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Synthesis of bicyclo[4.2.0]octane ring of kingianin via [2+2] ketene cycloaddition

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Abstract: Kingianins are pentacyclic polyketides isolated from *Endiandra kingiana*. They exhibit promising activity in inhibiting anti-apoptotic proteins (i.e Bcl-xL and Mcl-1) and anti-diabetic proteins (α-glucosidase) at micromolar levels. Due to their structural complexity and intriguing biological activity, researchers are increasingly focussing on designing total synthesis routes for these compounds. In this communication, we propose a new non-biomimetic synthesis strategy that utilises a [2+2] ketene cycloaddition reaction as a key-step to access the bicyclo[4.2.0]octane system of kingianins. To the best of our knowledge, this is the first report based on this approach.

Keywords: Kingianins; cyclic polyketides; bicyclo[4.2.0]octane system; [2+2] ketene cycloaddition reaction.

1. Introduction

Kingianins are formally Diels-Alder reaction products derived from two monomers with a bicyclo[4.2.0]octadiene backbone. It is assumed that they are formed by a stereospecific electrocyclisation cascade starting from polyenes. Kingianins are associated with interesting biological properties[1-5] and their synthesis is an exciting challenge for the organic chemist, requiring the development of original and powerful synthetic methods. Interestingly, the chemistry of these molecules is virtually unexplored. A strategy for the biomimetic synthesis of kingianins was developed by the groups of Moses, Parker and Sherburn and was based on the hypothesis of Black and

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the work of Nicolaou on the construction of endiandric acids.[6-8] This strategy suffers from regio- and stereochemistry problems, low yields of the final products and tedious purification steps.

In this study, we focus on the preparation of monomers of kingianins, i.e. functionalised bicyclo[4.2.0]octadiene subunits, by a [2+2] ketene cycloaddition at an early stage of the synthesis, starting from simple and easily accessible substrates. One of the main advantages of such a strategy is the rapid build-up of the carbon skeleton of the kingianins, improving the chances of good overall yields of the final products.

2. Background

Kingianin A was first isolated from the Malaysian *Endiandra kingiana* and described by our research group in 2010.[1] The pentacyclic backbone was presumably formed by a Diels-Alder reaction between two monomers having a bicyclo[4.2.0]octadiene skeleton, resulting from a stereospecific electrocyclization reaction of a compound of polyketide origin. In addition, sixteen kingianin analogues (Kingianin B-Q), were reported in the subsequent years.[2,3] These compounds were isolated as optically inactive white powders. Their respective spectroscopic data were very similar but their structures differed in the nature and position of the substitutions. *In vitro* biological screening of these compounds showed good binding affinity for the protein Bcl-xL (Kingianin G: K_i = 2.0 µM) and good inhibition of α-glucosidase (Kingianin A: IC_{50} = 11.9 µM and Kingianin F: IC_{50} = 19.7 µM) (Figure 1).[2,3,5] This class of new compounds offers a promising approach for the development of anti-cancer and anti-hyperglycaemic agents.

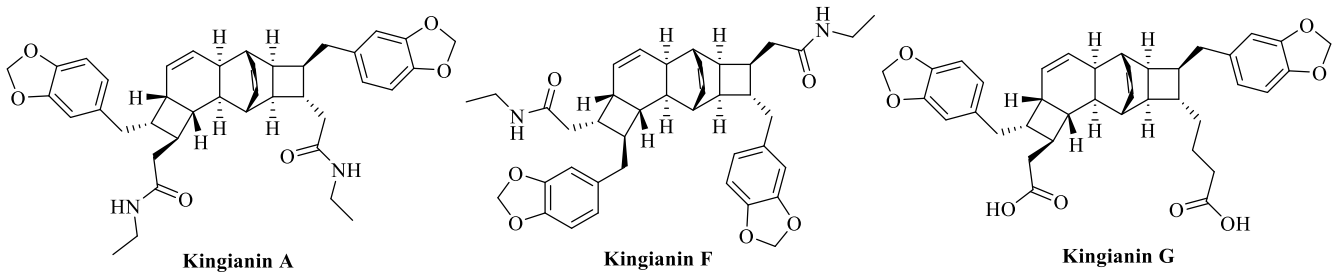


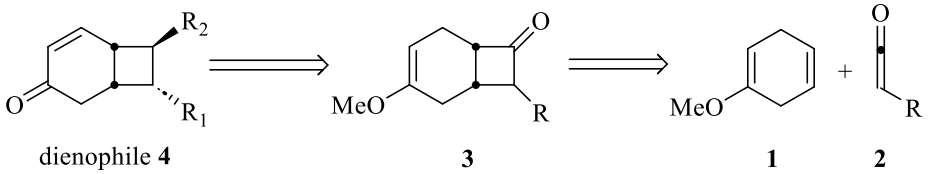
Figure 1. Selected kingianins isolated from Malaysian *Endiandra kingiana* Gamble

3. Experimental

The details of the experimental procedures for all described reactions and the complete characterisation data for all compounds can be found in the supporting information.

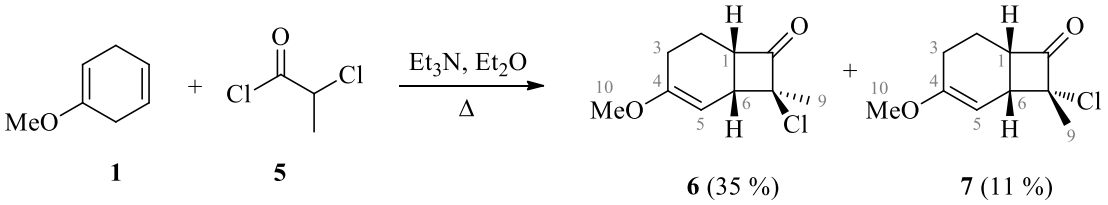
4. Present Study

Ketene cycloaddition chemistry was envisioned as a good strategy to synthesise the monomeric precursors of kingianins. At the beginning of this study, 4-methoxy-1,4-cyclohexadiene **1** and ketenes **2** were used to prepare dienophiles **4** (Scheme 1).



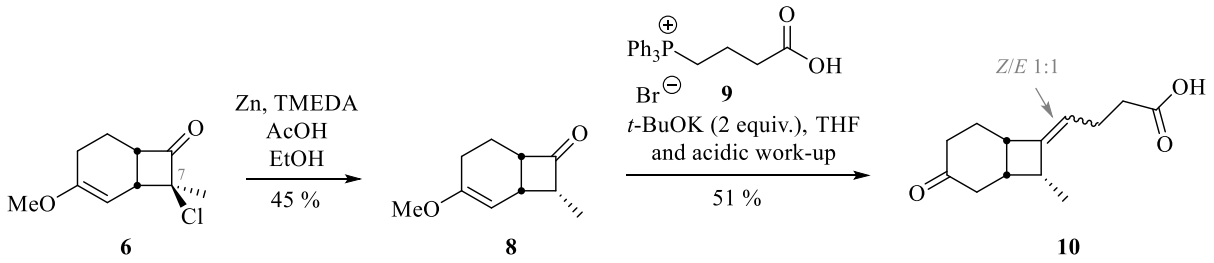
Scheme 1. Retrosynthetic analysis for the preparation of dienophiles **4**

The synthesis began with the preparation of cyclobutanones in gram quantities, as an adaptation of the sequence reported by Wu et al.[9] The reaction of 4-methoxy-1,4-cyclohexadiene **1** with 2-chloropropionyl chloride **5** and Et_3N in ether gave a separable mixture of 7-methylchloroketones **6** and **7** in a ratio of 3:1 (Scheme 2). A displacement of the double bond from C3−C4 to C4−C5 was observed during this transformation. This result is consistent with semi-empirical PM7 calculations, which indicated that compound **6** is thermodynamically more stable, by 2.39 kcal/mol, than the corresponding isomer having the C=C double bond located at C3−C4. In ^{1}H NMR, cyclobutanones **6** and **7** show characteristic signals corresponding to the olefinic proton H5, at δ_H = 4.73 and 4.69 ppm, respectively. Comparison of the ^{1}H NMR spectra shows that the proton signals for the ring junction protons H1 and H6 of compound **7** are more shielded than those of compound **6** [δ_H = 3.67 and 3.05 ppm respectively for **7**; 4.12 and 3.26 ppm for **6**). Furthermore, the formation of **6** and **7** was supported by analysis of the high-resolution mass spectra, showing peaks at *m/z* = 200.0599 and 200.0606, respectively, in agreement with a molecular formula of $C_{10}H_{13}{}^{35}ClO_2^{+\bullet}$ ($M^{+\bullet}$; calculated value 200.0599). The configuration of the methyl group (C9) for compound **7** was *exo*, as confirmed by a two-dimensional NOESY experiment. Indeed, a correlation were observed between H6 and H9 and no correlation between H5 and H9. Accordingly, this implied the *endo* configuration of the methyl group (C9) for compound **6**.



Scheme 2. Synthesis of cyclobutanone diastereoisomers **6** and **7**

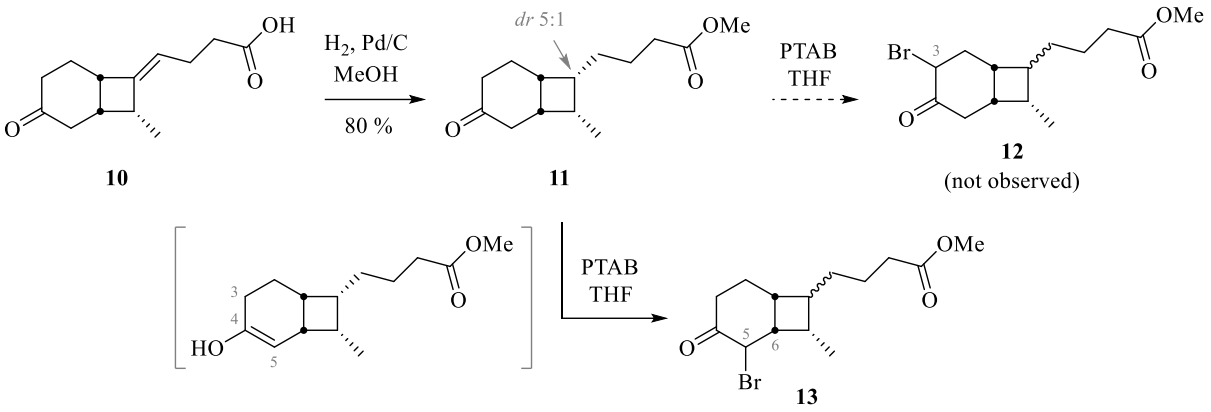
Next, the bicyclic[4.2.0]octane **6** was subjected to dechlorination at C7 using activated Zn, TMEDA and acetic acid to give cyclobutanone **8** in 45 % yield. The formation of cyclobutanone **8** was confirmed by ^{1}H NMR spectroscopy with signals at δ_H = 3.07 (qd, *J* = 8.4, 4.6 Hz) and 0.91 ppm (d, *J* = 8.4 Hz), corresponding to the proton and methyl group attached to C7, respectively. This compound proved to be relatively unstable and had to be rapidly used. The Wittig reaction of 7-methyl ketone **8** with the phosphorus ylide generated from **9** gave the expected 7-methyl product **10** as a 1:1 mixture of *Z/E* isomers, in 51 % yield (Scheme 3).



Scheme 3. Functionalisation of cyclobutanone **6**

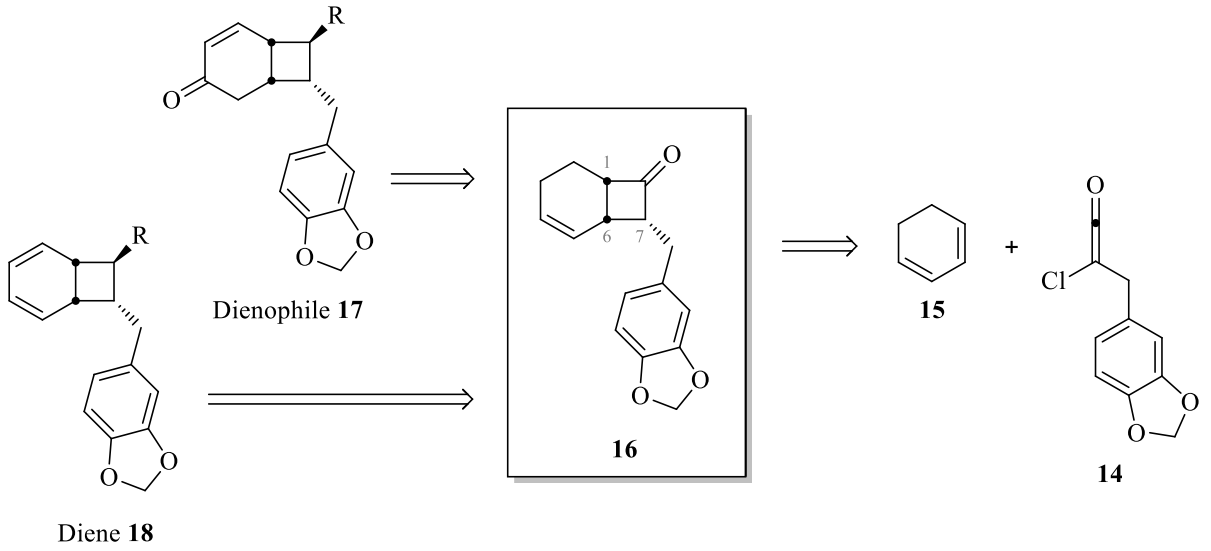
The sequence was continued by a palladium-catalysed hydrogenation of **10** in methanol to give compound **11** in 80 % yield (Scheme 4). On the basis of data found in the literature,[10] it was anticipated that bromination of **11** with phenyltrimethylammonium perbromide (PTAB) in THF (−78 to 0 °C) could afford the bromoketone **12** as the major product. However, examination by ^{1}H NMR spectroscopy of the crude product obtained under analogous conditions showed the typical signals of bromoketone **13** (not isolated). The doublet signal at δ_H = 4.86 ppm showed scalar coupling between the protons at C5 and C6. This selectivity in favour of bromination at C5 can be rationalised by the

preferential formation of the enol intermediate having the C=C double bond located at C4−C5 (displayed in the scheme), calculated to be more stable than the alternative enol having the C=C bond at C3−C4, by 1.82 kcal/mol (PM7). The synthesis was stopped at this stage and continued with another approach using 1,3-cyclohexadiene.



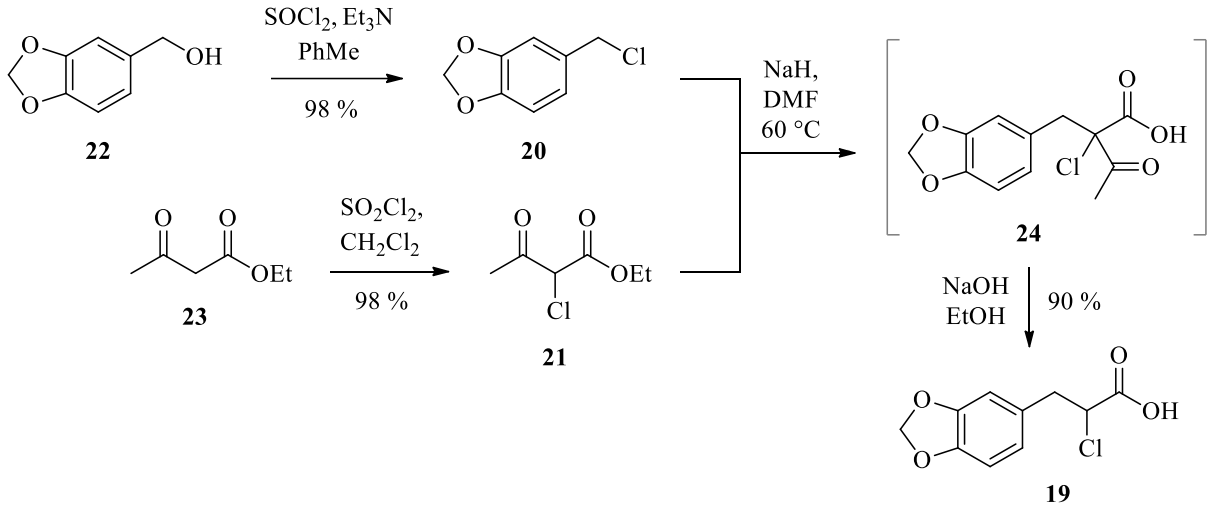
Scheme 4. Synthesis of compound **13**

This route was implemented with ketene **14**, having the methylenedioxybenzyl group of the kingianin structures. The aim was to synthesise compound **16**, which could be a common precursor of dienophile **17** and diene **18** (Scheme 5).



Scheme 5. Strategy for the synthesis of dienophile **17** and diene **18**

First, the ketene precursor 2-chlorocarboxyl chloride **14** was prepared from 2-chlorocarboxylic acid **19**.[11] The synthesis began with two fragments, namely piperonyl chloride **20** and ethyl-2-chloro-3-oxobutanoate **21** (Scheme 6). The chloride **20** was prepared from piperonyl alcohol **22**. Compound **21** can be synthesised in one step from commercial ethyl-3-oxobutanoate **23** using sulfuryl chloride. Nucleophilic substitution of **20** with **21** gave the chloroketone **24**, from which reaction with NaOH in ethanol afforded the acid **19** in 90 % yield (Scheme 6).



Scheme 6. Synthesis of 2-chlorocarboxylic acid **19**

With this 2-chlorocarboxylic acid **19** in hand, attention turned to the ketene [2+2] cycloaddition with 1,3-cyclohexadiene **15**. The reaction of **15** with chloro piperonyl ketene **14**, generated *in situ* from the corresponding acyl chloride in the presence of Et_3N, in diethyl ether at room temperature afforded the bicyclic cyclobutanone **25** in low amount (7% yield). Investigation of the use of different solvents under reflux conditions (Table 1) improved the yield to 25 % by carrying out the reaction in cyclohexane (b.p. 81 °C). Rationalisation of this observation is very uneasy. Indeed, no obvious correlation is identified between the results and the polarity of the solvent or the temperature applied. The reaction performs better in refluxing diethyl ether (b.p. 35 °C) than in refluxing THF, a more polar solvent having a higher boiling point (66 °C). It also performs better than in petroleum ether (40-60 °C), a less polar medium, but not as well than in cyclohexane, which boils at higher temperature and is also less polar than diethyl ether. Regardless of these considerations, the cycloadduct **25** was isolated as a single diastereoisomer having the methylenedioxybenzyl group in *endo* relative configuration. Its structure was analysed and confirmed by NMR experiments.

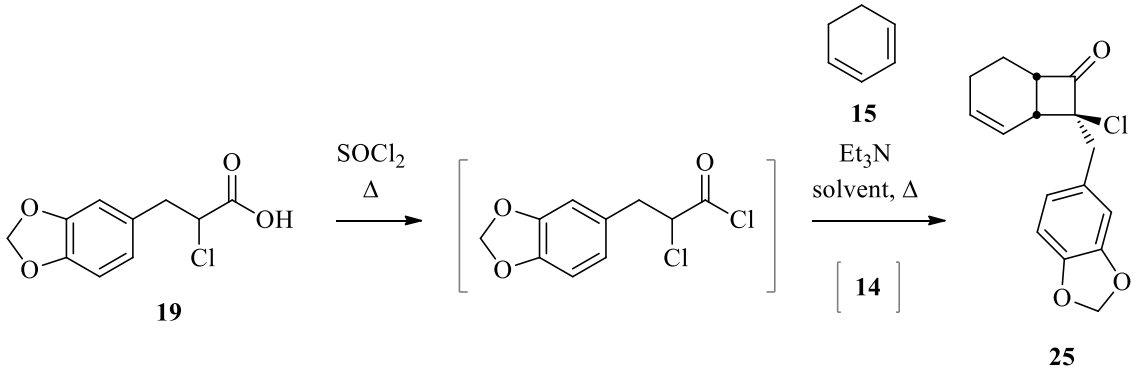


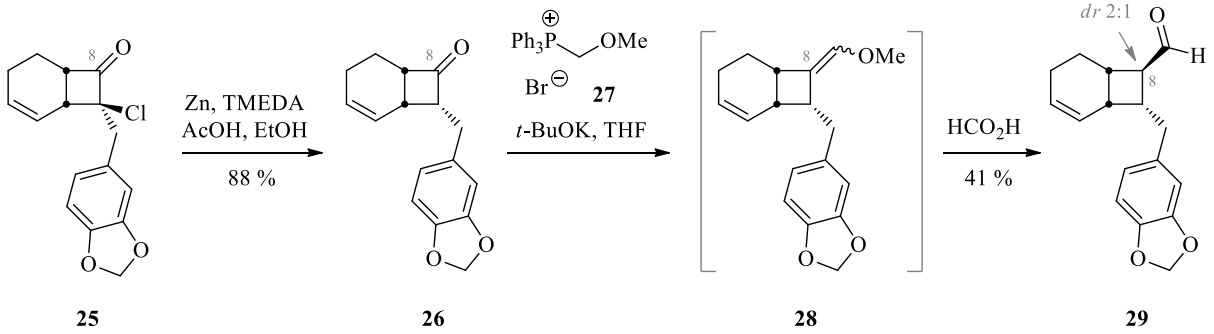
Table 1. Optimization of the [2+2] cycloaddition.

Entry[1]	Condition	Yield (%)[2]
1	Et_2O, room temperature	7
2	Et_2O, reflux	14
3	Cyclohexane, reflux	25
4	CH_2Cl_2, reflux	6
5	THF, reflux	7
6	Petroleum ether (40-60 °C), reflux	5
7	Toluene, 100 °C (oil bath)	5

[1] Reaction carried out on 2.0 mmol scale.

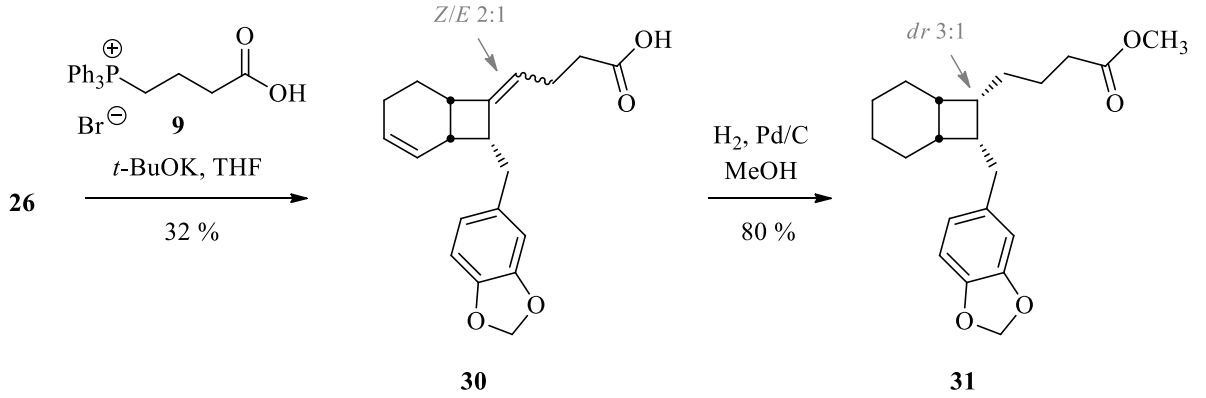
[2] Yield after purification by column chromatography. **25** was the sole product isolated.

Cycloadduct **25** was subjected to reduction with activated zinc in the presence of acetic acid to give the ketone **26** in 88% yield. The functionalisation of **26** was performed using Wittig reactions (Schemes 7 and 8). The first Wittig reaction was carried out with the phosphonium salt **27** to obtain enol ether **28**, which was directly subjected to hydrolysis with formic acid to produce the aldehyde **29**.



Scheme 7. Synthesis of aldehyde **29**

The second Wittig reaction was conducted with the phosphonium bromide **9** to afford the desired acid **30** with an *E*/*Z* isomer ratio of 1:2. Palladium-catalysed hydrogenation of both C=C double bonds, carried out in methanol, afforded the methyl ester **31** in 80 % yield. This structure, especially the minor diastereoisomer produced, bears high similarity with the western part of kingianins H, L and M and the eastern part of kingianins G, H, K and N.[2]



Scheme 8. Synthesis of bicyclo[4.2.0]octane derivative **31**

5. Conclusion

As a conclusion of this preliminary work, the goals of this project were partially achieved. The racemic syntheses of substructures of kingianins were successfully achieved on model compounds, in a few synthesis steps. These findings will be the benchmark for our future synthetic work on the kingianin series. The preparation of the bicyclo[4.2.0]octane core (for example compounds **11**, **29**, and **31**) may lead to a wider range of analogues that could be developed further. This approach allows the rapid construction of the kingianin carbon skeleton, maximising the chance of good overall yields of the final products. The proposed total synthesis of kingianins is currently in progress.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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