Tetrahedron xxx (2014) 1–7

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formal synthesis of nanaomycin D via a Hauser–Kraus annulation using a chiral enone-lactone

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ARTICLE INFO

Article history:
Received 4 May 2014
Received in revised form 27 June 2014
Accepted 5 September 2014
Available online xxx

Keywords:
Pyranonaphthoquinones
Hauser–Kraus annulation
Nanaomycin
γ-Lactone

ABSTRACT

A formal total synthesis of nanaomycin D has been achieved. The strategy employed made use of a one-pot cyclisation–stereoselective reduction of a hydroxyketone to install the pyranonaphthalene moiety after execution of a Hauser–Kraus annulation using a chiral enone-lactone as the Michael acceptor to append the γ-lactone ring. The chirality in the chiral enone-lactone was established using a Sharpless asymmetric dihydroxylation. The enone-lactone used herein represents an attractive chiral synthon for the construction of other γ-lactone containing pyranonaphthoquinones such as griseusin A and crisamicin A.

1. Introduction

The pyranonaphthoquinones are a large family of natural products that all share a common naphtho[2,3-*c*]pyran-5,10-dione ring system.[1] These natural products remain attractive synthetic targets in our research group.[2] The nanaomycins are a subgroup of the pyranonaphthoquinones that bear a naphthol at C9 and a methyl group with the (*S*)-configuration at C1 of the dihydropyran ring.[1a] Nanaomycins A **1** and B **2**, were the first members of the family to be isolated from the cultured broth of a *Streptomyces* sample during screening for anti-mycoplasmal agents (Fig. 1).[3] These compounds both contain a carboxylic acid substituent at C3, while nanaomycin B **2** has also undergone hydration across the C4a–C10a double bond. Since then, eight further nanaomycins have been isolated, including nanaomycin D **3**, in which the carboxylic acid side-chain is ring-closed to form a fused γ-lactone.[4] Nanaomycin D **3** is the enantiomer of previously isolated kalafungin.[4] Nanaomycin C **4** contains an amide side-chain[5] while nanaomycin E **5** bears an epoxide at C4a–C10a.[6] Other natural nanaomycins comprise methyl ester or reduced derivatives of the C3 side-chain (Fig. 1, **6**–**10**).[1a] The nanaomycins display an impressive range of biological activity against mycoplasma, fungi and both Gram positive and Gram negative bacteria.[1a,7] They have also been found to exhibit inhibitory activity against platelet aggregation,[8] topoisomerase II[2g] and DNA methyl transferase B,[9] with possible applications for the treatment of bleeding disorders and cancer.

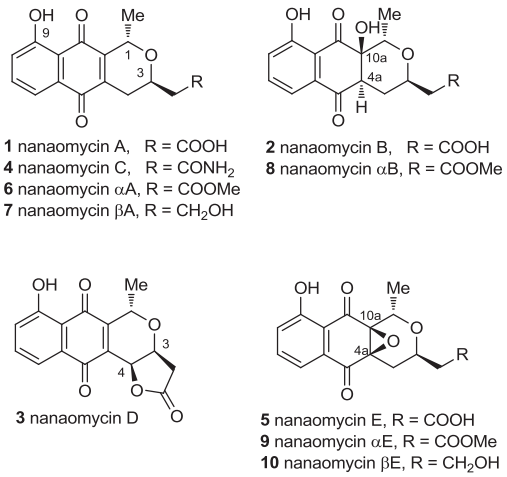

Fig. 1. Nanaomycin natural products.

A number of total and formal syntheses of nanaomycin D **3** have been reported.[10] One such synthesis involved construction of the pyranonaphthalene ring system using a Hauser–Kraus (HK)

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http://dx.doi.org/10.1016/j.tet.2014.09.014
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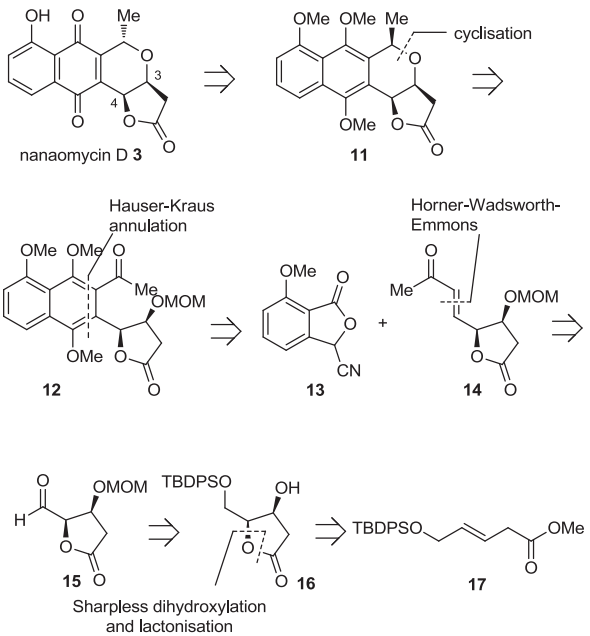
annulation between a pyranone and a phenylsulfonyl phthalide, with the lactone formed in the final steps of the synthesis.[10b,c] We have previously found the HK annulation to be a powerful method for the synthesis of a number of pyranonaphthoquinone and pyranonaphthalene frameworks.[2a,b,11] In a new approach to nanaomycin D **3**, we envisaged the use of an HK annulation employing an enone containing a pre-formed chiral lactone as a key step. Pyranonaphthalene **11** has been previously reported by Fernandes and Brückner in a total synthesis of nanaomycin D **3**,[10f] hence synthesis of this advanced intermediate **11** comprises a formal synthesis of nanaomycin D **3** (Scheme 1).



Scheme 1. Retrosynthesis from known nanaomycin intermediate **11**.

The formal synthesis of nanaomycin D **3** presented herein focusses on assembly of pyranonaphthalene-lactone **11**. Disconnection of the dihydropyran ring in pyranonaphthalene **11** gives trimethoxynaphthalene **12**, that in turn is assembled by an HK annulation of known cyanophthalide **13**[2b] with enone-lactone **14**. Enone-lactone **14** could be accessed from lactone aldehyde **15** using a Horner–Wadsworth–Emmons (HWE) reaction. The stereogenic centres in lactone aldehyde **15** can be readily constructed via a Sharpless asymmetric dihydroxylation of β,γ-unsaturated ester **17**, followed by lactonisation.

2. Results and discussion

Initial attention focussed on the synthesis of chiral enone-lactone **14** from unsaturated ester **17**. Accordingly, synthesis of unsaturated ester **17** began with readily available D-mannitol **18** (Scheme 2). Acetonide protection[12] and periodate cleavage[13] were carried out using literature procedures to give aldehyde **19**. HWE coupling with commercially available triethyl phosphonoacetate under mild aqueous conditions[14] cleanly afforded the desired *E*-alkene **20** in good yield. Alkene **20** was then converted via reductive cleavage to a β,γ-unsaturated ester **21** using Mg/MeOH,[15] in which transesterification with the solvent results in formation of the methyl ester. It was found that the outcome of the reductive cleavage step was very dependent on the particle size of the magnesium powder used and the reaction time. Use of coarser particle sizes afforded low yields whereas long reaction times resulted in undesired isomerisation to the α,β-unsaturated ester. It was also necessary to activate the magnesium powder by washing with hydrochloric acid.

Alcohol **21** was next protected as a TBDPS ether **17** and was subsequently subjected to Sharpless asymmetric dihydroxylation[16] with the $(DHQ)_2PHAL$ ligand. The resulting diol underwent concomitant lactonisation to give a 76% yield of lactone **16** in 79% enantiomeric excess, as determined by Mosher ester analysis. Protection of the alcohol in lactone **16** as an ethoxymethyl ether was unsuccessful using ethoxymethyl chloride with either diisopropylethylamine or sodium hydride as a base. The alcohol in lactone **16** was therefore protected as a methoxymethyl ether using dimethoxymethane and phosphorous pentoxide, a procedure that avoided the use of base given the presence of a base-sensitive γ-lactone. The TBDPS ether was then deprotected using TBAF buffered with acetic acid to give alcohol **22** in 92% yield. Oxidation of alcohol **22** to an aldehyde was unsuccessful with TPAP, IBX, PCC, TEMPO, Swern conditions and Dess–Martin periodinane (DMP) using pyridine as a base. Pleasingly, use of DMP buffered with sodium bicarbonate gave aldehyde **15**, which was immediately subjected to an HWE olefination with dimethyl 2-oxopropylphosphonate to furnish the desired enone-lactone **14** for the key HK annulation. Enone-lactone **14** represents an attractive chiral synthon for the construction of other γ-lactone containing pyranonaphthoquinones such as griseusin A[17] and crisamicin A.[18]

With an expedient route to enantiopure enone-lactone **14** established, we next investigated its use as a Michael acceptor in an HK annulation with cyanophthalide **13**, itself readily prepared from *o*-anisic acid as described previously.[2b] The mechanism of the Hauser–Kraus annulation is well-established, whereby the stabilised anion formed from the cyanophthalide undergoes a Michael addition to the enone and a subsequent Dieckmann-like condensation then delivers the cyclic product.[19] The reaction is known to produce a mixture of hydroquinone and quinone products; therefore it is common to carry out a subsequent reductive methylation step in order to trap the hydroquinone product as the dimethyl ether derivative. Hence, HK annulation between cyanophthalide **13** and enone-lactone **14** was attempted using *t*-BuOK and the crude material immediately subjected to reductive methylation conditions (Table 1, entry 1).[20] Disappointingly, only a complex mixture was recovered.

The HK annulation was attempted again without carrying out the methylation step. As found in previous HK annulation studies,[2a] the product obtained was not the desired naphthoquinone intermediate **24**, but the Michael addition product **23** (entry 2). Altering the base to *t*-BuOLi produced the same outcome (entry 3). Use of sodium hydride as a base gave naphthoquinone **24** (tentatively assigned based on the ^1H NMR spectrum of the crude material) in 16% yield, together with 56% of the Michael addition product **23** (entry 4). The naphthoquinone product **24** was found to degrade quickly, so a second attempt at the reaction was undertaken using sodium hydride as base for the annulation step immediately followed by reductive methylation using caesium carbonate and methyl iodide. These conditions furnished the desired trimethoxynaphthalene **12**, albeit in a low 13% yield (entry 5). The annulation was next attempted using potassium hydride as base followed by reductive methylation, affording a slightly higher 15% yield of methylated product **12** (entry 6). Next, the HK annulation step was conducted using potassium hydride, omitting the subsequent methylation step, affording naphthoquinone **24** and intermediate **23** that were separated by chromatography. Pure intermediate **23**, which was obtained in 64% yield, was then treated with sodium hydride followed by reductive methylation in combination with previously isolated naphthoquinone **24**, giving trimethoxynaphthalene **12** in a much improved 30% yield (entry 7). However, it was later discovered that this stepwise process was

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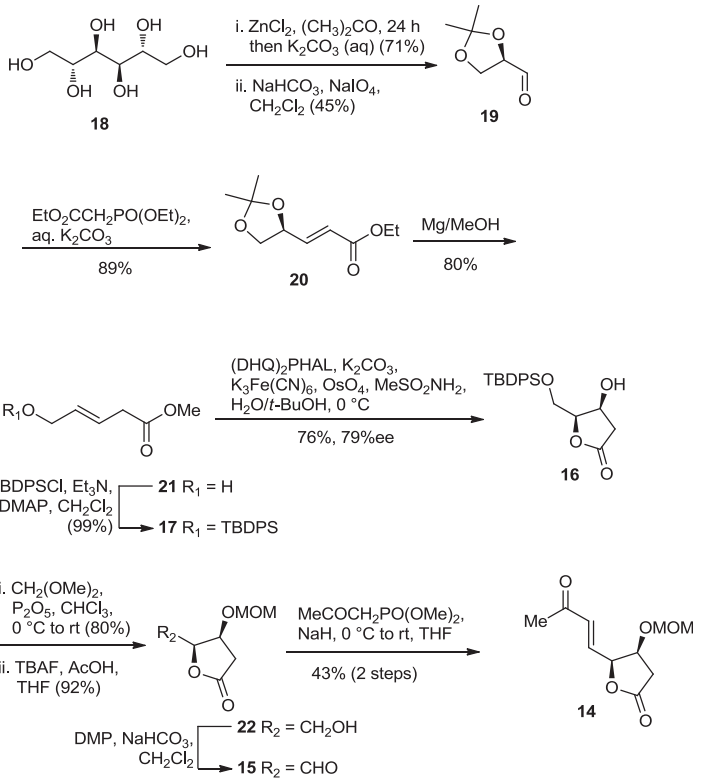
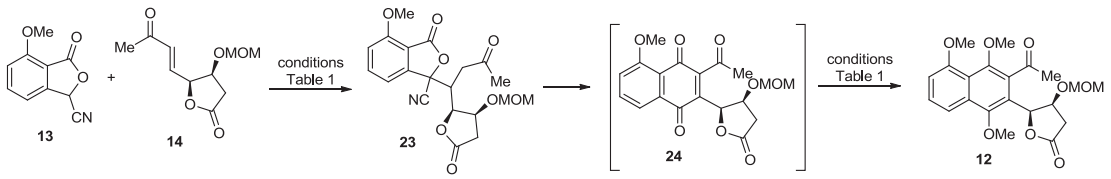


Scheme 2. Synthesis of chiral enone-lactone **14**.

Table 1
HK annulation of cyanophthalide **13** and enone-lactone **14**



Entry	Annulation conditions	Methylation conditions	Result
1[a]	*t*-BuOK (1.5 equiv), DMSO, rt, 30 min[a]	$Na_2S_2O_4$, TBAI, NaOH, H_2O/THF, Me_2SO_4, H_2, rt, 3 h	Complex mixture
2[a]	*t*-BuOK (1.5 equiv), DMSO, rt, 30 min[a]	—	9% **23**
3[a]	*t*-BuOLi (1.5 equiv), DMSO, rt, 30 min[a]	—	34% **23**
4[a]	NaH (3 equiv), THF, 0 °C, 2.5 h	—	16% **24**[c], 56% **23**
5[a]	NaH (3 equiv), THF, 0 °C, 2.5 h	$Na_2S_2O_4$, Cs_2CO_3, MeI, rt, 15 h	13% **12**
6[a]	KH (3 equiv), THF, 0 °C, 2.5 h	$Na_2S_2O_4$, Cs_2CO_3, MeI, rt, 15 h	15% **12**
7[a]	KH (3 equiv), THF, 0 °C, 2.5 h then NaH, EtOH, 0 °C, 4 h[d]	$Na_2S_2O_4$, Cs_2CO_3, MeI, rt, 15 h	30% **12**
8[b]	LDA (2.5 equiv), THF, −78 °C to rt, 30 min	$Na_2S_2O_4$, Cs_2CO_3, MeI, rt, 15 h	35% **12**

[a] Cyanophthalide **13** (1.5 equiv).
[b] Cyanophthalide **13** (2.5 equiv).
[c] Naphthoquinone **24** was not fully characterised due to instability.
[d] HK products **23** and **24** were separated (**24** not characterised), **23** cyclised to **24** using NaH, combined batches methylated to **12** without further purification.

unnecessary as use of lithium diisopropylamide (LDA) as base resulted in formation of the desired trimethoxynaphthalene **12** in 35% yield after reductive methylation (entry 8). This HK annulation sequence enabled formation of the naphthalene framework of nanaomycin D **3** with the chiral lactone already intact.

With the key trimethoxynaphthalene intermediate **12** in hand, the formal synthesis of nanaomycin D **3** could now be completed (Scheme 3). Removal of the MOM group was unsuccessful using Dowex 50W resin,[21] however, this step was achieved in 55% yield using anhydrous hydrochloric acid in THF. Surprisingly, the alcohol in **25** did not spontaneously cyclise onto the carbonyl group of the methyl ketone to form pyranonaphthalene **11**. It was postulated that the electrophilicity of the carbonyl group was lowered due to the presence of the highly electron-rich trimethoxynaphthalene ring system. Thus, oxidation to the 1,4-naphthoquinone was next investigated in order to promote formation of the lactol. Oxidative demethylation of **25** with ceric ammonium nitrate or AgO/HNO_3 gave an unstable product, identified by the ^1H NMR spectra of the crude material as naphthoquinone **26**. Disappointingly, spontaneous cyclisation of the hydroxyl group of the lactone on to the

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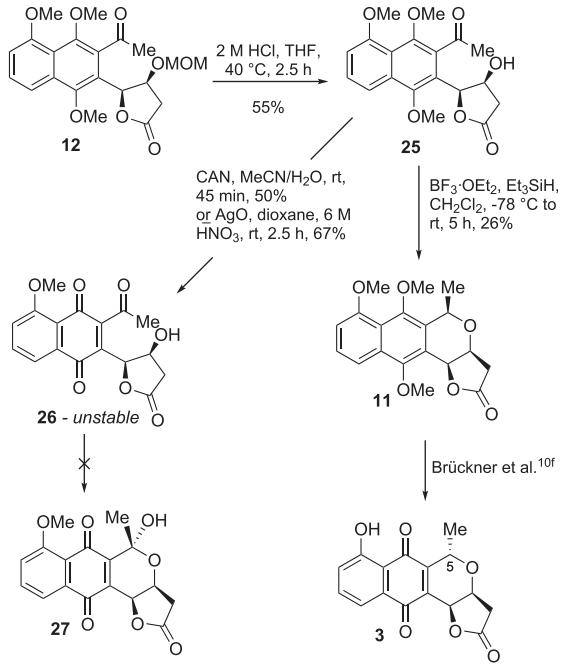

Scheme 3. Synthesis of pyranonaphthalene-lactone **11** and formal synthesis of nanaomycin D **3**.[10f]

methyl ketone in naphthoquinone **26** to afford desired lactol **27** did not occur. Pleasingly, it was discovered that hydroxyketone **25** underwent concomitant cyclisation and stereoselective reduction when exposed to $BF_3{\cdot}OEt_2$–Et_3SiH,[11b] giving pyranonaphthalene-lactone **11**, an advanced intermediate in the previously reported total synthesis of nanaomycin D and whose spectroscopic data was in full agreement with our own.[10f,22] Hence a formal synthesis of nanaomycin D had been accomplished.[10f] It is thought that the Lewis acid-mediated cyclisation of **25** takes place via formation of an oxonium intermediate derived from the initially formed lactol, followed by stereoselective reduction whereby hydride is delivered to the pseudo-axial position.[11]

3. Conclusion

In summary, the synthesis of pyranonaphthalene-lactone **11** completes a formal synthesis of the pyranonaphthoquinone natural product (−)-nanaomycin D **3**. Sharpless asymmetric dihydroxylation was used to generate the chirality in enone-lactone **14**. Importantly, subsequent Hauser–Kraus annulation of this chiral enone-lactone **14** with cyanophthalide **13** enabled construction of nanaomycin D **3** in a convergent manner. Chiral enone-lactone **14** comprises a key building block for the synthesis of other pyranonaphthoquinone antibiotics bearing fused γ-lactone rings. Additionally, a one-pot cyclisation–stereoselective reduction of a hydroxyketone was used to install the pyranonaphthalene moiety in an efficient manner.

4. Experimental section

4.1. General methods

Unless stated, all solvents and reagents were used as supplied from commercial sources. THF and dioxane were freshly distilled over sodium. CH_2Cl_2 was freshly distilled over CaH. MeOH was freshly distilled from magnesium. Analytical thin-layer chromatography (TLC) was performed using Kieselgel F_{254} 0.2 mm (Merck) silica plates with visualisation by ultraviolet irradiation (254 nm) followed by staining with vanillin or potassium permanganate. Flash chromatography was performed using Kieselgel S 63–100 μm (Riedel-de-Hahn) silica gel. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX300 or Bruker DRX400 spectrophotometer as stated. Chemical shifts were referenced to δ 7.26 and δ 77.0 ppm from chloroform for ^1H and ^{13}C, respectively, or δ 3.31 and δ 49.0 ppm from methanol for ^1H and ^{13}C, respectively, as stated. All coupling constants J are reported in hertz (Hz). All ^{13}C NMR spectra were acquired using broadband decoupled mode, and assignments were determined using DEPT, COSY, HSQC and NOESY sequences where required. Optical rotations were measured with a Rudolph Research Autopol IV automatic polarimeter at wavelength 589 nm, with the concentration of the solution measured in grams per 100 mL. Infrared (IR) spectra were recorded using a Perkin Elmer Spectrum One FT-IR spectrometer on a film ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were determined on a Kofler hotstage apparatus. Mass spectra were obtained by electrospray ionisation in positive ion mode using a VG70-SE spectrometer at a nominal accelerating voltage of 70 eV or on a Bruker micrOTOF-Q II mass spectrometer. Compound **13** was synthesised as described previously.[2b]

4.2. D-(*R*)-Glyceraldehyde acetonide (19)

$ZnCl_2$ (34.04 g, 0.25 mol) was stirred in AR grade acetone (185 mL, 2.52 mol) until dissolved. The mixture was cooled to 0 °C and D-mannitol **18** (18.28 g, 0.10 mol) added. The mixture was warmed to rt and stirred for 24 h. A 50 w/w% solution of K_2CO_3 (27.58 g) in H_2O (27 mL) was added at 0 °C and the mixture stirred for a further 1 h. The acetone layer was then decanted off and the precipitate extracted with EtOAc (3×50 mL). The acetone layer was brought to pH 8 by the addition of concentrated NH_3 solution (1–2 mL) and the resulting mixture was concentrated in vacuo. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3×30 mL). The combined EtOAc extracts were washed with H_2O (60 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting solid was dried under high vacuum overnight to give the acetonide intermediate (18.59 g, 71%) as a white powder; mp=108–110 °C (lit[23] 119.5–121 °C); $[\alpha]_D^{20}$ +3.5 (*c* 0.93, $CHCl_3$) (lit[24] +2.0 (*c* 2.38, $CHCl_3$)); δ_H (400 MHz; $CDCl_3$) 1.35 (s, 6H), 1.40 (s, 6H), 2.69 (br s, 1H), 2.70 (br s, 1H), 3.75 (t, *J*=6.2, 2H), 3.97 (m, 2H), 4.16 (m, 4H); δ_C (400 MHz; $CDCl_3$) 25.2 (2C), 26.7 (2C), 66.8 (2C), 71.2 (2C), 76.2 (2C), 109.2 (2C). NMR data, mp and $[\alpha]_D$ closely matched those previously reported.[23,24]

The acetonide intermediate (20.00 g, 0.076 mol) was dissolved in distilled CH_2Cl_2 (200 mL) and satd aq $NaHCO_3$ (8 mL) was added. $NaIO_4$ (32.62 g, 0.15 mmol) was added over 5 min keeping the temperature below 25 °C using a cool water bath. The reaction mixture was stirred at rt for 3 h under a reflux condenser. Anhydrous $MgSO_4$ (9 g) was added and the reaction mixture stirred for a further 30 min. The reaction mixture was filtered and the residue stirred with distilled CH_2Cl_2 (50 mL) for 10 min then filtered again. The solvent was concentrated in vacuo at 40 °C keeping the pressure above 150 mbar. The residue was vacuum distilled into a chilled receiver at 30 mbar (60–65 °C) to give the title compound **19** (11.36 g, 57%) as a colourless oil; $[\alpha]_D^{20}$ +39.5 (*c* 1.30, CH_2Cl_2) (lit[25] +53.8 (*c* 2.00, $CHCl_3$)); δ_H (400 MHz; $CDCl_3$) 1.37 (s, 3H), 1.44 (s, 3H), 4.09 (m, 2H), 4.34 (m, 1H), 9.66 (s, 1H); δ_C (400 MHz; $CDCl_3$) 25.1 (2C), 26.2, 65.5, 79.8, 201.7. NMR data and $[\alpha]_D$ matched those previously reported.[25]

4.3. Ethyl (*S*)-(*E*)-4,5-isopropylidenedioxy-2-pentenoate (20)

Aldehyde **19** (9.75 g, 74.92 mmol) in triethyl phosphonoacetate (30 mL, 0.15 mol) was cooled to 0 °C and aq K_2CO_3 (6 M, 120 mL)

was added. The mixture was warmed to rt and stirred for 20 h. The mixture was extracted with CH_2Cl_2 (3×60 mL), the combined organic extracts were washed with brine (60 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (hexanes/EtOAc 3:2) to give the title compound **20** (13.41 g, 89%) as a clear liquid; $[\alpha]_D^{20}$ +34.2 (*c* 1.02, CH_2Cl_2); δ_H (300 MHz; $CDCl_3$) 1.25 (t, *J*=7.1, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 3.63 (t, *J*=7.5, 1H), 4.15 (m, 3H), 4.63 (m, 1H), 6.06 (d, *J*=15.8, 1H), 6.83 (dd, *J*=5.8, 15.8, 1H); δ_C (400 MHz; $CDCl_3$) 14.1, 25.7, 26.4, 60.5, 68.7, 74.9, 110.1, 122.4, 144.6, 165.9. NMR data closely matched those previously reported.[26]

4.4. (*E*)-Methyl 5-hydroxypent-3-enoate (21)

A solution of alkene **20** (5.00 g, 24.97 mmol) in distilled methanol (125 mL) was cooled to −23 °C. Activated magnesium powder (20–230 mesh) (1.82 g, 74.9 mmol) was added and the reaction mixture was stirred at −23 °C for 15 h. The resulting grey suspension was diluted with diethyl ether (125 mL) then filtered through a pad of silica. The filtrate was concentrated in vacuo and the crude mixture was purified by flash chromatography (hexanes/EtOAc, 7:3) to give the title compound **21** (2.60 g, 20.0 mmol, 80%) as a pale yellow oil; δ_H (300 MHz, $CDCl_3$) 2.53 (s, 1H), 3.10 (d, *J*=5.3, 2H), 3.70 (s, 3H), 4.14 (d, *J*=4.0, 2H), 5.76–5.80 (m, 2H); δ_C (75 MHz, $CDCl_3$) 37.6, 51.9, 63.1, 123.7, 133.2, 172.0. NMR data closely matched those previously reported.[15]

4.5. (*E*)-Methyl 5-(*tert*-butyldiphenylsilyloxy)pent-3-enoate (17)

A solution of alcohol **21** (6.90 g, 53.0 mmol) in distilled CH_2Cl_2 (200 mL) was cooled to 0 °C. TBDPSCl (20.4 mL, 79.5 mmol), triethylamine (14.76 mL, 106 mmol) and 4-dimethylaminopyridine (647.5 mg, 5.30 mmol) were added. The resulting suspension was warmed to rt and stirred for 20 h. The reaction mixture was quenched upon addition of cold water (100 mL) and the organic phase was isolated. The aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting crude mixture was purified by flash chromatography (hexanes/EtOAc, 9:1) to give the title compound **17** (19.3 g, 52.5 mmol, 99%) as colourless oil; ν (neat)/cm^{-1} 3071, 2954, 2932, 2857, 1740, 1427, 1259, 1164, 1108, 971; δ_H (300 MHz, $CDCl_3$) 1.06 (s, 9H), 3.08 (m, 2H), 3.69 (s, 3H), 4.19 (m, 2H), 5.64–5.72 (m, 1H), 5.77–5.89 (m, 1H), 7.34–7.45 (m, 6H), 7.66–7.69 (m, 4H); δ_C (75 MHz, $CDCl_3$) 19.2, 26.8 (3C), 37.5, 51.8, 64.0, 122.1, 127.6 (4C), 129.6 (2C), 132.9, 133.6 (2C), 135.5 (4C), 172.1; HRMS (ESI) $[M+H]^+$ found 391.1690, calcd for $C_{22}H_{28}NaO_3Si$ 391.1700.

4.6. (4*S*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4-hydroxydihydrofuran-2(3*H*)-one (16)

To a mixture of *t*-BuOH/H_2O (1:1) (136 mL) were added K_2CO_3 (5.64 g, 40.8 mmol), $K_3Fe(CN)_6$ (13.4 g, 40.8 mmol), $(DHQ)_2PHAL$ (106 mg, 0.14 mmol, 1 mol %) and OsO_4 (0.71 mL, 2.5 wt % in *tert*-butanol, 0.054 mmol, 0.4 mol %). The reaction mixture was stirred until all the solids dissolved then methanesulfonamide (1.29 g, 13.6 mmol) was added. The reaction mixture was stirred vigorously for 2 h and then cooled to 0 °C. Olefin **17** (5.00 g, 13.6 mmol) in *t*-BuOH/H_2O (1:1) (10 mL) was added and the reaction mixture was stirred for 20 h. The mixture was warmed to rt and then quenched by the addition of satd aq Na_2SO_3 (110 mL). The resulting solution was extracted with EtOAc (3×150 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 3:2) to give the title compound **16** (3.83 g, 10.3 mmol, 76%, 79% ee) (as determined by Mosher ester, see Supplementary data) as a viscous pale brown oil; $[\alpha]_D^{20}$ −23.7 (*c* 1.12, $CHCl_3$); ν (neat)/cm^{-1} 3455, 3072, 2931, 2857, 1769, 1472, 1427, 1110, 1047, 822, 737; δ_H (300 MHz, $CDCl_3$) 1.07 (s, 9H), 2.60 (dd, *J*=2.9, 17.8, 1H), 2.77 (dd, *J*=6.5, 17.8, 1H), 3.26 (d, *J*=4.9, 1H), 4.03 (dd, *J*=5.4, 11.3, 1H), 4.10 (dd, *J*=4.2, 11.3, 1H), 4.41–4.45 (m, 1H), 4.66–4.72 (m, 1H), 7.38–7.48 (m, 6H), 7.65–7.85 (m, 4H); δ_C (75 MHz, $CDCl_3$) 19.1, 26.7 (3C), 38.5, 62.0, 68.9, 81.4, 128.0 (4C), 130.2 (2C), 131.8, 132.2, 135.4 (2C), 135.6 (2C), 174.9; HRMS (CI^+) $[M+H]^+$ found 371.1680, calcd for $C_{21}H_{27}O_4Si$ 371.1679. NMR data closely matched those previously reported.[27]

4.7. (4*S*,5*S*)-5-(Hydroxymethyl)-4-(methoxymethoxy)dihydrofuran-2(3*H*)-one (22)

To a stirred solution of alcohol **16** (6.30 g, 17.02 mmol) in $CHCl_3$ (102 mL) was added dimethoxymethane (102 mL, 1.20 mol) and the solution was cooled to 0 °C. Phosphorus pentoxide (21.7 g, 153.2 mmol) was added and the reaction mixture was warmed to rt and stirred for 15 h. Satd aq Na_2CO_3 (100 mL) was added and the organic phase was isolated. The aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layers were washed with brine (200 mL) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the crude mixture was purified by flash chromatography (hexanes/EtOAc, 7:3) to give the MOM ether (5.60 g, 13.5 mmol, 80%) as a colourless oil; ν (neat)/cm^{-1} 3073, 3049, 2932, 2858, 2893, 1784, 1472, 1428, 1153, 1111, 1035, 997, 823; δ_H (300 MHz, $CDCl_3$) 1.05 (s, 9H), 2.68–2.83 (m, 2H), 3.30 (s, 3H), 3.92–4.03 (m, 2H), 4.49–4.55 (m, 2H), 4.61–4.71 (m, 2H), 7.36–7.47 (m, 6H), 7.67–7.72 (m, 4H); δ_C (75 MHz, $CDCl_3$) 19.1, 26.7 (3C), 36.4, 55.8, 61.4, 73.1, 82.3, 96.3, 127.75 (2C), 127.78 (2C), 129.8, 129.9, 132.8, 132.9, 135.6 (4C), 174.6; HRMS (CI^+) $[M+NH_4]^+$ found 432.2205, calcd for $C_{23}H_{34}NO_5Si$ 432.2206.

To a solution of the MOM ether (3.10 g, 7.46 mmol) in distilled THF (150 mL) was added glacial acetic acid (0.85 mL, 14.3 mmol) and the reaction mixture was stirred for 10 min prior to the addition of TBAF (1 M sol in THF, 14.9 mL, 14.9 mmol). The resulting solution was stirred for 3 h then concentrated in vacuo. The crude mixture was purified by flash chromatography (hexanes/EtOAc, 7:3) to afford the title compound **22** (1.21 g, 6.87 mmol, 92%) as a pale yellow oil; $[\alpha]_D^{20}$ +15.5 (*c* 1.00, $CHCl_3$); ν (neat)/cm^{-1} 3421, 2939, 2899, 2829, 1774, 1406, 1357, 1201, 1152, 1101, 1034, 994,,938,918; δ_H (300 MHz, $CDCl_3$) 2.43 (br s, 1H), 2.70 (dd, *J*=3.2, 17.8, 1H), 2.82 (dd, *J*=5.9, 17.8, 1H), 3.40 (s, 3H), 3.93 (dd, *J*=4.6, 12.4, 1H), 4.02 (dd, *J*=4.6, 12.4, 1H), 4.55–4.63 (m, 2H), 4.67–4.73 (m, 2H); δ_C (75 MHz, $CDCl_3$) 36.3, 56.0, 60.6, 73.7, 82.3, 96.3, 174.4; HRMS (CI^+) $[M+H]^+$ found 177.0761, calcd for $C_7H_{13}O_5$ 177.0763.

4.8. (4*S*,5*S*)-4-(Methoxymethoxy)-5-((*E*)-3′-oxobut-1′-enyl)dihyrofuran-2(3*H*)-one (14)

Dess–Martin periodinane (168 mg, 0.95 mmol) and $NaHCO_3$ (159.6 mg, 1.90 mmol) were added to distilled CH_2Cl_2 (30 mL) and the resulting suspension was stirred for 15 min. A solution of alcohol **22** (1.0 g, 5.7 mmol) in distilled CH_2Cl_2 (1 mL) was added and the reaction mixture stirred for 3 h. Satd aq $Na_2S_2O_3$ (25 mL) was added and the organic phase was isolated. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the intermediate crude aldehyde **15**.

To a suspension of sodium hydride (45.6 mg, 60% dispersion in mineral oil, 1.14 mmol) in distilled THF (5 mL) was added dimethyl-(2-oxopropyl)phosphonate (0.16 mL, 1.14 mmol) at 0 °C. The reaction mixture was stirred until gas evolution ceased (30 min). A solution of crude aldehyde **15** in distilled THF (8 mL) was added, the

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cooling bath removed and the reaction mixture was stirred for 4 h at rt. Satd aq NH_4Cl (10 mL) was added and the organic phase was isolated. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 7:3) to afford the title compound **14** (71.0 mg, 0.41 mmol, 43% over two steps) as a pale yellow viscous oil; $[\alpha]_D^{23}$ −11.5 (*c* 0.40, $CHCl_3$); ν (neat)/cm^{-1} 2999, 2957, 2900, 2837, 1773, 1673, 1649, 1252, 1148, 1096, 1013, 978; δ_H (400 MHz, $CDCl_3$) 2.30 (s, 3H), 2.69 (dd, *J*=2.8, 17.7, 1H), 2.79 (dd, *J*=5.7, 17.7, 1H), 3.34 (s, 3H), 4.57 (ddd, *J*=2.7, 5.2, 5.2, 1H), 4.61 (d, *J*=7.0, 1H), 4.64 (d, *J*=7.0, 1H), 5.10 (m, 1H), 6.42 (dd, *J*=1.5, 16.0, 1H), 6.81 (dd, *J*=5.4, 16.0, 1H); δ_C (100 MHz, $CDCl_3$) 28.0, 36.0, 56.0, 74.2, 81.5, 95.8, 132.0, 138.0, 173.8, 197.2; HRMS (EI^+) $[M]^+$ found 214.0837 calcd for $C_{10}H_{14}O_5$ 214.0841.

4.9. 3-Cyano-7-methoxy-3-(1′-((2*S*″,3*S*″)-3″-(methoxymethoxy)-5″-oxotetrahydofuran-2″-yl) 3′-oxobutyl)-1-isobenzofuranone (23)

To a suspension of potassium hydride (11.2 mg, 60% dispersion in mineral oil, 0.28 mmol) in distilled THF (1.5 mL) at 0 °C was added phthalide **13** (35.2 mg, 0.19 mmoL) and the reaction mixture was left to stir for 20 min. A solution of enone **14** (20 mg, 0.093 mmol) in distilled THF (1 mL) was added and the reaction mixture was stirred for a further 2.5 h. Satd aq NH_4Cl (20 mL) was added and the organic phase was isolated. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 1:1) to afford the title compound **23** (24.0 mg, 0.06 mmol, 64%) as a pale yellow oil. Naphthoquinone **24** (6.37 mg, 0.016 mmol, 17%) was also obtained; $[\alpha]_D^{20}$ −39.0 (*c* 0.2, $CHCl_3$); ν (neat)/cm^{-1} 2927, 2853, 1782, 1719, 1599, 1489, 1440, 1366, 1289, 1211, 1151, 1010, 966, 908, 802, 779, 692; δ_H (300 MHz, $CDCl_3$) 2.33 (s, 3H), 2.47–2.70 (m, 3H), 3.14 (dd, *J*=7.6, 18.5, 1H), 3.33 (s, 3H), 3.85–3.89 (m, 1H), 4.02 (s, 3H), 4.35–4.40 (m, 2H), 4.60 (s, 2H), 7.08 (d, *J*=8.4, 1H), 7.35 (d, *J*=7.4, 1H), 7.77 (dd, *J*=7.6, 8.4, 1H); δ_C (75 MHz, $CDCl_3$) 30.1, 35.9, 40.4, 40.7, 56.3, 56.3, 74.2, 78.6, 79.7, 96.0, 111.5, 113.1, 114.6, 115.8, 138.0, 148.1, 159.0, 165.1, 172.9, 203.5; HRMS (ESI^+) $[M+Na]^+$ found 426.1158, calcd for $C_{20}H_{21}NNaO_8$ 426.1159.

4.10. (4*S*,5*S*)-5-(3′-Acetyl-1′,4′,5′-trimethoxynaphthalen-2′-yl)-4-(methoxymethoxy)dihydrofuran-2(3*H*)-one (12)

A solution of phthalide **13** (220 mg, 1.16 mmol) in distilled THF (5 mL) was added slowly to a freshly prepared solution of LDA (1.16 mmol) in distilled THF (2 mL) at −78 °C [prepared from addition of *n*-butyllithium in hexanes (1.6 M, 0.17 mL, 1.16 mmol) to diisopropylamine (0.75 mL, 1.16 mmol) at 0 °C] and the reaction mixture was stirred for 15 min. To the resulting bright yellow solution was added enone **14** (100 mg, 0.47 mmol) in THF (2 mL), and the reaction mixture was warmed to rt with stirring over 1 h. Satd aq NH_4Cl (5 mL) was added and the organic phase was isolated. The aqueous layer was extracted with EtOAc (3×25 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Then the resulting crude residue was taken up in DMF (5 mL) and sodium dithionite (645 mg, 3.72 mmol) was added. After stirring for 30 min, caesium carbonate (1.21 g, 3.72 mmol) was added followed by methyl iodide (0.23 mL, 3.72 mmol). The reaction mixture was stirred for 15 h under an atmosphere of nitrogen. Satd aq NH_4Cl (5 mL) and CH_2Cl_2 (10 mL) were added and the organic phase was isolated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with water (3×10 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes/EtOAc, 1:1) to afford the title compound **12** (65.8 mg, 0.16 mmol, 35% over two steps) as a yellow oil; $[\alpha]_D^{20}$ −11.9 (*c* 0.52, $CHCl_3$); ν (neat)/cm^{-1} 2996, 2935, 2842, 1788, 1738, 1695, 1615, 1572, 1458, 1449, 1363, 1341, 1268, 1246, 1148, 1069; δ_H (300 MHz, $CDCl_3$) 2.63 (s, 3H), 2.64 (dd, *J*=5.4, 18.0, 1H), 3.14 (dd, *J*=8.1, 18.0, 1H), 3.32 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), 4.03 (s, 3H), 4.64 (d, *J*=6.9, 1H), 4.67 (d, *J*=6.9, 1H), 4.74 (ddd, *J*=5.7, 5.7, 7.6, 1H), 5.73 (d, *J*=5.1, 1H), 6.97 (d, *J*=7.8, 1H), 7.50 (dd, *J*=7.8, 8.4, 1H), 7.69 (d, *J*=8.4, 1H); δ_C (75 MHz, $CDCl_3$) 32.9, 36.4, 55.8, 56.2, 63.2, 63.9, 78.9, 81.2, 96.3, 107.2, 115.3, 120.8, 123.9, 127.8, 131.1, 132.2, 149.8, 150.8, 156.5, 174.7, 206.4; HRMS (EI^+) $[M+H]^+$ found 405.1571, calcd for $C_{21}H_{25}O_8$ 405.1544.

4.11. (4*S*,5*S*)-5-(3′-Acetyl-1′,4′,5′-trimethoxynaphthalen-2′-yl)-4-hydroxydihydrofuran-2(3*H*)-one (25)

To a solution of trimethoxynaphthalene **12** (82.0 mg, 0.203 mmol) in distilled dioxane (7 mL) was added hydrochloric acid (4 M sol in dioxane, 7 mL) and the resulting solution was stirred at 40 °C for 3 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (hexanes/EtOAc, 3:7) to yield the title compound **25** (40 mg, 0.11 mmol 55%) as a pale yellow oil; $[\alpha]_D^{20}$ −20.8 (*c* 0.24, $CHCl_3$); ν (neat)/cm^{-1} 3539, 2935, 2848, 1775, 1697, 1572, 1459, 1365, 1341, 1265, 1245, 1186, 1145, 1065, 1009; δ_H (400 MHz, $CDCl_3$) 2.64 (dd, *J*=5.8, 18.0, 1H), 2.68 (s, 3H), 2.75 (br s, 1H), 3.11 (dd, *J*=8.3, 18.0, 1H), 3.76 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 4.80 (m, 1H), 5.52 (d, *J*=4.9, 1H), 6.97 (dd, *J*=0.6, 7.8, 1H), 7.52 (dd, *J*=7.8, 8.4, 1H), 7.67 (d, *J*=0.9, 8.5, 1H); δ_C (75 MHz, $CDCl_3$) 32.9, 37.4, 56.2, 63.1, 63.8, 74.1, 83.6, 107.2, 115.1, 120.5, 124.1, 128.0, 131.3, 131.8, 150.2, 150.6, 156.6, 174.6, 206.9; HRMS (ESI) $[M+Na]^+$ found 383.1109, calcd for $C_{19}H_{20}NaO_7$ 383.1101.

4.12. 3-Acetyl-2-((2′*S*,3′*S*)-3′-hydroxy-5′-oxotetrahydrofuran-2′-yl)-5-methoxynaphthalene-1,4-dione (26)

To a solution of alcohol **25** (8.60 mg, 0.024 mmol) in distilled dioxane (2 mL) was added silver(II) oxide (12.0 mg, 0.095 mmol) followed by nitric acid (0.1 mL, 6 M) and the reaction mixture was stirred at rt for 45 min. Another portion of silver(II) oxide (6.0 mg, 0.048 mmol) and nitric acid (6 M, 0.5 mL) were added and the stirring was continued for 20 min. Two more portions of silver(II) oxide (6.0 mg, 0.048 mmol; 18 mg, 0.14 mmol in total) and nitric acid (6 M, 0.5 mL; 1.5 mL in total) were added at 20 min intervals. Water (10 mL) was added and the organic phase was isolated. The aqueous layer was extracted with EtOAc (3×15 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo and the crude mixture was subjected to preparative thin-layer chromatography (hexanes/EtOAc, 1:1) to give the title compound **26** (5.30 mg, 0.016 mmol, 67%) as a bright yellow solid; δ_H (300 MHz, $CDCl_3$) 2.54 (s, 3H), 2.62 (dd, *J*=4.1, 18.3, 1H), 3.05 (dd, *J*=8.1, 18.3, 1H), 4.03 (s, 3H), 4.57 (m, 1H), 5.36 (d, *J*=3.3, 1H), 7.39 (m, 1H), 7.75 (m, 2H).

4.13. (3a*S*,5*R*,11b*S*)-6,7,11-Trimethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one (11)

To a solution of alcohol **25** (8.60 mg, 0.024 mmol) in distilled CH_2Cl_2 (2 mL) at −78 °C was added boron trifluoride diethyl etherate (0.04 mL, 0.29 mmol) followed by triethylsilane (0.046 mL, 0.29 mmol). The solution was stirred at −78 °C for 15 min then allowed to warm to rt over 5 h. Satd aq $NaHCO_3$ (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography

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(hexanes/EtOAc, 7:3) gave the title compound **11** (2.14 mg, 0.0062 mmol, 26%) as a light yellow solid; mp 230–234 °C; $[\alpha]_D^{19}$ −60.7 (*c* 0.45, $CHCl_3$); ν (neat)/cm^{-1} 2998, 2924, 2852, 1775, 1593, 1571, 1499, 1449, 1435, 1402, 1373, 1345, 1288, 1261, 1229, 1203, 1153, 1112, 1061, 1033, 995, 805; δ_H (300 MHz, $CDCl_3$) 1.75 (d, *J*=6.3, 3H), 2.78 (dd, *J*=17.3, 1H), 2.92 (dd, *J*=4.5, 17.3, 1H), 3.75 (s, 3H), 4.02 (s, 3H), 4.10 (s, 3H), 4.36–4.38 (m, 1H), 5.06–5.10 (m, 1H), 5.59 (d, *J*=2.3, 1H), 6.94 (d, *J*=7.8, 1H), 7.44 (dd, *J*=7.8, 8.3, 1H), 7.73 (d, *J*=8.3, 1H); δ_C (100 MHz, $CDCl_3$) 22.4, 38.4, 56.3, 61.6, 64.5, 70.2, 71.3, 73.0, 107.3, 115.2, 119.2, 121.6, 126.6, 129.2, 130.3, 149.4, 152.9, 156.2, 175.7; HRMS (ESI) $[M+H]^+$ found 345.1341, calcd for $C_{19}H_{21}O_6$ 345.1333.

Acknowledgements

The authors wish to thank the Staff Scholarship funded by Universiti Teknologi MARA (NPSH) and Maurice Wilkins Centre for Molecular Biodiscovery for financial support. We thank Professor Reinhard Brückner for providing relevant spectroscopic data.

Supplementary data

These include ^1H NMR and ^{13}C NMR spectra for all novel compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.09.014.

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