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Towards the Total Synthesis of Mycaperoxide B: Probing Biosynthetic Rationale

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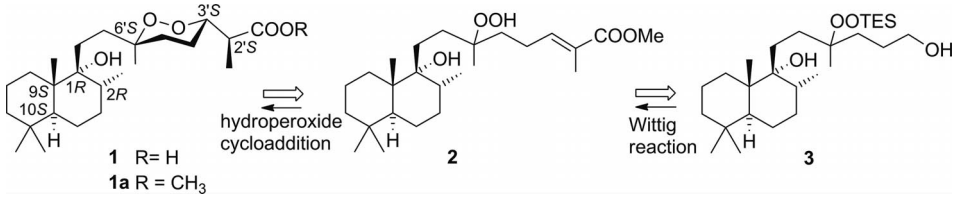
Studies towards the biomimetic synthesis of mycaperoxide B (**1**) are described. We have established the synthesis of four diastereoisomers of mycaperoxide B methyl ester (**1a**) by employing a Michael addition across an α,β-unsaturated ester precursor **2** as the key step. This result strongly suggests stereocontrol in the addition of the hydroperoxide functionality to the *E* double bond and discloses the importance of choosing the correct geometry of the α,β-unsaturated double bond when attempting to synthesise mycaperoxide B. Four diastereoisomeric tetrahydrofurans derived from an intramolecular rearrangement of the 1,2-dioxolane enolate **12** were also isolated and characterised.

Introduction

The mycaperoxide family[1–5] consists of eight structurally related marine norsesterterpenes with a common carbon skeleton that consists of a tetramethyldecalin nucleus possessing a side-chain at the C-1 position that bears a 1,2-dioxolane ring. Mycaperoxide B (**1**; Scheme 1) was isolated in 1993 from marine sponges of the genus Mycale and exhibits significant cytotoxicity against various cancer cell lines as well as antiviral activity.[1] Mycaperoxide B (**1**) contains an interesting cyclic peroxide moiety in its structure and its absolute configuration was assigned to be 2′*S*,3′*S*,6′*S*,1*R*,2*R*,9*S*,10*S*.[1] For these reasons, mycaperoxide B (**1**) represents a novel and synthetically challenging target and development of an efficient facile synthetic route presents a rewarding and important objective. Following previous work,[6] our group has been particularly interested in investigating the viability of a synthetic methodology based on the second proposed biosynthetic pathway reported by Capon for the formation of this family of norsesterterpene cyclic peroxides.[7] According to this hypothesis, it was expected that the generation of a tertiary hydroperoxide and subsequent intramolecular Michael cyclisation across an α,β-unsaturated ester (Scheme 1) would allow the preparation of the desired target.[7]

The method that seemed to be most suitable for obtaining the 1,2-dioxolane in a single step consisted of an intramolecular addition of a tertiary hydroperoxide group to an α,β-unsaturated ester. The conjugate addition of the hydroperoxide to an α,β-unsaturated ester was first described by Bartlett and Chapuis in an approach towards the synthesis of polyether tetrahydrofurans.[8] More recently, Massanet and co-workers described the preparation of 1,2-dioxolane, 1,2-dioxane or 1,2-dioxepane rings by the intramolecular Michael addition of a secondary hydroperoxide group onto an α,β-unsaturated ester as the key step.[9] In addition, 3-methoxy-6-[(methoxycarbonyl)methyl]-1,2-dioxane,[10a–10g] 3-methoxy-5-[(methoxycarbonyl)methyl]-1,2-dioxolane[10h] and spiro-peroxides,[10i] some of which have anti-malarial activity, have been synthesised by the intramolecular Michael addition of hydroperoxy ketals to α,β-unsaturated esters. Posner and co-workers have described the



Scheme 1. Retrosynthetic analysis of mycaperoxide B (**1**) inspired by the second biosynthetic pathway proposed by Capon.[7]

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intramolecular attack of a tertiary hydroperoxide group on the α,β-unsaturated carbonyl of carvone.[11] In this case, the spatial proximity of the two groups favoured the reaction. Finally, Woerpel and co-workers have recently synthesised 1,2-dioxane systems by intramolecular palladium-catalysed addition of hydroperoxides to olefins.[12] This method, however, appears to be specific to tertiary hydroperoxides because less substituted substrates did not cyclise.

Recently, we demonstrated for a series of model alkene substrates the introduction of the hydroperoxide functional group into the required position for a biosynthetically inspired synthesis of mycaperoxide B (**1**).[13] We also demonstrated that the introduction of a triethylsilylperoxy substituent into analogues of a potential synthetic precursor to the mycaperoxides is dependent on hydroxy protection and this has led to the successful synthesis of triethylsilyl peroxide **3** (Scheme 1).[13]

Herein we describe the successful, although non-stereoselective, synthesis of four diastereoisomers of mycaperoxide B (**1**) by using the (*E*)-α,β-unsaturated methyl ester precursor **2**, as well as the formation of four diastereoisomeric tetrahydrofuran compounds by intramolecular rearrangement of an enolate intermediate involved in the formation of the dioxolane ring.

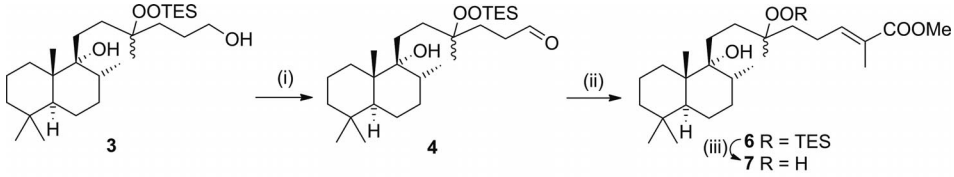
Results and Discussion

With the methodology for preparing the protected hydroperoxide precursor **3**[13] in hand, the next objective was to assemble the remaining parts of the side-chain and, finally, to prepare the 1,2-dioxolane ring. According to the retrosynthetic analysis outlined in Scheme 1, the remaining parts of the side-chain were to be assembled by a Wittig reaction between the aldehyde **4** and a stabilised ylide **5** that would be expected to set up the desired *E* stereochemistry for **2** (Scheme 2).

The primary alcohol in the side-chain of **3** was selectively oxidised to the aldehyde **4** in quantitative yield by using Dess–Martin periodinane (Scheme 2) with the crude material being used in the next step without further purification. A triplet at δ_H = 9.70 ppm (J = 2.5 Hz) in the ^{1}H NMR spectrum and a carbonyl stretch at 1725 cm^{-1} in the IR spectrum indicated successful formation of the desired product. The ylide **5** (Scheme 2) required for the Wittig reaction with **4** was synthesised according to the literature procedure from commercially available triphenylphosphane and methyl 2-bromopropionate in the presence of triethylamine.[14] A solution of the aldehyde **4** in dichloromethane was added dropwise to a solution of the ylide **5** in dichloromethane (Scheme 2). The reaction mixture was stirred overnight at room temperature under an inert atmosphere, after which time TLC analysis of the mixture indicated complete consumption of the starting material along with the formation of a new component. The crude material was purified by flash column chromatography, eluting with petroleum ether/diethyl ether (9:1), to furnish the desired product **6** in 69% yield. The ^{1}H NMR spectrum of compound **6** shows a new olefinic signal at δ_H = 6.78–6.74 ppm and a three-proton singlet at δ_H = 3.73 ppm, which corresponds to the methyl ester group. A singlet at δ_H = 1.84 ppm was assigned to the resonance of the methyl group attached to the newly created double bond. Given that only one signal is associated with both these functional groups in both the ^{1}H and ^{13}C NMR spectra of **6**, it is credible to assume that the Wittig reaction had taken place with complete stereocontrol, as expected. The completion of the synthesis of the proposed biomimetic precursor **7** (Scheme 2) was achieved in a yield of 81% by removal of the triethylsilyl group from the hydroperoxide **6** using a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The ^{1}H NMR spectrum of deprotected compound **7** shows two singlets at δ_H = 9.24 and 8.89 ppm in an approximately 1:1 ratio, which correspond to the resonances of two hydroperoxide protons, which reveals that the product had been obtained as a mixture of two diastereoisomers.

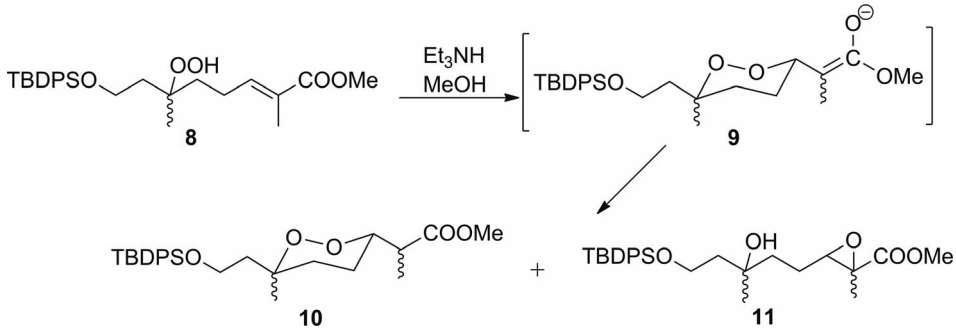
With all the key features of the natural product in place the most critical and important step in this synthesis had now been reached: the construction of the cyclic peroxide ring. The intramolecular cyclisation of the hydroperoxide onto the conjugated methyl ester in **7** was first studied in model system **8** (Scheme 3), which was prepared by using a methodology similar to that previously reported.[13] It was initially decided to attempt the cyclisation reaction under basic conditions (Table 1, entries 1–8). The conditions that resulted in the optimum formation of the desired 1,2-dioxolane ring **10** (15%) along with the undesired epoxide **11** (40%) involved the use of 0.2 equiv. of triethylamine in methanol (Table 1, entry 3).

It was reasoned that the best way to improve the low yield of the desired product **10** would be to promote the rapid protonation of the intermediate enolate **9** and thereby disfavour the formation of the unwanted epoxide **11**.[15] The formation of an epoxide, by cleavage of the O–O bond, had previously been reported in a publication concerning the structure elucidation of the marine natural product plakor-



(i) Dess-Martin, CH_2Cl_2, rt, 2 h, quant; (ii) $(CH_3)C(PPh_3)CO_2Me$ **5**, CH_2Cl_2, r.t., overnight, 69 %; (iii) PPTS, EtOH, r.t., 6 h, 81 %.

Scheme 2. Preparation of the α,β-unsaturated methyl ester **7**.



Scheme 3. Preparation of 1,2-dioxolane **10** by using model system **8**.

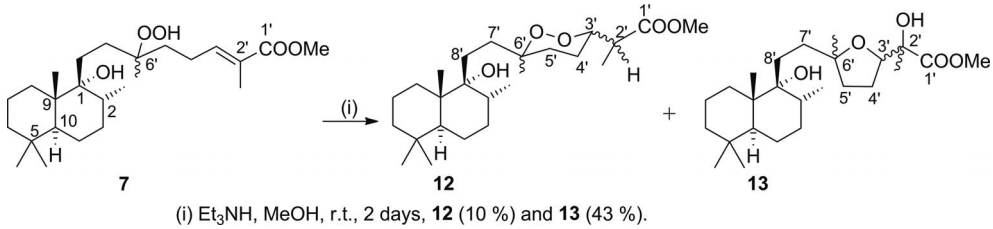
Table 1. Optimisation of the conditions for the cyclisation step with compound **8**.

Entry	Conditions	Yield [%]		
		10	**11**	**8**
1	KF, 18-crown-6, THF	–	65	–
2	Et_3N (0.1 equiv.), MeOH	14	48	–
3	Et_3N (0.2 equiv.), MeOH	15	40	–
4	Hünig's base, MeOH	9	37	–
5	NaOMe, MeOH	8	68	–
6	LHMDS, –78 °C, THF	–	93	–
7	LHMDS, TMSCl, –78 °C, THF	–	–	68
8	Et_2NH (0.4 equiv.), MeOH/CF_3CH_2OH (1:1), 0 °C	–	–	–
9	$MgBr_2{\cdot}OEt_2$, MeOH	–	–	47
10	$BF_3{\cdot}OEt_2$, toluene	no reaction		
11	$SnCl_4$, toluene	decomposition		
12	$Yb(CF_3SO_3)_3$, THF, H_2O	–	–	66

tin.[16] This interesting rearrangement occurred on treatment of plakortin with sodium methoxide in methanol, which led to the formation of the epoxide through ring contraction followed by the final formation of a tetrahydrofuran. By using trimethylsilyl chloride it was hoped to capture and isolate the intermediate **9** as its silyl enol ether and therefore avoid the formation of epoxide **11**. Unfortunately, no reaction was observed and only the starting material was recovered (Table 1, entry 7). The use of Lewis acid conditions resulted in no reaction or decomposition (Table 1, entries 9–12).

The preparation of both the desired product **10** and the hydroxy epoxide **11** was confirmed by analysis of the NMR spectroscopic data. The ^1H NMR spectrum of compound **10** shows a new multiplet at δ_H = 4.11–4.07 ppm attributed to the single proton of the peroxide ring. Also, the appearance of two new double quartets at δ_H = 2.67 and 2.56 ppm, which integrate to one proton and correspond to the resonance of the proton adjacent to the methyl ester, concomitant with the loss of the olefin signal and the two hydroperoxide signals of the starting material, confirmed the formation of **10**. The ^1H NMR spectrum of compound **11** shows a new multiplet at δ_H = 3.93–3.86 ppm attributed to the single proton of the epoxide ring. Two new singlets at δ_H = 1.54 and 1.53 ppm, which integrate to three protons and correspond to the resonance of the methyl group geminal to the methyl ester, also confirmed the formation of epoxide **11**. As the highest yield for the formation of the desired 1,2-dioxolane ring in the model compound was achieved by using triethylamine in methanol (Table 1, entry 3), it was decided to apply these same conditions to substrate **7** (Scheme 4). Thus, a methanolic solution of freshly distilled triethylamine (0.05 M, 2 equiv.) was added dropwise over a period of 2 h to a solution of the hydroperoxide **7** in methanol and the reaction was monitored by TLC (petroleum ether/diethyl ether, 2:1). After half the base had been added, TLC analysis revealed the concurrent formation of two products. The first spot had an R_f value higher than the starting material and the second spot appeared almost on the baseline. The solution was stirred under nitrogen for 48 h in total and the crude material was purified by flash column chromatography by using a mixture of petroleum ether/diethyl ether (2:1) as eluent.

The least polar fraction was isolated as a colourless oil in a yield of 10% and NMR spectroscopic analysis (see Table S1, Supporting Information) suggested it was the desired dioxolane product **12**. The second fraction to be isolated consisted of recovered starting material (21%) and the most polar fraction, which was obtained in 43% yield, was confirmed to be the tetrahydrofuran byproduct **13** by NMR

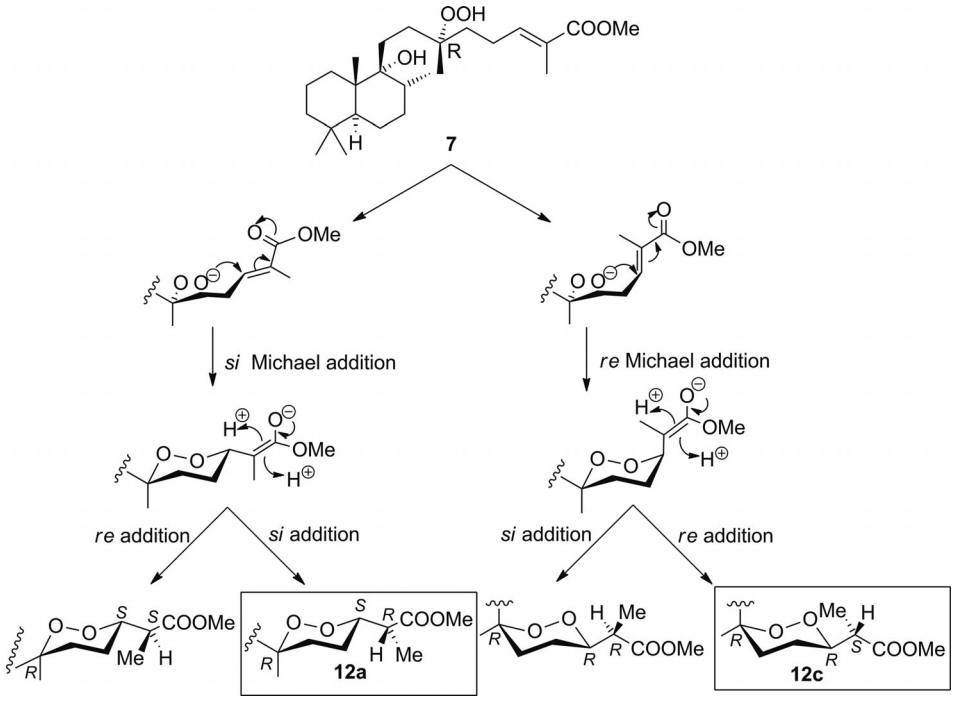


Scheme 4. Preparation of the six-membered peroxide ring **12**.

analysis (see Table S2, Supporting Information; Scheme 4). The ^{1}H NMR spectrum of the first fraction (see Table S1, Supporting Information) shows the appearance of two new double double doublets at δ_H = 4.104 (J = 7, 7, 7 Hz) and 4.141 ppm (J = 7, 7, 7 Hz), which combined integrate as one proton, along with two new double quartets at δ_H = 2.658 (J = 7, 7 Hz) and 2.620 ppm (J = 7, 7 Hz), which also integrate to one proton, concomitant with the loss of the olefin signal and the two hydroperoxide signals from the starting material. Examination of the ^{1}H–^{1}H COSY, HSQC and HMBC spectra showed that the two new double double doublets at δ_H = 4.104 and 4.141 ppm correspond to the proton at C-3′ on the peroxide ring and that the two new double quartets at δ_H = 2.658 and 2.620 ppm correspond to the proton adjacent to the methyl ester group at C-2′. From these results it was evident that cyclic peroxide formation had occurred and the colourless oil was tentatively assigned the gross structure **12** of the mycaperoxide skeleton. However, although the ^{1}H NMR spectroscopic data for the least polar material were very similar to those previously reported for mycaperoxide B (**1**), they did not match exactly. Examination of the ^{13}C NMR spectrum of **12** was extremely revealing. Many of the signals were "tripled" (see Table S1, Supporting Information), but C-3′ and C-8′ both appeared as four distinct resonances, which indicates the presence of four inseparable diastereoisomers. Given that there are three stereogenic centres at C-2′, C-3′ and C-6′, and therefore eight possible diastereoisomers, the observed formation of only four such isomers implies some form of stereoselectivity during the cyclisation reaction. As for the ^{1}H NMR spectrum, although the chemical shifts of the majority of the carbon signals compared very favourably with both mycaperoxide B (**1**) and its methyl ester (**1a**),[1] there was a significant discrepancy between our observations and the chemical shifts quoted for C-5′ and C-7′. In our sample these signals were extremely broad and poorly resolved in the ^{13}C NMR spectrum, which made assignment difficult; indeed some of the assignments for C-5′ and C-7′ reported in Table S1 (see the Supporting Information) were more easily made on the basis of 2D experiments.

The formation of four of the possible isomers starting from the *R* diastereoisomer at C-6′ of **7** is illustrated in Scheme 5. The hydroperoxide can perform a Michael addition to either the *Re* or *Si* face of the double bond conjugated to the ester and the resulting enolate could subsequently be protonated on either the *Si* or *Re* side, thus allowing the formation of up to four products from this single diastereoisomer, and a total of eight if both C-6′ epimers of **7** are considered. As intramolecular attack of the hydroperoxide on both the *Re* and *Si* faces of the double bond appears to be equally probable, we propose that the observed stereoselectivity results from an overall stereoselective *trans* addition across the *trans* double bond (i.e., either *Si* addition of H^+ to the enolate from the *Si* Michael addition or *Re* addition of H^+ to the enolate from the *Re* Michael addition). The four diastereoisomers that would result from the operation of such a selective mechanism on both the 6′*R* and 6′*S* substrates are depicted in Figure 1 and possess either a 1,4-*trans* (**12a**,**b**) or a 1,4-*cis* (**12c**,**d**) relationship across the 1,2-dioxolane ring.

Capon and MacLeod developed an empirical rule designed to assign the relative stereochemistry about the C-2′, C-3′ and C-6′ atoms of the mycaperoxides.[17] It was proposed that the relative configuration between C-2′ and C-3′ in cyclic peroxy systems such as mycaperoxide B (**1**) could be assigned on the basis of the ^{1}H NMR shift for the



Scheme 5. Possible formation of up to four diastereoisomers in the Michael addition reaction when using the 6′*R* diastereoisomer.

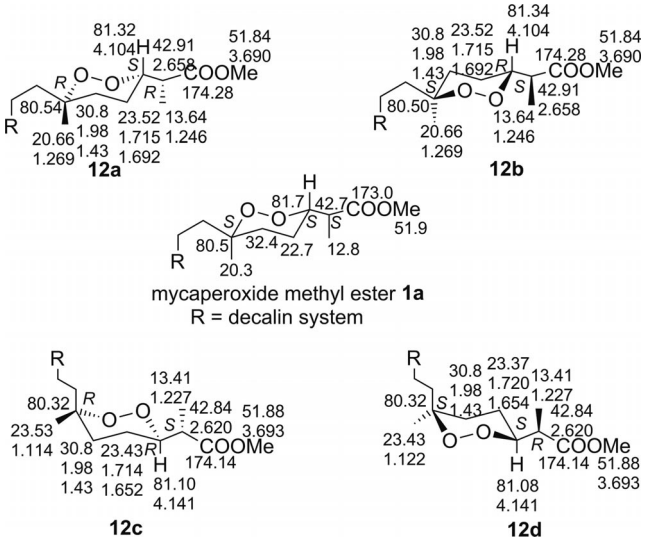


Figure 1. NMR spectroscopic data for the cyclic peroxide ring of the four diastereoisomers isolated and ^{13}C NMR spectroscopic data for mycaperoxide B methyl ester (**1a**).

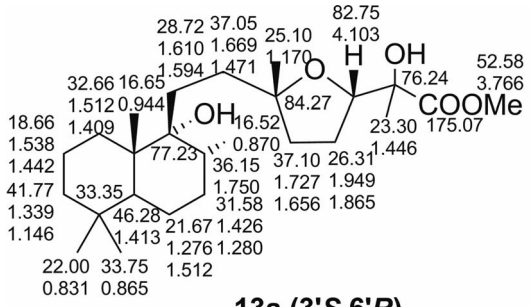
C-2′ secondary methyl group. Examination of the ^1H NMR shifts for the C-2′ secondary methyl group in several dioxolane-containing natural products revealed that, in those cases in which C-2′ and C-3′ are in an *erythro* configuration (*R*,*R* or *S*,*S*), the ^1H NMR shift for the C-2′ methyl is more upfield (δ = 1.13–1.14 ppm) than in those examples in which they are *threo* (*R*,*S* or *S*,*R*; δ = 1.24–1.26 ppm).[17] The authors state that this observation is independent of the stereochemistry of C-6′, but all the examples considered possess an axial C-3′ oxymethine proton. Consequently, this technique cannot be extended to assign the stereochemistry about C-2′ in compounds in which the C-3′ proton is equatorial.

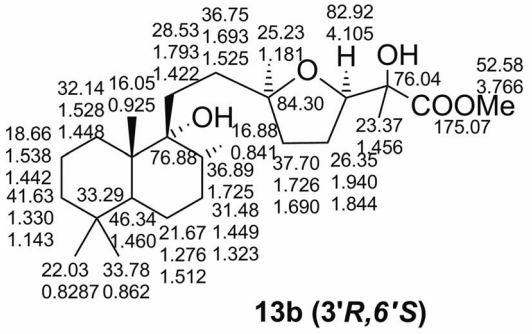
The stereochemistry of the 1,2-dioxolane ring bearing substituents has been deduced for several different natural products containing this functionality by applying this empirical rule.[1,4,17,18] In our case, the chemical shift of the C-2′ methyl group in compounds **12a**–**d** is between δ_H = 1.23 and 1.25 ppm (Figure 1), which suggests that the stereochemistry of the C2′–C3′ fragment is *threo* and lends support to our proposal of a stereoselective *trans* addition across the double bond.

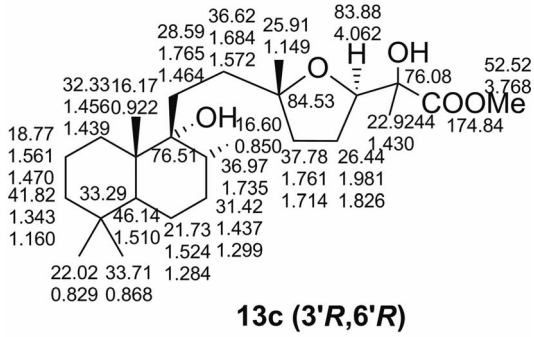
The relative stereochemistry at C-6′ in **12a**–**12d** (Figure 1) is consistent with the chemical shifts observed in the ^{13}C NMR spectra for the C-6′ methyl group of these diastereoisomers. Six-membered cyclic peroxides are reported to exist predominantly in chair conformations and equatorial methyl groups (δ_C = 23.5–24.0 ppm) are known to resonate significantly downfield relative to axial methyl groups (δ_C = 20.5–20.9 ppm).[17] The chemical shifts of the 6′-methyl group in **12a** and **12b** (δ_C = 20.66 ppm) suggest that this group should be axial and for **12c** and **12d** (interchangeably δ_C = 23.53/23.43 ppm) this methyl group should be equatorial. The *cis* relationship between the substituents at the 6′- and 3′-positions of **12c/12d** was then confirmed by the observation of a weak nuclear Overhauser enhancement between the 3′-H (δ_H = 4.141 ppm) and the 6′-Me (interchangeably δ_H = 1.114/1.122 ppm), which was absent for the corresponding protons in **12a/12b**. The observation of such a weak correlation between the rather distant 1- and 4-positions of this *cis*-dioxolane ring may be related to its conformational mobility, as revealed by line-broadening in the ^{13}C NMR spectrum (particularly severe for C-5′ and C-7′). Such line-broadening was also observed by Tanaka et al. when characterising mycaperoxide A, the structure of which was later confirmed by X-ray crystallography.[1]

These same *cis* and *trans* relationships were observed very clearly for the tetrahydrofuran ring in the byproducts **13a**–**13d**. As shown in Scheme 3, these compounds arise from an alternative reaction of the enolate produced by addition of the hydroperoxide group to the alkene in **7**. HRMS revealed a molecular formula of $C_{25}H_{44}O_5$ for the most polar fraction. The ^1H NMR spectrum of this fraction shows a series of double doublets at δ_H = 4.048 (*J* = 9, 5.5 Hz), δ_H = 4.062 (*J* = 9, 5.5 Hz), δ_H = 4.105 (*J* = 7.5, 7.5 Hz) and δ_H = 4.104 ppm (*J* = 7.5, 7.5 Hz), which correlate to tetrahydrofuran methine protons (Figure 2, see Table S2, Supporting Information). Singlets at δ_H = 3.45, 3.33, 3.093 and 3.086 ppm were shown to be the protons associated with the tertiary alcohol 2′-OH adjacent to the ester group as they underwent exchange with D_2O. The presence of an alcohol was also confirmed by the presence of a strong absorption band at 3435 cm^{-1} in the IR spectrum. The appearance of four distinct signals for this group indicated once again that four diastereoisomers were present. The presence of four diastereoisomers was also confirmed by examination of the ^{13}C NMR spectrum, which shows four distinct carbon signals associated with almost every carbon. The structures of the four diastereoisomers and the NMR spectroscopic data associated with each are represented in Figure 2.

NOE studies suggest that for compounds **13a** and **13b**, 3′-H and 6′-CH_3 are in a *cis* relationship to each other, and that for compounds **13c** and **13d**, 3′-H and 6′-CH_3 are in a *trans* relationship. However, the NMR spectroscopic data assigned to structures **13a** and **13b** are interchangeable, as are the data assigned to structures **13c** and **13d**. There is no means, by NMR studies, of deciding which *cis*-tetrahydrofuran is derived from the 6′*S* diastereoisomer and which is derived from the 6′*R* hydroperoxide starting material. Similarly, it is impossible to assign the relative stereochemistry of the *trans*-tetrahydrofurans. To conclude, the relative stereochemistries of the cyclised materials **12a**–**d** are proposed to be 2′*R*,3′*S*,6′*R*, 2′*S*,3′*R*,6′*R*, 2′*S*,3′*R*,6′*S* and 2′*R*,3′*S*,6′*S*, respectively. Unfortunately, none of these four diastereoisomers have data that exactly match the NMR spectra of mycaperoxide B methyl ester (**1a**) with a 2′*S*,3′*S*,6′*S* stereochemistry. It is suggested that to synthesise mycaperoxide B by using this methodology it will be necessary to start with the *Z* alkene of **7** to furnish the correct stereochemistry about the C-3′ position instead of the *E* alkene, which was used in our studies. Assuming that the Michael addition step remains stereospecifically *trans*, as in Scheme 5 (i.e., *Si* addition of the hydroperoxide is fol-







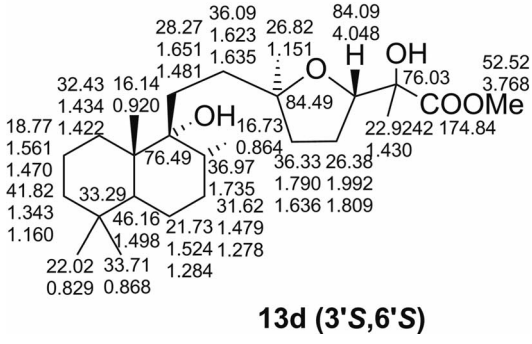


Figure 2. NMR spectroscopic data of the four diastereoisomers of **13**.

lowed by *Si* addition of H^+ to the resulting enolate), then it should be possible to produce the natural diastereoisomer of mycaperoxide B starting from the 6′*S* diastereoisomer of the *Z* alkene of **7**.

Conclusions

The key objective of this project has been accomplished, namely the first synthesis of a compound having the gross structure of mycaperoxide B (**1**) by a pathway following the proposed biosynthesis of Capon.[7] All the steps leading to the formation of compound **12** progressed efficiently until the Michael addition cyclisation step. The formation of the cyclic peroxide occurred in a low yield and examination of the NMR spectroscopic data revealed the formation of four diastereoisomers of mycaperoxide B (**1**). Nonetheless, the successful formation of the cyclic peroxide **12** and the tetrahydrofuran **13** provide evidence to support Capon's second biosynthetic proposal concerning the formation of the characteristic cyclic peroxide common to the mycaperoxide family. Following these results, future work will involve the preparation of a (*Z*)-α,β-unsaturated methyl ester precursor analogue of **2** and the preparation of the 1,2-dioxolane ring from this substrate.

Experimental Section

General Methods: ^{1}H NMR spectra were recorded with either a Bruker AV500 (500 MHz), a Bruker AMX400 (400 MHz) or a Bruker DPX250 (250 MHz) spectrometer. Spectra were referenced to the residual solvent peak or TMS as the internal standard. ^{13}C NMR spectra were recorded with the same spectrometers listed above at either 125, 100 or 62.5 MHz. 2D NMR spectra, such as HSQC, HMBC, ^{1}H–^{1}H COSY and NOESY, were all recorded at high resolution in order to make full assignments of **12a**–**12d** and **13a**–**13d**. HRMS were recorded under conditions of CI with ammonia as the ionising source or ESI. Finnigan MAT 95 and Bruker micro TOF mass spectrometers were used, respectively. IR spectra were recorded as a thin film between two sodium chloride plates with a Perkin–Elmer 1720-X FT-IR spectrometer. Flash column chromatography was performed according to the procedure developed by Still et al.[19] by using Merck 60 silica gel (particle size 0.040–0.063 nm, 230–400 mesh ASTM) with head pressure produced by means of hand bellows. TLC was performed with Merck aluminium plates coated with 0.25 mm silica 60 containing F254. Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were either used directly as supplied or following purification according to procedures described by Perrin and Armarego.[20]

6′-(9,10-*trans*-1α-Hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1β-yl)-4′-methyl-4′-(triethylsilylperoxy)hexanal (4): Dess–Martin periodinane (0.61 g, 15 wt.-%, 0.22 mmol) was added dropwise over 5 min to a stirred solution of 1-[6′-hydroxy-3′-methyl-3′-(triethylsilylperoxy)hexyl]-9,10-*trans*-2α,5,5,9β-tetramethyldecahydronaphthalen-1α-ol (**3**; 85 mg, 0.18 mmol) in dichloromethane (8 mL) under nitrogen. The resulting solution was stirred at room temperature for a further 2 h. The reaction mixture was diluted with diethyl ether (15 mL), washed with sodium hydroxide (1 M, 15 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (15 mL), dried with Na_2SO_4 and concentrated in vacuo to furnish the aldehyde **4** as a colourless oil (84 mg, quant.) which was used without further purification. R_f = 0.33 (20% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 3539, 2948, 2934, 2867, 1725, 1460, 1372, 1238, 1017, 975, 802, 741 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ_H = 9.70 (t, *J* = 2.5 Hz, 1 H, 1′-H), 2.43–2.37 (br. t, *J* = 7.5 Hz, 2 H, 2′-H), 1.85–1.77 (m, 2 H, 3′-H), 1.75–1.01 (m, 16 H, 2-, 3-, 4-, 6-, 7-, 8-, 10-H and 5′-, 6′-H), 1.07 (s, 3 H, 4′-CH_3), 0.93–0.86 (m, 12 H, $SiCH_2CH_3$ and 9-CH_3), 0.80–0.76 (m, 9 H, 2-CH_3 and 5-CH_3), 0.59 (q, *J* = 7.5 Hz, 6 H, $SiCH_2CH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ_C = 203.1

(C-1′), 84.0 and 83.9 (COOTES), 77.4 and 77.3 (C-1), 46.7 and 46.6 (C-10), 43.82 and 43.80 (C-6), 42.2 (C-2′), 37.0 and 36.8 (C-2), 34.2 (5α-CH_3), 33.7 (C-5), 33.3 and 33.2 (C-5′), 32.5 and 32.4 (C-8), 31.8 (C-6′), 30.7 (C-3′), 28.0 and 27.9 (C-3), 22.4 (5β-CH_3), 22.1 (C-4), 22.0 (4′-CH_3), 19.1 and 19.0 (C-7), 16.9 and 16.8 (2-CH_3), 16.7 and 16.6 (9-CH_3), 7.3 and 7.2 ($SiCH_2CH_3$), 3.9 ($SiCH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{27}H_{52}O_4NaSi$ [M + Na]$^{+\cdot}$ 491.3533; found 491.3539.

Methyl (2′*E*)-8′-(9,10-*trans*-1α-Hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1β-yl)-2′,6′-dimethyl-6′-(triethylsilylperoxy)oct-2′-enoate (6): A solution of 6′-(9,10-*trans*-1α-hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1β-yl)-4′-methyl-4′-(triethylsilylperoxy)hexanal (**4**; 50 mg, 0.11 mmol) in dichloromethane (2 mL) was added dropwise over 15 min to a stirred solution of methyl 2-(triphenylphosphanyl)propionate (**5**; 44 mg, 0.13 mmol) in dichloromethane (2 mL) under nitrogen. The resulting solution was left to stir overnight at room temperature. The solvents were removed in vacuo and the crude residue was purified by flash column chromatography on silica, eluting with petroleum ether/diethyl ether (9:1), to give the title compound as a colourless oil (39 mg, 69%). R_f = 0.89 (20% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 3561, 2951, 2873, 1714, 1461, 1280, 1018, 805, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.78–6.74 (m, 1 H, 3′-H), 3.73 (s, 3 H, $COOCH_3$), 2.21–2.15 (m, 2 H, 4′-H), 1.841 and 1.838 (s, 3 H, 2′-CH_3), 1.76–1.11 (m, 18 H, 2-, 3-, 4-, 6-, 7-, 8-, 10-H and 5′-, 7′-, 8′-H), 1.164 and 1.158 (s, 3 H, 6′-CH_3), 0.98 (t, J = 8.0 Hz, 9 H, $SiCH_2CH_3$), 0.94 and 0.93 (s, 3 H, 9-CH_3), 0.866 (d, J = 6.5 Hz, 3 H, 2-CH_3), 0.867 (s, 3 H, 5α-CH_3), 0.83 (s, 3 H, 5β-CH_3), 0.67 (q, J = 7.4 Hz, 6 H, $SiCH_2CH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 168.7 (C=O), 142.7 (C-3′), 127.4 (C-2′), 84.0 (COOTES), 76.9 (C-1), 51.7 ($COOCH_3$), 46.2 (C-10), 43.43 and 43.37 (C-9), 41.8 and 41.7 (C-6), 36.6 and 36.4 (C-2), 35.5 and 35.4 (C-5′), 33.8 (5α-CH_3), 33.3 (C-5), 32.7 and 32.6 (C-8), 32.1 and 32.0 (C-3), 31.4 (C-7′), 27.6 and 27.5 (C-8′), 23.34 and 23.27 (C-4′), 22.0 (5β-CH_3), 21.9 and 21.8 (6′-CH_3), 21.7 (C-4), 18.7 and 18.6 (C-7), 16.5 and 16.4 (2-CH_3), 16.3 and 16.2 (9-CH_3), 12.3 (2′-CH_3), 6.8 ($SiCH_2CH_3$), 3.9 ($SiCH_2CH_3$) ppm. HRMS (ESI): calcd. for $C_{31}H_{58}O_5NaSi$ [M + Na]$^{+\cdot}$ 561.3939; found 561.3946.

Methyl (2′*E*)-6′-Hydroperoxy-8′-(9,10-*trans*-1α-hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1β-yl)-2′,6′-dimethyloct-2′-enoate (7): A solution of methyl (2′*E*)-8′-(9,10-*trans*-1α-hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1β-yl)-2′,6′-dimethyl-6′-(triethylsilylperoxy)oct-2′-enoate (**6**; 42 mg, 0.078 mmol) and pyridinium *p*-toluenesulfonate (2.1 mg, 0.0083 mmol) in absolute ethanol (2 mL) was left to stir at room temperature for 6 h. The solvents were removed in vacuo and the crude residue was purified by flash column chromatography on silica, eluting with petroleum ether/diethyl ether (2:1), to give the title compound as a colourless oil (27 mg, 81%). R_f = 0.21 (20% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 3535, 3390, 2934, 2868, 1699, 1460, 1438, 1283, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.24 (s, 0.5 H, OOH), 8.89 (s, 0.5 H, OOH), 6.81–6.74 (m, 1 H, 3′-H), 3.733 and 3.729 (s, 3 H, $COOCH_3$), 2.37–2.13 (m, 2 H, 4′-H), 1.89–1.11 (m, 21 H, 2-, 3-, 4-, 6-, 7-, 8-, 10-H, 5′-, 7′-, 8′-H and 2′-CH_3), 1.19 and 1.09 (s, 3 H, 6′-CH_3), 0.95 (s, 3 H, 9-CH_3), 0.90 (d, J = 6.7 Hz, 1.5 H, 2-CH_3), 0.88 (s, 3 H, 5α-CH_3), 0.87 (d, J = 6.4 Hz, 1.5 H, 2-CH_3), 0.83 (s, 3 H, 5β-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 168.8 and 168.7 (C=O), 142.7 and 142.4 (C-3′), 127.6 and 127.5 (C-2′), 84.3 and 84.1 (C-6′), 77.2 (C-1), 51.7 ($COOCH_3$), 47.3 and 47.0 (C-10), 43.7 and 43.6 (C-9), 41.6 (C-6), 37.2 and 36.8 (C-2), 36.0 and 35.1 (C-5′), 33.8 (5α-CH_3), 33.5 (C-5), 32.4 and 31.9 (C-8), 31.7 and 31.6 (C-3), 31.4 (C-7′), 26.1 and 25.9 (C-8′), 23.1 and 23.0 (C-4′), 22.0 (5β-CH_3), 21.5 and 21.4 (C-4), 20.5 (6′-CH_3), 18.6 (C-7), 16.9 and 16.8 (2-CH_3), 16.3 and 16.0 (9-CH_3), 12.3 (2′-CH_3) ppm. HRMS (ESI): calcd. for $C_{25}H_{44}O_5NaSi$ [M + Na]$^{+\cdot}$ 447.3082; found 447.3081.

Methyl 2-{6-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-6-methyl-1,2-dioxan-3-yl}propanoate (10): Freshly distilled triethylamine (0.32 mL, 32.0 μmol, 0.1 M in methanol) was added dropwise to a solution of methyl (2*E*)-8-(*tert*-butyldiphenylsilanyloxy)-6-hydroperoxy-2,6-dimethylocta-2-enoate (**8**; 152 mg, 0.32 mmol) in methanol (5 mL) under nitrogen. The resulting solution was stirred at room temp. for a further 24 h. The solvents were subsequently concentrated in vacuo and the crude material was purified by flash chromatography on silica. Elution with petroleum ether/diethyl ether (9:1) gave a first fraction, pure compound **10**, obtained as a colourless oil (23 mg, 15%) as a mixture of inseparable diastereoisomers. Further elution gave a second fraction, pure compound **11**,obtained as a colourless oil (73 mg, 40%) as a mixture of inseparable diastereoisomers.

Methyl 2-{6-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-6-methyl-1,2-dioxan-3-yl}propanoate (10): R_f = 0.63 (20% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 1711, 1586 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.74–7.65 (m, 4 H, Ph), 7.47–7.35 (m, 6 H, Ph), 4.11–4.07 (m, 1 H, 3-H), 3.76 (m, 2 H, 8-H), 3.68 (s, 3 H, COOMe), 2.67 (dq, 0.5 H, 2-H), 2.56 (dq, 0.5 H, 2-H), 2.13–1.87 (m, 1 H, CH_2), 1.83–1.73 (m, 1 H, CH_2), 1.71–1.50 (m, 2 H, CH_2), 1.66 (s, 1.5 H, CH_3), 1.59 (s, 1.5 H, CH_3), 1.43–1.20 (m, 2 H, CH_2), 1.12 (s, 3 H, 2-CH_3), 1.05 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 174.7 and 174.6 (C=O), 136.0 (Ph), 135.9 (Ph), 134.1 (Ph), 130.2 (Ph), 128.1 (Ph), 81.7 and 81.6 (C-3), 80.1 (C-6), 79.8 (q), 60.5 and 59.9 (C8), 52.3 ($COOCH_3$), 43.3 and 43.2 (C-2), 37.9 (C-7), 32.9 and 32.3 (C-5), 27.2 (*t*Bu), 24.0 and 23.6 (C-4), 22.7 (6-CH_3), 19.5 (q, *t*Bu), 14.0 and 13.9 (2-CH_3) ppm. HRMS (CI): calcd. for $C_{27}H_{39}O_5Si$ [M + H]$^+$ 471.2567; found 471.2574.

Methyl 8-(*tert*-Butyldiphenylsilanyloxy)-6-hydroxy-2,3-epoxy-2,6-dimethylocta-6-enoate (11): R_f = 0.17 (20% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 3550, 1712, 1591 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.69–7.66 (m, 4 H, Ph), 7.46–7.41 (m, 6 H, Ph), 3.93–3.86 (m, 1 H, 3-H), 3.87 (t, J = 12 Hz, 2 H, 8-H), 3.83 (s, 3 H, COOMe), 1.85–1.51 (m, 6 H, 3 CH_2), 1.54 (s, 1.5 H, 2-CH_3), 1.53 (s, 1.5 H, 2-CH_3), 1.25 (s, 1.5 H, CH_3), 1.23 (s, 1.5 H, CH_3), 1.04 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 172.1 (C=O), 135.6 (Ph), 132.6 (Ph), 130.0 (Ph), 127.9 (Ph), 72.2 (C-6), 62.7 and 62.6 (C-3), 61.7 (C-8), 57.8 (C-2), 52.6 ($COOCH_3$), 41.6 (CH_2) 41.3 (CH_2), 38.5 (CH_2), 38.4 (CH_2), 26.8 (*t*Bu), 26.6 and 26.3 (6-CH_3), 22.8 (CH_2), 19.0 (q), 13.5 (2-CH_3) ppm. HRMS (ESI): calcd. for $C_{27}H_{39}O_5Si$ [M + H]$^{+\cdot}$ 471.2567; found 471.2548.

Methyl 2-{6-[2-(9,10-*trans*-1-Hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1-yl)ethyl]-6-methyl-1,2-dioxan-3-yl}propanoate (12): A solution of freshly distilled triethylamine (3.95 mL, 0.05 M in methanol) was added dropwise to a solution of methyl (2′*E*)-6′-hydroperoxy-8′-(9,10-*trans*-1α-hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1β-yl)-2′,6′-dimethyloct-2′-enoate (**7**; 42 mg, 0.10 mmol) in methanol (1 mL) under nitrogen. The resulting solution was stirred at room temperature for 2 d. The reaction mixture was subsequently concentrated in vacuo and the crude material purified by flash column chromatography on silica. Elution with petroleum ether/diethyl ether (2:1) gave a first fraction, pure compound **12**, obtained as a colourless oil (4.1 mg, 10%) as a mixture of inseparable diastereoisomers. Further elution allowed the recovery of the starting material (8.7 mg, 21%) and a second fraction, pure compound **13**, obtained as a colourless oil (17.9 mg, 43%) as a mixture of inseparable diastereoisomers.

Methyl 2-{6-[2-(9,10-*trans*-1-Hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1-yl)ethyl]-6-methyl-1,2-dioxan-3-yl}propanoate (12): R_f = 0.83 (30% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 2932, 2867, 1735, 1458, 1375, 1264, 1199, 1162, 909 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{44}O_5Na$ $[M + Na]^{+\cdot}$ 447.3081; found 447.3076. For the NMR spectroscopic data, see Table S1, Supporting Information.

Methyl 2-Hydroxy-2-{5-[2-(9,10-*trans*-1-hydroxy-2α,5,5,9β-tetramethyldecahydronaphthalen-1-yl)ethyl]-5-methyltetrahydrofuran-2-yl}propanoate (13): R_f = 0.12 (30% diethyl ether/petroleum ether). IR (thin film): $\tilde{\nu}_{max}$ = 3435, 2932, 2867, 1730, 1460, 1372, 1261, 1179, 1060, 977 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{44}O_5Na$ $[M + Na]^{+\cdot}$ 447.3081; found 447.3076. For the NMR spectroscopic data, see Table S2, Supporting Information.

Supporting Information (see footnote on the first page of this article): NMR spectroscopic data for compounds **12a**–**d** and **13a**–**d**.

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