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PAPER

Studies towards the synthesis of the northern polyene of viridenomycin and synthesis of *Z*-double bond analogues†

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Viridenomycin is a structurally challenging, potentially biologically valuable molecule which has yet to succumb to total synthesis. Its instability, perhaps particularly associated with the northern polyene may contribute to the difficulties of piecing this molecule together. The synthesis of northern polyene models, including potentially stabilised analogues incorporating benzene rings as *Z*-alkene replacements, have been prepared using an efficient series of cross-coupling reactions. The resulting polyenes and polyene surrogates have been converted into tetraene ester and amide models of the viridenomycin system. These analogues have sufficient stability compared with the unsubstituted northern polyene analogue to be viable for future developing a strategy for the construction of viridenomycin and analogues.

Introdcution

Viridenomycin **1**[1] is a 24-membered, *E*:*Z*-mixed polyene macrolide isolated from *Streptomyces gannmycius* and *Streptomyces viridochromogenes*. It has been shown to have cytotoxic activity against Gram-positive bacteria and certain protozoa. Studies have also demonstrated that it prolongs the survival period of mice bearing B16 melanoma. The structure of viridenomycin was elucidated in 1991, and it is a complex, challenging and inherently unstable structure. Particularly notable are the unstable tetraene systems, especially the *Z*,*Z*-containing northern tetraene, and also the densely functionalised cyclopentanone-derived core. Both the absolute stereochemistry of the oxygenated cyclopentanone-derived ring and the relative stereochemistry of the benzylic amide-substituted carbon remain unknown. This creates the requirement to synthesise all four possible stereoisomers of viridenomycin in order to determine which stereoisomer is naturally occurring. To date, none of the possible stereoisomers have been prepared,[2] though ongoing efforts in our laboratories have resulted in the efficient synthesis of useful building blocks and in this paper, we report the synthesis of fragments suitable for building viridenomycin and novel analogues.[3]

Retrosynthetically, viridenomycin can be disconnected into three main fragments (Scheme 1), *i.e.* a densely-functionalized cyclopentanone ring derivative **2** and two triene units: a northern polyene **3** and southern polyene **4**. A Heck–Mizoroki (HM)-type coupling, possibly intramolecular depending on order of assembly, was envisaged between the core and northern hemisphere. This would leave an amide coupling to the southern polyene **4** and finally enol-ester formation to complete the synthesis.

As part of our ongoing studies to develop a synthesis of viridenomycin, a synthesis of the northern triene **6**[1c] has been reported (eqn (1)), along with mechanistic studies with regard to the focal HM cross-couplings employed. It was observed that the northern polyene **3** and its precursors (in particular, the alkenyl iodides) were extremely susceptible to light-induced decomposition and isomerisation, especially under ambient conditions and even with low light exposure. Clearly, these properties have the potential

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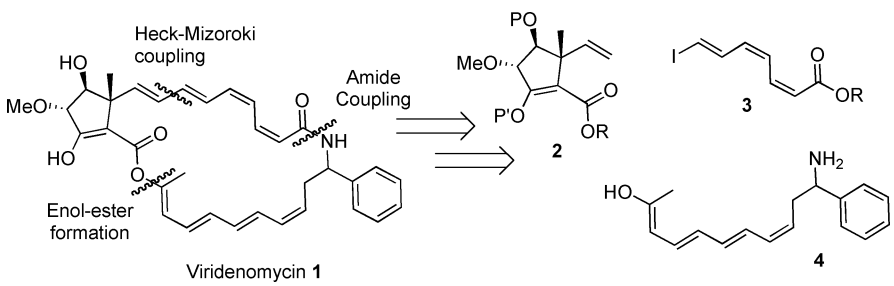
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for compounds **8**, **9**, **11**, **13**, **14**, **17**, **19**, **20**, **23–26**, **28**, **29** and **31–34**. See DOI: 10.1039/c0ob00977f

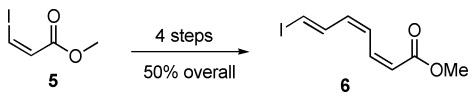


Scheme 1 Retrosynthetic strategy for the synthesis of viridenomycin.

Table 1 Conditions examined for the HM reaction shown in eqn (2)

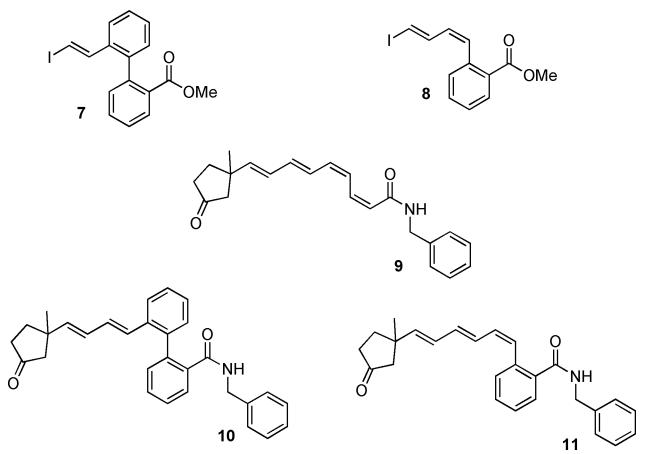
Entry	Solvent	Base	Temp/°C	Time/h	Ligand	Catalyst loading (%)	Yield **13** (%)
1	MeCN	AgOAc	60	45	P(*o*-Tol)$_3$	5	19
2	MeCN	AgOAc	80	45	P(*o*-Tol)$_3$	5	25
3	EtCN	AgOAc	60	96	P(*o*-Tol)$_3$	5	<5
4	MeCN	AgOAc	60	96	P(*o*-Tol)$_3$	10	20
5	DMF	AgOAc	60	48	P(*o*-Tol)$_3$	5	19
6	MeCN	Ag_2CO_3	60	72	P(*o*-Tol)$_3$	5	10
7	MeCN	AgOAc	60	24	—	5	70

to make subsequent coupling reactions to the southern polyene building block **5** and cyclopentanone derivative **2** challenging, considering the reaction conditions likely to be required.



5 **6** (1)

Bearing this in mind, potentially more stable analogues of the northern polyene became attractive synthetic targets, not only for modelling the final assembly of viridenomycin **1**, but also as overall targets to compare the biological activity of the final products. Hence, the synthesis of substituted analogues of viridenomycin with *cis*-alkene replacements built into the northern polyene section would allow us to probe whether this part of the molecule was critical for biological activity. Indeed, such analogues may in fact exhibit more potent cytotoxic activity, especially considering the probable instability of viridenomycin *in vivo*. Therefore, because much of the instability of the northern polyene building block **6** seemed to be centred in the ester carbonyl-substituted alkene, this was the obvious area for modification. Alkene analogues of this fragment would require prohibiting isomerisation of the *Z*-double bond, resulting in locking its *Z*-configuration. A potentially good solution would be to build in either two *ortho*-disubstituted benzene rings to replace both *Z*-double bonds, or a sole *ortho*-disubstituted benzene ring in place of the least stable double bond, *i.e.* replacing **3** with the corresponding analogues **7** and **8**.



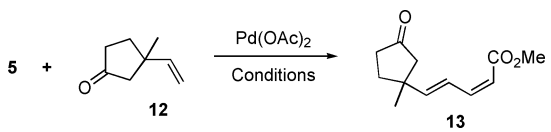
7 **8** **9** **10** **11**

In order to determine if building blocks such as **7** and **8** would be good surrogates for triene iodide **6**, it was necessary to ascertain the impact of benzene rings upon the resulting polyene derivatives. In order to examine this, it was decided to prepare two models of the northern polyene amide section of viridenomycin **1**, *i.e.* structures **10–11** using building blocks **6–8** respectively. In this paper, we report the synthesis of the viridenomycin northern polyene surrogates **9–11** and the resulting effects on stability towards isomerisation afforded by the inclusion of benzene functions.

Results and discussion

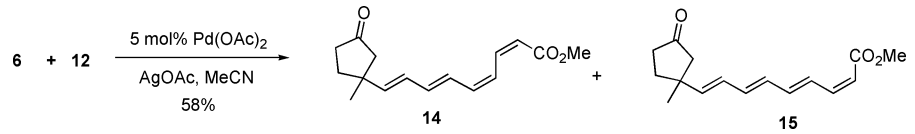
Synthesis of 3-methyl-3-vinylcyclopentanone 12

In order to access the systems **9–11**, the cyclopentanone derivative **12** was required, which was prepared similarly to a literature method by the addition of a vinylcuprate to 3-methylcyclopentenone.[4] Initial attempts at the HM coupling of **12** were then performed using vinyliodide **5** rather than trienyl iodide **6**, in order to assess the efficiency of the reaction without matters being complicated by instability of the resulting product(s), *i.e.* as outlined in eqn (2). It should be noted that the HM reactions of iodide **5** are non-trivial due to competition from the competing reductive dimerisation side-reaction.[5] Indeed, we have previously reported that employing tri(*o*-tolyl)phosphine is one of the few ways of suppressing this reaction.[3c] The results of these studies were not initially promising (see Table 1), since the use of the standard conditions developed especially for the coupling of iodide **5** with vinylboronate esters[3c] were highly inefficient (Table 1, Entry 1), resulting in a low yield of the desired product **13**.



12 **13** (2)

The reaction (eqn (2)), run under varying conditions and time periods, was found to be generally slow, requiring two days or more to achieve sufficient conversion to allow product isolation (Table 1, Entries 1–6). Although the yield was slightly improved by increasing the temperature (Table 1, Entries 1 and 2), given the sensitivity of the substrates to be used for the actual synthesis of viridenomycin (*i.e.* **6**), it was decided to avoid pursuing such conditions due to fears over the stability of the products from this type of reaction. Changing solvent also had little impact on the efficiency of the reaction (Table 1, Entries 1, 3 and 5) and increasing the catalyst loading failed to improve the yield (Table 1, Entries 1 and 4). A change of base to sodium carbonate also failed to improve matters (Table 1, Entry 6). Finally, ligand-free conditions, which had previously been discovered to be moderately successful in the HM coupling of iodide **5** with vinylboronate esters,[6] were successfully employed (Table 1, Entry 7) providing the desired diene **13** in 70% yield with excellent stereoselectivity.



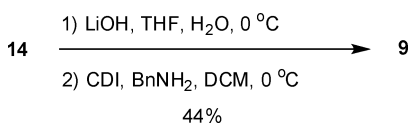
(3)

Having discovered suitable conditions for the reaction of **5** with **12**, application of these new conditions (Table 1, Entry 7) to trienyl iodide **6** was attempted (eqn (3)) in order to access tetraene **14**. The initial results were also not promising; not only was the overall yield poor (27%) using the ligand-free conditions, but significant isomerisation of the product was also observed. Hence, **14** was isolated as a 2 : 1 mixture of the intended *Z*,*Z*,*E*,*E*-isomer together with the *Z*,*E*,*E*,*E*-isomer **15**.

It was feared that the use of ligand-free palladium was at least partly to blame for this degree of isomerisation given that in previous HM reactions of similar substrates little or no isomerisation was observed. In order to try and reduce this isomerisation, the reaction was repeated employing two equivalents of olefin **12**, partly in order to increase the rate of the reaction but also to act as a labile ligand for the palladium catalyst. This approach proved to be successful and, when combined with the use of chilled eluent for the silica gel-based column purification, the product **14** was isolated in a reasonable 58% yield with acceptable isomeric purity, with a *Z*,*Z*,*E*,*E* : *Z*,*E*,*E*,*E* ratio of 5 : 1, *i.e.* **14** : **15**, respectively. It was felt that given the extremely sensitive nature of the substrate **6**, this level of yield and selectivity was acceptable and attention was turned to accessing the corresponding amide derivative.

Synthesis of tetraene benzamide 9

Saponification of the methyl ester **12** using lithium hydroxide in aqueous THF at 0 °C was sluggish and required ten equivalents of lithium hydroxide for the reaction to proceed to completion. The intermediate was not purified but used directly in the next step, *i.e.* exposed to a CDI-mediated amide bond formation with benzylamine as a model for the southern hemisphere amine. The reaction provided the benzamide **9** in moderate yield (eqn (4)), however, some further isomerisation of the product occurred giving a reduced *Z*,*Z*,*E*,*E* : *Z*,*E*,*E*,*E* ratio of 3 : 1. Given the mild nature of this type of coupling reaction, this result clearly demonstrates the high degree of sensitivity of these types compounds towards isomerisation.

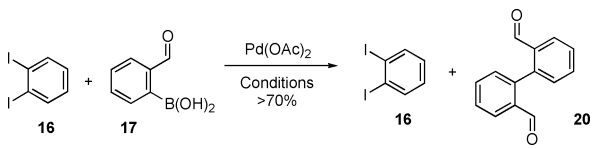


(4)

Synthesis of biaryl analogue 7

It was anticipated that accessing both the biaryl benzamide analogue **10** and *ortho*-disubstituted benzamide analogue **11** would follow a synthetic sequence equivalent to that applied to the assembly of tetraene benzamide **9** (eqn (1), (3)–(4)) with application of analogous conditions throughout. In the case of the biaryl analogue **7**, this would require an initial Suzuki–Miyaura (SM)[7] coupling in place of the original HM conditions and as such, start with the commercially available *ortho*-diiodobenzene **16**. This would then be followed by a one-pot Oxone[8] mediated oxidation–esterification (Scheme 2).

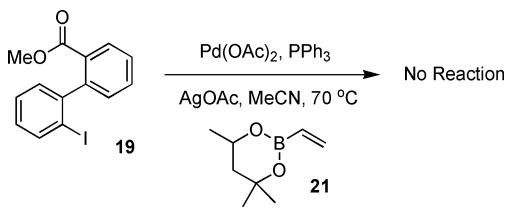
The SM coupling to access the building block **18** proved difficult and inconsistent, despite considerable variation of the reagents and reaction conditions, with the best conditions (Scheme 2) providing a moderate 48% yield. Indeed, the dominant reaction under the vast majority of the reaction conditions examined, and despite vigorous degassing, was the oxidative coupling of the boronic acid **17** to provide the biaryl **20**, leaving the diiodide **16** untouched and often resulting in yields upwards of 70% (eqn (5)).



(5)

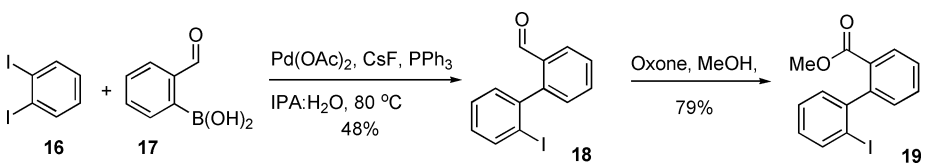
In spite of these difficulties, the aldehyde **18** could be exposed to a one-pot oxidation–esterification to provide the biaryl iodide **19** in 79% yield (Scheme 2) which was to be the HM precursor.

Application of the original HM conditions employed in the synthesis of triene **6** (eqn (6)) was unsuccessful, *i.e.* biaryl iodide **19** could not be converted under any conditions into the corresponding vinylboronate derivative by reaction with vinylboronate **21**. That, together with the initial difficulties encountered with the SM coupling (Scheme 2), led to the development of a new synthetic approach.

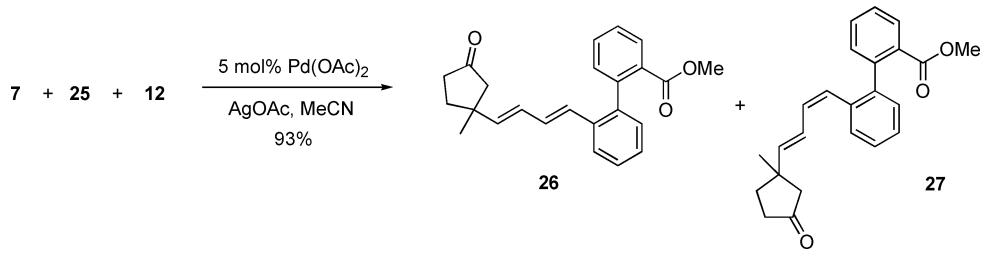


(6)

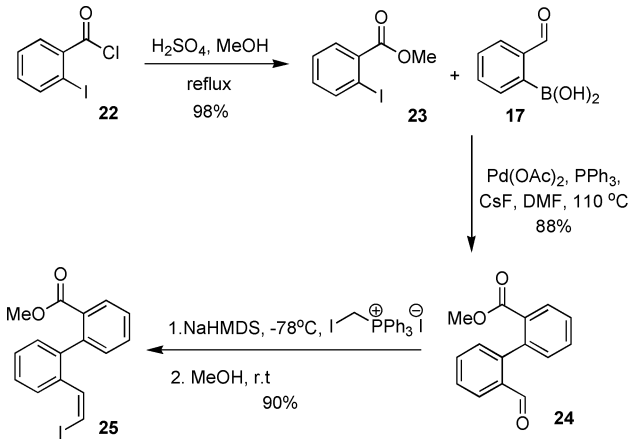
Speculating that the inherent problem with the initial sequence lay with the nature of the starting materials, the alternative synthetic sequence involved a SM coupling and Wittig reaction[9] sequence (Scheme 3) to install the double bond, hence eliminating the requirement of a HM accessible intermediate.



Scheme 2 Assembly of biaryl iodide intermediate **19**.



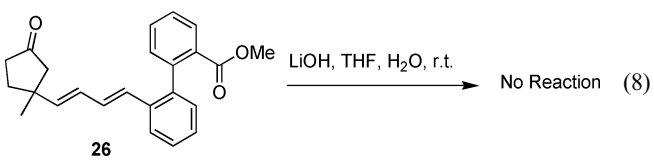
(7)



Scheme 3 Alternative assembly of intermediate vinyliodide **7**.

SM coupling of the iodide **23** proceeded well to provide the biaryl unit **24** in excellent yield and subsequent Wittig reaction with iodomethyltriphenylphosphonium iodide–NaHMDS which provided iodide **25** as the predominant *Z*-isomer in a ratio of 97 : 3, *Z* : *E* respectively. As the *E*-isomer **7** was required for this analogue, Schlosser[10] methodology was applied in place of the original Wittig conditions in Scheme 3 to try to access the *E*-isomer directly, however, this remained unsuccessful with the biaryl aldehyde remaining inactive. It was hoped that favourable *Z*–*E*-isomerization of intermediate iodide **25** would be possible during the final stages of the synthetic sequence, and hence, providing the desired isomer at the final product stage (*vide infra*).

To access the cyclopentanone derivative **26**, identical HM conditions for the synthesis of tetraene **14** were applied to the mixture of alkenyl iodides **7** and **25**, which proceeded in excellent yield (eqn (7)), demonstrating some of the required isomerisation in the process, *i.e.* providing a ratio of the desired *E*,*E*-isomer **26** to the *Z*,*E*-isomer **27** in a ratio of 1 : 2, respectively (eqn (7)). At this stage, separation of the isomers **26** and **27** was achieved *via* silica gel chromatography allowing continuation to the final stages to proceed with a pure sample of diene **26** isolated in 31%.



(8)

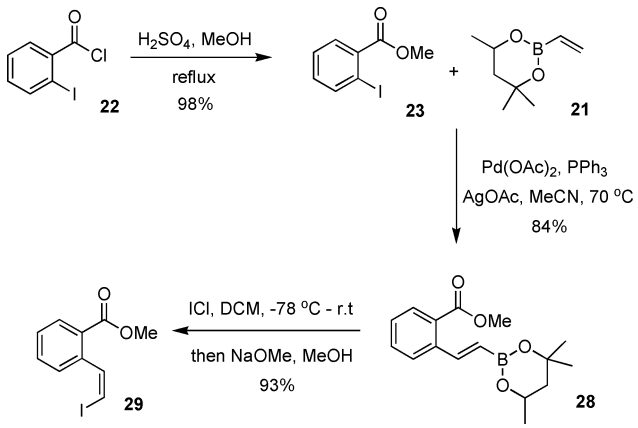
Synthesis of dienyl benzamide 10

Application of the saponification conditions in construction of tetraene benzamide **9** proved unsuitable with ester **26**, showing no reaction even after 72 h (eqn (8)).

This remained the case, even after an increase in molarity of lithium hydroxide used, from 1.5 to 8 M! Changing the source of hydroxide from lithium to sodium gave similar results at lower molarities, and eventual destruction of the starting material **26** once the concentration of sodium hydroxide rose to 6 M. It is also worth noting that a very similar lack of reactivity was observed on applying identical conditions to biaryl ester **7**, suggesting that nucleophilic attack at these di-*ortho*-substituted biaryl ester systems is too sterically demanding. This finding led to the conclusion that these types of biaryl systems may therefore be unsuitable for the construction of accessible, stable analogues of viridenomycin.

Synthesis of dienyliodide 8

It was anticipated that following a synthetic sequence equivalent to that applied to the assembly of tetraene benzamide **9** (eqn (1) and 3–4) would be more successful in accessing the *ortho*-disubstituted benzamide analogue **11** than for biaryl analogue **10**. Hence, the synthesis started with commercially available *ortho*-iodobenzoyl chloride **22** (Scheme 4).



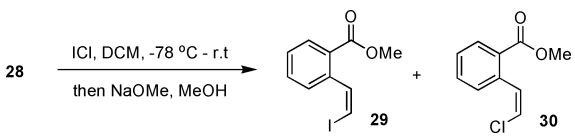
Scheme 4 Assembly of *Z*-iodide intermediate **18**.

Following ester formation to give **23**, HM coupling was attempted with vinylboronate **21**. Initial attempts at this HM coupling to form boronate **28** was found to be only moderate yielding (51%) using of tri(*o*-tolyl)phosphine as had been employed in all HM couplings in the synthesis of triene **6** (*vide supra*). As previously reported,[3c] the benefit of using tri(*o*-tolyl)phosphine was primarily to provide steric bulk around the palladium(II) intermediate species, in order to prevent competitive iodide homocoupling.[5] We have already mentioned that this substrate does not undergo reductive dimerisation, which seems more likely to do with the difficultly in adding palladium across an aromatic double bond rather than any steric differences, and hence, because

Table 2 Attempted iodo-deoboronation of **28** using molecular iodine

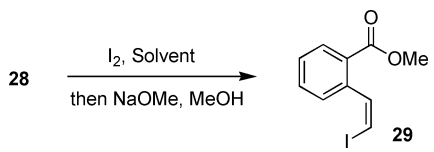
Entry	I_2 (equiv.)	Solvent	Temp/°C	*E* : *Z* ratio **29**	Yield **29** (%)
1	1.25	DCM	–78 –rt	—	0
2	3	DCM	rt	1 : 1	89
3	3	Et_2O–THF	rt	3 : 7	92

we knew that reductive dimerisation was not an issue in this case, PPh_3 could be safely employed. With this in mind, it was hoped that in this instance, the use of aromatic iodide **23** would provide enough steric bulk around the palladium complex and prevent the undesirable homocoupling by itself, as previously discussed (*vide supra*), which again meant that the less bulky triphenylphosphine would facilitate an increase in reaction rate and yield. Indeed, the yield was increased to 84%, with there was no sign of the homocoupled iodide species, as outlined in Scheme 4. Subsequent stereoselective iodo-deboronation of **28** to install the *Z*-double bond and furnish **29** proved to be more problematic than expected when applying the previously reported optimised conditions to this new substrate.[3] The problem in this case being control of chemoselectivity; also a process which has been encountered previously.[11] This was confirmed by the identification of the corresponding *Z*-chloride **30** as the major product (eqn (9)), which was produced in varying, but significant ratios (up to 1 : 1) with respect to the desired iodide **29**.



(9)

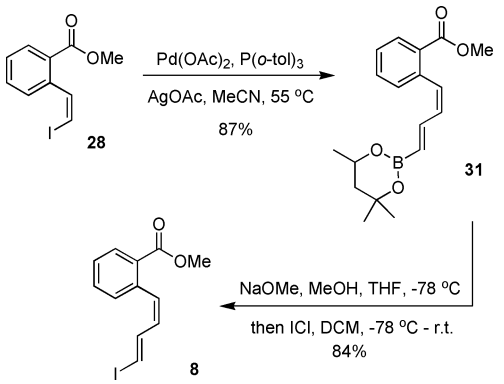
The use of diiodine for such transformations is well documented,[12] however, it usually requires more electron-rich substrates due to the less reactive nature of diiodine compared to iodine monochloride. In order to determine whether boronate **28** was sufficiently reactive towards diiodine, the reaction outlined in eqn (10) was examined. The results (Table 2) showed that excess diiodine was required to convert **28** to the corresponding iodide **29**, however, the *E* : *Z*-ratio remained unsuitable for further use.



(10)

Re-examination of the ICl reaction of **28** (Scheme 4), and particularly the reaction concentration, number of equivalents of ICl and rate of addition of ICl, provided the solution to the problem. Reducing the number of equivalents of ICl from 1.2 to 1.05, reducing the reaction concentration to 0.075 M and slowing the rate of addition of the ICl at –78 °C provided consistent results, *i.e.* the iodide to chloride ratio was consistently >9 : 1 (*i.e.* **29**:**30**) and high yields were obtained.

To complete the synthesis of the northern hemisphere surrogate **7**, a further HM coupling of **29** was required (Scheme 5). For the conversion of **29** to the dienylboronate **31**, the tri(*o*-tolyl)phosphine ligand system was required, since the substrate **29** was less sterically hindered. Hence, **29** was efficiently converted to **31** in 79% yield, followed by iodo-deboronation using ICl with

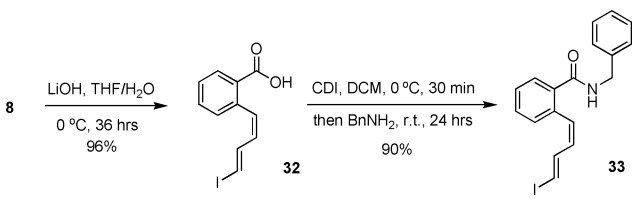


Scheme 5 Completion of northern hemisphere surrogate analogue **8**.

retention of stereochemistry (Scheme 5) to give **8** as a 94 : 6 mixture of *Z* : *E*-stereoisomers in good yield.

Synthesis of dienyliodide amide 33

The dienyliodide **8** was found to be more air and light sensitive compared to its boronate counterpart **29**, which meant that mild reaction conditions were required for its conversion to the corresponding amide **33**. This was accomplished by a saponification–amidation sequence as outlined in Scheme 6. During the saponification step, notable isomerisation occurred to iodide **8**, after which, a 12 : 1 mixture of *E*,*Z*- to *E*,*E*-stereoisomers of **32** was obtained.



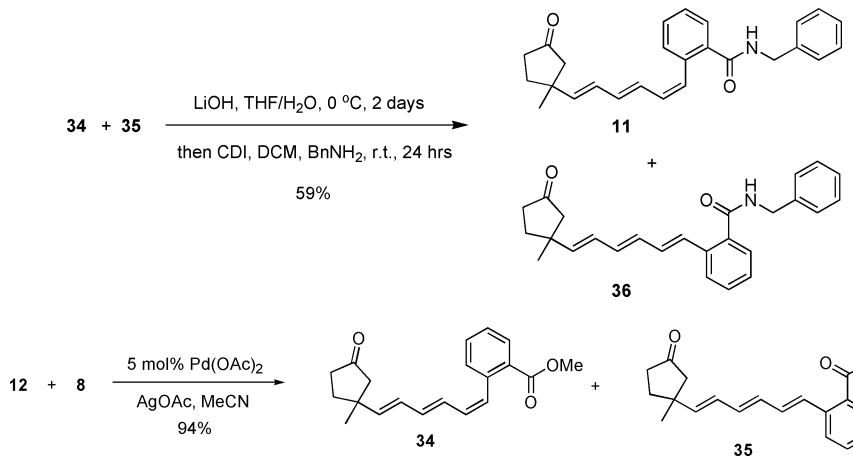
Scheme 6 Conversion of ester **8** to amide **33**.

Given this encouraging result, attention turned to the HM coupling to the model cyclopentanone core **11**, using conditions for the analogous coupling to the triene **6** (eqn (3)). Hence, application of these conditions on dienyliodide **8** (eqn (11)) resulted in an excellent yield of a mixture of *Z*,*E*,*E*- and *E*,*E*,*E*-isomers **34** and **35**, respectively, in a ratio of 50 : 1.

Exposing the resulting mixture of trienes **34** and **35** to the amide coupling conditions resulted in a similar mixture of isomers being formed, *i.e.* a 20 : 1 ratio of isomers **11** to **36**, respectively (eqn (12)), demonstrating that triene **9** remained more susceptible to isomerisation under the saponification–amide coupling conditions. However, the amide derivatives are generally more susceptible to isomerisation in general than the corresponding esters, which is noteworthy in the context of the synthesis of viridenomycin and its lactam moiety.

Comparison of the stabilities of viridenomycin northern polyene models 14 and 34

To determine whether the incorporation of the benzene ring had any effect on the stability of the northern hemisphere building blocks, stability tests were run in parallel and the results assessed using ^{1}H NMR on esters **14** and **34**. This involved the exposure of



(11)

(12)

Table 3 Relative stabilities of tetraenes **14** and **34** by ^{1}H NMR

Entry	Sample (starting isomer ratio)	Time/days	Conditions	Ratio minor isomer
1	**14** (5 : 1)	2	Dark	3 : 1
2	**14**	2	Light	2 : 1
3	**14**	8	Light	2 : 1
4	**34** (50 : 1)	2	Dark	30 : 1
5	**34**	2	Light	18 : 1
6	**34**	8	Light	15 : 1

the NMR samples dissolved in $CDCl_3$ being exposed to ambient laboratory light and air over prolonged periods. None of the NMR samples showed instability to air; they did however undergo isomerisation in ambient laboratory light, and the results of these studies are reported in Table 3. These studies show that both of the compounds **14** and **34** were particularly unstable to light-promoted *cis–trans* isomerisation, with minimal isomerisation in the absence of fluorescent light, even after 3 weeks. In addition, in both cases, it was clear from the NMR spectra in each case that decomposition did not occur, merely the isomerisation process which appeared to reach equilibrium within a period of light exposure of two days. As expected, the mono-phenyl ring derivative of the northern tetraene **34** was less susceptible to isomerisation that its tetraene analogue **14**, and it therefore might be predicted that its incorporation into the synthesis of viridenomycin could be a viable strategy for analogue synthesis.

Conclusion

The development of methods suitable for the construction of the northern hemisphere of viridenomycin has been achieved, with the synthesis of amide tetraene **9**, and a phenyl ring-containing model amide derivative **36**. ^{1}H NMR studies conducted on both the ester derivatives, *i.e.* **14** and **34** in tandem under varying light conditions, illustrated not only vastly improved isomeric ratios (*Z*,*E*,*E* : *E*,*E*,*E*) but also a slower rate of isomerisation for the phenyl-ring containing system **34**. Analogous results are anticipated for the equivalent amide-containing counterparts **9** and **36**, however, qualitative observations show that the amides are less stable than the corresponding ester counterparts. These results indicate that this type of model may be promising for constructing models of viridenomycin itself, and as such, may provide an opportunity in assisting the development of reaction conditions suitable for the final construction of this target compound and its different stereoisomers.

Experimental

3-Methyl-3-vinylcyclopentanone 12

To a stirred suspension of copper(I) iodide (2.3 g, 12 mmol) in dry THF (30 mL) was added tributylphosphine (3.2 mL, 13 mmol), the mixture cooled to −40 °C, vinylmagnesium bromide (29 mL of a 1.0 M solution in THF, 29 mmol) added dropwise followed by methylcyclopenteneone (1.0 mL, 10 mmol). The reaction was stirred for 3 h, warmed to −10 °C over 1 h and quenched by the addition of sat. aq. NH_4Cl (24 mL). The mixture was filtered through Celite eluting with Et_2O (100 mL), washed with 5% HCl (40 mL) and brine (60 mL), the combined organic phase extracted with Et_2O (80 mL) and the combined organic phase dried ($MgSO_4$) and evaporated to afford the crude product as an orange oil. Purification by silica gel chromatography (EtOAc : pet. ether 40–60 °C, 1 : 19 then 1 : 9 as eluent) gave the title compound (750 mg, 60%) as a pale yellow oil. All spectroscopic and analytical properties were identical to those reported in the literature.[4]

(2*Z*,4*E*)-5-(1-Methyl-3-oxo-cyclopentyl)-penta-2,4-dienoic acid methyl ester 13

To a dried Schlenk tube under a positive pressure of argon was added palladium(II) acetate (8 mg, 33 μmol), silver(I) acetate (160 mg, 0.96 mmol) and dry MeCN (3 mL), the mixture was degassed using the freeze–pump–thaw method (1×), iodide **5** (160 mg, 0.75 mmol) and a solution of olefin **12** (70 mg, 0.56 mmol) in dry MeCN (0.15 mL) were added, the mixture was further degassed (2×) and heated to 60 °C with vigorous stirring. After 24 h the mixture was cooled, diluted with Et_2O (40 mL), passed through Celite and evaporated to give the crude product as a green oil. Purification by silica gel chromatography (gradient elution, EtOAc : pet. ether, 1 : 19 to 1 : 4 as eluent) gave the title compound **13** (81 mg, 70%) as a yellow oil. ν_{max}/cm^{-1} (film) 2955, 1737, 1711, 1637, 1601, 1263 and 1170; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, s, Me), 1.86–1.92 (1H, m, C*H*HCH$_2$C=O), 2.03–2.09 (1H, m, CH*H*CH$_2$C=O), 2.15 (1H, d, *J* 18, MeCC*H*HC=O),

2.28–2.35 (2H, m, CH_2CH_2C═O), 2.35 (1H, d, *J* 18, MeCCH*H*C═O), 3.72 (3H, s, OMe), 5.65 (1H, d, *J* 11, C*H*CO_2Me), 6.10 (1H, d, *J* 15.5, MeCC*H*═), 6.56 (1H, t, *J* 11, C*H*═CH–CO_2Me) and 7.41 (1H, dd, *J* 15.5, 11, MeCCH═C*H*); δ_C (126 MHz, $CDCl_3$) 25.5 (Me), 35.3 (CH_2), 36.8 (CH_2), 42.5 (*C*Me), 51.3 (OMe), 51.6 (CH_2), 116.9 (alkene), 124.1 (alkene), 145.0 (alkene), 151.0 (alkene), 166.9 (CO_2Me) and 218.1 (*C*═O); LRMS (ES^+) *m/z* 278 (M + NH_4^+, 100%), 261 (M + H^+), 229; HRMS (ES^+) 226.1437 ($C_{12}H_{20}NO_3$, M + NH_4^+, requires 226.1438).

(2*Z*,4*Z*,6*E*,8*E*)-9-(1-Methyl-3-oxo-cyclopentyl)-nona-2,4,6,8-tetraenoic acid methyl ester 14

A solution of iodide **6** (210 mg, 0.80 mmol) and olefin **12** (200 mg, 1.6 mmol) in dry MeCN (4 mL) in a dry Schlenk tube under argon was degassed using the freeze–pump–thaw method (1×), palladium(II) acetate (8 mg, 0.086 mmol) and silver(I) acetate (170 mg, 1.02 mmol) were added, the mixture was further degassed (2×) and heated to 60 °C with vigorous stirring in the absence of light. After 2.5 h the mixture was cooled, diluted with Et_2O (60 mL), passed through Celite and washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (EtOAc : pet. ether, 1 : 9 then 1 : 4 cooled to 0 °C as eluent) gave the title compound **14** (120 mg, 58%, 5 : 1 mixture with minor *Z*,*E*,*E*,*E*-isomer **15**) as a light red oil. ν_{max}/cm^{-1} (film) 2951, 1736, 1707, 1593, 1446, 1209 and 1164; δ_H (700 MHz, $CDCl_3$) 1.20 (3H, s, CMe), 1.83 (1H, m, C*H*H), 1.98 (1H, m, CH*H*), 2.09 (1H, d, *J* 18, C*H*H), 2.27 (2H, m, CH_2), 2.30 (1H, d, *J* 18, CH*H*), 3.73 (3H, s, OMe), 5.67 (1H, d, *J* 12, H1), 5.86 (1H, d, *J* 16, H8), 6.10 (1H, dd, *J* 16, 11, H7), 6.33 (1H, dd, *J* 15, 11, H6), 6.34 (1H, t, *J* 12, H4), 6.68 (1H, dd, *J* 15, 12, H5), 7.06 (1H, t, *J* 12, H2) and 7.25 (1H, t, *J* 12, H3); δ_C (176 MHz, $CDCl_3$) 26.0 (C*Me*), 35.8 (CH_2), 36.8 (CH_2), 42.3 (*C*Me), 51.4 (CH_2), 51.5 (OMe), 117.4 (alkene), 124.6 (alkene), 126.2 (alkene), 127.6 (alkene), 137.1 (alkene), 137.3 (alkene), 138.7 (alkene), 144.4 (alkene), 167.0 (CO_2Me) and 218.5 (ketone); LRMS (ES^+) *m/z* 226 (M + NH_4^+, 100%), 209 (M + H^+), 177; HRMS (ES^+) 278.1751 (M + NH_4^+, $C_{16}H_{24}NO_3^+$ requires 278.1751).

(2*Z*,4*Z*,6*E*,8*E*)-9-(1-Methyl-3-oxo-cyclopentyl)-nona-2,4,6,8-tetraenoic acid benzylamide 9

To a stirred solution of methyl ester **14** (50 mg, 0.19 mmol) in THF (3 mL) at 0 °C under argon was added a solution of $LiOH.H_2O$ (80 mg, 1.9 mmol) in water (3 mL) dropwise, the reaction was stirred for 19 h, diluted with Et_2O (40 mL), acidified with 5% HCl (5 mL) and separated. Drying ($MgSO_4$) and evaporation gave the crude acid (62 mg) as a brown oil. δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s, Me), 1.82–1.87 (2H, m, CH_2), 1.96–2.07 (1H, m, C*H*H), 2.13 (1H, d, *J* 18, C*H*H), 2.26–2.32 (1H, m, CH*H*), 2.34 (1H, d, *J* 18, CH*H*), 5.72 (1H, d, *J* 10, H1), 5.91 (1H, d, *J* 16, H8), 6.14 (1H, dd, *J* 16, 11, H7), 6.38 (1H, dd, *J* 15, 11, H6), 6.40 (1H, t, *J* 10, H4), 6.72 (1H, dd, *J* 15, 10, H5), 7.18 (1H, t, *J* 10, H2) and 7.23 (1H, t, *J* 10, H2). To a stirred solution of the crude acid in dry DCM (3 mL) at 0 °C under argon was added CDI (30 mg, 0.19 mmol), the mixture was stirred for 15 min and benzylamine (0.040 mL, 0.32 mmol) was added dropwise. The reaction was stirred for 9 h, warmed to room temperature, stirred for a further 13 h, diluted with EtOAc (40 mL) and washed with 5% HCl (10 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown tar. Purification by silica gel chromatography (EtOAc : pet. ether, 1 : 1 as eluent, cooled to 0 °C) gave the title compound **9** (28 mg, 44%) as a light brown oil. ν_{max}/cm^{-1} (film) 3296 (br), 2962, 1734, 1640, 1595, 1523, 1496 and 1240; δ_H (500 MHz, $CDCl_3$) 1.23 (3H, s, Me), 1.83–1.90 (1H, m, C*H*H), 1.96–2.04 (1H, m, CH*H*), 2.12 (1H, d, *J* 18, C*H*H), 2.28–2.32 (2H, m, CH_2), 2.32 (1H, d, *J* 18, CH*H*), 4.40 (1H, brs, NH), 4.50 (2H, d, *J* 5.6, CH_2Ph), 5.63 (1H, d, *J* 11, H1), 5.87 (1H, d, *J* 16, H8), 6.12 (1H, dd, *J* 16, 10, H7), 6.31 (1H, t, *J* 12, H4), 6.34 (1H, dd, *J* 16, 10, H6), 6.75 (1H, dd, *J* 15, 12, H5), 6.94 (1H, t, *J* 12, H2), 7.24–7.32 (5H, m, aryl) and 7.41 (1H, t, *J* 12, H3); δ_C (126 MHz, $CDCl_3$) 26.0 (Me), 35.8 (CH_2), 36.8 (CH_2), 42.2 (*C*Me), 43.7 (CH_2NH), 51.4 (CH_2), 124.9, 126.4, 127.8, 127.7, 127.7, 128.1, 128.8, 128.9, 135.4, 135.9, 136.2, 143.7, 166.2 and 218.8; LRMS (ES^+) *m/z* 226 (M + NH_4^+, 100%), 209 (M + H^+), 177; HRMS (ES^+) 336.1960 ($C_{22}H_{26}NO_2^+$, M + H^+ requires 336.1958).

2,2′-Iodoformyl biphenyl 18

A stirred solution of 1,2-diiodobenzene (0.99 g, 3.0 mmol), caesium(I) fluoride (1.8 g, 12 mmol), 2-formylphenylboronic acid **17** (0.90 g, 2.0 mmol) and triphenylphosphine (16 mmol, 0.06 mmol) in IPA (20 ml) and water (2 mL) was degassed by bubbling argon through the suspension for 30 min. After further degassing using freeze–pump–thaw (2 × cycles), palladium(II) acetate (6.7 mg, 0.03 mmol) was added, and the solution evacuated and filled with argon (3 × cycles). After stirring under argon, at 35 °C for 4 h, the reaction was cooled to room temperature, filtered through celite, diluted with diethyl ether (150 mL) and washed with 5% HCl (2 × 50 mL), water (75 mL) and brine (75 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a brown oil. Purification by silica gel chromatography (pet. ether : EtOAc, 15 : 1 as eluent) gave the title compound **18** as white needles (0.44 g, 48%). M.p. 89–90.5 °C; δ_H (400 MHz, $CDCl_3$) 7.04 (1H, dt, *J* 1.6, 7.7, *meta* Ar*H*), 7.19 (1H, d, *J* 8.0, *ortho* Ar*H*), 7.24 (1H, dd, *J* 1.6, 7.6, *ortho* Ar*H*), 7.37 (1H, dt, *J* 1.2, 7.6, *meta* Ar*H*), 9.69 (1H, d, *J* 0.8, CO_2H); δ_C (400 MHz, $CDCl_3$) 99.0 (I*C*) 126.4, 127.1, 127.6, 128.7, 129.5, 129.7, 132.4, 132.6, 138.1, 141.9, 146.7, 190.4. All spectroscopic and analytical data were identical to those stated in the literature.[13] Also identified was an and oxidative biproduct [1,1′-biphenyl]-2,2″dicarbaldehyde **20** as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.35 (2H, dd, *J* 1.2, 7.6, *ortho* Ar*H*), 7.59 (2H, t, *J* 7.6, *meta* Ar*H*), 7.67 (2H, dt, *J* 1.6, 7.6, *meta* Ar*H*), 8.05 (1H, dd, *J* 1.6, 7.6, *ortho* Ar*H*), 9.83 (1H, d, *J* 0.6, CO*H*); δ_C 128.7, 129.0, 131.9, 133(*C*OH). All spectroscopic and analytical data were identical to those stated in the literature.[14]

Methyl 2′-iodobiphenyl-2-carboxylate 19

To a solution of biaryl aldehyde **18** (0.10 g, 0.33 mmol) in methanol (2 mL), heated to 45 °C was added Oxone™ (0.20 g, 0.36 mmol) portion-wise. After stirring for 40 h the mixture was cooled to room temperature, diluted with EtOAc (50 mL), acidified with 5% HCl (10 ml) and extracted with EtOAc (3 × 20 ml). The organic extracts were then washed with water (2 × 40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product and

dark brown oil. Purification with silica gel chromatography (pet. ether : EtOAc 10 : 1, as eluent) gave the title product as a light yellow oil (88 mg, 79%). Rf 0.50 (pet. ether 5 : 1, as eluent); UV (CH_3CH_2OH, nm) 200 (ε 76 075); ν_{max}/cm^{-1} (film) 3067 (w, Ar C–H), 1726 (s, C═O), 1599 (m, Ar C═C), 1461, 1444, 1431, 1286, 1254; δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, CO_2CH_3), 7.05 (1H, dt, *J* 1.6, 7.6, meta IAr*H*), 7.21 (2H, dd, *J* 1.6, 7.6, *meta* IAr*H* and *meta* CO_2MeAr*H*), 7.39 (1H, dt, *J* 1.2, 7.2, *para* IAr*H*), 7.48 (1H, dt, *J* 1.2, 8.0, *meta* CO_2MeAr*H*), 7.59 (1H, dt, 1.6, 7.6, *para* CO_2MeAr*H*), 7.90 (1H, dd, *J* 1.2, 8.0, *ortho* IAr*H*), 8.04 (1H, dd, *J* 1.4, 8.0, *ortho* CO_2MeAr*H*); δ_C (400 MHz, $CDCl_3$) 52.1 (OCH_3), 98.8 (I*C*), 127.7, 128.0, 128.6, 128.9, 129.7, 130.2, 131.0, 131.9, 138.5, 145.5, 146.8, 167.0 (CO_2Me); LRMS (ES$^+$) *m*/*z* 361 (M^+ + Na^+), 356 (M^+ + H_2O, 100%), 339 (M^+ + H^+); HRMS (ES$^+$) *m*/*z* found (M^+ + H^+) 338.9744 calculated for $C_{14}H_{12}O_2I$ [H^+] 338.9882.

Methyl 2-iodobenzoate 23

A mixture of 2-iodobenzoyl chloride (10 g, 38 mmol), concentrated H_2SO_4 (0.30 mL) and methanol (60 mL) was heated to reflux and left overnight. The reaction was neutralised with Na_2CO_3 (25 mL), extracted with diethyl ether (3 × 75 mL) and washed with brine (75 mL). Drying ($MgSO_4$) and evaporation gave the title product **23** as a clear liquid (9.8 g, 98%). δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, OMe), 7.08 (1H, dt, *J* 1.6, 7.6, *para* Ar*H*), 7.35 (1H, dt, *J* 0.8, 6.8, *meta* Ar*H*), 7.73 (1H, dd, *J* 1.6, 7.6, *ortho* Ar*H*), 7.93 (1H, d, *J* 8, *ortho* Ar*H*). δ_C (400 MHz, $CDCl_3$) 52.5 (OCH_3), 94.0 (*C*I), 127.9, 130.9, 132.6, 135.2, 141.3, 167.0 (CO_2Me). All spectroscopic and analytical data were identical to that reported in the literature.[15]

Methyl 2′-formylbiphenyl-2-carboxylate 24

To a solution of iodide **23** (0.53 g, 2.00 mmol) in dimethylformamide (20 mL) was added triphenylphosphine (52 mg, 0.20 mmol), caesium fluoride (0.92 g, 6.02 mmol) and 2-formylphenylboronic acid (0.60 g, 4.02 mmol). The suspension was degassed by evacuation and refill (3 × cycles), to which was then added palladium(II) acetate (23 mg, 0.10 mmol). The suspension was further degassed as previously described (3 × cycles) before heating to 100 °C and leaving to vigorously stir. After 3 days the black suspension was cooled to room temperature, diluted with diethyl ether (100 mL) and filtered through Celite. The dark orange solution was washed with 10% HCl (2 × 60 mL), water (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to give the crude product as a dark orange oil. Purification by silica gel chromatography (pet. ether : EtOAc, 10 : 1 as eluent) gave the title compound **24** as a clear oil (0.42 g, 88%). δ_H (400 MHz, $CDCl_3$) 3.59 (3H, s, CO_2CH_3), 7.22 (1H, ddd, *J* 0.4, 1.2, 7.2, *ortho* Ar*H*), 7.28 (1H, ddd, *J* 0.4, 1.6, 7.6, *ortho* Ar*H*), 7.47–7.51 (2H, m, *para* Ar*H*), 7.54–7.61 (2H, m, *para* Ar*H*), 7.99 (1H, ddd, *J* 0.4, 1.6, 7.6, *ortho* Ar*H*), 8.00 (1H, ddd, *J* 0.4, 1.6, 7.6, *ortho* Ar*H*), 9.77 (1H, d, *J* 0.8, C*H*O); δ_C (400 MHz, $CDCl_3$); 52.2 (CO_2CH_3), 127.6, 128.1, 128.4, 130.3, 131.8, 131.9, 133.3, 134.1, 139.6 (*C*CO2Me), 145.3 (*C*CHO), 167.3 (*C*O2Me), 191.8 (*C*HO); LRMS (ES$^+$) *m*/*z* 295 (M^+ + CO_2H), 363 (M^+ + Na^+, 100%), 241 (M^+ + H^+); HRMS (ES$^+$) *m*/*z* found (M^+ + H^+) 365.00331 calculated for $C_{16}H_{13}O_2I$[H^+]: 365.00331. All spectroscopic and analytical data were identical to those stated in the literature.[16]

(*Z*)-Methyl 2′-(2-iodovinyl)biphenyl-2-carboxylate 25

To a suspension of (iodomethyl)phosphonium iodide (0.99 g, 1.25 mmol) in dry THF (9 mL) at −78 °C under argon was added NaHMDS (0.99 mL of a 2 M solution in THF). After stirring for 30 min at room temperature, the reaction was cooled back down to −78 °C followed by dropwise addition of aldehyde **24** (0.30 g, 1.25 mmol) under argon. After stirring for 3 h at −78 °C, methanol (10 mL) was added dropwise, and the reaction was allowed to warm to room temperature. The resulting mixture was washed with a mixture of $CHCl_3$ (20 mL) and water (10 mL) twice, dried ($MgSO_4$) and evaporated. Purification using silica gel chromatography (pet ether : EtOAc 15 : 1, as eluent) gave the title compound **25** as a yellow oil (0.41 g, 90%). UV (CH_3CH_2OH, nm) 260 (ε 45 691); ν_{max}/cm (neat) 2981 (w, C–H), 1739 (s, C═O), 1666 (s, C═C), 753 (*ortho* disubstituted aromatic); δ_H (400 MHz, $CDCl_3$) 3.49 (3H, s, CO_2CH_3), 6.26 (1H, d, *J* 8.4, ArC═C*H*), 6.71 (1H, d, *J* 8.4, IC═C*H*), 7.04–7.06 (1H, m, *para* Ar*H*), 7.10 (1H, dd, *J* 0.6, 7.2, *para* Ar*H*), 7.22–7.26 (2H, m, *ortho* and *para* Ar*H*), 7.29 (1H, dd, *J* 1.4, 7.6, *ortho* Ar*H*), 7.37 (1H, dt, *J* 1.6, 7.6, *para* Ar*H*), 7.60–7.62 (1H, m, *ortho* Ar*H*), 7.77 (1H, ddd, *J* 0.4, 1.6, 7.6, Ar*H*); δ_C (400 MHz, $CDCl_3$); 52.3 (CO_2CH_3), 82.1 (C═*C*I), 127.0, 127.8, 128.0, 128.1, 129.1, 130.2, 131.5, 131.6, 135.7, 138.7, 141.3, 141.6, 167.9 (CO_2Me). LRMS (ES$^+$) *m*/*z* 386 (M^+ + Na^+), 382 (M^+ + H_2O, 100%), 365 (M^+ + H^+); HRMS (ES$^+$) *m*/*z* found (M^+ + H^+) 365.00331 calculated for $C_{16}H_{13}O_2I$ [H^+] 365.00331.

Methyl 2′-((1*E*,3*E*)-4-(1-methyl-3-oxocyclopentyl)buta-1,3-dienyl)biphenyl-2-carboxylate 26

To a solution of iodide **25** (0.17 g, 0.47 mmol) in dry MeCN (5 mL) under bright light and argon was added silver(I) acetate (93 mg, 0.56 mmol), and palladium(II) acetate (5 mg, 0.02 mmol). The solution was then degassed by evacuating and refilling with argon (3 × cycles) before adding a solution of olefin **12** (75 mg, 0.61 mmol) in dry MeCN (0.75 mL) dropwise. The solution was further degassed in the same manner (3 × cycles) before heating to reflux with vigorous stirring. The starting material disappeared (monitored by TLC) after 24 h, the reaction was left for a further 48 h to encourage isomerism. After 72 h in total the reaction was cooled to room temperature, diluted with diethyl ether (60 mL), washed with 5% aqueous HCl (25 mL), water (3 × 40 mL) and brine (40 mL). After drying ($MgSO_4$) and evaporating, the crude product was left as a yellow oil. Purification on silica gel chromatography (pet ether : EtOAc, 4 : 1 as eluent) gave the title compound **26** as a clear oil (52 mg, 31%); UV (CH_3OH, nm) 204 (ε 25 586), 205 (ε 25 671); ν_{max}/cm (neat) 2951 (w, C–H), 1728 (s, C═O), 1684 (s, C═C), 751 (*ortho* disubstituted aromatic); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, s, CHCC*H*$_3$), 1.80–1.85 (1H, m, CMeC*H*$_2$), 1.93–2.01 (1H, m, CMeC*H*$_2$), 2.07 (1H, d, *J* 16, COC*H*$_2$), 2.25 (1H, d, *J* 4, COC*H*$_2$), 2.29 (2H, d, *J* 8, COC*H*$_2$), 3.53 (3H, s, CO2C*H*$_3$), 5.81 (1H, d, *J* 16, CMeC*H*═C), 5.95 (1H, d, *J* 12, ArC*H*═C), 6.04 (1H, t, *J* 12, CMeC═C*H*), 6.46 (1H, dd, *J* 16, ArC═C*H*), 7.18–7.24 (2H, m, *para* Ar*H*), 7.29–7.34 (3H, m, *ortho* and *para* Ar*H*), 7.38 (1H, dt, *J* 0.8, 7.6, *ortho* Ar*H*), 7.49 (1H, dt, 0.8, 7.6, *ortho* Ar*H*), 7.88 (1H, dd, *J* 1.2, 7.6, *ortho* Ar*H*); δ_C (400 MHz, $CDCl_3$) 26.2, 25.8, 37.0, 42.2, 51.8, 52.1 (OCH_3), 124.1, 127.2, 127.5, 128.8, 129.2, 129.4, 130.1, 130.2, 131.2, 131.5, 131.6, 135.7, 141.3, 142.2, 143.4 (*C*═C), 167.9 (CO_2Me), 218.9 (*C*═O cyclic); LRMS (ES$^+$)

m/z 383 ($M^+ + Na^+$), 378 ($M^+ + H_2O$, 100%), 361 ($M^+ + H^+$); HRMS (ES^+) *m/z* found ($M^+ + H^+$) 361.17984 calculated for $C_{24}H_{24}O_3$ [H^+]: 361.17982.

Methyl 2-((*E*)-2-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)vinyl)benzoate 28

To a dried Schlenk tube under positive pressure of argon was added a solution of iodobenzoate **23** (1.8 g, 3.8 mmol) in dry MeCN (35 mL). Added to the solution was palladium(II) acetate (21 mg, 0.095 mmol), triphenylphosphine (50 mg, 0.19 mmol) and silver(I) acetate (0.77 g, 4.6 mmol). The mixture was degassed using the freeze–pump–thaw method (2 × cycles), vinyl boronate **21** (0.71 g, 4.6 mmol) was then added and the mixture further degassed (2 × cycles) and heated to 70 °C with vigorous stirring. After 2 h, the mixture was cooled to room temperature to give a dark yellow solution which was diluted with Et_2O (160 mL), filtered through Celite, washed with 5% HCl (aq) (80 mL), water (160 mL) and brine (160 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a thick, orange oil. Purification by silica gel chromatography (pet. ether : EtOAc, 10 : 1 as eluent) yielded the title **28** product as a clear oil (0.93 g, 84%). Rf 0.28 (pet. ether : EtOAc 10 : 1 as eluent); ν_{max}/cm^{-1} (neat) 1731 (s, C═O), 1587 (w, Ar C═C), 1438 (s), 1308 (m), 1293 (m), 1132 (m), 1112 (m), 1132 (w), 996 (w), 25.9 (m); UV (CH_3OH, nm) 204 (ε 25 586), 205 (ε 25 671); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.0 BOCHC*H*$_3$), 1.34 (6H, s) (BOCC*H*$_3$), 1.55 (1H, dd, *J* 12, 14 BOCC*H*$_2$), 1.81 (1H, dd, *J* 3.0 Hz, 14 Hz) (BOCC*H*$_2$), 3.92 (3H, s) (OC*H*$_3$), 4.23–4.32 (1H, m, BOC*H*), 6.02 (1H, d, *J* 18) (C═C*H*BO), 7.33 (1H, dt, *J* 1.2, 7.6, ArC*H*═C), 7.44–7.47 (1H, m, *para* Ar*H*), 7.64 (1H, d, *J* 7.6, *ortho* Ar*H*), 7.84 (1H, dd, *J* 1.2 Hz, 8.0, *meta* Ar*H*), 7.99 (1H, d, *J* = 18.0 Hz) (*ortho* Ar*H*); δ_C (400 MHz, $CDCl_3$) 23.2 (*C*H$_3$), 28.2 (*C*H$_3$), 31.3 (*C*H$_2$), 46.0 (O*Me*), 52.0 (BO*C*), 64.8 (C═*C*), 70.9, 127.4, 127.6, 129.1, 130.1, 130.9, 140.0, 145.0, 168.0 (*C*OMe); $\delta_{B\{1H\}}$ (400 MHz, $CDCl_3$) 25.9; LRMS (ES^+) *m/z* 311 ($M^+ + Na^+$), 289 ($M^+ + H^+$, 100%), 243 (M + -CO_2H); HRMS (ES^+) *m/z* found ($M^+ + H^+$) 289.16066 calculated for $C_{16}H_{21}BO_4$ [H^+] 289.16057.

Methyl 2-((*Z*)-2-iodovinyl)benzoate 29

To a dry Schlenk flask under positive pressure of argon was added a solution of boronate **28** (0.50 g, 1.7 mmol) in dry DCM (11 mL). The mixture was degassed using the freeze–pump–thaw method (2 × cycles) and then cooled to −78 °C. ICl (1.8 mL, 1.8 mmol, 1 M in DCM) was then added dropwise and the solution was left to stir for 90 min. After warming to room temperature the solution was left to stir for a further 2 h, after which NaOMe (3.6 mL, 1.7 mmol, 0.5 M in methanol) was then added to produce a pale yellow/purple solution. The reaction was then stirred for 30 min, diluted with diethyl ether (60 mL), washed with sodium metabisulfite (40 mL), water (60 mL) and brine (60 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a pale yellow oil. Purification using silica gel chromatography (pet. ether : EtOAc, 15 : 1 as eluent) gave the title product **29** as a pale yellow oil (0.49 g, 93%). ν_{max}/cm^{-1} (neat) 2948 (w, C–H), 1715 (s, C═O), 1596 (w, C═C alkene), 1478 (w, C═C aromatic), 1433 (m, C═C aromatic), 1259 (s, C–OCH_3); UV (CH_3OH, nm) 308 (ε 4507); δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, OC*H*$_3$), 6.62 (1H, d, *J* 8.4, CI*H*═C), 7.42 (1H, dt, *J* 2.0, 8.0, *meta* Ar*H*), 7.53–7.58 (2H, m, *ortho* and *meta* Ar*H*), 7.73 (1H, d, *J* 8.4, *Z*-iodide CI═C*H*), 8.02 (1H, d, *J* 7.6 *ortho* Ar*H*),; δ_C (400 MHz, $CDCl_3$); 52.1 (O*Me*), 81.9 I*C*═C), 128.0, 128.5, 130.3, 130.6, 132.0, 139.5, 140.2, 144.1, 166.9(*C*O_2Me); LRMS (ES^+) *m/z* 311 ($M^+ + Na^+$), 289 ($M^+ + H^+$, 100%), 161; HRMS (ES^+) *m/z* found ($M^+ + H^+$) 288.97192 calculated for $C_{10}H_9IO_2$ [H^+]: 288.97201.

Methyl 2-((1*Z*,3*E*)-4-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)buta-1,3-dienyl)benzoate 31

In a dry Schlenk flask under argon was added a solution of vinyl iodide **29** (0.30 g, 1.0 mmol) in dry MeCN (4.5 mL). To the solution was added P(*o*-tol)$_3$ (32 mg, 0.10 mmol), Palladium(II) acetate (12 mg, 0.05 mmol), silver(I) acetate (0.21 g, 1.3 mmol). The reaction was degassed using the freeze–pump–thaw method (2 × cycles). Vinyl boronate **21** (0.19 g, 1.3 mmol) was then added and the mixture further degassed (2 × cycles), and then heated to 50 °C with vigorous stirring. After 2 days, the reaction was cooled to room temperature, diluted with diethyl ether (80 mL), filtered through Celite and then washed with 5% HCl (aq) (2 × 20 mL), water (40 mL) and brine (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a thick, orange oil. Purification by silica gel chromatography (pet. ether:EtOAc, 20 : 1 as eluent) yielded the title product **31** as a yellow oil (0.29 g, 87%). Rf 0.15 (pet. ether : EtOAc, 10 : 1 as eluent); ν_{max}/cm^{-1} (neat) 2972 (w, C–H), 1719 (C═O), 1621 (m, C═C), 1589 (m, Ar–H), 1257 (C–O), 766.3 (*ortho* Ar–H); UV (CH_3OH, nm) 315 (ε 5441); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.0, BOC*H*Me), 1.25 (3H, s, BOCMeC*H*$_3$), 1.26 (3H, s, BOCMeC*H*$_3$), 1.46 (1H, dd, *J* 12, 13, BOCMe$_2$C*H*$_2$), 1.75 (1H, dd, *J* 2.8, 14, BOCMe$_2$C*H*$_2$), 3.86 (3H, s, CO_2CH_3), 4.18 (1H, qt, *J* 2.8, 12, BOC*H*Me), 5.65 (1H, d, 17, *trans* BC*H*═C), 6.36 (1H, dt, *J* 0.8, 11, *cis* C*H*═C), 7.00 (1H, d, 12, *cis* C═C*H*), 7.12 (1H, ddd, *J* 1.2, 11, 17, *trans* C═C*H*), 7.34 (1H, dt, *J* 1.2, 7.6, *meta* Ar*H*), 7.40 (1H, d, *J* 7.2 *ortho* Ar*H*), 7.51 (1H, dt, *J* 1.2, 7.6, *meta* Ar*H*), 7.85 (0.04H, dd, *J* 1.2, 8.0, *ortho* Ar*H* minor isomer), 7.98 (1H, dd, *J* 1.2, 7.6, *ortho* Ar*H*); δ_C (400 MHz, $CDCl_3$) 23.1 (*C*H$_3$), 28.1 (*C*H$_3$), 31.2 (*C*H), 46.0 (*C*H$_2$), 52.0(O*C*H$_3$), 64.7 (C═*C*H), 70.7 (*C*Me$_2$), 127.1, 129.1, 130.6, 131.6, 131.8, 131.9, 132.1, 138.8, 142.3, 167.4 (*C*O_2Me); $\delta_{B\{1H\}}$ (400 MHz, $CDCl_3$) 25.91 (s); LRMS (ES^+) *m/z* 337 ($M^+ + Na^+$), 332 ($M^+ + H_2O$), 315 (M + H^+, 100%); HRMS (ES^+) *m/z* found ($M^+ - C_{18}H_{23}BO_4 + H^+$) 315.17634 calculated for $C_{18}H_{23}BO_4$[H^+]: 315.17622.

Methyl 2-((1*Z*,3*E*)-4-iodobuta-1,3-dienyl)benzoate 8

To a solution of boronate **31** (0.55 g, 1.75 mmol) in dry THF (12 mL) was added NaOMe (0.5 M in MeOH, 4.20 mL, 2.101 mmol) at −78 °C, and left to stir for 30 min. ICl (1 M in DCM, 1.80 mL, 1.80 mmol) was then added followed by further stirring at −78 °C for 1 h. After warming to room temperature, the solution was diluted with diethyl ether (80 mL), washed with sodium metabisulfite (60 mL), water (80 mL) and brine (80 mL), dried ($MgSO_4$) and evaporated to leave the crude product as a bright yellow oil. Purification using silica gel chromatography (pet. ether : EtOAc 5 : 1, as eluent) gave the title compound **8** as a bright yellow oil (0.46 g, 84%);. Rf (pet. ether : EtOAc, 5 : 1 as eluent); ν_{max}/cm^{-1} (neat) 1714 (s, C═O), 1258 (s, C–O), 763 (m, *o*-substituted Ar ring); UV (CH_3OH, nm) 318 (ε 48 600), 209

(ε 48 366), δ_H (400 MHz, $CDCl_3$) 3.87 (1H, s, CO_2CH_3), 6.23 (1H, t, *J* 12, *Z* ArC=C*H*), 6.43 (0.05H, dd, *J* 1.2, 10), 6.50 (1H, d, *J* 14, *E* IC*H*=C), 6.89 (0.05H, ddd, *J* 1.2, 7.6, 10.4, *Z* IC=C*H*) 6.95 (1H, d, *J* 12, *Z* ArC*H*=C), 7.20 (1H, ddd, *J* 1.2, 11, 14, *E* IC=C*H*), 7.31 (1H, d, *J* 7.6, *ortho* Ar*H*), 7.37 (1H, dt, *J* 0.8, 7.6, *meta* Ar*H*), 7.51 (1H, dt, *J* 1.2, 7.2, *meta* Ar*H*), 7.99 (1H, dd, *J* 1.2, 8.0, *ortho* Ar*H*); δ_C 52.1, 82.1, 127.6, 129.0, 129.1, 130.8, 130.9, 131.4, 132.0, 138.2, 141.5, 167.2; LRMS (ES^+) *m/z* 378, 315 ($M + H^+$, 100%), 278; HRMS (ES^+) *m/z* found ($M^+ + H^+$) 314.98773 calculated for $C_{12}H_{11}IO_2$ [H^+] 314.89766.

2-((1*Z*,3*E*)-4-Iodobuta-1,3-dienyl)benzoic acid 32

To a stirred solution of iodide **8** (0.10 g, 0.3 mmol) in THF (1 mL) at 0 °C, under a positive pressure of argon, in the absence of light, was added a solution of $LiOH{\cdot}H_2O$ (80 mg, 1.9 mmol) in water (1 mL). After stirring for 16 h, the solution was warmed to room temperature and left to stir for a further 6 h. The solution was then diluted with diethyl ether (40 mL), washed with 5% HCl (2 × 10 mL) and water (40 mL). Drying ($MgSO_4$) and evaporation gave the crude product as a light yellow solid. Purification using silica gel chromatography (2 : 1 pet. ether : EtOAc) gave the title compound **32** as a white solid (91 mg, 96%). M.p. 101–103 °C, Rf 0.21 (2 : 1 pet. ether : EtOAc), ν_{max}/cm^{-1} (neat) 2965, 2812, 2643 (w, O–H), 1675 (s, C=O), 1565 (s, Ar–H), 753 (m, *o*-substituted Ar ring); UV (CH_3OH, nm) 205 (ε 8203), 317 (ε 2154); δ_H (400 MHz, $CDCl_3$) 6.25 (1H, t, *J* 7.4, *cis* ArC=C*H*), 6.52 (1H, d, *J* 14, *trans* IC*H*=C), 6.99 (1H, d, *J* 12, *cis* ArC*H*=C), 7.20 (1H, ddd, *J* 1.2, 11, 14, *trans* IC=C*H*), 7.35 (1H, d, *J* 8.0, *ortho* Ar*H*), 7.40 (1H, dt, *J* 0.8, 7.6, *meta* Ar*H*), 7.58 (1H, dt, *J* 1.2, 7.6, *meta* Ar*H*), 8.13 (1H, dd, *J* 1.2, 8.0, *ortho* Ar*H*), δ_C 82.4 (*C*I), 127.7, 129.2, 130.8, 131.6, 131.8, 133.0, 139.1, 141.4, 172.2 (*C*O_2H); LRMS (ES^+) *m/z* 300 (M^+), 299 ($M - H^+$, 100%); HRMS (ES^-) *m/z* found (M^+ $C_{11}H_9O_2I - H^+$) 298.95728 calculated for $C_{12}H_8O_2I$: 298.95745.

N-Benzyl-2-((1*Z*,3*E*)-4-iodobuta-1,3-dienyl)benzamide 33

To a solution of benzoic acid **32** (60 mg, 0.19 mmol) in DCM (0.8 mL) cooled to 0 °C was added CDI (40 mg, 0.25 mmol). After stirring for 30 min, benzylamine (30 mg, 0.25 mmol) was added, and the mixture was allowed to warm to room temperature, and stirred overnight. The mixture was diluted with dichloromethane (5 mL), washed with 5% HCl (2 × 20 mL) water (2 × 10 mL), brine (1 × 20 mL), dried ($MgSO_4$) and evaporated to leave the crude product as a pale yellow solid. Purification by silica gel chromatography (pet. ether : EtOAc 2 : 1, as eluent) gave benzamide **33** as a white solid (67 mg, 90%). M.p. 112–115 °C; Rf 0.30 (pet. ether : EtOAc 2 : 1, as eluent); ν_{max}/cm^{-1} (neat) 1676 (s, aryl C=O), 1479 (m, OH); UV (CH_3OH, nm) 325 (ε 3450); δ_H (400 MHz, $CDCl_3$) 4.36 (1H, s, NCH_2), 4.60 (1H, d, *J* 5.6, NCH_2), 5.01 (1H, br s, N*H*, which disappears on shaking with D_2O), 6.24 (1H, t, *J* 12, ArC*H*=C), 6.57 (1H, d, *J* 14, IC*H*=C), 6.69 (1H, d, *J* 11, ArC=C*H*), 7.25–7.28 (3H, *m*, *ortho* BnAr*H* and IC=C*H*), 7.30–7.37 (5H, m, *ortho* and *para* Ar*H*), 7.43 (1H, t, *J* 7.2, *ortho* Ar*H*), 7.63 (1H, d, *J* 7.6, *para* Ar*H*); δ_C (400 MHz, $CDCl_3$) 126.5, 128.8, 129.9, 131.3, 131.5, 131.8, 132.3, 132.7, 132.9, 139.4, 141.0, 172.9 (*C*O_2H); LRMS (ES^+) *m/z* 403 ($M^+ + NH_4^+$, 100%), 390 ($M^+ + H^+$); HRMS (ES^+) *m/z* found (M^+ $C_{18}H_{16}NOI + H^+$) 390.40265 calculated for $C_{18}H_{16}NOI$ [H^+]: 390.23819.

Methyl 2-((1*Z*,3*E*,5*E*)-6-(1-methyl-3-oxocyclopentyl)hexa-1,3,5-trienyl)benzoate 34

To a solution of iodide **8** (0.22 g, 0.70 mmol) in dry MeCN (6 mL) in a dry Schlenk flask, under positive pressure of argon, in the absence of light, was added AgOAc (0.12 g, 0.71 mmol) and palladium(II) acetate (7.00 mg, 0.03 mmol). The mixture was degassed using freeze–pump–thaw (3 × cycles) and olefin **12** (113 mg, 0.92 mmol) was then added. The mixture was degassed further using freeze–pump–thaw (2 × cycles). After heating and stirring overnight at 60 °C, the reaction was cooled to room temperature, diluted with diethyl ether (40 mL), washed with 5% HCl (2 × 20 mL), water (2 × 30 mL) and brine (30 mL) and was then dried ($MgSO_4$). Evaporating under vacuum gave the crude product as a deep orange oil. Purification by silica gel chromatography (pet. ether : EtOAc, 10 : 1 as eluent) gave the title compound **34** as a bright orange oil (0.50 mmol, 94% yield) as a single diastereoisomer. Rf = 0.24 (pet. ether : EtOAc 5 : 1, as eluent); ν_{max}/cm^{-1} (neat) 1736 (C=O), 1716 (C=O), 1561 (C=C), 768 (*o*-substituted Ar ring); UV (CH_3OH, nm) 319 (ε 21 228), 322 (ε 21 200); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, s, C=CHCCH_3), 1.79–1.86 (1H, m, CCH_3CH_2), 1.93–2.00 (1H, m, C=OCH_2), 2.08 (1H, d, *J* 18, C=OCH_2), 2.25–2.29 (2H, m, C=OCH_2 and CCH_3CH_2), 2.32 (1H, s, C=OCH_2), 3.86 (3H, s, CO_2CH_3), 5.77 (1H, d, *J* 16, CCH_3CH=C *E*), 5.99 (1H, dd, *J* 10, 15, CCH_3C=C*H E*), 6.22 (1H, dd, *J* 5.8, 10, ArC=C*H Z*), 6.27 (1H, d, *J* 11, C*H*=C *E*), 6.30–6.38 (1H, m, C=C*H E*), 6.93 (1H, d, *J* 11, ArC*H*=C *Z*), 7.31–7.38 (2H, m *ortho* and *para* Ar*H*), 7.50 (1H, dt, *J* 1.3, 7.6, *para* Ar*H*), 7.97 (1H, dd, *J* 1.4, 8.0, *ortho* Ar*H*); δ_C (400 MHz, $CDCl_3$) 26.2, 35.9, 36.9, 42.2, 51.6 (O*C*H_3), 52.2, 127.3, 127.9, 128.4, 129.3, 129.9, 130.3, 130.8, 131.6, 132.0, 134.8, 139.1, 142.1, 167.7 (*C*O_2Me). 218.8 (*C*=O); LRMS (ES^+) *m/z* 333 ($M^+ + Na^+$, 100%), 328 ($M^+ + H_2O$), 311 ($M^+ + H^+$); HRMS (ES^+) *m/z* found ($M^+ + H^+$) 311.16421 calculated for $C_{20}H_{22}O_3$ [H^+] 311.16417.

N-Benzyl-2-((1*Z*,3*E*,5*E*)-6-(1-methyl-3-oxocyclopentyl)hexa-1,3,5-trienyl)benzamide 11

To a stirred solution of triene **34** (0.14 g, 0.44 mmol) in THF (3 mL) under positive pressure of argon, at 0 °C, in the absence of light was added a solution of $LiOH{\cdot}H_2O$ (0.18 g, 4.35 mmol) in H_2O (3 mL). After stirring for 30 h, the bright yellow solution was diluted with diethyl ether (60 mL), washed with 5% HCl (2 × 30 mL) and H_2O (30 mL), dried ($MgSO_4$) and evaporated to produce the dark orange crude product (0.14 g) containing the corresponding acid. To a solution of the crude acid (0.14 g, 0.47 mmol) in dry DCM (5 mL) under positive pressure of argon at 0 °C, in the absence of light, was added CDI (92 mg, 0.57 mmol). After stirring for 30 min, benzylamine (61 mg, 0.57 mmol) was added and was left to stir for 48 h. The bright yellow solution was then diluted with diethyl ether (60 mL), washed with 5% HCl (2 × 30 ml) and H_2O (30 mL), dried ($MgSO_4$) and evaporated to give the crude product as a bright orange oil. Purification by silica gel chromatography (pet ether : EtOAc, 4 : 1, as eluent) gave the title compound **11** as a bright yellow oil (0.25 mmol, 59%). Rf = 0.24 (pet. ether : EtOAc 5 : 1, as eluent); ν_{max}/cm^{-1} (neat) 1732 (s, C=O), 1639 (s, C=C), 1527 (s, NH), 731 (m, *o*-substituted Ar ring), 3024, 3607, 3395 (w, CONH); UV (CH_3OH, nm) 287 (ε 182 110), 250 (ε 119 605); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, s, C=CHCCH_3), 1.81

(1H, dt, *J* 8.0, 12, CCH_3CH_2), 1.96 (1H, dt, *J* 8.0, 12, C═OCH_2), 2.06 (1H, d, *J* 16, C═OCH_2), 2.23–2.27 (2H, m, C═OCH_2 and CCH_3CH_2), 2.29–2.32 (1H, m, C═OCH_2), 4.58 (2H, d, *J* 4.0, NCH_2), 5.79 (1H, d, *J* 16, CCH_3CH═C *E*), 5.99 (1H, dd, *J* 8, 16, CCH_3C═C*H E*), 6.24 (1H, br s, N*H* which disappears on shaking with D_2O), 6.22 (1H, dd, *J* 5.8, 10, ArC═C*H Z*), 6.27 (1H, d, *J* 11, C*H*═C *E*), 6.30–6.38 (1H, m, C═C*H E*), 6.93 (1H, d, *J* 11, ArC*H*═C *Z*), 7.31–7.38 (2H, m *ortho* and *para* Ar*H*), 7.50 (1H, dt, *J* 1.3, 7.6, *para* Ar*H*), 7.97 (1H, dd, *J* 1.4, 8.0, *ortho* Ar*H*); δ_C (400 MHz, $CDCl_3$) 26.2, 35.9, 36.9, 42.2, 51.6 (OCH_3), 52.2, 127.3, 127.9, 128.4, 129.3, 129.9, 130.3, 130.8, 131.6, 132.0, 134.8, 139.1, 142.1, 167.7 (CO_2Me). 218.8 (*C*═O); LRMS (ES^+) *m*/*z* 408 ($M^+ + Na^+$), 386 ($M^+ + H^+$, 100%); HRMS (ES^+) *m*/*z* found ($M^+ + H^+$) 386.29959 calculated for $C_{26}H_{27}NO_2$ [H^+] 386.21200.

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