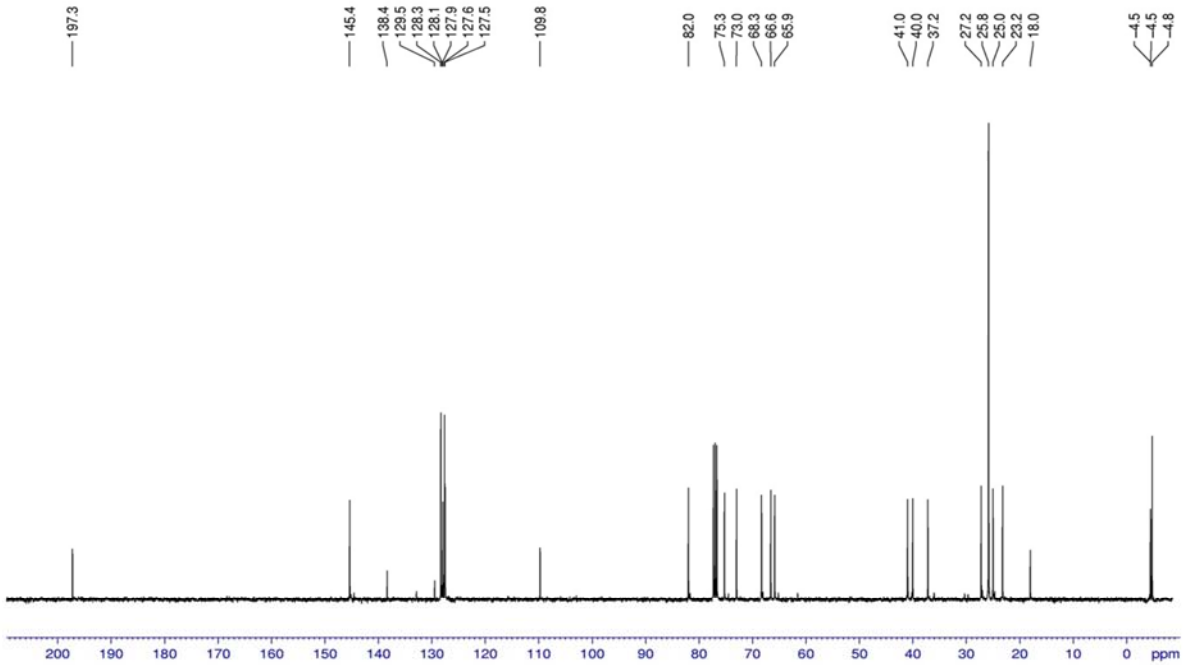
Enone, 23



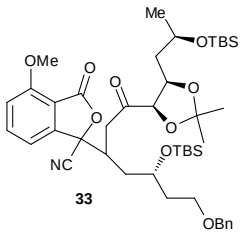
^{1}H NMR (400 MHz, $CDCl_3$)



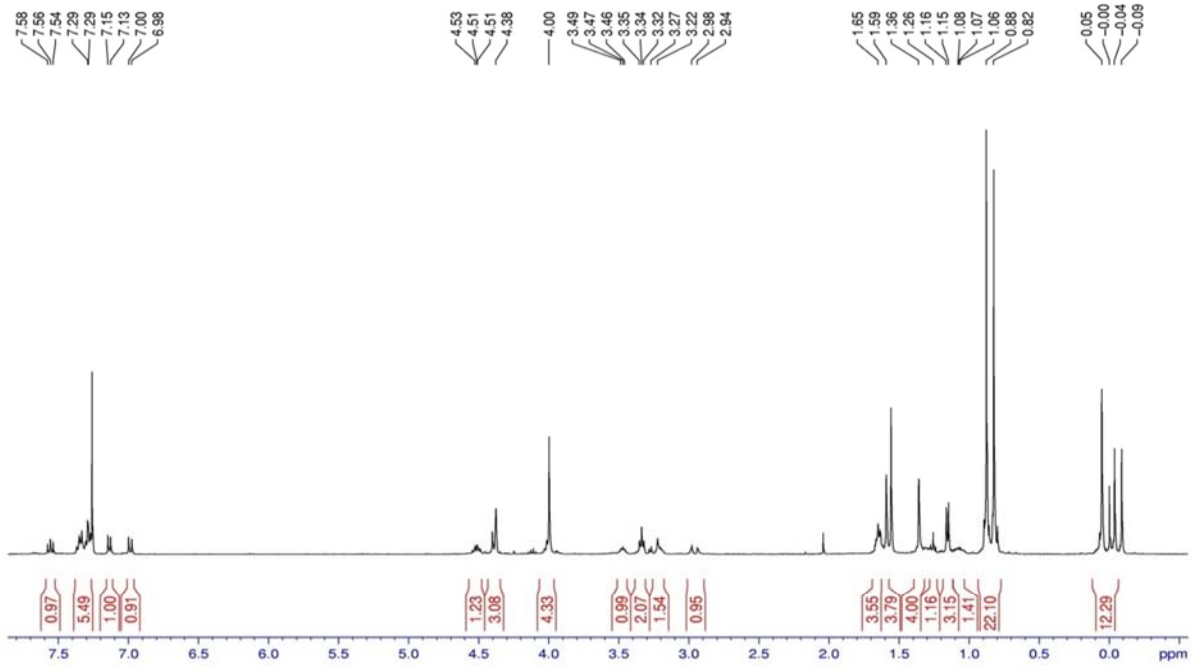
^{13}C NMR (400 MHz, $CDCl_3$)



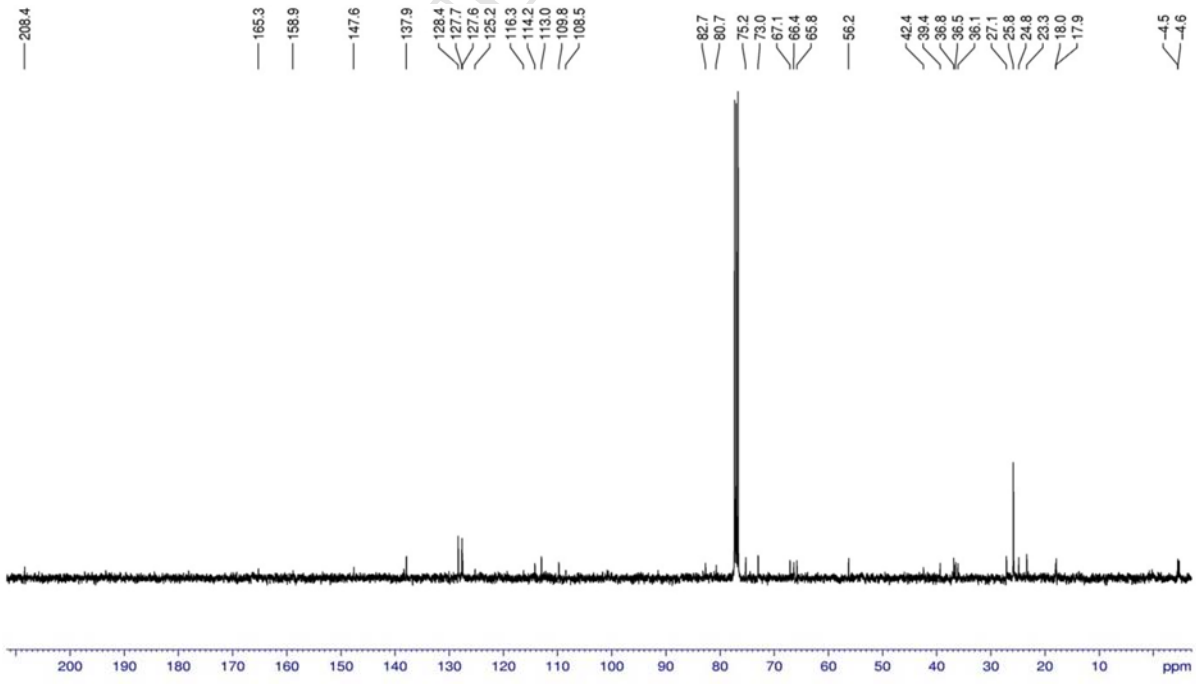
Michael addition product, 33



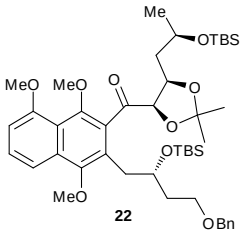
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)

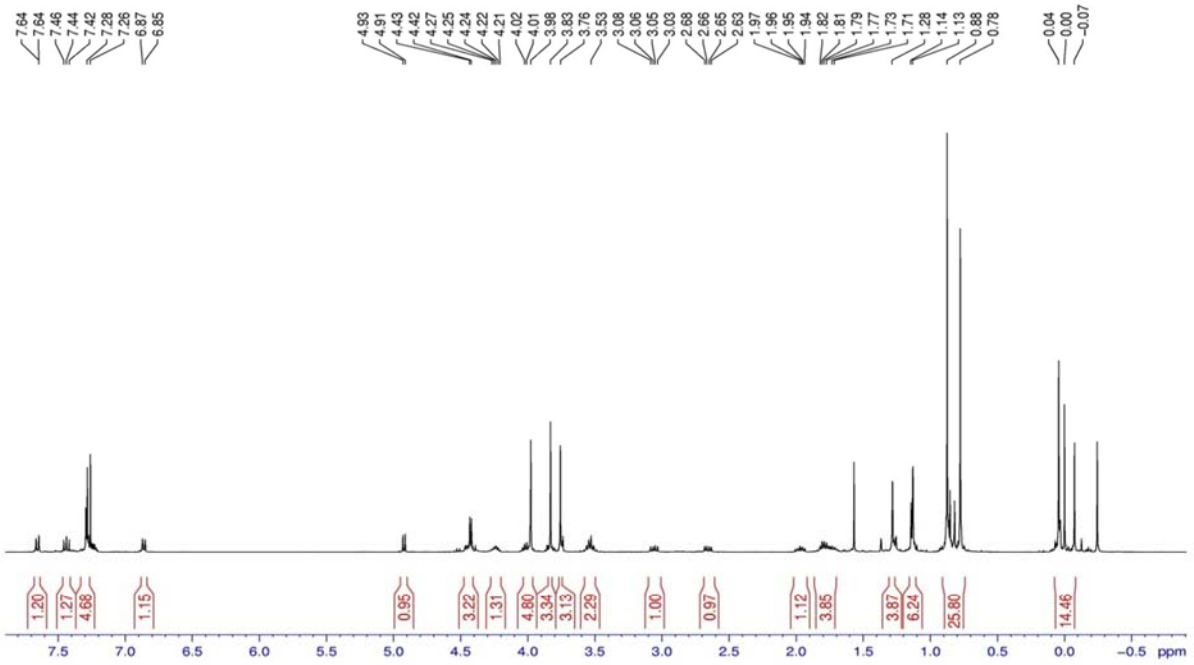


Dimethoxynaphthalene, 22

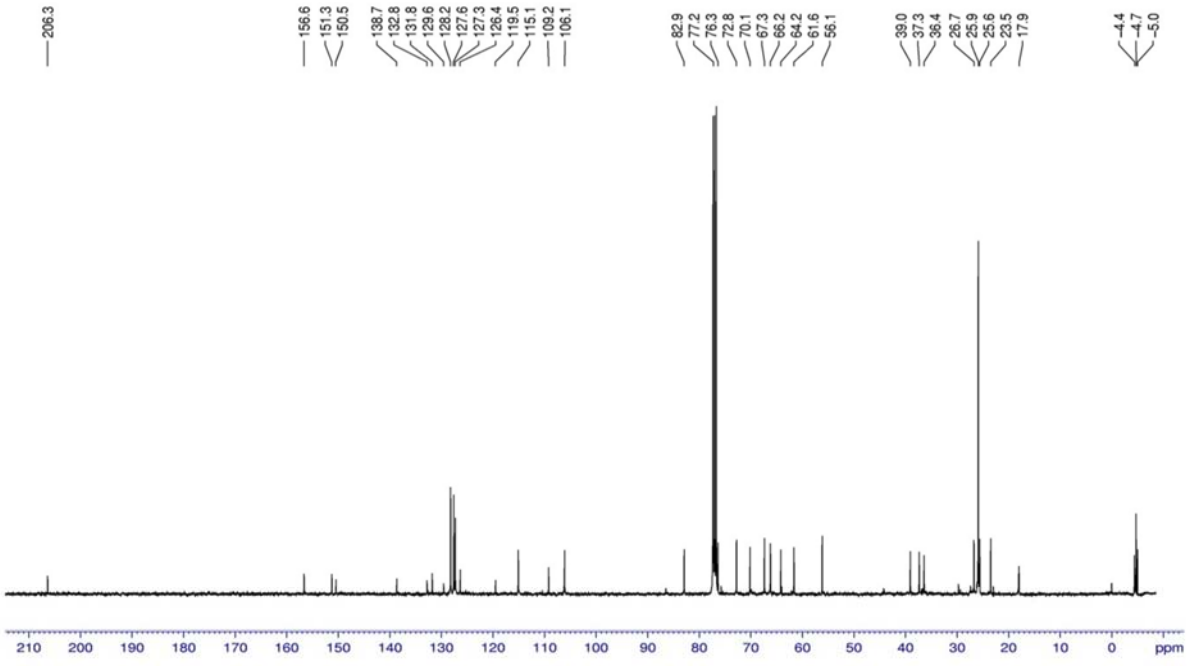


22

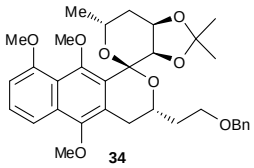
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)

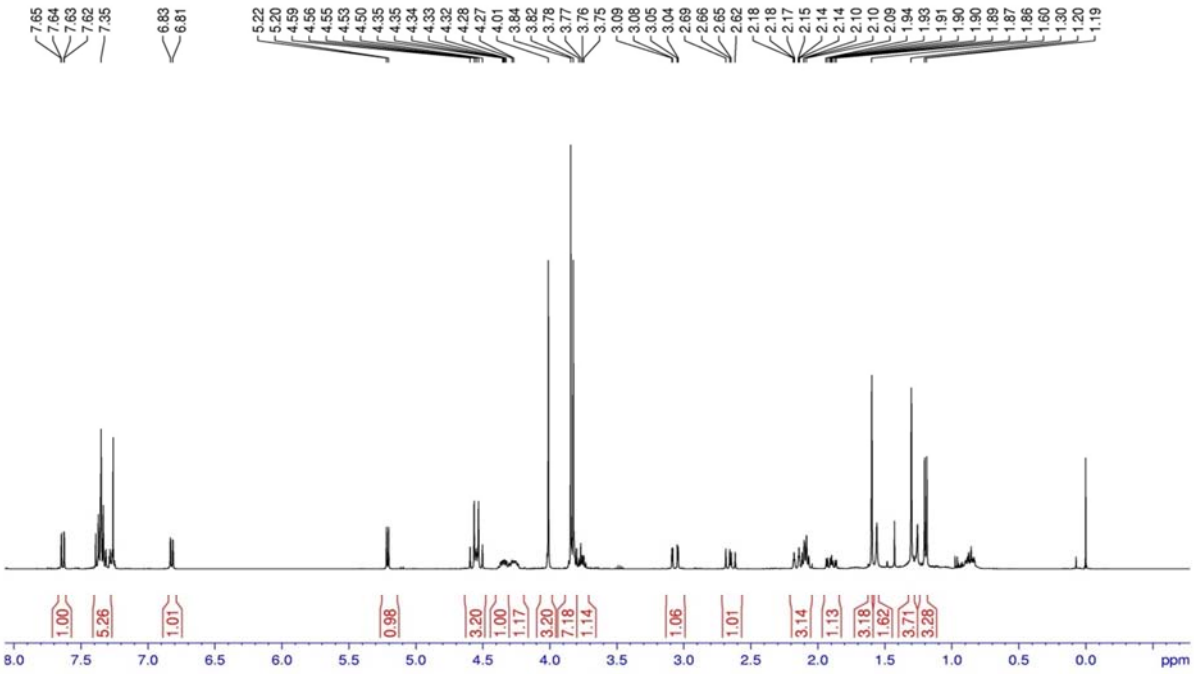


Spiroketal, 34

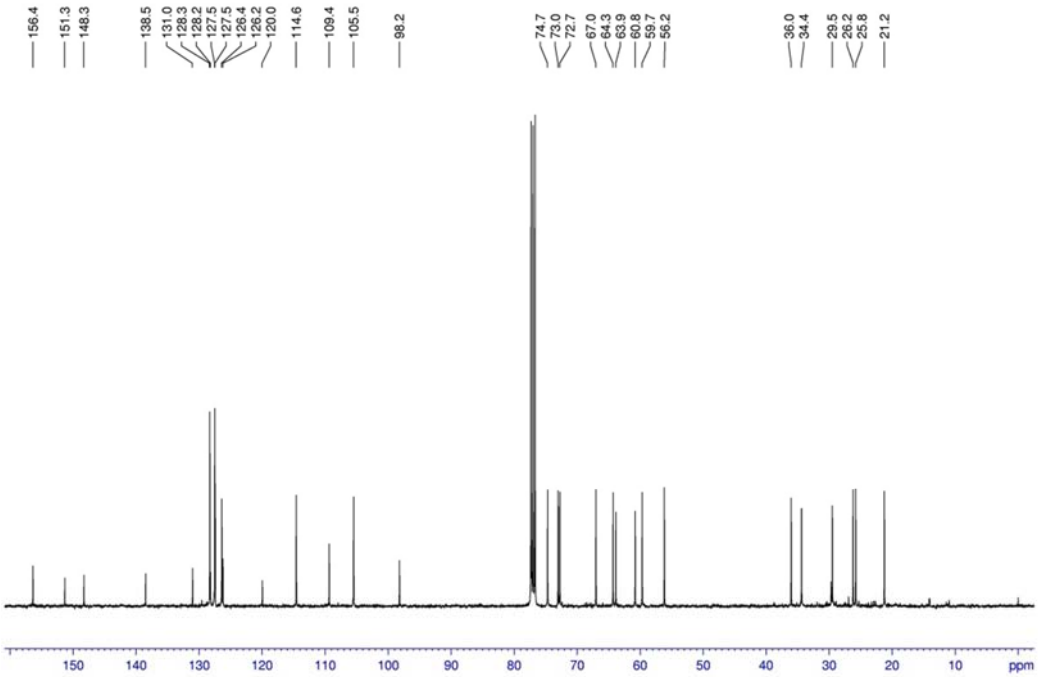


34

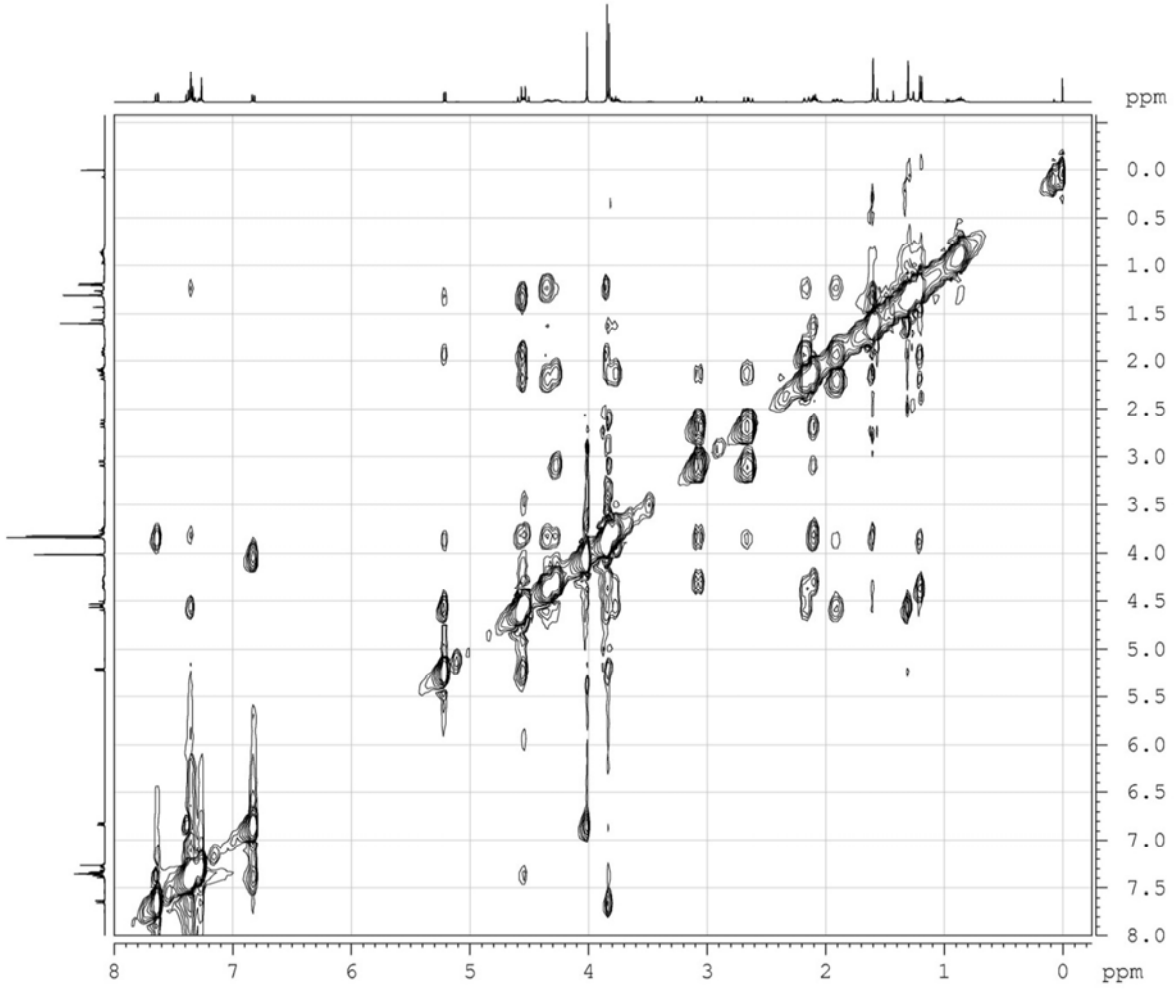
^{1}H NMR (400 MHz, $CDCl_3$)



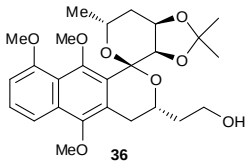
^{13}C NMR (400 MHz, $CDCl_3$)



NOESY NMR (400 MHz, $CDCl_3$)

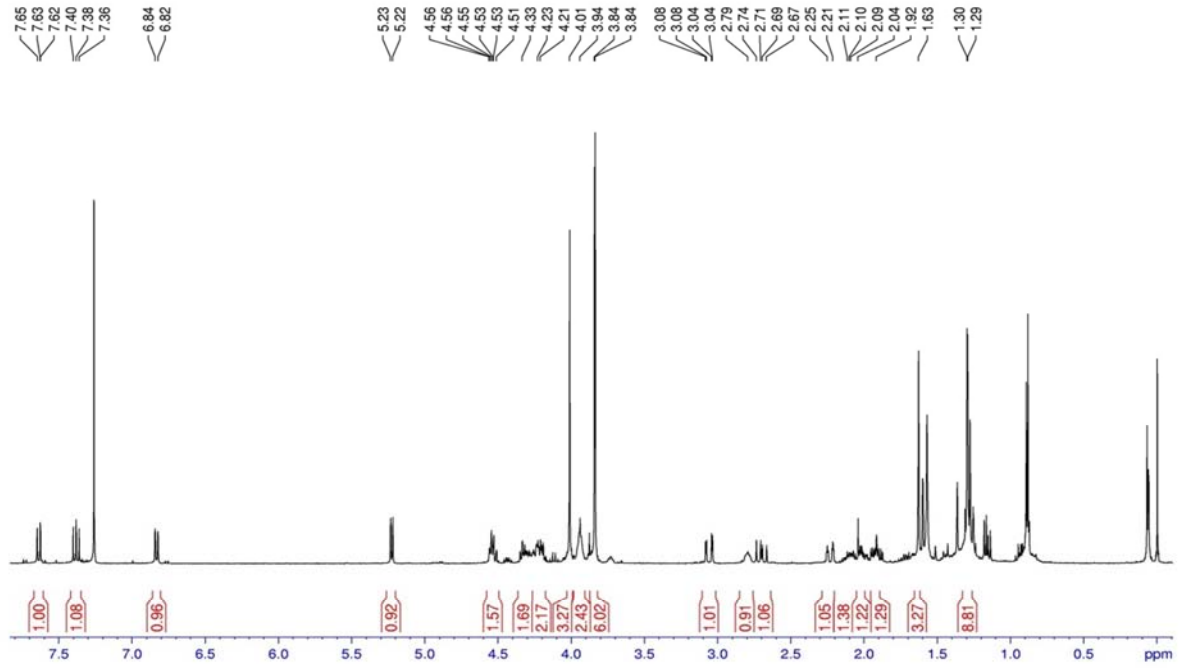


Spiroketal alcohol, 36

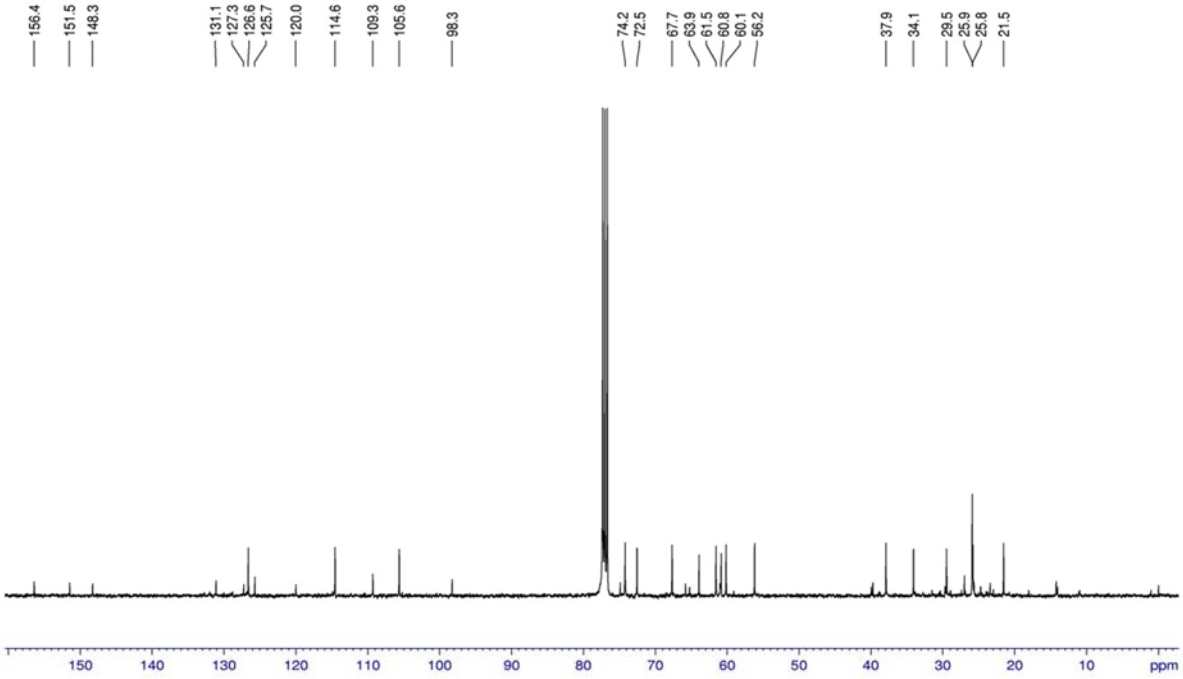


36

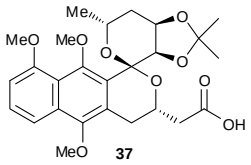
^{1}H NMR (400 MHz, $CDCl_3$)



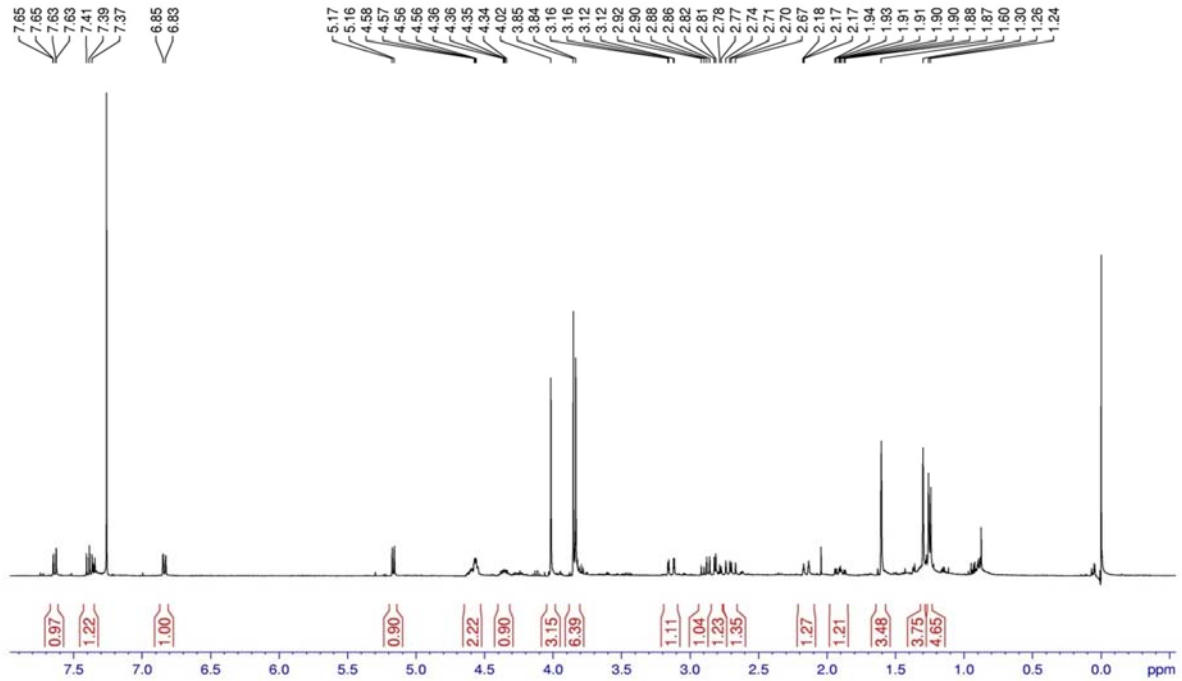
^{13}C NMR (400 MHz, $CDCl_3$)



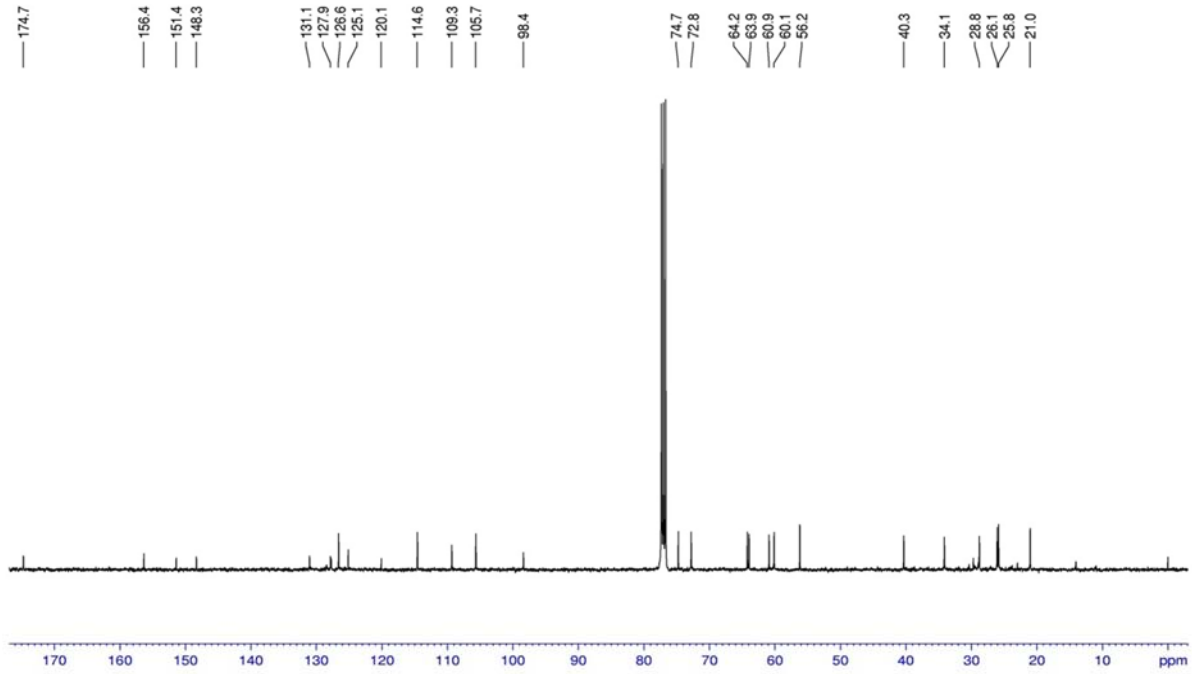
Spiroketal acid, 37



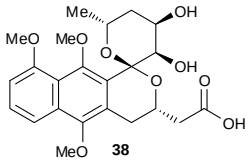
^{1}H NMR (400 MHz, $CDCl_3$)



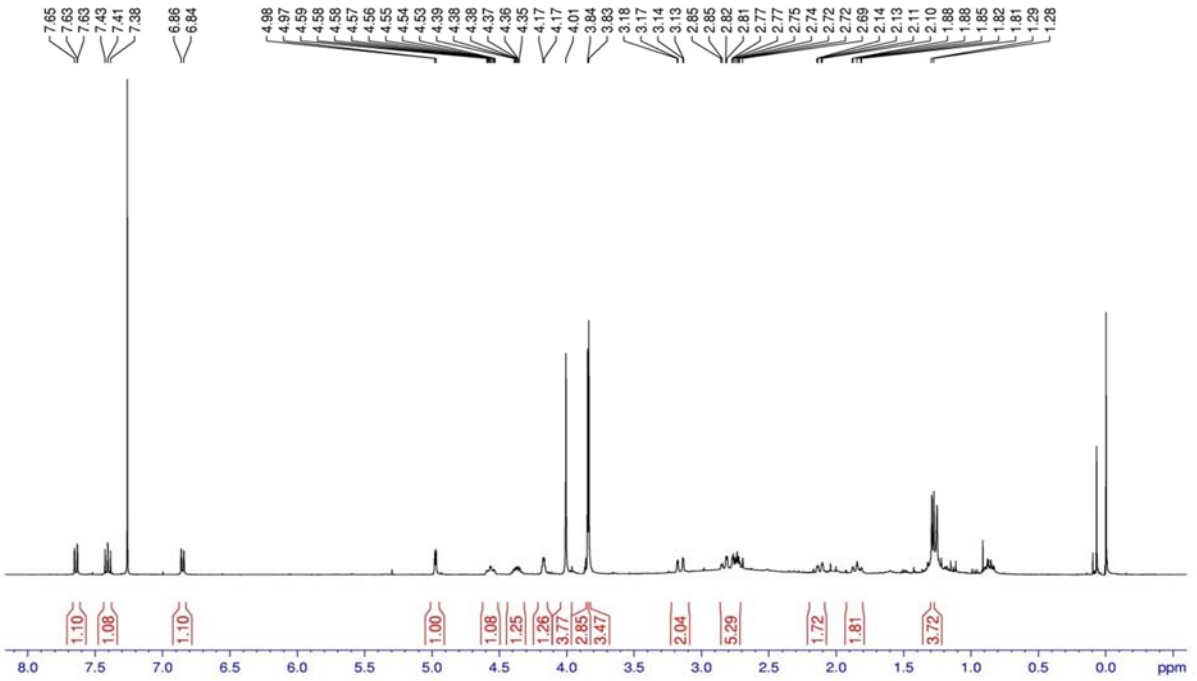
^{13}C NMR (400 MHz, $CDCl_3$)



Spiroketal diol, 38



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (400 MHz, $CDCl_3$)