

Chapter 2

Synthesis of the Tridachiahdropyrone and their Biomimetic Precursors

2.1 Revised Synthetic Route

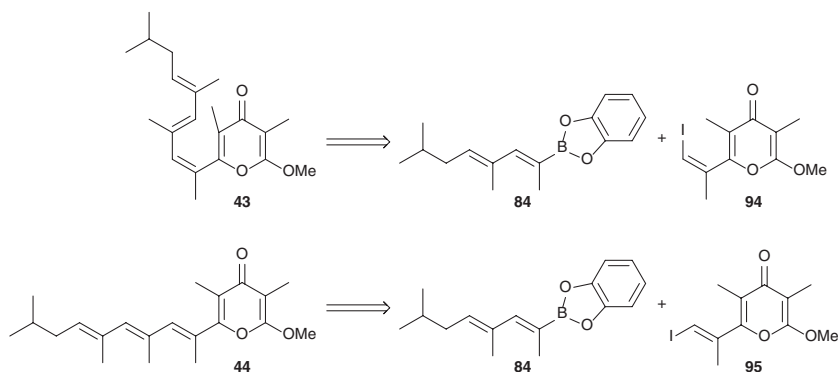
The main problem with the original synthetic route to tridachiahdropyrone (**9**) was the Suzuki coupling step of the boronic ester **84** with the bromo-pyrone fragments **85** and **39** to form the biomimetic precursors **43** and **44** (see Sect. 1.3, Schemes 16 and 18) [1, 2]. In addition to being fairly low yielding the yields themselves were found to be inconsistent. As this occurred at such a late stage in the synthesis it was thought preferable to improve upon this reaction if possible.

It was postulated that using the iodo-pyrone **94** and **95** in place of their bromo-analogues could improve the efficiency of this step, as iodo compounds are known to be more reactive in cross coupling reactions due to the lower strength of their bonds to carbon in comparison with the other halides [3]. Thus the original retrosynthesis was revised (Scheme 2.1).

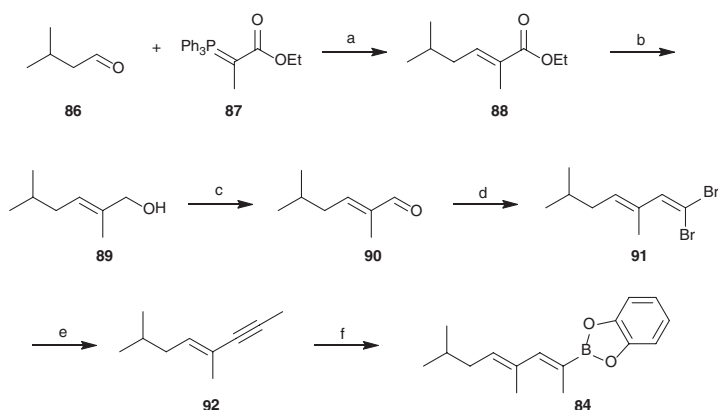
2.2 Synthesis of the Boronic Ester Coupling Fragment

This synthetic strategy towards the polyenes **43** and **44** had a common intermediate in the boronic ester **84**. This was synthesised from isovaleraldehyde (**86**) in six steps following the known methodology (Scheme 2.2) [1].

The synthesis proceeded smoothly, with yields comparable to the literature. One modification was made, with Dess-Martin periodinane (DMP) being used for the oxidation of the allylic alcohol **89** to the aldehyde **90** instead of the original MnO_2 -mediated strategy. This improved the yield from 71 to 93 %, whilst significantly reducing the reaction time from overnight to just 30 min.



Scheme 2.1 Revised retrosynthesis of the polyenes **43** and **44**

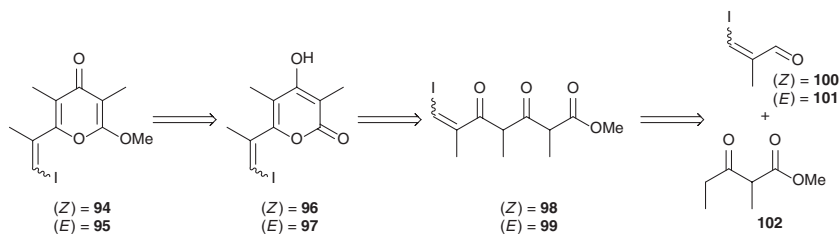


Scheme 2.2 Synthesis of the coupling fragment **84** from isovaleraldehyde (**86**). Reagents and conditions: *a* CH_2Cl_2 , 72 h, Δ , 98 %; *b* DIBAL-H, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow \text{rt.}$, 16 h, 97 %; *c* DMP, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt.}$, 30 min, 93 %; *d* CBr_4 , PPh_3 , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt.}$, 1.5 h, 92 %; *e* $^n\text{BuLi}$, MeI, THF, $-78^\circ\text{C} \rightarrow \text{rt.}$, 18 h, 71 %; *f* catecholborane, 80°C , 2 h, >99 %

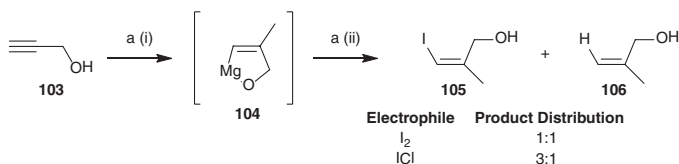
2.3 Synthesis of the Vinyl Iodopyrone Fragments

The *Z* and *E* vinyl iodopyrones **94** and **95** had been utilised by Trauner et al. in their syntheses of cyercene A and the placidenes [4]. Their synthetic strategy centred on cyclisation of the triketides **98/99**, formed from aldol addition of the dianion of β -ketoester **102** onto the appropriate iodoaldehyde **100/101** and subsequent oxidation (Scheme 2.3).

The (*Z*)-iodoaldehyde **100** was synthesised in two steps from commercially available propargyl alcohol (**103**). Addition of Grignard reagent MeMgBr to **103** followed by trapping of the intermediate metallocycle **104** with a source of



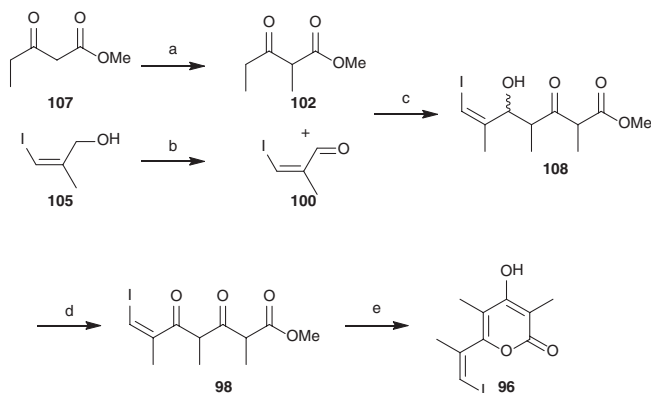
Scheme 2.3 Retrosynthesis of the vinyl iodopyrones **94** and **95**



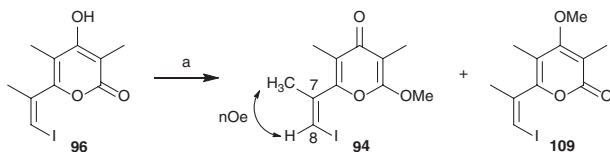
Scheme 2.4 Synthesis of the (Z)-iodoalcohol **105**. Reagents and conditions: *a* (i) MeMgBr, CuI, Et₂O, -10 °C → rt., 3 h then (ii) ICl, Et₂O, -10 °C → rt., 19 h, 49 % (isolated yield of **105**)

electrophilic iodine furnished the (Z)-iodoalcohol **105**, the required alkene geometry installed stereoselectively by chelation control (Scheme 2.4). Initial use of I_2 as the electrophile [5] afforded a 1:1 mixture (determined by analysis of the ^1H NMR spectrum of the crude reaction mixture) of the desired iodinated and protonated products (**105** and **106** respectively). Whilst these were chromatographically separable, the use of an alternative, more effective electrophile was investigated in order to influence the product ratio in favour of the iodinated product. The use of iodine monochloride [6] proved successful, giving an improved product distribution of 3:1 in favour of the desired product.

Oxidation of **105** with MnO_2 yielded the unstable (Z)-iodoaldehyde **100** [5], which was immediately taken forward to the aldol reaction (Scheme 2.5). The aldol reaction of **100** with the β -ketoester **102** (itself formed by the facile methylation of methyl propionylacetate (**107**)) [7] proceeded smoothly upon a slight modification to Trauner's reported procedure [4]. Formation of the dianion of **102** was reportedly formed by stirring a solution of **102** in THF with NaH for 10 min at 0 °C and then adding $nBuLi$ and stirring at 0 °C for a further 10 min. A solution of iodoaldehyde **100** in THF was then added to the solution and the mixture stirred at room temperature. However it was found that a stirring time of 10 min at 0 °C was insufficient in this work to promote anion formation, with no product formation observed, and just the β -ketoester **107** recovered upon following this procedure. Stirring the solution at room temperature for 30 min between additions rectified this, with the aldol product **108** formed in good yields as a diastereomeric mixture. Dess-Martin oxidation of **108** and DBU-mediated cyclisation of the resulting triketide **98** furnished the γ -hydroxy α -pyrone **96** in 73 % yield over three steps (from **100** and **102**, Scheme 2.5) [4].



Scheme 2.5 Synthesis of the γ -hydroxy α -pyrone **96**. Reagents and conditions: *a* K_2CO_3 , THF, Δ , 2.5 h then MeI, 0°C , 18 h, 97 %; *b* MnO_2 , CH_2Cl_2 , rt., 2 h, 79 %; *c* **102**, NaH, THF, $0^\circ\text{C} \rightarrow \text{rt.}$, 0.5 h then $^n\text{BuLi}$, $0^\circ\text{C} \rightarrow \text{rt.}$, 0.5 h then **100**, $0^\circ\text{C} \rightarrow \text{rt.}$, 1.5 h, 80 %; *d* DMP, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{rt.}$, 3 h, 96 %; *e* DBU, toluene, 70°C , 4 h, 95 %

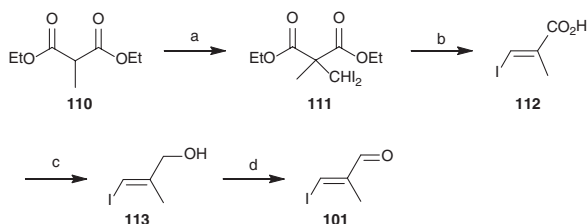


Scheme 2.6 Formation of the (*Z*)-coupling fragment **94**. Reagents and conditions: *a* Me_2SO_4 , Li_2CO_3 , acetone, Δ , 96 h, 34 % (isolated yield of **94**)

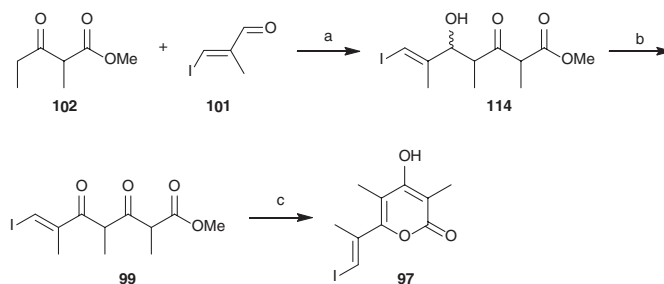
MeOSO_2F is the most effective methylating agent for regioselective α -methylation of γ -hydroxy α -pyrones to form α -methoxy γ -pyrones, and was used by Trauner for the conversion of **96** into the coupling fragment **94** [4]. However, due to its extremely high toxicity alternative methylating agents Me_2SO_4 [8] and Me_3OBF_4 [9] have also been utilised in γ -pyrone-containing natural product synthesis to achieve analogous transformations.

Treatment of the γ -hydroxy α -pyrone **96** with dimethyl sulfate afforded a mixture of the corresponding γ - and α -pyrones, **94** and **99**, which were easily separable by column chromatography. The desired coupling fragment **94** was thus isolated in 34 % yield (Scheme 2.6). The geometry of the alkene was at this point confirmed as *Z* by nOe studies, a strong through-space correlation observed between the olefinic proton (C8-H) and methyl group (C7- CH_3).

The route to the corresponding *E* isomer **95** was slightly longer, but proved unproblematic, following a published synthesis of the (*E*)-iodoaldehyde **101** in four steps from commercially available diethyl methylmalonate (**110**) (Scheme 2.7) [10]. The key transformation was a base-promoted hydrolysis-decarboxylation-elimination sequence of **111**, itself formed by the nucleophilic substitution reaction between diethyl methylmalonate (**110**) and iodoform. LiAlH_4



Scheme 2.7 Synthesis of the (*E*)-iodoaldehyde **101**. Reagents and conditions: *a* NaH, Et₂O, Δ, 2.5 h then CHI₃, Δ, 24 h, 82 %; *b* KOH, EtOH-H₂O, Δ, 24 h, 90 %; *c* LiAlH₄, THF, 0 °C → rt., 20 h, 84 %; *d* MnO₂, CH₂Cl₂, rt., 2 h, 72 %

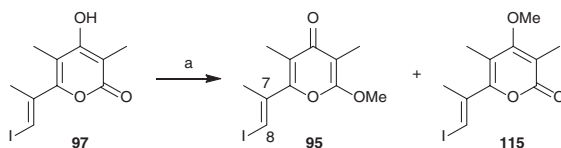


Scheme 2.8 Synthesis of the γ -hydroxy α -pyrone **97**. Reagents and conditions: *a* **102**, NaH, THF, 0 °C → rt., 0.5 h then ⁿBuLi, 0 °C → rt., 0.5 h then **101**, 0 °C → rt., 18 h, 71 %; *b* DMP, CH₂Cl₂, 0 °C → rt., 1 h, 98 %; *c* DBU, toluene, 70 °C, 2 h, 95 %

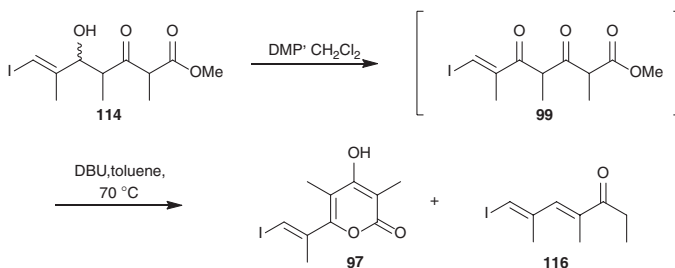
reduction of the carboxylic acid **112** afforded the corresponding alcohol **113** smoothly, which was oxidised to the desired (*E*)-iodoaldehyde **101** in an analogous manner to its *Z* isomer **100**.

The aldol reaction between (*E*)-iodoaldehyde **101** and β -ketoester **102** proved more sluggish than the analogous reaction with the *Z*-analogue **100**. Whilst addition of **102** to **100** (Scheme 2.5) was complete (as judged by aldehyde consumption by TLC analysis) within 1.5 h, an extended reaction time of 18 h was required for the reaction to go to completion in the case of the (*E*)-iodo aldehyde **101**. Shorter reaction times of 2–4 h resulted in incomplete consumption of **101** and disappointing yields of 38–54 %. The subsequent oxidation of **114** and DBU-mediated cyclisation of the resultant tricarboxyl **99** afforded the γ -hydroxy α -pyrone **97** in 66 % yield over three steps (Scheme 2.8).

The γ -hydroxy α -pyrone **97** was converted into the coupling fragment **95** under the same conditions used for methylation of the *Z* isomer (Scheme 2.9). Again an easily separable mixture of isomers was formed, with the desired product **95** isolated in 42 % yield. The geometry of the alkene was again confirmed by nOe studies, with no significant nOe observed between the olefinic proton (C8-H) and methyl group (C7-CH₃).



Scheme 2.9 Formation of the (*E*)-coupling fragment **95**. Reagents and conditions: *a* Me₂SO₄, Li₂CO₃, acetone, Δ, 18 h, 42 % (isolated yield of **95**)



Scheme 2.10 Unexpected byproduct formation

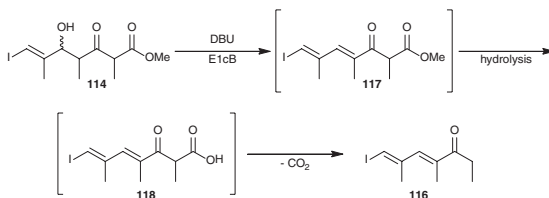
During the synthesis of the γ -hydroxy α -pyrone **97** an interesting side reaction was discovered. The conversion of **114** into **97** was attempted in a telescoped manner, without the usual chromatographic purification of the intermediate triketide **99**. At the end of this reaction sequence an unexpected non-polar compound was isolated in addition to the desired pyrone **97**. Spectroscopic analysis revealed this byproduct to be the novel diene **116** (Scheme 2.10).

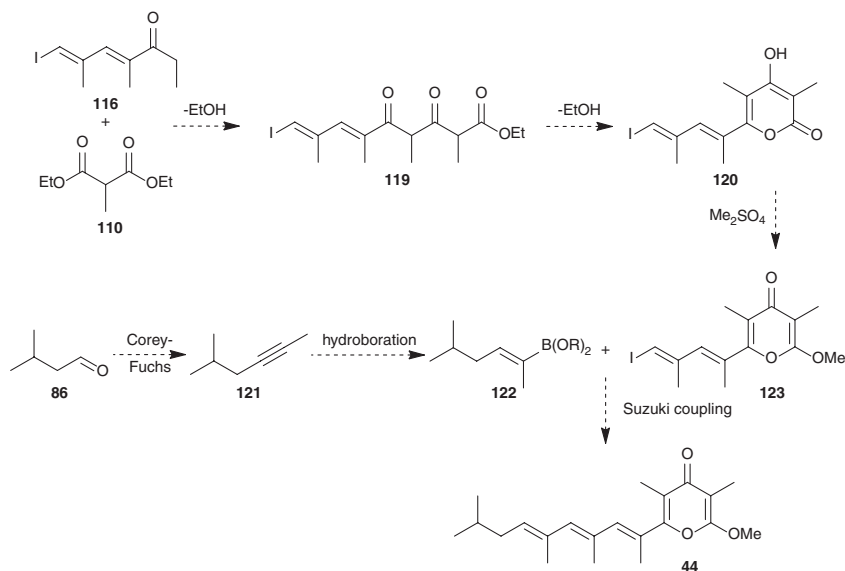
Analysis of the ¹H NMR spectrum of the crude product **99** used in the cyclisation reaction revealed a significant quantity of the unoxidised alcohol **114** to be present. It is thus highly probable that **116** was generated from **114** upon heating in the presence of DBU by an elimination-saponification-decarboxylation sequence, as outlined in Scheme 2.11.

This side reaction was deemed of interest because the byproduct **116** could potentially be used in an adapted route to the desired polyene pyrone **44**, which would be shorter than the existing route used. This potential new route is outlined in Scheme 2.12.

Of this proposed synthetic sequence, the initial condensation step between **116** and diethylmethylmalonate (**110**) to form the extended tricarbonyl **119** was

Scheme 2.11 Generation of the byproduct **116**: likely mechanism



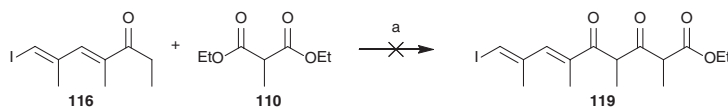


Scheme 2.12 Proposed new route to the pyrone **44** via **116**

potentially problematic, with several self- and cross-condensation products possible. In addition, literature precedent for this reaction was scarce, the only examples of malonates used as electrophiles in condensation reactions generally involving an activated derivative such as the acyl chloride [11–13].

NaHMDS was chosen as a strong bulky base for the initial deprotonation of **116**. This deprotonation was carried out at -78°C with stirring for 0.5 h, with the development of a strong yellow colour indicating this step had been successful. This solution was then transferred into a solution of malonate **110** in THF also at -78°C , and the mixture stirred at -78°C for 0.5 h. TLC analysis indicated no reaction after this time and so the temperature was increased to -30°C , to rt., and then further to 50°C . However still no reaction was observed to have occurred, and upon work up both unreacted starting materials were present in the ^1H NMR spectrum of the crude reaction mixture as the only components (Scheme 2.13).

There are two possible explanations for the observed outcome in this case. Firstly it is possible that no reaction at all occurred between **110** and the deprotonated **116**, with the anion of **116** remaining stable in solution until the reaction



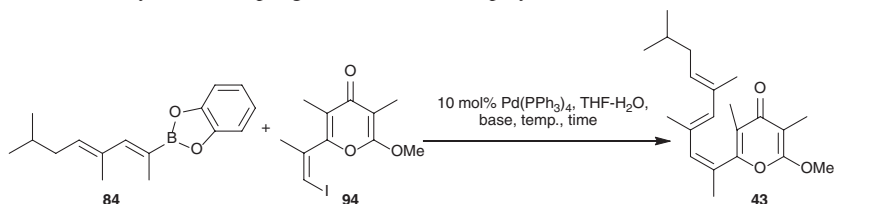
Scheme 2.13 Attempted condensation of **116** with diethylmethylmalonate (**110**). Reagents and conditions: *a* NaHMDS , **116**, THF, -78°C , 0.5 h then **110**, $-78^\circ\text{C} \rightarrow 50^\circ\text{C}$, 20 h

was quenched, whereupon it would have been reprotonated, regenerating the starting material. However, as the temperature was raised to 50 °C during the course of the reaction it seems unlikely that the system would have remained so completely inert. A second plausible explanation then is that, instead of nucleophilic attack of the anion of **116** onto the ester moiety of **110** in a Claisen-type condensation reaction, deprotonation of the acidic malonate proton by the anion of **116** occurred, regenerating **116** in addition to a relatively stable malonate anion, which remained in solution until being reprotonated upon quenching of the reaction mixture.

2.4 Suzuki Coupling: Synthesis of the Biomimetic Precursors

With the boronic ester **84**, and the iodopyrones **94** and **95**, in hand, the key Suzuki coupling step was attempted. The (*Z*)-iodopyrone **94** and **84** were first exposed to the coupling conditions used in the original Moses group synthesis with the bromo analogue **85** (see Sect. 1.3) [1]. This used a slight excess of the boronic ester fragment **84**, with KOH as base in an aqueous THF solvent system, and Pd(PPh₃)₄ as the catalyst. Heating at 80 °C for 20 h afforded the desired product **43** in a disappointing 19 % yield (Table 2.1, Entry 1). Whilst after this time unreacted starting material was present in the crude reaction mixture (as judged by analysis of TLC and ¹H NMR post-work up), increasing the reaction time to 48 h did not increase the yield, or result in full consumption of the limiting substrate **94** (Table 2.1, Entry 2). This suggested that the catalyst was becoming inactive before the reaction went to completion. It was reasoned that increasing the rate of reaction would likely improve the yield.

Table 2.1 Key Suzuki coupling to form the (*Z,E,E*)-polyene **43**: conditions screened

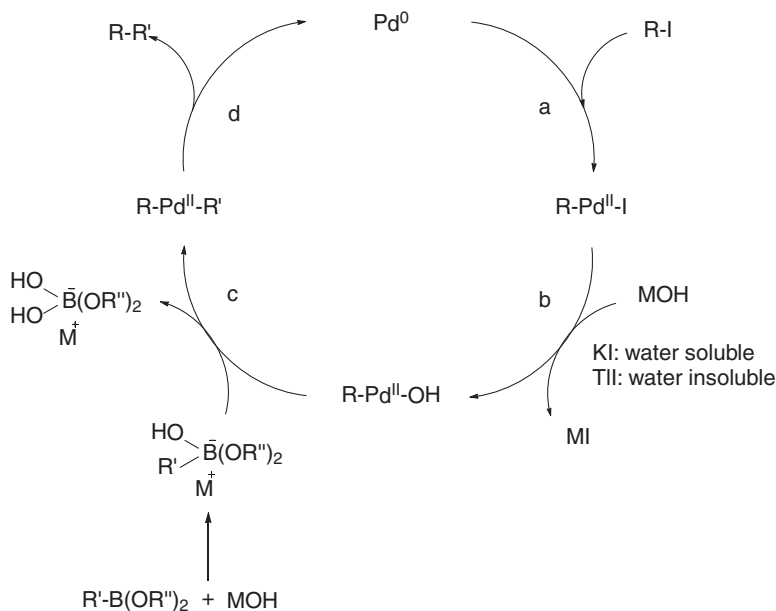


Entry	Ratio 84:94	Base	Temp. (°C)	Time (h)	Yield (%)
1	1.3:1	KOH	80	20	19
2	1.3:1	KOH	80	48	18
3	3.5:1	TIOEt	50	3	65
4	3:1	TIOEt	50	3	66
5	2.5:1	TIOEt	50	3	77
6	2:1	TIOEt	50	4	95

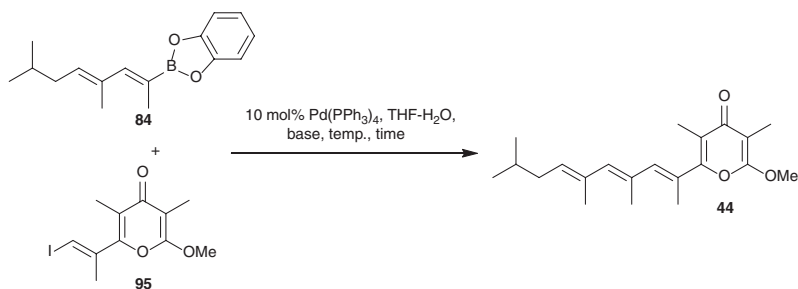
Use of TIOEt, in place of more commonly utilised bases such as KOH, K_2CO_3 and NaOMe, has been reported by Roush to greatly accelerate Suzuki coupling reactions and lead to improved yields [14]. Thus the use of TIOEt as base was investigated. The result of the initial experiment (Table 2.1, Entry 3) was encouraging, with a greatly improved yield of 65 % being obtained, at a lower temperature of 50 °C and much reduced reaction time. Whilst the reaction did indeed go to completion under these conditions, the separation of **43** from the excess unreacted boronic ester **84** proved difficult due to their similar polarities, accounting for the less than perfect 65 % yield. A ratio of 3.5:1 boronic ester **84**: iodo **94** had been chosen based on the published representative experimental procedure. Roush et al. had discovered that in many cases a large excess of the boronic acid/ester coupling component was required, due to issues with the solubility of the ate complex formed in situ.

A series of reactions was next conducted, systematically lowering the equivalence of the boronic ester **84** used. It was found that lowering the ratio of **84**:**94** increased the isolated yield of **43**, by increasing the ease of chromatographic purification (Table 2.1, Entries 3–6). 2 equivalents of **84** gave an excellent 95 % yield (Table 2.1, Entry 6).

The improvement in yield upon switching to TIOEt as base can be rationalised by reference to the catalytic cycle of the Suzuki coupling reaction. A general cycle is depicted in Scheme 2.14. Kishi et al. suggest step b to be the rate determining step of the cycle for many substrates [15]. When the metal counterion of the base



Scheme 2.14 General catalytic cycle for the Suzuki coupling reaction, depicting *a* oxidative addition, *b* ligand exchange, *c* transmetalation and *d* reductive elimination steps

Table 2.2 Key Suzuki coupling to form the (*E,E,E*)-polyene **44**: conditions screened

Entry	Ratio 84:94	Base	Temp. (°C)	Time (h)	Yield (%)
1	1.1:1	KOH	80	20	14
2	3:1	TIOEt	50	3	58
3	2.5:1	TIOEt	50	4.5	74
4	2:1	TIOEt	50	4	92
5	1.3:1	TIOEt	50	20	23

used is potassium or sodium, the metal iodide byproduct is soluble in the reaction medium. However, when the base is TIOH (generated in situ from TIOEt and H₂O), the TII salt formed is insoluble, precipitating out, and thus driving the step forward. Thus the rate of the reaction is increased, allowing the reaction to go to completion before the catalyst becomes deactivated, and resulting in improved yields.

This interpretation also accounts for the lack of improvement in reaction outcome observed in switching from the bromopyrone fragment **85** (Sect. 1.3, Scheme 16: 30 %) to its iodo analogue **94** (Table 2.1, Entry 1: 19 %), under the same coupling conditions. The higher reactivity of iodides over bromides in coupling reactions lies in the relative strengths of their bonds to carbon. A carbon-iodine bond is weaker and thus undergoes oxidative addition (step a) more readily. However, if the oxidative addition step is not rate limiting then the reaction outcome is unlikely to be affected by this factor.

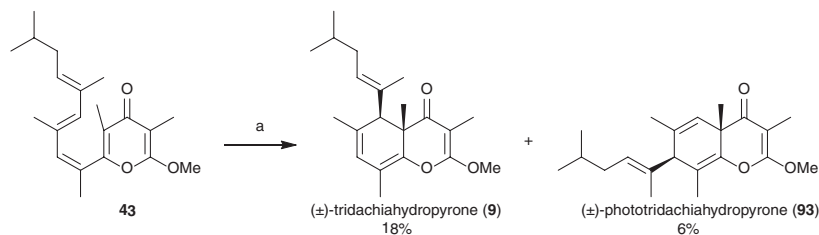
A similar trend in yields was observed for the synthesis of the (*E,E,E*)-polyene pyrone **44** (Table 2.2).

Again, substituting KOH for TIOEt resulted in higher yields, and lowering the equivalence of the boronic ester **84** improved the yields due to increasing the ease of purification. Lowering the equivalence of **84** below 2 however had a detrimental effect, with the yield dropping from an excellent 92 % for 2 equivalents (Table 2.2, Entry 4) to just 23 % when 1.3 equivalents was used instead (Table 2.2, Entry 5). At such a low concentration, solubility of the ate complex presumably becomes a hindrance.

2.5 Biomimetic Synthesis of the Tridachiahypyrone Family

The key biomimetic conversion of the (*Z,E,E*)-polyene **43** into tridachiahypyrone (**9**) was next investigated. A sample of **43** was dissolved in anhydrous methanol, and the solution thoroughly purged with argon. The solution was then irradiated using a medium pressure mercury lamp (125 W). Previous work had shown that after 7 h, further exposure to UV light promoted the rearrangement of the product tridachiahypyrone (**9**) into phototridachiahypyrone (**93**) [2]. In order to try to avoid this, and maximise tridachiahypyrone (**9**) synthesis, after an initial 6 h of irradiation the solvent was removed under reduced pressure and the product **9** isolated by preparative TLC. However, an additional band was observed on the TLC plate, attributable to the rearranged product **93**. Both products were isolated, and the remaining starting material **43** re-dissolved in anhydrous methanol, re-purged with argon, and re-exposed to UV light. To try and prevent further isomerisation the reaction was this time stopped after 5 h, and the isolation process repeated. As still some phototridachiahypyrone (**93**) production was observed, the next two cycles of irradiation were limited to 3 h each. After a total 17 h of irradiation (6 h + 5 h + 3 h + 3 h) tridachiahypyrone (**9**) had been isolated in 18 % yield, along with 6 % of the rearranged photoproduct **93**, and 70 % recovered starting material, (*Z,E,E*)-polyene **43** (Scheme 2.15).

This technique, with multiple cycles of irradiation and purification, was labour intensive and time consuming, the 17 h of total irradiation time requiring 4 days work in order to isolate a relatively small quantity of the desired natural product **9**, and still not preventing formation of the phototridachiahypyrone (**93**) byproduct. In order to discern whether this technique was really beneficial, an NMR study into the photoconversion of **9** to **93** was conducted. Work previously conducted in the group had found that 24 h irradiation promoted full conversion of **9** to **93** [2]. As that work had also led to the generation of comparable yields of tridachiahypyrone (**9**) (25 % yield of **9** from **44** in 7 h, see Sect. 1.3, Scheme 19) in shorter times than the current work (Scheme 2.15), it was deemed worthwhile to reinvestigate the kinetics of the photoconversion.



Scheme 2.15 Biomimetic conversion of **43** into **9** and **93**, using multiple purification technique. Reagents and conditions: a hv, MeOH, rt., 17 h total irradiation time (with purification carried out after 6, 5, 3, 3 h irradiation periods) (70 % starting material **43** also recovered)

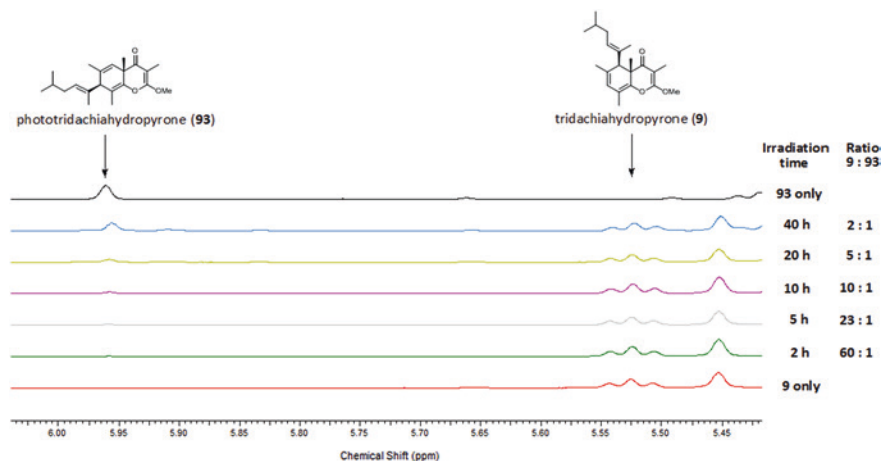


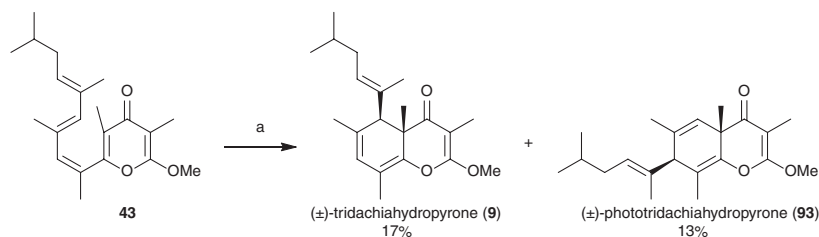
Fig. 2.1 NMR study into the photochemical conversion of **9** into **93**

Thus a solution of tridachiahypyrone (**9**) was dissolved in CDCl_3 , degassed by purging with argon, and then irradiated. The photochemical sigmatropic rearrangement to form phototridachiahypyrone (**93**) was monitored over time by analysis of the ^1H NMR spectrum of the reaction mixture. The relative intensities of the olefinic proton signals of the two compounds were used in order to determine the ratio of **9**:**93** at various intervals. The results are depicted in Fig. 2.1.

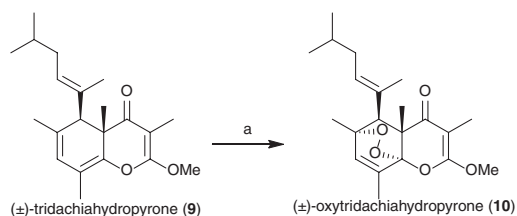
From this study it can be seen that after even 40 h irradiation time tridachiahypyrone (**9**) is the major component in the reaction mixture, the ratio of **9**:**93** at this point being 2:1. Whilst the same lamp was used for irradiation in the current and previous work, the differences in reaction rates can perhaps be explained by small experimental differences such as the distance between the reaction vessel and UV light source. From these results it was decided that the time consuming strategy of multiple purification steps after short irradiation times was not necessary in order to prevent significant depletion of the desired tridachiahypyrone (**9**).

In light of this, the biomimetic photochemical electrocyclicisation of the (*Z,E,E*)-polyene pyrone **43** into **9** was repeated, this time exposing the substrate to 37 h continuous irradiation (Scheme 2.16). Whilst this strategy did increase the isolated yield of phototridachiahypyrone (**93**), the longer overall irradiation time afforded comparable yields of **9** in a shorter space of time, and with just a single purification step required at the end of the irradiation time.

Having optimised the synthetic strategy for synthesis of tridachiahypyrone (**9**), its conversion into the related natural product oxytridachiahypyrone (**10**) was next conducted. This was achieved by irradiation of a methanolic solution of **9** in the presence of molecular oxygen and the photosensitiser methylene blue. The [4 + 2] cycloaddition of singlet oxygen to **9** proceeded smoothly, generating the desired product **10** in 97 % yield (Scheme 2.17).



Scheme 2.16 Biomimetic conversion of **43** into **9** and **93**, by continuous irradiation. Reagents and conditions: *a* hv, MeOH, rt., 37 h (62 % starting material **43** also recovered)



Scheme 2.17 Synthesis of oxytridachiahypyrone (**10**). Reagents and conditions: *a* MeOH, methylene blue, O₂, hv, 5 h, 97 %

As in the previous photochemical reactions studied, a longer irradiation time was again required in comparison with that reported in earlier work (5 h cf. 0.5 h, see Sect. 1.3, Scheme 20) [2].

Having successfully synthesised the compounds of the tridachiahypyrone family, namely tridachiahypyrone (**9**), phototridachiahypyrone (**93**) and oxytridachiahypyrone (**10**), along with their proposed biomimetic precursors the (*Z,E,E*)-polyene pyrone **43** and the (*E,E,E*)-polyene pyrone **44**, via an optimised synthetic route, attention was next turned to investigating the feasibility of the sunscreen hypothesis, using a range of biophysical techniques.

References

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Tridachiahdropyrone Family of Natural Products

Powell, K.J.

2016, XIX, 136 p. 151 illus., 17 illus. in color., Hardcover

ISBN: 978-3-319-22068-0